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ABSTRACT BOOK

IX international conference on novel psychoactive substances

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IX INTERNATIONAL CONFERENCE ON NOVEL PSYCHOACTIVE SUBSTANCES

In recent years, there has been a dramatic increase in the number of new psychoactive substances (NPS) detected across the world. The NPS market remains resilient and highly dynamic and is characterised by the emergence of large numbers of new substances reported in a growing number of countries. Between 2009 and 2021, 134 countries and territories reported the emergence of 1 127 NPS to the United Nations Office on Drugs and Crime (UNODC), through the UNODC Early Warning Advisory on NPS. In Europe, since 1997, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), has been monitoring and responding to NPS appearing on the market through the EU Early Warning System on NPS. At the end of 2021, the EMCDDA was monitoring over 880 NPS. The increase in the number and availability of NPS in recent years has largely been driven by globalisation, the internet and rapid changes in technology. Yet, recently, there have been some encouraging signs. For example, the number of NPS reported annually for the first time in Europe has dropped from a high of around 100 in 2014 and 2015 to around 50 in 2017 and in successive years. Nevertheless, NPS continue to pose numerous challenges in terms of: detecting, measuring and monitoring; understanding patterns of use and harms caused; and developing appropriate public health responses. In Europe, around one new substance is still detected every week, increasing the overall number to be monitored. Major new problems have also emerged, that have led to an increasing number and range of risks for people who use psychoactive substances. These include an increase in the number of highly potent NPS on the market — many of which are synthetic cannabinoids or synthetic opioids — and the impact of the COVID-19 pandemic. Faced with the numerous challenges posed by NPS, the International Society for the Study of Emerging Drugs (ISSED) strives to strengthen multidisciplinary and international collaboration, enhance knowledge and improve the quality of information-sharing in this complex area. In this context, this NPS conference series is the major international forum on NPS, attracting hundreds of participants worldwide. This year's conference is jointly organised by the ISSED, UNODC, the EMCDDA, the World Anti-Doping Agency (WADA), the University of Hertfordshire (UH), the Centre for Forensic Science Research & Education (CFSRE), the Government of Panama, the Regional Anti-Doping Organization of Central America and the Panamanian Anti-Doping Organization. This year marks the 25th anniversary of the EU Early Warning System on NPS — the first regional early-warning mechanism set up to monitor and respond to NPS in Europe. It is also nine years since this series of international conferences on NPS started in Budapest. The increasing impact of NPS, and the role of global factors in shaping related threats, highlight both the key role of early-warning systems in providing reliable information in a timely manner and the need for international collaboration.

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IX NPS CONFERENCE ABSTRACTS

(in alphabetical order)

Development and validation of a chiral LC-MS/MS method for the separation and quantification of (R)- and (S)-enantiomers of four synthetic cathinones in human whole blood

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Introduction: Synthetic cathinones, a subclass of new psychoactive substances, have gained high popularity on the recreational drugs market over the past years. As these drugs contain a chiral center, pharmacological, pharmacokinetic and metabolic properties of their enantiomers are expected to differ. However, these drugs are often sold as a racemic mixture, and therefore differentiation of their (R)- and (S)- enantiomers is relevant in clinical and forensic toxicology. Information about single enantiomers of synthetic cathinones is relatively scarce due to challenges of their chiral analysis. Methods: a sensitive and reliable liquid chromatography–tandem mass spectrometry method was developed and validated for the separation and quantification of 4 synthetic cathinones in human whole blood samples. Results: The method was fully validated in terms of linearity, limit of detection, limit of quantification, bias, precision, carryover, interferences, matrix effects, recovery and processed sample stability using published guidelines, and successfully applied to evaluate the stability of single enantiomers under various storage conditions. Conclusions: Both enantiomers for each target analyte were shown to degrade over time with stability of E1-enantiomers being slightly better than their E2-enantiomers, except for MDPV, but these differences were statistically insignificant.

Preventing drug harm in Aotearoa, New Zealand. Part 1. High alert: New Zealand's drug earlywarning system works to identify NPS and prevent drug harm

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Introduction:High Alert is the public face of Drug Information and Alerts Aotearoa New Zealand (DIANZ), New Zealand's drug early warning system. DIANZ consists of representatives from government agencies and is supported by a network of health professionals and social services. The core function of DIANZ is to gather and analyse data from various sources to build an understanding of the illicit drug environment and reduce drug harm. This includes the identification of new psychoactive substances (NPS) to New Zealand. Methods: Information on NPS is gathered from several sources including police data, customs seizures, ambulance incidence data, drug checking services and public submissions. When identified, samples that possibly contain NPS are sent to the ESR for confirmational analysis. Results: Since launching in June 2020, High Alert has published 4 notifications for NPS that had not previously been identified in New Zealand, including synthetic cannabinoids, synthetic cathinones and synthetic opioids. High Alert has also identified several NPS that have not been publicly notified but were discussed with network partners. Conclusion: The integration of many information sources has resulted in High Alert supporting the identification of NPS in New Zealand and has allowed for the development and implementation of harm reduction methods.

Large scale retrospective identification of new psychoactive substances in clinical routine samples

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Introduction: New psychoactive substances (NPS) pose a particular health threat through unpredictable toxicity, but also due to their unknown prevalence, high turn-over, and frequent structural changes that limit the analytical information available to healthcare professionals. Techniques and strategies for monitoring of NPSs in clinical samples therefore need to be further developed. Retrospective identification of NPS in raw data from liquid chromatography-high resolution mass spectrometry (LC-HRMS) has, to our knowledge, not been used previously on clinical routine samples in a scale allowing for epidemiological analyses or for evaluation of its clinical potentiality. Methods: Retrospective identification of 88 NPS was performed in raw data from a LC-HRMS based multidrug panel analysis on more than 14,000 clinical samples requested during 2019 mainly from psychiatric and addiction care clinics in Sweden. Results: Thirty-four substances were identified in approximatively 1% of samples and 2% of patients. Differences in NPS use in relation to patient's gender, age and use of traditional drugs, as well as type of clinic and legal (scheduling) status of NPS, were observed and will be discussed. Conclusions: Retrospective identification of NPS appears to be a useful tool when prioritizing which NPSs to include in clinical routine analysis, and when studying NPS epidemiology.

Trends in the international use of novel psychoactive substances through wastewater analysis

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Introduction: Wastewater analysis has become a key tool in the monitoring of novel psychoactive substances (NPS) and is complementary to traditional methods such as surveys, drug seizures and forensic information. More than 1100 substances have been reported to the United Nations Office of Drugs and Crime Early Warning Advisory on NPS from

all continents. With new NPS being identified every year, it is crucial from a public health standpoint to continue to monitor these compounds. In this work, influent wastewater was collected from up to 50 sites over three consecutive New Year periods (2019-20, 2020-21 and 2021-22). The number of sites and countries involved in the campaigns has increased from 12 sites (8 countries) to more than 50 sites in 15 countries. The New Year was chosen as the sampling period because it is a time internationally renowned for parties and increased drug use. The comparison of these three campaigns allows us to distinguish specific trends in international use of NPS and potentially predict where and which NPS will next emerge. Methods: 24-hour composite influent wastewater samples were collected for up to 10 days from every site over the New Year period. Samples were collected from sites in eight countries in 2019-20, (Australia, United States, New Zealand, Italy, Spain, Norway, China, and the Netherlands) from 10 countries in 2020-21 (Australia, New Zealand, China, Spain, Italy, Canada, United States, Fiji, Republic of Korea and Belgium) and 15 countries in 2021-22 (Australia, New Zealand, China, Spain, Italy, Canada, United States, Republic of Korea, Greece, Brazil, Slovenia, Cyprus, Iceland, France and Sweden). These sites contained small towns, large cities, and sites a known influx of holidaymakers. Samples were either sent directly to Australia for analysis or first loaded onto solid-phase extraction cartridges. All samples were analysed using liquid chromatography – mass spectrometry instruments and validated methods for a variety of classes including synthetic cathinones, phenethylamines, synthetic cannabinoid receptor agonists, opioids, designer benzodiazepines as well as plant-based NPS. Results: With three years of data collected, trends in NPS use are becoming apparent. Across the three sampling periods, a total of 15 NPS were quantified including synthetic cathinones (e.g. eutylone, N-ethylpentylone, 3-methylmethcathinone (3-MMC) and mephedrone), phenethylamines (e.g. 4-fluoroamphetamine), benzoidiazepines (e.g. etizolam) as well as plant-based NPS (e.g. mitragynine). It was found that 3-MMC had highest levels in sites in Europe, while eutylone and mephedrone was in Oceania and mitragynine in North America. The dynamic nature of NPS was also observed. For example, N-ethylpentylone was one of the more prevalent synthetic cathinones in the first collection but was later replaced by eutylone. Moreover, 3-MMC was initially only seen in Europe, but in later campaigns was also seen in Oceania. Conclusions: This work has highlighted the utility of wastewater analysis as a tool in the surveillance and detection of novel psychoactive substances. Through the analysis of up to 15 countries, both country- and continent-specific preferences could be ascertained. It has the potential to act as a global early warning system and can help international public health agencies to better focus their efforts to reduce harm.

Optimisation of a gas chromatography coupled to mass spectrometry (GC-MS) method for simultaneous detection and quantification of psilocybin and psilocin

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Introduction: Psilocybin is the main mushroom hallucinogen, being rapidly dephosphorylated into its bioactive metabolite, psilocin, upon ingestion. Given the nonspecificity of the adverse/toxic effects induced by magic mushrooms ingestion, the correct identification of intoxications depends on the detection of these compounds in the consumer system and/or the consumed product. We aimed to develop and optimise a GC-MS methodology for the simultaneous detection and quantification of psilocybin and psilocin. Methods: Methanol solutions of psilocybin, psilocin and their mixtures were evaporated to dryness using a SpeedVac concentrator, resuspended with the derivatisation agent MSTFA (N-trimethylsilyl-N-methyl trifluoroacetamide) with 1% TMCS (trimethylchlorosilane), and incubated in a thermoblock for 1 h at 90 oC. After cooling down to room temperature, the dry residue was dissolved in ethyl acetate and 1 µL injected in the GC-MS equipment. The analysis was performed in SIM mode using a GC-2010 Plus coupled to a MS QP2020 (Shimadzu, Japan), with an SH-Rxi-5ms capillary column (30mx0.25mmx0.25µm). Based on previously published methodologies, the chromatographic conditions were optimised to allow detection of the target compounds. Results: Bis(trimethylsilyl)psilocin (m/z 290 and 348) was detected with a mean retention time (RT) of 6.821 min. A correlation coefficient higher than 0.90 was determined, evidencing the method linearity within the range of 0.07812–10 µg/mL. Tri(trimethylsilyl)psilocybin (m/z 442, 455 and 485) was detected with a mean RT of 8.430 min, however there was no linearity at the tested range (1.25–160 µg/mL). We were able to simultaneously detect the drugs at the highest concentrations tested for the mixture (50 and 100 µg/mL). Conclusions: In this preliminary work, both psilocin and psilocybin were detected in a time- efficient way, but further optimisation is required to improve the detection and quantification of psilocybin. Acknowledgements: FCT projects UIDP/04378/2021, UIDB/04378/2021, LA/P/0140/2021 and PhD grant 2021.04999.BD.

Public health impacts of novel pharmacologically active adulterants in international drug supply

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Introduction: The drug supply is ever changing in terms of the main pharmaceutical ingredient as evidenced by the proliferation of novel psychoactive substances reported by EMCDDA, UNODC, NPS Discovery and others. With increasing frequency these street drug supplies are cut or adulterated with substances designed to add bulk, but also with pharmacologically active substances many of which have toxic effects of their own. This presentation will review the most prevalent substances internationally identified as toxic adulterating substances, including many banned substances, NPS, and veterinary drugs. Methods: The Colombo Plan collaborates with forensic laboratory directors internationally to collect information on the multiple constituents identified in street drug samples and works with the Center for Forensic Science Research and Education (CFSRE) to test seized drug samples in the United States

specifically to identify both legacy and new adulterants. Results: This work has identified many NPS substances such as designer benzodiazepines (e.g. bromazolam, flualprazolam, and etizolam), added to the fentanyl supply and sold as "benzo dope" in the midwestern United States, and Xyalizine, a veterinary tranquilizer and sedative is now routinely found in fentanyl in the northeast of the United States. Other novel substances reported as adulterating agents include anticoagulant drugs such as the superwarfarins which have been identified in drug intoxication outbreaks in the United States and Jordan. These emerging substances all have significant adverse public health effects and complicate drug treatment and drug user education. Reports of patterns of drug adulterants are reported through the Colombo Plan's International Toxic Adulterants Database (ITAD). Conclusions: Toxic adulterating substances should not be overlooked for their public health impact and the Colombo Plan has made significant investments in making drug toxicity data, adverse effects profiles and treatment regimens for exposure to these substances available to stakeholder communities.

The role of The Burke Test in measuring the cognitive efficiency of the drug impaired driver

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Introduction: Driving is a divided attention (psychophysical) task in which the operator must be able to process information from the ever-changing external environment, while physically manipulating the controls of a motor vehicle. Methods: The Burke Test requires an impaired subject to collect $2.42 in US coins while sorting through multiple objects such as European and US coins, nuts, bolts, washers, game tokens, and buttons. As the subject is sorting, a marble is rolled every five seconds through the subject's field of vision. This targets vigilance, judgment, reaction time and peripheral vision, all of which are critical for the safe operation of a motor vehicle. Being that there is only $1.73 in US currency, it is impossible for the subject to collect the requested $2.42. Results: Pending but positive. Conclusions: The Standardized Field Sobriety Tests (SFST) have been used for decades by American law enforcement (ALE) during impaired driving investigations. Novel Psychoactive Substances (NPS) that have flooded the American drug market, and the legalization of marijuana have seen the SFST become antiquated, because they were created to measure impairment at, or near certain breath/blood alcohol levels. Due to marijuana, and many of the NPS causing a high degree of cognitive impairment, it is crucial that ALE use tests the target cognitive efficiency during impaired driving investigations.

Flipped point-of-use detection of psychoactive substances by coupling Raman spectroscopy to computational approaches

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Introduction: New psychoactive substances misuse represents a critical social and health problem. It is often reported that abuse of these substances often leads to negative outcomes such as violence and aggression, sympathomimetic effects, acute organ failures as well as fatalities. This is compounded by the fact that still little is known about the acute and chronic health effects for such a diverse range of substances and thus targeted treatment are continually lagging behind. The recent increase in the control status requested tailored analytical methods that are capable of monitoring the sheer number and inherent chemical diversity of NPS and their products. Herein, a novel flipped approach is presented for the detection of these substances in complex mixtures using portable Raman spectroscopy and computational approaches. Methods: To demonstrate it, three structurally diverse NPS (5F-PB-22, phenibut and N-Me2-AI) and four commonly used adulterants (benzocaine, caffeine, creatine and sodium glutamate) were selected. A Design-of-Experiments guided approach was employed to simulate samples, ranging from binary to quinary mixtures of varying concentrations. Spectra were acquired for all mixtures using a portable Raman spectrometer and examined using projection analysis on model systems, developed via principal component analysis using reference materials. Results: For all 31 mixtures investigated, the innovative flipped methodology resulted in isolated and unequivocal detection of the NPS. Interestingly, the NPS signatures were consistent across all mixtures investigated and were 1712, 1000 and 777/1022 cm-1 for 5FPB-22, phenibut and N-Me-2-AI, respectively. Thus, indicating that the developed model systems could be applicable to structural analogues. NPS were detected to concentrations as low as 6.0% w/w. This flipped methodology was benchmarked to the instrument's output algorithms and outperformed these in terms of NPS detection, particularly for low concentration ternary and quinary mixtures. Conclusions: As a result, this study represents a critical change in the conceptualization of novel approaches for the detection of psychoactive substances and further denotes a blueprint for the development of detection methodologies of target analytes in complex mixtures.

Early and effective detection of addictive and hallucinogen potential in the next generation of NPS. The first steps of the NextGenPS project

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Introduction: At the end of 2019, the EMCDDA had identified more than 700 NPS. These include new psychostimulants and hallucinogens from which there is a lack of information about their properties and adverse effects. The aim of the NextGenPS project is to provide scientific-based evidence of the health consequences associated with NPS to speed up the implementation of control measures by the EU. Methods: After generating a list of recently

emerged NPS, we will process them using a structure-activity relationship software (PredictNPS) obtaining a ranked list by their drug dependence/hallucinogenic potential score. Moreover, 8 candidates will be selected, synthetized and an analytical protocol using HPLC-MS will be designed. Finally, the mechanism of action will be studied using radioligand binding, uptake inhibition assays and microdialysis. Behavioral responses related to addiction and hallucinogenic effects will be also assessed in experimental animals: locomotor activity, conditioning place and self-administration paradigms, as well as head-twitch response. Results: 8 candidates (4F-3Me-alpha-PVP, α-D2PV, 3F-NEB, 5-MeO-pyr-tryptamine, 5-Cl-DMT, 5-MeO-MALT, 25I-NBF and 25B-NBF) have been selected according to their novelty, lack of information, structural and scientific criteria, as well as their drug dependence and/or hallucinogenic score obtained using PredictNPS software. Conclusions: The NextGenPS project will provide, for policies and actions worldwide, a rapid and predictive information about the capability of NPS to induce drug dependence or psychedelic effects.

In silico studies on recreational drugs: 3D-QSAR prediction of classified and de novo designer benzodiazepines

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Introduction. Currently, increasing availability and popularity of designer benzodiazepines (DBZDs) constitutes a primary threat to public health. To assess this threat, the biological activity/potency of DBZDs was investigated using in silico studies. Methods.Specific Quantitative Structure Activity Relationship (QSAR) models were developed in Forge for the prediction of biological activity (IC50) on the γ-aminobutyric acid A receptor (GABA-AR) of previously identified classified and unclassified DBDZs. A set of new potential ligands resulting from scaffold hopping studies conducted with MOE® was also evaluated. Results. Two generated QSAR models (i.e., 3D-field QSAR and RVM) returned very good performance statistics (r2= 0.98 (both) and q2 0.75 and 0.72 respectively). The DBZDs predicted to be the most active were flubrotizolam, clonazolam, pynazolam and flucotizolam, consistently with available information in literature and drug discussion fora. The scaffold hopping studies strongly suggests that replacement of the pendant phenyl moiety with a five-membered ring could increase biological activity and highlight the existence of a still unexplored chemical space for DBZDs. Conclusions. QSAR could be of use as a preliminary risk assessment model for (newly) identified DBZDs, as well as scaffold hopping for the creation of computational libraries that could be used by regulatory bodies as support tools for scheduling procedures.

Changing trends and pattern of mephedrone drug in Mumbai — challenges for investigation agencies in India

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Ganja, charas, opium, heroin, methamphetamine, lysergic acid (LSD), ephedrine, benzodiazepines…etc. are types of drug seized by investigation agencies in Mumbai and Mumbai suburban. Since year 2012, the seizer of mephedrone increased drastically. In India, mephedrone a psychoactive drug comes under NDPS act in year 2015 as per Notification of Ministry of Finance (Department of Revenue) dated 5th February 2015. Forensic data shows that the pattern of mephedrone changing day by day. It shows earlier crystals (crystalline form) Mephedrone received for analysis, it was pure form of mephedrone. The trend changed and monosodium glutamate (Aginomoto) or magnesium sulphate was started to mixed with Mephedrone. The appearance of Mephedrone, magnesium sulphate and monosodium glutamate are similar. Further, crystalline powder form of mephedrone came in gray market, phenacetine, lignocaine types of adulterants started to mix with drug. Sometimes ketamine too used with drug. Further there is trend of preparing mephedrone in liquid form. It is difficult for investigation agencies to differentiate crystals of mephedrone, magnesium sulphate and monosodium glutamate and similarly, it is difficult to differentiate powder form mephedrone, lignocaine and phenacetine on field. Hence Forensic science laboratory prepared two kits to use on field. Kit 1 can use to differentiate Mephedrone, magnesium sulphate and monosodium glutamate. Kit 2 can use to differentiate mephedrone, lignocaine, cocaine, ketamine, methamphetamine, phenacetine…etc.

Preventing drug harm in Aotearoa, New Zealand. Part 2. The role of drug-checking services in detecting NPS and the associated challenges

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Introduction: Drug checking services play a key role in providing drug testing to the public, and at events such as music festivals, to inform users of their drug composition, provide information on safe drug use practices and ultimately to minimise potential harm related events. These services may indicate if a drug sample is not consistent with a user's expectations or identify when a new drug or drug trend appears. In November 2021, the Drug and Substance Checking Legislation Bill was passed, making Aotearoa the first country to legalise drug checking. Methods: Generally, drug checking services utilise rapid testing methods, such as reagent colour tests and spectroscopy techniques. New psychoactive substances (NPS) present challenges for drug checkers as their reactions with common reagent tests are unknown and they are unlikely to be present in spectroscopy libraries. A process has been developed for the further testing of suspected NPS by the Institute of Environmental Science and Research (ESR), the sole forensic service provider in NZ. Results: This presentation will provide an overview of the drug checking process in Aotearoa, from the on-site testing carried out to the process developed for when 'unknown' suspected NPS are detected. This will include

the role played by ESR in supporting the drug checkers, further confirmatory analysis, and the communication of test results by New Zealand's drug early warning systems, Drug Information and Alert NZ (DIANZ) and High Alert. A summary of the NPS detected in drug checking samples by ESR will also be provided. Conclusions: Working collaboratively in a multi-agency approach, there is an ability to increase the impact of drug checking in Aotearoa to further reduce drug-associated harms. Providing full laboratory analysis for new or unknown samples also allows NPS to be detected early and the appropriate information released to minimise the impact of drug-related harm incidents.

'Croaking on Kambô': intoxications and fatalities associated with use of secretions from phyllomedusa bicolor (giant leaf frog, giant monkey frog)

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Introduction:Secretions from amphibians' skins have been used for psychoactive and other purposes.Interest in using 'Kambo' from the giant leaf frog (Phyllomedusa bicolor) in shamanistic 'healings' ,'cleansings' and 'purges' has grown in recent years in 'Western' countries due to the many peptides it contains. It is usually applied topically. However, this secretion is a toxin and has led to reported poisonings and 'associated' deaths. There is no solid scientific epidemiological information on such events; this evidence gap needs filling. Methods: A 'state of the art' review was undertaken in April - May 2022 of scientific databases (e.g., Google Scholar, Scopus, PubMed), social media platforms (e.g., Facebook, Twitter, Reddit) as well as the surface internet for reports of such deaths. Search terms used included: ('Kambo' or 'Phyllomedusa bicolor' or 'Sapo') and ('death' or 'fatal*' or 'lethal' or 'toxic*' or 'intoxication' or 'poisoning' or 'overdose'). Searches were conducted in English and six other European languages. Qualitative information will be investigated using content/thematic analyses. Quantitative data will be considered using simple statistical techniques. Results: Information on about 12 fatalities in Australis, Europe, and Central and South America will be presented, including about the types of events leading to death and decedents' motives for taking 'kambo'. The role of 'kambo' in deaths and the mechanisms of death will be presented, and also key characteristics of decedents. The difficulties of obtaining reliable and detailed case-reports (only two published to date) will explored. Based on entries on internet websites, the number of cases identified here is an underestimate. Conclusions: This is the first academic attempt to collate epidemiological data on deaths related to 'kambo' use. It indicates that such events are international and are likely to continue. Improved case reporting and epidemiological surveillance is needed. Disseminating this study's findings to 'kambo' practitioners and (potential) clients may help reduce future occurrences.

Trends in hospital presentations following analytically confirmed synthetic cannabinoid receptor agonist exposure before and after implementation of the 2016 UK Psychoactive Substances Act

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Introduction: The 2016 UK Psychoactive Substances Act (PSA) made the production, supply, and sale of all non-exempted psychoactive substances illegal. The aim of this study was to examine trends in hospital presentations for severe toxicity following analytically confirmed synthetic cannabinoid receptor agonist (SCRA) exposure before and after implementation of the PSA. Methods: As part of the IONA Study, biological samples were collected from 627 patients presenting to participating UK hospitals with severe acute toxicity following suspected novel psychoactive substance (NPS) use between July 2015 – December 2019. Samples were analysed using LC-MS/MS. Time-series analysis was conducted on the monthly number of patients with (and without) analytically confirmed SCRA exposure using Poisson segmented regression. Results: SCRAs were detected in 35.7% (n=224) of patients. After adjusting for seasonality, models showed no clear evidence of an upward or downward trend in the number of SCRA exposure cases in the period before (IRR: 1.12, 95% CI: 0.99 – 1.26, p=0.068) or after (IRR: 0.97, 95% CI: 0.94 – 1.01, p=0.202) the implementation of the PSA. Conclusions: In the first study to examine UK trends in hospital presentations following analytically confirmed SCRA exposure, we saw no clear evidence of an increase or decrease since the PSA was implemented.

An overview of presentations involving new psychoactive substances (NPS) to the Euro-DEN Plus Emergency Departments in Europe.

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Introduction: There are limited systematic data on acute NPS-related harm which represents a significant gap in the understanding of the public-health implications of NPS. The Euro-DEN Plus project uses a sentinel-centre model in 36 Emergency-Departments in 24 European countries. We describe here NPS-presentations over the 6-year period 2014-2019. Methods: Data were extracted from the Euro-DEN Plus purpose-designed dataset to enable analysis of NPS-presentations. Results: 3,304 (7.6%) presentations involved an NPS. The proportion involving NPS fell (11.9%(2015) to 5.7-6.2%(2017-2019)), and varied by centre (four-centres: no NPS-presentations, six-centres:>20% NPS-presentations). 2014: 78.4% NPS-presentations involved cathinones, 3.4% synthetic cannabinoids; 2019: 11.6%, 72.2% respectively. NPS-presentations were younger (median30(IQR23–37)-vs-32(25–40)years,p<0.001) than those not involving NPS. NPS-presentations: more likely to self-discharge (22.8%-vs-15.1%), less likely to be admitted to

critical care (3.6%-vs-6.1%); longer length of hospital stay for NPS-presentations (median 5.1(IQR 2.7-18.7)hours), than those not involving NPS (4.7(2.5-9.2)hours,p<0.001). Conclusions: This large multicentre European series demonstrates the value of this sentinel-centre model. Triangulation of these data with complementary sources e.g. drug seizures, poison-centre enquiries, self-report surveys, drug-related deaths will enable a greater understanding of the public-health implications of NPS use.

A game of tug of war between legislation and NPS: the case of fluetizolam

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Introduction: Benzodiazepines (BZDs) are among the most commonly misused prescription drugs worldwide. Increased demands, quick profit gains and scheduling by law cause rapid shifts in their availability and the need for new compounds. As of 2021, the EMCDDA is monitoring 30 such designer BZDs. Methods: Tablets originating from a known Dutch web shop were discovered by the Belgian Customs and screened for the presence of established drugs and new psychoactive substances. Following tentative identification, they were sent to the European Commission's Joint Research Centre for confirmation and nuclear magnetic resonance (NMR) structure elucidation. Results: 54 orange tablets labelled "fluetizolam" were seized. NMR analysis confirmed the presence of this new designer BZD. No other BZDs or psychoactive substances were discovered in the tablets. Peer-reviewed information on its pharmacology is missing, user forums agree on strength/effects comparable to etizolam itself. At around the same time, very similar tablets were seized by the Finnish Customs, also containing fluetizolam. Conclusions: We present the first ever detection of the designer BZD fluetizolam. Since the scheduling of etizolam in the Dutch Opium law, popular web shops seem to have switched from selling etizolam to selling fluetizolam, with some even recommending it as the legal alternative.

Profiling users of image and performance enhancing drugs during the COVID-19 lockdown: a cross-cultural perspective

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Background: Image and performance enhancing drugs (IPEDs) are a wide range of products presented as having the potential to improve mental and physical function. Little is known about IPEDs consumption during COVID-19 lockdown, a period characterized by physical distancing, isolation and altered lifestyle habits. The aim of the present study was to profile IPEDs users during COVID-19 lockdown using a cross-cultural methodology. Methods: An online questionnaire was disseminated between April and May 2020 in eight countries (United Kingdom, Italy, Lithuania, Hungary, Portugal, Spain, Brazil, Japan). Type of IPEDs consumed and purchasing methods were investigated. The Exercise Addiction Inventory (EAI), the Appearance Anxiety Inventory (AAI) and the Self-Compassion Scale (SCS) were also administered. Results: A total of 736 IPEDs users were included in the survey. The mean age of the sample was 33.05 ± 10.06 years, with a female rate of 64.2%. The majority of participants (n = 409, 55.6%) purchased IPEDs at pharmacy/specialised shops, while 304 (n = 41.3%) purchased IPEDs on the Internet. Those purchasing IPEDs online were mainly males ($p < 0.001$) and showed higher scores at EAI ($p = 0.004$). One or more IPEDs classifiable as "potentially at risk" were used by 488 respondents (66.3%). Users of potentially at risk IPEDs were younger ($p < 0.001$) and mainly males ($p < 0.001$). They showed higher scores both at EAI ($p < 0.001$) and at AAI ($p < 0.001$). Discussion: This study profiled users of IPEDs during the the peak of lockdown policies due to COVID-19 breakdown. Both purchasing methods and types of IPEDs consumed were associated with distinct socio-demographical aspects and psychometric traits. Some relevant cross-cultural differences were highlighted. Further investigation will be needed to determine impact of COVID-19 lockdown on IPEDs consumption and further investigation are needed to explore the impact of socially restrictive measures among specific groups to implement more targeted responses.

Off-target activity of NBOMes and NBOMe analogs at the μ opioid receptor

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Introduction: The exact effects and molecular targets of new psychoactive substances are often inadequately elucidated. Guided by recent literature, we investigated the μ opioid receptor (MOR) activation potential of psychedelics, which typically activate the serotonin receptor (5-HT2AR). Methods: Using a activity-based MOR-βarr2 recruitment assay, a large panel of psychedelics was screened for opioid activity. Based on this initial screening, MOR activity of a selected panel of NBOMe analogs was evaluated using 2 distinct cell-based assays, monitoring both βarr2 recruitment and G protein signaling. Results: Ten NBOMe analogs could activate MOR, as indicated via two distinct bioassays. Similar to the structure-activity relationship found at the 5-HT2A receptor, MOR activity increased with an increasing size of the halogen or alkyl substituent of NBOMes, which were more active than their NBOH counterparts. Furthermore, MOR activation by NBOMes could be blocked by naloxone, indicating that these compounds occupy the same binding pocket as conventional opioids. Conclusion: As MOR activity of these psychedelics was only noticed at high concentrations, it is unlikely that these will contribute to pronounced opioid toxicity at physiologically relevant concentrations. However,

modifications to the original NBOMe structure may yield 'dual' agonists acting at both MOR and 5-HT2A receptor at relevant concentrations.

New generic ban evading synthetic cannabinoids shaking up the market?

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Introduction: To avoid the recent Chinese class-wide ban, synthetic cannabinoids (SCRAs) with previously unknown structural features have appeared on the recreational drug market, e.g. the recently detected ADB-FUBIATA (carrying an additional methylene group between core and linker) and the "OXIZID" SCRAs (with a new oxoindolin core). This study was the first to pharmacologically characterize these compounds at both CB1 and CB2 cannabinoid receptors. Methods: Potency and efficacy were assessed using activity-based βarr2 recruitment assays, based on the functional complementation of a nanoluciferase enzyme. Results: Overall, these new SCRAs were found to be only moderately active at CB1 (EC50 ≥ 85 nM). Focusing on five OXIZID SCRAs, the n-hexyl analog was the least efficacious and potent. Shortening the tail to a pentyl group led to increased activity at both CB1 and CB2. The cyclohexyl methyl analog BZO-CHMOXIZID was the most active analog. All OXIZIDs showed a CB2 preference, whereas ADB-FUBIATA failed to activate CB2 and even showed antagonistic properties. Conclusion: As new SCRAs containing never-seen-before structural features are expected to appear in the future, this characterization will contribute to a broader insight into the properties of recently detected substances, thereby informing about their potential harms and allowing prioritization of legal responses.

Pharmacokinetics, pharmacodynamics, and clinical aspects of psilocybin

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Introduction: Psilocybin is a classic hallucinogen produced by mushrooms, most of them belonging to the genus Psilocybe. These fungi have a long history of use by Mexican indigenous cultures for religious, therapeutic, and divination purposes. Modern cultures have recently demonstrated interest for both recreational use and clinical research. Herein, we critically reviewed the pharmacokinetics, pharmacodynamics, psychological and physiological effects, and therapeutic applications of magic mushrooms/psilocybin. Methods: An extensive English literature search was performed in PubMed (US National Li- brary of Medicine) and Scopus. Results: Magic mushrooms, cooked or in their raw/dried form, and pure psilocybin are usually consumed through oral ingestion, being rapidly absorbed from the gastrointestinal tract. Psilocybin is rapid and extensively dephosphorylated to its active metabolite, psilocin. Contrary to psilocybin, psilocin can easily cross the blood brain barrier and exert the psychoactive effects. Psilocin is subsequently subjected to phase-I and phase-II metabolism, rendering inactive metabolites. The effects are mediated by a partial agonism at the 5-HT2A receptor. Nevertheless, the pharmacodynamics of psilocin is much more complex and still uncomprehended. The therapeutic properties of psilocybin are well recognised among the scientific community and have been an important research subject in recent clinical studies, especially its antidepressant and anxiolytic potential. Long-lasting (up to 6.5 months) beneficial effects after just one or two psilocybin sessions (0.2–0.4 mg/Kg, oral) have been reported by patients with moderate to severe treatment-resistant depression, sometimes associated with a terminal cancer diagnostic. Adverse effects reported in the clinical studies were transient and well-manageable. Conclusions: Despite the promising therapeutic efficacy and low harm, the widespread misuse of magic mushrooms/psilocybin and consequent outcomes have given a bad reputation to these drugs. Additionally, law restrictions in several countries and relative limited knowledge on psilocybin's pharmacology and toxicology impose significant limitations to its clinical application.

An overview on toxicokinetics and toxicodynamics of Salvia divinorum and Salvinorin A

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Introduction: Salvinorin A is a non-nitrogenous diterpenoid, and the only known non-alkaloidal hallucinogen. This compound is naturally produced by a psychoactive mint from the Lamiaceae family, named Salvia divinorum Epling and Játiva, which is endemic to Mexico. S. divinorum had been used for centuries by Mazatecans for divinatory, religious, and medicinal purposes. In recent years, its recreational, especially among adolescents and young adults, has progressively increased worldwide. Here, we comprehensively reviewed the toxicokinetics and toxicodynamics of S. divinorum and salvinorin A, highlighting their psychological and physiological adverse effects, and toxicity. Methods: An extensive English literature search was performed in PubMed (US National Li- brary of Medicine) and Scopus. Results: The leaves of S. divinorum can be chewed, drunk as an infusion, smoked, or vaporised. Salvinorin A is rapidly broken down in the gastrointestinal system to its major inactive metabolite, salvinorin B. Salvinorin A is rapidly distributed, with accumulation in the brain. Unlike the classical hallucinogens (e.g., LSD, psilocybin, DMT, mescaline), salvinorin A activates potent k-opioid receptors, which seems to be responsible for most of its effects. The most common reported adverse effects include tiredness, confusion, hallucinations, drowsiness, heaviness of head, tachycardia, and dizziness. Other symptoms like fear, panic, paranoia, agitated delirium, sadness, irritability, augmented perspiration, chills, nausea, and vomiting were also reported. A variety of therapeutic applications have been proposed for S. divinorum which includes the treatment of chronic pain, gastrointestinal and mood disorders, neurological

diseases, and treatment of drug dependence. Conclusions: There is still limited knowledge regarding the pharmacology and toxicology of S. divinorum and salvinorin A, and this is needed due to its widespread use. Additionally, the clinical acceptance of salvinorin A has been hampered, especially due to the psychotropic side effects and misuse, turning the scientific community to the development and study of analogues with better pharmacological profiles.

Differentiation of structurally similar fentanyl analogs with theoretical and experimental analysis by surface-enhanced Raman spectroscopy (SERS).

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Introduction: New synthetic opioids, especially fentanyl and its analogs, are causing the most recent acceleration in opioid abuse. The presence of fentanyl analogs as mixtures in illicit drugs makes it hard to estimate their potencies. This makes the detection and differentiation of fentanyl analogs important. Most of the screening methods in current use have difficulty in detecting the full range of opioid analogs due to a wide variety of structural variations. However, Raman spectroscopy, specifically surface-enhanced Raman spectroscopy (SERS) is quite capable of detecting and identifying previously known and/or unknown fentanyl analogs. The SERS technique uses Raman spectroscopy combined with colloidal metal nanoparticles to yield highly sensitive SERS spectra. It can also differentiate structurally similar fentanyl analogs due to its ability to yield spectroscopic fingerprints for the detected molecules. Certain fentanyl analogs such as carfentanil, furanyl fentanyl, acetyl fentanyl, 4-fluoroisobutyryl fentanyl, and cyclopropyl fentanyl, have gained popularity and constitute 76.4 percent of the fentanyl analogs identified in drug seizures. Several of these have been already described using Raman spectroscopy. However, there are many other fentanyl analogs that are structurally similar to 4-fluoroisobutyryl fentanyl or cyclopropyl fentanyl. Thus, it is important to differentiate these analogs from similar molecules in order to track and identify trends in illicit distribution. In this presentation, we develop methods for the differentiation of structurally similar fentanyl analogs using theoretical and experimental methods. Methods: For theoretical approach, Density Functional Theory (DFT) calculations were done by using the Gaussian 16 package. The Raman frequency calculations were performed after optimization of molecular geometries. This was done by utilizing the hybrid exchange correlation functional wB97XD coupled with the basis set ccpVTZ. The obtained Raman frequencies and activities was converted to simulated spectra by GaussView 6.1. For NR and SERS experiments, fentanyl and fentanyl analogs was prepared in methanol as a 0.4 mg/ mL solution. For NR, the solutions was mixed with water in 1:1 ratio to be able to form drops. 1 μL of the mixed solution was deposited onto aluminum foil and allowed to dry. This process was repeated until a solid form of the drug was obtained. SERS experiments were performed using Ag/Au nanostars prepared from 0.01M AuCl4 and 0.01M AgNO3. 245μL of colloidal nanoparticles was mixed with 2.5μL of 1.67x10-2 M magnesium chloride (MgCl2) and was allowed to aggregate for 5 minutes. Then 2.5μL of each fentanyl analog will be added to the aggregated colloidal solution and was incubated for another 5 minutes. SERS measurements was performed conducted portable Raman spectrometer fitted with an excitation laser in 785nm. Results: The characteristic bands in DFT−simulated, SERS and Normal Raman spectra are shown in Figure 2,3 and 4 respectively. The wavelengths obtained using NR spectroscopy demonstrate common characteristics amongst the fentanyl analogs tested; however, spectral shifts in the SERS and DFT results were observed in the spectra. The bands at 993, 1020, 1450, and 1640 cm-1 were observed throughout all fentanyl analogs. On the other hand, each fentanyl analog had signature bands that allow us to differentiate them from each other. For IBF and FIBF, the band at 960 cm-1 shows the presence of isobutyryl on the amide group. Also, the strongest band at 815 cm-1 in FIBF is due to a fluorine in the aniline ring. 4FF also has a band at 815 cm-1 for the same reason but because of the lack of isobutyryl group, it does not have a band at 960 cm-1. In 4'FF, fluorine is in the benzene ring that presents in the N-Alkyl chain. This causes the existence of many characteristic bands for 4'FF such as 745, 827, and 849 cm-1. Conclusions: In this project, structurally similar fentanyl analogs have been analyzed using DFT calculations, normal Raman, and SERS. The DFT results obtained in this project permit the assignment of spectral bands. These results are then compared with experimental spectra. The outcome of these experiments demonstrates the applicability of SERS to detect and differentiate fentanyl analogs using handheld spectrometers.

Citotoxicity and addictive potential of novel ethcathinone derivatives

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Introduction: Novel synthetic cathinones are constantly emerging thanks to structural modifications to the chemical structure of cathinone, leading to an enormous group of compounds whose pharmacological and toxicological effects are unknown. Thus, the present study is focused on five different N-ethyl substituted cathinones; Ethcathinone, N-ethyl-buphedrone (NEB), N-ethyl-pentedrone (NEPD), N-ethyl-hexedrone (NEH) and N-ethyl-heptedrone (NEHP) that only differ in the length of the aliphatic side chain, a common structural modification found in the NPS's market. Methods: The cell line PC12 has been used for cytotoxicity assays. Cell viability was assessed using the CCK-8 Cell Counting Kit, based on 2-(2-methoxy-4-nitrophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2H-tetrazolium, monosodium salt (WST-8). The potential of the studied compounds to induce reward was determined in CD-1 male mice (3, 10 and 30 mg/kg, i.p.) using a place conditioning paradigm. Results: A significant reduction in cell viability was observed for all the cathinones tested, showing higher cytotoxic properties than methamphetamine. Moreover, all the compounds induced a significant increase in the conditioned preference score at the medium dose tested. Ethcathinone and NEB

also revealed rewarding properties at the lowest dose tested. Conclusions: Our results demonstrate the high cytotoxic potential induced by the recently emerged synthetic cathinones NEH and NEHP. Moreover, the present study also demonstrates for the first time the rewarding properties of some novel ethcathinone derivatives such as NEB, NEH and NEHP.

Understanding the evolving nature of novel psychoactive substances: a scientometric perspective

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Introduction: In the 2000s, a new group of substances was introduced in the markets as a legal alternative to illicit drugs. Considering the challenges posed by novel psychoactive substances (NPSs) for countries' drug monitoring and surveillance, a scientific understanding of the phenomenon becomes of high social and political valence. Methods: The current study adopted a scientometric approach to systematically identify and review the impactful publications and the thematic developments in the literature regarding novel psychoactive substances. An amount of 2,365 documents was downloaded from Scopus and imported into CiteSpace. An optimized Document Co-Citation Analysis (DCA) was computed on the downloaded sample with a g-index having k set at 15. Results: The generated network consisted of 567 nodes and 2,641 links. The highest citation burstness – an index of scientific impact - was recorded by Peacock et al. (2019), which describes the complexity of definition, surveillance, and response to NPSs. Moreover, according to the Generate Narrative function, four major significant thematic clusters were identified: (i) "Availability and use of new psychoactive drugs" (centroid year of publication = 2010), (ii) "New synthetic cannabinoids" (2013), (iii) "New synthetic cathinone" (2013), and (iv) "Neuropharmacology of new psychoactive substances" (with 2015 as the average year of document publication). Although not significant, a fifth cluster on (v) "New synthetic opioids" (2017) was recorded, and its content was highly relevant for the past few years of research on NPSs. Conclusions: After the initial epidemiological studies, scholars have focused on the neuropharmacology of specific NPSs. The rapid introduction of new drugs has forced researchers to move from the specific drugs' mechanisms of action to the general understanding of the neuropharmacology of NPSs.

Rise of ketamine as a designer drug in Chile — risks and consequences

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Introduction: El Instituto de Salud Pública de Chile es el encargado de efectuar las determinaciones a las incautaciones realizadas por las policías del país a excepción de cannabis. En este contexto, alrededor del 80-70% de los decomisos corresponden a muestras de cocaína. Sin embargo, en los últimos 10 años se ha observado un marcado cambio en el patrón de consumo de drogas de abuso, en que, si bien las sustancias más consumidas continúan siendo los derivados de cannabis y estimulantes como la cocaína, han aparecido las llamadas drogas de diseño. En Chile desde el año 2013 hemos advertido la aparición de nuevas sustancias, así como también una reaparición de drogas más tradicionales, pero en nuevas formas de presentación o con nuevos adulterantes, como es el caso de la Ketamina. Methods: Se analizaron los resultados de decomisos desde 2014 a 2021,utilizando herramientas estadísticas con datos obtenidos delSistema informático del Laboratorio "Control de Ilícitos" Results: De las muestras analizadas por el Instituto de Salud Pública de Chile en 2021, incautadas como presunto 2C-B o "TUSI", podemos decir que del total de muestras, 2.364 corresponden realmente a ketamina y solo 27 a algún derivado sintético de la familia de los 2C-X. Ahora si analizamos la tendencia desde 2014 a 2021 podemos decir que la ketamina ha desplazado notoriamente a las fenetilaminas. Por otra parte, en cuanto a la presentación mayormente incautada de ketamina, podemos informar que, del total de muestras de ketamina analizadas en 2021, el 91.3% corresponde a polvos de colores conocidos como "TUSI", mientras que el 6.6% corresponde a ketamina liquida posiblemente proveniente de desvíos del mercado veterinario. Conclusions: Uno de los principales riesgos de intoxicación se produce por la comercialización de drogas bajo el nombre de otra droga, como es el caso de los derivados 2C o TUSI, en que realmente están traficando Ketamina u otros fármacos con efectos diferentes a los esperados por el usuario de 2C, lo que genera consumo de dosis equivocadas, sumado además al alto potencial adictivo de la ketamina.

Adulterants in samples of cocaine and NPS analysed in 2017–2020 in the forensic laboratory of the National Anti-Drug Secretariat, Paraguay

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La mayor incautación de cocaína en 2017 llegó a 1,3 toneladas, en 2018 tuvo un descenso el cual fue de 0.77 toneladas, en el 2019 aumento a 4,3 toneladas, mientras que en el 2020 llegó a 2,4 toneladas. El objetivo de este trabajo fue determinar los distintos adulterantes presentes en muestras depositadas en el laboratorio, incautadas por la Secretaría Nacional Antidrogas. Fueron analizadas 3.967 muestras. Los procedimientos de análisis fueron realizados según las recomendaciones de la UNODC. El año 2017 el número de muestras analizado fue de 1.094, 339 contenían adulterantes. La variedad de adulterantes identificados fueron; cafeína, lidocaína, fenacetina, benzocaína, levamisol e imidazol. En el 2018 de 935 muestras analizadas, 231 contenían adulterantes, en ese año fueron identificados dos nuevos adulterantes que fueron aminopirina y paracetamol. En el 2019 de 974 muestras analizadas, 358 contenían adulterantes. La particularidad de este año fue la identificación de un nuevo adulterante que es la tetracaína, en cambio el imidazol no fue detectado en este año. En el 2020 de 964 muestras analizadas, 239 contenían adulterantes. En tanto la

variedad de adulterantes identificados fueron las mismas que el 2019. Cabe destacar en los años de estudios fueros identificados aisladamente variedades de pastillas, entre las cuales; MDMA, pirovalerona, pseudoefedrina, Metanfetamina, difenhidramina con flunitrazepam, entre otros. El trabajo pretende exhortar a las autoridades correspondientes sobre la necesidad de desarrollar un mecanismo que permita el análisis sistemático de todas las muestras de drogas incautadas, como fuente permanente de conocimiento y como alarma sobre las drogas de consumo y adulterantes, impacto de cada y la toxicidad de estas.

Health Canada Drug Analysis Service (DAS) data story: how to use enforcement data in support of harm reduction initiatives

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Introduction: The role of DAS is to provide independent, impartial scientific analysis to identify the presence of controlled substances in seized samples from law enforcements agencies across Canada. DAS was first funded for enforcement activities. In light of Canada's response to the Opioid Crisis, DAS mandate was expanded to support harm reduction activities. DAS is a unique data source since it is the only Canadian laboratory accredited to analyze drug seized by all law enforcement agencies and it owns historical data since 1988. The objective of this work is to describe how laboratory data produced for administrative purpose can be used to support harm reduction and substances use initiatives. Methods: In 2017, DAS has implemented three Information Products (IP), Drug Notification, Analyzed Drug Summary Report and Monthly Raw Data, to support the response to the opioid crisis. DAS performed a review of those information products in 2019 to understand the audience, the process for producing information products and identify needs for improvement. The framework used for this review was based on understanding the process by looking at the characteristics of the various IPs, of the dissemination strategy, of the users and of the content. The review was conducted through telephone or in-person interviews and online questionnaires. Results: Twenty-two (22) telephone interviews were conducted and 67 completed online questionnaire (30%) were received over a two (2) months period in June and July 2019. Our data are used across the country. In smaller areas, only health partners are using our data, but in larger areas, audience includes non-governmental organizations, provincial and federal public health and law enforcement partners. The review allowed for the identification of improvements for the current IPs and emerging needs to ensure usefulness of DAS' IPs. The most significant improvement is related to the timeliness of our IPs on emerging of new substances and co-occurrences. Other improvements include adding variables, modifying format, modifying dissemination and increase accuracy. Conclusions: This work led to the improvement of current IPs and development of new IPs. DAS will be able to fulfil emerging needs by exploiting its administrative data. Next steps include the development of a Strategic Data Analysis Plan to support the implementation and development in a sustainable manner.

Analytical method for the identification of new psychoactive substances using retention index and GC-MS

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Introduction: New Psychoactive Substances (NPS) are substances designed to circumvent existing norms. They have a high introduction rate into the market and represent a huge challenge from a regulatory and forensic point of view. In this context, the need for a method capable of identifying NPS, without the availability of certified analytical standards arises. Methods: The methodology of the work relies on the development of a GC/MS method, to apply to a wide diversity of existing NPS; its validation, using figures of merit such as selectivity, precision, and robustness; and calculation of the Kovats' Retention Index for the substances analyzed. This index was selected because it was reported in the literature as a tool for high-precision identification. A total of twenty-two illicit drugs were used. They are four synthetic cannabinoids (AM-2201, MAM-2201, JWH-081, JWH-210), one synthetic cathinone (*N*-ethylpentylone), three phenylethylamines (5-MAPB, 2-FA, 25C-NBOMe), two piperazines (o-CPP, p-CPP), one opioid (U-47700), one tryptamine (5-MeO-MiPT), one aminoindane (5-IAI), one plant-based substance (*Salvia divinorium*), one listed as "other" (methiopropamine) and seven traditional drugs (THC, heroin, amphetamine, methamphetamine, MDMA, cocaine, ephedrine). Results: The method presented only one Selectivity limitation, represented by the coelution of methiopropamine and methamphetamine. The calculated Resolution values were higher than 1.25, indicating separation of the signals, and the figures of merit Separation Factor, Number of Theoretical Plates, and Tailing also presented satisfactory results. The evaluation of the Intermediate Precision indicated Relative Standard Deviations in the range of 0.02 - 0.29%, values lower than those found in the literature. The Robustness evaluation using a Fractional Factorial Design identified that the change in the column polarity was the most influential factor, while the column brand, gas flow, split rate, injector temperature, and ramp temperature did not interferences with high magnitude values. Kovats' Retention Index for all the substances was calculated without overlap and the Global Confidence Interval for t21,95% varied from 0,5 to 20,6 Retention Index Unity and the Relative Standard Deviation (RSD) varied from 0,02 to 0,29%, inferior to the range found in the literature. The values from the Retention Index evaluated during this study can be applied in routine analysis of the forensic centers in Brazil. Conclusions: The figures of merit analyzed were all satisfactory indicating that the method is a suitable alternative for the identification of New Psychoactive Substances using Kovats' Retention Index. The results of the method's development and validation using a total of twenty-two illicit drugs indicate the adequacy of the method that uses Kovats' Retention Index in the identification of NPS. The

collection of Retention Index values calculated in this study can be updated with other substances and made available to other forensic institutes in Brazil to be used as a tool in NPS identification.

Identification of 4F-MDMB-BINACA metabolites in human blood and urine with LC-QTOF

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Introduction: Synthetic cannabinoid receptor agonists occupy one of the leading positions in the structure of new psychoactive substances detected both in Russia and in the world. Their use often causes acute poisoning, including fatal. In order to timely establish the cause of poisoning with psychoactive substances, it is necessary to study the metabolic pathways of new synthetic cannabimimetics. Methods: 25 urine samples, 2 blood samples from living individuals, and 2 post-mortem urine samples were used to search for 4F-MDMB-BINACA metabolites and their glucuronides. 1290 Infinity II LC liquid chromatograph equipped with a Zorbax Eclipse Plus C18 column with a 6545 Q-TOF mass spectrometer (Agilent Technologies). Results: 49 metabolites of cannabimimetic 4F-MDMB-BINACA have been found in human urine. These substances have been identified as products of hydrolysis, hydroxylation of various moieties, defluorination with hydroxylation or carboxylation, dihydrodiol formation, carboxylation of a neopentane residue, N-dealkylation, and combinations of these reactions. In addition, dehydrogenation products of the tert-leucine residue were found, the properties of which suggest intramolecular cyclization with the formation of a lactone. Metabolites were present in the urine in free form and as glucuronides. Conclusions: The results of this study can be used to diagnose acute poisoning with 4F-MDMB-BINACA, as well as to predict the metabolic pathways of new synthetic cannabimimetics with similar structural fragments.

Associations of concomitant psychiatric disorders and kratom (Mitragyna Speciose Korth) use

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Introduction: Kratom (Mitragyna speciosa), a psychoactive plant native to Southeast Asia, is gaining popularity in Western countries, including among people with health conditions. However, few kratom-related surveys have incorporated standardized psychometric scales. We sought to better understand the correlations between kratom consumption, demographic, and psychosocial factors among consumers with underlying psychiatric conditions. Methods: An anonymous online survey was distributed using Qualtrics between July 2019 to 2020. All participants were assessed for self-reported health conditions, kratom use, and other substance use; approximately half of the participants were also evaluated using standardized psychometric scales (Euro-QOL-5D-5L, ASRS-v1.1, PC-PTSD-5, and SCL-90). A total of 4,945 valid responses were analysed. Bivariate and interval analysis were conducted; statistical significance was set at $p \leq 0.05$. Results: A total of 2,296 respondents (46.4%) met criteria for >1 psychiatric condition. Except for those with PTSD, most respondents were male. Most respondents were between 31-50 years-old, while those with a psychiatric condition were younger (18-40 years-old). For all psychiatric conditions, cannabis and benzodiazepine use was more likely. Less depressive and anxious mood, and reduced PTSD symptoms, were reported as beneficial effects from kratom; adverse effects of vomiting and irritability were described. Quality-of-life was lower across all conditions. A higher percentage of those with a psychiatric condition took 3-5 g of kratom/dose and used >4 times/day, compared to those without a condition ($p=0.01$ and $p=0.03$). Conclusions: Self-treatment of psychiatric conditions with kratom is common and indicates a unique user base compared to those seeking pain relief or substance use disorder management. The unique pharmacology of kratom alkaloids indicates a potential therapeutic use. Kratom's safety and risk requires further investigation.

N-MOC-MDMA, a novel "masked" variant found by Argentina Federal Police

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Introduction: NSP encompass both the appearance of new substances and the variation of other classic ones, among which are N-substituted derivatives of MDMA with substituents that function as a protective group or 'mask' in order to evade legal controls. Methods: Two different unrelated seizures were examined, physical characteristics and presentation indicating they would be destined directly for consumer use. Samples were analyzed with PE Clarus600 - 600T GC-MSD. In both cases, the amphetamine derivative N-MOC-MDMA (N-methoxycarbonyl-3,4-methylenedioxymethamphetamine) was identified as a minor component mixed with MDMA, with ephedrine also present in the second one. Identification was carried out from theoretical deconvolution with the support of predictive software and SWGDRUG's v. 3.09 spectral library matching. Results: Obtained results are congruent in N-MOC-MDMA identification according to revised bibliography. Conclusions: Bibliographic background indicates N-MOC-MDMA, among others, as a possible prodrug made with the aim of eluding controls for its distribution, and subsequent reconversion to the typical drug in a simple form. This hypothesis could be supported by the mixture identified in the samples, a consequence of a possible inefficient conversion. Detection of this new "masked"-type MDMA in Argentina demonstrates the need for its inclusion in the local lists of prohibited substances.

A comprehensive action plan of Department of Narcotics Control (DNC) to address the NPS challenge in Bangladesh

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Introduction The United Nations Office for Drugs and Crime (UNODC) has defined NPS as ‘substances of abuse, either in a pure form or a preparation, that are not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but which may pose a public health threat." The use and misuse of new psychoactive substances (or ‘legal highs’) has increased significantly around the world in the past 10 years. The NPS problem in Bangladesh has been seen since 2018 and has become important due to geographical location. The Golden Triangle and Golden Crescent have given a degree of vulnerability to NPS trafficking and drug abuse in the country. Besides, the pharmacy and drug regulatory systems in Bangladesh are patient-friendly. For those, malpractices like ‘prescription hopping’ are a common modus operandi followed by the abusers to procure controlled drugs from pharmacies. Abusers also misuse the prescriptions of their family members, friends, etc. to obtain drugs, and some of them resort to "doctor shopping," i.e., procuring prescriptions from different doctors to procure controlled drugs from pharmacies. A comprehensive action plan was in place to overcome NPS challenges. Methods DNC's Director General has developed a comprehensive action plan. Under this approach, the Narcotics Control Act of 1990 was repealed and replaced by the Narcotics Control Act of 2018. New areas of the NPS issue have been included in this act, such as LSD, DOB, MDMA, Magic Mushroom, phenethylamine, Khat, Tapentadol HCl, Tramadol, Nalbuphine, and others. The temporary probationary period for newly emerging NPSs was preserved. This control measure is only in place because of the legal structure in place at the national level. The severity of the penalty and punishment was increased. The airport, seaport, and land port have all been upgraded. The inspection of local pharmacies and drugs has been intensified. A technical session for clinicians was held to restrict the prescription of these medications. DNC undertook a number of NPS training programs as part of its capacity-building operations for law enforcement agencies and transportation-related personnel. It is necessary to expand the digitalization of medicine marketing and its monitoring system. Results All attempts to infiltrate the newly formed NPS were traced through the implementation of a complete action plan in accordance with the guidelines, and all attempts to infiltrate failed. As a result, Bangladesh was the first country to seize plant-based NPS Khat in 2018. A total of 4.5 metric tons of Khat was seized at Dhaka and Chottogram airports. , a considerable amount of LSD was seized in 2019. Phenethylamine, an organic substance, was seized in 2020. In the year 2021, psilocybin mushrooms were discovered. Dimethoxybromoamphetamine (DOB) was recently discovered in 2022. Because the method of operation is similar to that of an ATS, locally made tapentadol HCl is abused instead of an ATS. Its use and promotion are similarly regulated. The capacity of law enforcement agencies and transportation employees has expanded. As a result, no attempt to penetrate NPS has succeeded at any time or in any form. With the collaboration of the mass community, drug pharmacists, physicians, and other national and international authorities, the Department of Narcotic Control has been able to successfully monitor and regulate the overall situation. Conclusions The DNC's comprehensive response plan is still in full swing, and Bangladesh's NPS problem is under control. If the problem worsens, the plan will be reevaluated, and a different approach, such as genetic control, will be used.

New Psychoactive Substances Emerging in Poly-substance Combinations in the United States

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Introduction: Hundreds of new psychoactive substances (NPS) have been identified in the past decade and are being monitored domestically in the United States and internationally. NPS sometimes emerge in combinations with other drugs/substances of abuse which pose particular threats to the public health and safety in the United States and countries around the world. Methods: Using data from the Drug Enforcement Administration’s (DEA) National Forensic Laboratory Information System (NFLIS-Drug), an analysis of NPS in the United States focusing on those co-reported with other drugs and drug classes will be presented. NFLIS-Drug provides comprehensive, timely, accurate, chemically and/or otherwise verified data which is used to identify emerging drugs as well as diversion of pharmaceuticals, trafficking, and abuse patterns geographically and over time in support of federal, state, and international drug policy initiatives. Keeping in mind that the identification and reporting of drug combinations is heavily dependent on individual lab policies and procedures, insights based on co-reported substances are obtained through statistical and graph theory analyses. Detailed highlights of some select NPS that have emerged in the United States illicit drug market are presented. Results: A summary of results at the drug and drug class level are presented along with detailed results pertaining to some select NPS. Select substances highlighted include new fentanyl-related substances, benzimidazole-opioids, benzodiazepines, and synthetic cannabinoids. Conclusions: Investigating the emergence of NPS in combination with other substances of abuse can assist our understanding and policy setting for NPS abuse in today’s dynamic, illicit-drug market and polysubstance-abuse environment.

An Australian national prompt response network for emerging drugs

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Introduction: The rapid emergence of new psychoactive substances (NPS) is a key public health challenge in Australia and internationally. Recent clusters of drug toxicity of a range of NPS, including novel benzodiazepines, highlight that the lack of a well-coordinated response leads to sector-wide communication gaps, making the development of a Prompt

Response Network (PRN) an urgent priority in Australia. Methods: We conducted a collaborative, co-design process with existing jurisdictional networks and key organisations to develop the PRN. This process identified the components necessary to ensure a broad health-focused national network; that would support, enable and coordinate the efforts of existing and emerging regional and specialist networks, while respecting and not duplicating established processes and existing efforts towards addressing these challenges from a public health perspective and harm reduction focus. Results: The stakeholder mapping and co-design processes found the necessary implementation of two main components. First: convening a broad national community network of stakeholders involved with regional and national networks, including networks of people who use drugs, to share information, insights and opportunities. Second: a custom-built digital platform to provide a national dashboard of real-time incidents utilising minimum de-identified data from contributing agencies. Conclusions: Through the iterative process employed to establish the PRN, an evolving network has been established. Implementation and expansion of the PRN will lead to coordinated and evidence-based information being shared cross-jurisdictionally and to the public.

The importance of international cooperation in the detection of new psychoactive substances (NPS) and other emerging drugs

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Introduction: New psychoactive substances (NPS) and other new drugs have been spreading across the countries in the Americas. While the drug problem is different in each country in the Americas and new drugs, and combinations of drugs are often local, the drug problem as a whole does not respect borders. International organizations such as the Inter-American Drug Abuse Control Commission and the United Nations Office on Drugs and Crime have a long-term collaboration on supporting countries in the Americas to detect, identify, and report on new and emerging drugs, in particular NPS. Key aspects of international cooperation between CICAD and UNODC are the development of early warning systems to help countries detect and respond to NPS and other emerging substances. This presentation will discuss importance of international collaboration and support to countries developing EWS to detect NPS and other emerging drug issues.

Towards better understanding SCRAs and metabolites in recreational drug intoxications associated with 5F-MDMB-PICA use

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Introduction: Synthetic cannabinoid receptor agonists (SCRAs) pose a danger to public health. This study focused on individuals experiencing recreational drug toxicity who had used 5F-MDMB-PICA. Methods: Patient records were evaluated regarding vital signs, Glasgow Coma Scale (GCS) and clinical features. Liquid chromatography coupled to high-resolution mass spectrometry (LC-HRMS) confirmed and quantified the presence of 5F-MDMB-PICA (and/or metabolites) as the only SCRA present in the serum of 71 patients. Cannabinoid activity was evaluated by a cannabinoid receptor (CB1) bioassay, to assess the relationship between serum concentrations and ex vivo human CB1 activation potential. Furthermore, associations with clinical effects were appraised. Results: 5F-MDMB-PICA and metabolites were pharmacologically profiled in vitro, revealing theoretically possible contributions of two active in vivo metabolites to overall cannabinoid activity. Serum concentrations of 5F-MDMB-PICA were correlated to the ex vivo cannabinoid activity, revealing a sigmoidal relationship. Moreover, the in vitro pharmacological characterization allowed close prediction of an individual's ex vivo CB1 activity. Clinically, the level of consciousness (GCS) showed a significant trend (decrease) with increasing ex vivo cannabinoid activity. Conclusion: This is the first study to evaluate possible toxic effects of 5F-MDMB-PICA in a unique large patient cohort, allowing a better understanding of 5F-MDMB-PICA and metabolites in humans.

Sensing HIF stabilisation: a proactive effort to screen for performance enhancing HIF stabilisers based on their activity

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INTRODUCTION: The cellular response to low-oxygen environments (e.g. high altitude) is mediated by hypoxia-inducible factors (HIFs), heterodimeric transcription factors consisting of an unstable HIFα- and a constitutive HIFβ subunit, leading to the production of various proteins (e.g. erythropoietin). Small-molecule HIF stabilizers are being misused in sports to 'artificially' increase red blood cells. WADA banned their use, but the field is rather new and quickly evolving. Therefore, a future-proof strategy was envisaged, capable of detecting ANY HIF stabilizer. METHOD: Two cell-based activity-based bioassays were developed to follow the upstream mechanism of HIF activation (heterodimerization of HIF1α/2α with HIF1β) via fusing HIFα/HIFβ subunits to parts of a split-nanoluciferase to monitor this protein-protein interaction. RESULTS: The HIF bioassays were more sensitive than the current state-of-the-art gene-reporter assay (measuring downstream transcriptional read-out). The generation of stable cell lines showed potential to further increase sensitivity. The bioassays functionally characterized eight clinical

HIF stabilizers and concentration-dependent effects were demonstrated for other, non-clinical HIF stabilizing compounds with different mechanisms of action, demonstrating broad specificity of this untargeted approach. CONCLUSION: The newly developed HIF bioassays are promising platforms to detect multiple performance-enhancing HIF stabilizing compounds that induce HIF heterodimerization, irrespective of their structure or precise mechanism of action.

Structure-activity relationships of novel synthetic substituted lysergamides and tryptamines at the human serotonin 2a receptor

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Introduction: There is growing interest in the putative benefits of psychedelic compounds either for the treatment of refractory psychiatric conditions or for recreational use. Many psychedelic substances act to modulate the body's serotonin receptors, such as the type 2a serotonin receptor (5HT2a). Synthetic derivatives of many of these compounds are available in the illicit supply where they are sold as novel psychoactive substances. In Canada, the Controlled Drugs and Substances Act (CDSA) provides a legislative framework for the control of substances that can alter mental processes and that may cause harm to the health of an individual or to society when misused or diverted to the illicit market. Three tryptamines, psilocin, LSD and the salts of these compounds are currently controlled under Schedule III of the CDSA. The purpose of this project is to generate data that can be used to assess whether select emerging psychedelics are efficacious serotonin receptor agonists. Seventeen potential psychedelic compounds were tested at 5HT2a (their potencies, efficacies, and biases) and that pharmacology was related to important regulatory and control measures for the safety and well-being of Canadians. Methods: Compounds (0.1 nM -10 μM) were screened for their binding to 5HT2a, $G\alpha_{q/11}$-depednent intracellular Ca^{2+} release, and βarrestin2 recruitment in Chinese hamster ovary cells stably expressing human 5HT2a. Concentration-response curves were fit using non-linear regression and used to calculate K_D, EC_{50}, and E_{max}. LSD was used as a reference agonist for all assays (*i.e.* E_{max} = 100%). Results: All compounds displayed competitive binding at h5HT2a in the presence of [^{3}H]ketanserin with affinity values ranging from 0.3 nM (1cP-LSD) to 760 nM (4-acetoxy DMT). All compounds also yielded 5HT2a-dependent release of intracellular Ca^{2+} with wide ranging potency and efficacy from psilocin (EC_{50} 0.54 nM, E_{max} 72%) to ergotamine (EC_{50} > 10,000 nM, E_{max} 44% at 10 μM). Compounds generally displayed markedly different potency and efficacy in the β arrestin2 recruitment assay where potency and efficacy values ranged between 5-methoxy MiPT (EC_{50} 1.2 nM, E_{max} 62%) to ALD-52 (EC_{50} 270 nM, E_{max} 115%). Among the compounds tested, 4-substitued tryptamines displayed consistent bias toward βarrestin2 recruitment relative to Ca2+ release whereas 5-substituted tryptamines and substituted lyergamides did not display bias. Conclusion: The pharmacology of these psychoactive substrances is multi-factorial and complex beyond what traditional single compound pharmacodynamic experiments are capable of modelling. Here, we took a reductionist approach to understand how single molecules behave at the human 5HT2a receptor and observed a range of potencies, efficacies, and biases. In the case of the tryptamines, bias appears to correlate with the position of substitution. Ongoing studies will help determine whether binding kinetics effect bias for these ligands and whether these ligands have activity at receptors beyond 5HT2a. Acknowledgements: Funding for this project was provided by a Health Canada Research Contract and a University of Saskatchewan Research Chair award to RBL. HJJK is supported by the graduate fellowship from the University of Saskatchewan. ALB was supported by a research award from the National Research Council (NRC).

Assessment of developmental neurotoxicity in mice after repeated postnatal exposure to MDPV

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Introduction: Synthetic cathinones constitute one of the most frequently abused group of Novel Psychoactive Substances. They potentiate brain signalling by elevating levels of monoamine neurotransmitters: dopamine, noradrenaline and serotonin. We investigated the effects of repeated exposure to MDPV (methylenodioxypyrovalerone), primarily enhancing dopaminergic neurotransmission, during postnatal days 11-20 (PD11-20, corresponding to the 3rd trimester of human pregnancy) on cognitive function in young adult mice. Methods: All experiments were performed using C57BL/6J mice of both sexes. Mice were injected subcutaneously with MDPV (10 mg/kg or 20 mg/kg) or saline twice a day with an inter-dose interval of 2 h during PD11-20. Animals were weighted daily during administration period. At the age of 12 weeks spatial working memory of mice were assessed using Y-shaped maze during 5-min trials of free exploration. Results: MDPV caused a decrease in body weight gain in mice. The effect was more pronounced in males. MDPV induced decrease of continuous spontaneous alternation of arms in Y-maze test in young adult male mice, however, it has no impact on females' performance. Conclusions: MDPV administered to mice during infancy cause developmental neurotoxicity that persist into adulthood impairing cognitive abilities.

Methodical analysis of unconventional adulterants in diacetylmorphine from 2019-2021 in Delhi, India

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Despite strenuous measures by drug law enforcement agencies the seizures of illicit drugs are escalating persistently. The magnitude of the challenge increases when novel compounds are added as additives to the conventional and

prominent drugs of abuse. The traditional potent drug 'Heroin' is steadily emerging as a vehicle to circulate other drugs. The suspected samples of drugs pertaining to 'Heroin' (1135 in number) seized by law enforcement agencies in the National Capital Region of India, Delhi, during the years 2019, 2020 and 2021 were submitted to the Forensic Science Laboratory for chemical analysis. The present study presents a compendium of analysis carried out extensively over a period of three years, in which unconventional adulterants like trimethoprim, dextromethorphan, olanzapine and sertraline as additives in diacetylmorphine along with the common additives Paracetamol, Caffeine, Alprazolam, etc., were detected. Preliminary examination of the samples was performed and subsequent confirmatory studies were carried out by Gas Chromatography - Mass Spectrometry technique. This analytical study is significant as unconventional adulterants were detected, thus spreading awareness to strengthen drug monitoring and regulation.

A qualitative study of people who use new psychoactive substances and harm reduction services in eight countries of Eastern Europe and Central Asia region

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Introduction: Research examines the use of new psychoactive substances (NPS) and the harm reduction response in eight countries of Eastern Europe and Central Asia (EECA) region: Belarus, Estonia, Lithuania, Moldova, Serbia, Kazakhstan, Kyrgyzstan, and Georgia. The aim is to generate a more accurate picture of current patterns of NPS use and harms associated with it in each country through recording the lived experience of people who use drugs and harm reduction service providers in order to inform the harm reduction response. Methods: The study involved desk research and semi-structured interviews and focus groups with 166 people who use drugs and 69 health and harm reduction service providers in eight countries. Results: People who use drugs in all countries were aware of NPS. Synthetic cannabinoids and synthetic cathinones are predominant groups of NPS and widely available, whereas synthetic opioids seem to be more present in Estonia and Lithuania. NPS users generally reflected two groups: those who have more experience with drug use, who have shifted to the use of NPS for a variety of reasons, and young people with no/ little previous history of drug use. A main risk of NPS is the absence of drug checking, because users don't know what they are actually consuming. Other health-related risks include overdoses, mental health issues and increased risk of transmission of human immunodeficiency virus (HIV) and hepatitis C virus (HCV) caused by unsafe use of drugs (mainly by frequent injections, sometimes up to 30 injections per night), often combined with increased number of sexual contacts and riskier sex practices. In most of countries providers of harm reduction, drug treatment programs and ambulance services are not prepared to provide people who use drugs with quality support and counselling to reduce risks associated with NPS use. Conclusions: The study identified patterns of NPS use, risk behaviours and drug-related harms. It presented more accurate picture of NPS use in 8 countries of EECA region. Research identified gaps in the current treatment and harm reduction response. These findings may inform and improve current harm reduction services to meet the needs of people who use NPS.

New psychoactive substance trends in the United States

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Introduction: New psychoactive substances (NPS) have continually evolved since appearing in the United States in 2009. The timely dissemination of information outlining the NPS currently in the market provides useful information to the law enforcement and health communities. This presentation will illustrate NPS identifications and trends tracked by Drug Enforcement Administration's (DEA) laboratory system. Methods: Data was collected for this analysis through a query of archived seizure and analysis information. The information targeted in this query included the date and location of the seizure and substances identified during the chemical analysis performed by the eight DEA chemistry laboratories. These seizure details and analytical results are used to compile drug intelligence, detect the appearance of new drugs of abuse, and monitor drug trends. Results: The most prevalent NPS identified in the United States fall within the categories of synthetic cannabinoids, cathinones, and opioids. Other chemical classes identified during the first half of CY 2022 include benzodiazepines, tryptamines, hallucinogens, and several other classes. Conclusions: Due to the ever-changing nature of NPS, the criminal justice system is confronted with a unique set of challenges. Understanding the current trends and monitoring the emergence of NPS within the United States enables the health, forensic, enforcement, and legislative communities to be better prepared to fight the NPS epidemic.

Synthetic Cannabinoids Scheduling Impacts on Positivity and Markets

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Introduction: Synthetic cannabinoids remain one of the most challenging classes on novel psychoactive substances. Their popularity has risen and fallen since their first appearance in 2008, and there have been successive waves of structural families. This presentation will describe the latest changes in chemical subclasses of synthetic cannabinoids, examine how these are changing based on regulation and scheduling and report on the most prevalent substances present in various populations. Methods: The data are generated from NPS Discovery sample mining for the identification of synthetic cannabinoids in postmortem and clinical toxicology samples provided from death investigators, clinicians, and forensic samples, and seized drug samples. Results: While the major and most frequently detected drugs in this class in 2021 and 2022 continue to be MDMB-4-en-PINACA, ADB-BINACA, and 5F-MDMB-

PICA, several new synthetic cannabinoids have been reported since China passed a ban on the legacy synthetic cannabinoids in May of 2021. By June 2021, we identified a synthetic cannabinoid not covered the ban: 5F-AB-PFUPPYCA. In subsequent months, online reviews of gray market vendors showed the gradual disappearance of compounds that were now illegal, and the emergence of novel subclasses and compounds that were not covered. These include members of the oxoindolinylidene class, 5F-BZO-POXIZID, BZO-HEXOXIZID, BZO-CHMIXIZID, ADB-FUBIATA, and others. In addition, compounds missing key functional groups for activity have been reported including MDMB-5Br-INACA. Another emerging trend is gray market websites offering precursors for home synthesis of synthetic cannabinoids. Conclusions: As markets become more scrutinized and regulated illicit suppliers are turning quickly to innovative new compounds and marketing strategies in an effort to circumvent the laws.

Improvement of the Brazilian regulatory model for substance control through the creation of an inter-institutional working group

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Independent Brazilian institutes share the responsibility of controlling and monitoring the illicit drug market. The phenomenon of New Psychoactive Substances (NPS) created the necessity to increase integration and facilitate communication between competent institutes. To provide a propitious environment for the discussion, an inter-institutional Working Group (WG) was created. The main objective of the WG is to discuss and improve the regulatory model for the classification and control of substances, especially NPS. The Group associates various fields involved in the combat of drug trafficking, such as forensic and legal experts, along with drug police and public health representatives. Method: The WG was established within the scope of the National Health Surveillance Agency (Anvisa), through Portaria number 898, on June 6th, 2015. It also has participation from the Ministry of Justice and Public Security, which is represented by the Federal Police (PF/MJSP), the National Secretariat of Public Security (SENASP/MJSP), and the National Secretariat of Drug Policies (SENAD/MJSP). The Group meets periodically and systematically to share knowledge and experiences faced by its representatives' institutes, as well as promote discussions that enable advances in legislation regarding drug control. Results: In favor of optimizing the control of NPS, the WG elaborated the generic classification for synthetic cannabinoids, synthetic cathinones, and phenylethylamines, which were included in Brazilian legislation in 2016, 2017, and 2019, respectively. In 2016, the Working Group also developed an online form for direct communication between Anvisa and forensic laboratories responsible for drug analysis and detection. This allows quick communication with Anvisa, which will evaluate the inclusion of the substance on the country's drug list. The Grou creation developed better communication between the entities involved in the drug problem. Along with measures taken by Anvisa to simplify the regulatory process of including a substance under national control, the period between a new drug identification and its inclusion in the country's control lists has drastically decreased. As an example, RH-34 was notified via the online form on December 27th, 2018 and its prohibition was published on February 2nd, 2019, only 45 days after receiving the notification. As for the substance 4-HO-MIPT, the notification took place on June 17th, 2018 resulting in its prohibition on August 21st, 2018, 60 days after the notification. Finally, the WG also prepares, annually, subsidies for Brazil's position regarding international control of new substances on the Expert Committee on Drug Dependence (ECDD) of the World Health Organization (WHO). Conclusion: Improved communication between the Working Group's member entities positively impacted the time elapsed between the detection of an NPS and its inclusion in the national control lists. This means that repression measures are effectively taken to prevent the spread of new drugs. The Group members are also habituated to monitoring and comparing the international context to what happens in Brazil, to develop strategies for the problems encountered, such as the generic classification for different drug classes. As a space for interaction between all institutions responsible for drug combat, the WG facilitates the agile development of efficient regulation, based on practical experiences and the knowledge of various actors working on the same problem.

The in vitro profile of 5-MeO-tryptamine derivatives on the serotoninergic system — a structure-activity study

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Introduction: New synthetic tryptamines became popular due to the similar hallucinogenic properties to already controlled psychedelics such as LSD. Despite the lack of information, these compounds are supposed to interact with the serotonergic system. Thus, this study focuses on the in vitro effects of nine amino-substituted 5-MeO-tryptamines with different modifications in the amino-group: 5-MeO-DMT, 5-MeO-MET, 5-MeO-DET, 5-MeO-NiPT, 5-MeO-MiPT, 5-MeO-EiPT, 5-MeO-DiPT, 5-MeO-MALT, 5-MeO-DALT. Methods: HEK293 cells expressing the human isoforms of serotonin (5-HT) transporter (hSERT) were used for the 5-HT uptake inhibition and transporter binding assays. Membranes from CHO-K1cells expressing the human isoform of 5-HT1A or 5-HT2A receptors were used for receptor binding assays. Results: Our results demonstrate that the amino group does not play an important role in 5-HT uptake inhibition. However, the affinity of the compounds for hSERT seems to increase with bulkier substituents. Moreover, all the compounds tested show a very high 5-HT1A receptor affinity and such interaction decreases with the presence of amino-isopropyl groups. Finally, all the compounds, especially allyl-amino derivatives, possess high 5-HT2A receptor affinity. Conclusions: Our results point to a high probability of inducing potent hallucinogenic effects, especially by the recently emerged allyl-amino derivatives 5-MeO-MALT and 5-MeO-DALT, due to their high 5-HT2A

affinity. Moreover, more studies are needed in order to evaluate changes in the thermoregulatory system, due to the high 5-HT1A affinity of these compounds.

Toxicokinetics and toxicodynamics aspects of ayahuasca and N,N-dimethyltryptamine (DMT)

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Introduction: Ayahuasca is a hallucinogenic beverage with a long traditional use by indigenous Amazonian tribes in religious ceremonies and therapeutic practices. While ethnobotanical surveys still indicate its spiritual and medicinal uses, consumption of ayahuasca has been progressively extended to recreational contexts worldwide. Herein, the toxicokinetics and toxicodynamics of ayahuasca, and its main psychoactive constituent N,N-dimethyltryptamine (DMT), were comprehensively covered. Methods: An extensive English literature search was performed in PubMed (US National Li- brary of Medicine) and Scopus. Results: Ayahuasca is typically prepared from the leaves of the DMT-containing Psychotria viridis, and the stem and bark of Banisteriopsis caapi, the plant source of harmala alkaloids. DMT freebase can be smoked or nasally insufflated, while fumarate salts are typically consumed through intravenous injection, leading to an almost immediate onset of potent hallucinogenic effects, that last for less than 1 hour. DMT is rapidly and extensively metabolised by MAO-A to its inactive metabolite 3-indole-acetic acid. However, when orally ingested in the form of ayahuasca, the harmala alkaloids act as potent MAO-A inhibitors, preventing the extensive degradation of DMT. DMT psychotropic effects are mainly related with the activation of 5-HT2A receptors. Mildly to rarely severe adverse effects are reported following consumption of ayahuasca or its alkaloids individually. Conclusions: The evidence has pointed to potential psychotherapeutic benefits in the treatment of depression, anxiety, and substance use disorders; and although recreational misuse of ayahuasca/DMT, and consequent occurrence of unpredictable health hazards, has been diverting attention away from such clinical potential, research onto its therapeutic effects has now strongly resurged.

Underground treatments: emerging trends in substance-assisted therapy

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Introduction The last two decades have witnessed the repositioning of ketamine, a widely used anaesthetic agent, as an antidepressant as well as the resurfacing of psychedelics for the treatment of major depressive disorder (MDD) and trauma-related disorders. The mechanism of action of ketamine appear to different significantly from the conventional antidepressants and is characterized by a rapid-onset (within 24-hours) and sustained effect (7-10 days) following a single intravenous infusion. Recently, the association of psychotherapy and/or counselling has emerged as a strategy to maintain the antidepressant effect of ketamine. For psychedelics there is also the option of "integration" after the session. Aims This study aims to survey the different approaches to rapid acting antidepressants and psychedelic assisted psychotherapy. Methods We conducted a search of the scientific literature on this topic and subsequently we surveyed websites of providers, internet fora and mailing lists, including the dark web. Results A limited number of randomized clinical trials is available on this subject and we noticed a significant heterogeneity in the clinical settings with practitioners administering therapeutic sessions concomitantly, within 24 hours, or several days/weeks following the administration of the drug. We also noticed that different therapeutic approaches have been implemented, from CBT to psychodynamic therapy to counselling. The qualifications of the therapists are also variable. Further, there are also reports of practitioners offering therapy to individuals that are sourcing ketamine or psychedelics on the black market, as harm reduction intervention. Conclusions Although psychotherapy assisted treatments appear promising, as many other authors have pointed out, further research is warranted. There is a lack of consensus on the definition of rapid acting antidepressant assisted therapy, type of psychotherapy and qualification of the therapy providers. We advocate therefore for the scientific community to come with an agreed definition of rapid acting antidepressants assisted therapy that clarifies the following items: 1. length of time between administration of the substance and the therapy sessions 2. the modality of the therapy 3. the qualification of the therapists.

New psychoactive substances identified in Canada

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Introduction: New psychoactive substances (NPS) are often marketed under generic names such as 'legal highs', research chemicals, etc. Since general population surveillance approach is time consuming, Health Canada (HC) developed an Online NPS Survey tool to improve its surveillance efforts. Methods: The Online NPS Survey was implemented on an ongoing basis starting in March 2020. Respondents were asked about a specific episode of NPS use and respond to quantitative and qualitative questions about their use. Results: As of March 2022, 655 responses were collected with 130 unique substances reported. The majority of respondents were between 25 and 64 years old (56%), where the average age was approximately 30 years. Roughly two-thirds of respondents were male. Thirty percent (30%) of the respondents were currently enrolled in school, and 63% were currently employed. Approximately one-third of responses were for substances which are not controlled in Canada. The most frequently reported pharmacological classes included classic hallucinogens (30%), stimulants (17%), opioids (13%), sedatives (11%) and dissociatives

(11%). In the first year of the study, the three most commonly self-reported substances were magic-mushrooms (21%), 1P-LSD (14%) and LSD (8%) – all classic hallucinogens. The same trend was observed in the second year, with an increase in reported magic-mushroom use (32%). Conclusions: The data will be used to understand trends in the Canadian illegal drug market and contribute to HC's drug monitoring and surveillance platform, i.e. Early Warning System (EWS). The results will also support to achieve the Controlled Drugs and Substances Strategy (CDSS) in Canada.

Detection of the superwarfarin drugs and synthetic cannabinoids in human biological samples

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Introduction: Anticoagulants, specifically the superwarfarin drug class, recently have been identified as a threat and have been reported in combination with the novel psychoactive substance (NPS) subclass of synthetic cannabinoids. When consumed in toxic amounts, anticoagulants can result in severe bleeding and death. In the United States (Chicago, Illinois) in 2018, a large number of cases of synthetic cannabinoids laced with brodifacoum have been reported. More than 150 patients presented to hospitals with coagulopathy and severe bleeding, which resulted in four deaths. More recently in December 2021, a similar outbreak occurred in Florida where synthetic cannabinoid products were adulterated with anticoagulants resulting in several hospitalizations. Methods: A method was developed and validated using liquid chromatography tandem mass spectrometry for the analysis of ten anticoagulants. The analytical range of the method was 5-250 ng/mL. Following the outbreak in December 2021, deidentified samples (n=78) were submitted for the analysis for anticoagulants and synthetic cannabinoids. Results: In 74 samples, brodifacoum was detected and quantitated. The median concentration for brodifacoum in blood (n=13) was 110 ng/mL (range 48-429 ng/mL). In serum (n=45), the median brodifacoum concentration was 575 ng/mL (range of 86-1,995 ng/mL), and in plasma the median was 53 ng/mL (range of 11-365 ng/mL). Difenacoum was also detected in six serum samples with brodifacoum. No anticoagulants were detected in the urine samples (n=8). Analysis of the urine samples identified the metabolite of 4F-MDMB-PICA. Analyses of other matrices for synthetic cannabinoids is ongoing. Conclusions: Incidents involving seized material adulterated with anticoagulant have become a public health threat. Identification of anticoagulants like brodifacoum and difenacoum in biological specimens requires specialized testing, as routine testing protocols lack the necessary sensitivity and selectivity. Further, additional testing may be required for synthetic cannabinoids as both outbreaks in the United States have involved this NPS subclass.

Ibogaine/Noribogaine in the treatment of Substance Use Dis-orders: a systematic review and Meta-analysis of side effects

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Introduction: Ibogaine and noribogaine are psychedelic substances with dissociative properties naturally occurring in plants of the Apocynaceae family. Research has shown their efficacy in the treatment of substance use disorders (SUD), particularly in opiate detoxification but its efficacy and toxicity are still unclear. The aim of this review is to assess the anti-addictive role of ibogaine and evaluate its side effects. Methods: A systematic literature review was conducted on 29 November 2021 using PubMed, Scopus and Web of Science databases. For data gathering purposes, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was followed. Research methods were registered on PROSPERO (CRD42021287034). Results: Thirtyone articles were considered for analysis. The results were organised according to the type of study: case reports/ case series, randomised-controlled trials (RCTs), open-label, survey and observational study. The main outcomes were related to the anti-addictive effect of ibogaine and its cardiac toxicity. A meta-analysis of side effects was conducted using RevMan 5.4 software showing a significative risk to develop headache after ibogaine/noribogaine treatment. Conclusions: The results show some efficacy of ibogaine in the treatment of SUDs, but its cardiotoxicity and mortality are worrying. Further studies are needed to assess its therapeutic efficacy and actual safety.

Emergence of new psychoactive substances with enhanced toxicities caused by intentional adulteration and/or presence of contaminants in seizures

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Introduction: The presence of an additional potent drug/s even in a minute quantity due to intentional adulteration and/or impurities produced under non-standardized clandestine manufacturing practices of new psychoactive substances is highly influential for the efficacy of the drug itself. It enhances the potency of the psychoactive effects and may contribute to high addictive potential towards the drug. Hence, the chemical characterization studies over seizures containing new psychoactive substances are vital to establish the mandatory supply control measures on the origin of precursors, illegal synthesis methods and supply networks as well as for introducing awareness platforms on health aspects. Method: This study presented herein is related to seizures of blotter papers made upon possession and trafficking through postal services respectively, made by Sri Lanka Police and Sri Lanka Customs during the period

2018 to 2022. The blotter samples were of four different types in physical appearance and have been suspected as LSD stamps. Detailed chemical analysis and characterization studies were conducted at the National Narcotics Laboratory of the National Dangerous Drugs Control Board using Gas Chromatography-Mass Spectrometry (GC-MS). Results: The spectral analysis revealed the presence of phenethylamines (2C-B, 2C-C, 25C- NBOMe) as major constituents and further identified significant amount of drugs having hallucinogenic and psycho-stimulant properties such as ketamine, brolamfetamine (DOB) and mixtures of other phenethylamine substituents like 2C-E and 2C-I. Conclusion: Recent toxicological studies have grabbed the attention more towards these seizures containing new psychoactive substances mixed intentionally or unintentionally with other potent psycho-stimulant substances, as several fatal intoxication cases have been reported on consumption of phenethylamines containing blotter papers; with special reference to NBOMe series substances. These findings are helpful for strengthening awareness and urge focusing towards the potential risk associated with consumption of unknown newly emerging synthetic drugs by younger generations.

Hierarchical Cluster Analysis Application on Suspected Plant-based New Psychoactive Substances (NPS) Found in the Philippines using FT-IR/ATR Spectral Data

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Due to the crackdown on traditional drugs, there has been significant abuse reports on plant-based NPS, most specially in countries wherein they are naturally available, have social importance, and are legal to abuse. In the Philippines, there are existing plant-based NPS namely kratom and angel's trumpet. Therefore, an efficient method to discern such substances is vital. In this study, hierarchical cluster analysis using FT-IR/ATR spectral data was explored as a statistical grouping model to discriminate authenticated kratom and angel's trumpet plants. Important factors to interpret grouping results such as extracting solvent and soaking period, FT-IR/ATR fingerprint region range, and geographical locations were investigated. Results revealed that samples soaked in methanol-chloroform (10:1) either in 12 or 24 hours, and with FT-IR/ATR spectral data range at 650-1500cm-1, appears to be the most suitable conditions for the explored statistical method. Importantly, angel's trumpet Brugmansia candida samples from Tagaytay, Cavite and Los Baños, Laguna which are geographically close clustered significantly hence, further indicates that plant location might be an additional key factor that can affect grouping results. The proposed protocol indeed has the potential to create grouping models, that can be used to quickly assess the species level identities of claimed kratom and angel's trumpet in a simple and cost-effective manner. As closeness of geographical location indicates that it can be a factor during cluster analysis as manifested by the present study, it is further recommended to acquire more samples in other Philippine regions for validation purposes. The use of other plant parts and multivariate techniques can also be investigated in the future. Lastly, this kind of undertaking is beneficial in the standpoint of drug-policy-making in the country, as it could provide quick and reliable reports about dominant plant-based NPS species being abused in the Philippines.

The Ibiza Experience: NPS and traditional substance use among a sample of inpatients of Can Misses Hospital Psychiatric ward

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Introduction: The current psychoactive substances scenario raises enormous concerns for public health at a national and international level. The risks posed by traditional and Novel Psychoactive Substances (NPS) require adequate training for health professionals, effective harm reduction interventions and updated policies: in this context, Ibiza, one of the most popular nightlife resorts for summer holidays in Europe, appears as a crucial setting to explore psychopathological issues related to both traditional drugs and NPS. Previous studies confirmed a higher prevalence of risky behaviors for both residents and tourists in Ibiza; furthermore, anecdotal cases of NPS intoxication have been reported in recent years; in such a dynamic setting, naive customers are frequently seen by traffickers as test subjects for trialing new and potentially dangerous compounds for the first time. Methods: Patients admitted to the psychiatry ward of the Can Misses Hospital in Ibiza due to psychiatric symptoms related to recent use of psychoactive substances were recruited. Sociodemographic factors, familiar and personal anamnesis, substance use habits, general and psychopathological features were investigated. Urine samples were collected and analyzed in a toxicology laboratory using gas chromatography and mass spectrometry. Results: A total of 110 patients were included in the study. Most patients (n=77, 70%) declared multiple substance use, and 33% of patients reported more than two substances. NPS use was disclosed by 20% of the patients, although almost half of the participants (46%) declared to have used a substance without knowing what it was at. 37 subjects (40%) disclosed the use of prescription drugs without medical supervision. Psychomotor agitation, reference, and paranoid delusions, affective symptoms, consciousness disorders, and aggressiveness represented some of the most frequent symptoms at entry evaluation. A positive association with a lifetime diagnosis of bipolar disorder was found (two-tailed Fisher's exact test: $p = 0.013$). Positive associations were also found with temporal disorientation at admission (two-tailed Fisher's exact test $p = 0.022$). Conclusions: In this study, we described the acute psychiatric presentations related to recreational drug use in subjects on holiday in Ibiza. The use of psychoactive substances was characterized by poly-use of both traditional and novel substances, with several psychopathological consequences. Future research should focus on a better understanding of the psychopathological effects of specific substances, to help differential diagnosis and prospectively examine long-term effects.

NPS-related health responses implemented in Europe through the lens of an intersectional risk environment approach

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Introduction: NPS users are diverse in their motivations and social profiles, and so are the health needs and harms associated with their drug use behaviour. Health responses that accompanied enforcement measures adopted across Europe seem to mitigate health harms among NPS users, yet they have been less successful in hindering NPS consumption. Methods: As relational matters, drug-related risks and harms are differently experienced across drug-using populations. We applied an intersectional risk environment approach to analyse public health responses to NPS implemented at national and supranational levels across Europe. It involves the analysis of the social and physical spaces in which risk and harm are produced or mitigated by intersecting micro- and macro-level environmental factors exogenous to individuals. Results: NPS-related health responses accompanying enforcement measures across Europe have mostly focused on prevention, monitoring and harm reduction. Policy developments at both national and supranational levels have generally adopted a one-dimensional approach that merely focus on singular social locations such as sexual orientation (men who have sex with men) or age (school students and young people). Targeted to more noticeable groups of users, these strategies have failed in developing approaches that account for complexity between and within groups of NPS users, which are given by specific environmental risk factors such as drug policy, availability of drug and harm reduction services, drug use settings, peer relationships and social environments, cultural and political contexts. Conclusions: As other drug-related issues such as opioids overdose crisis, public health responses to NPS would be improved through an intersectional risk factor framework to better assess social differences that yield specific health needs and rend some NPS users more exposed to harm. The close collaboration with users in the policy-making processes may also contribute to the design and implementation of more pertinent public health strategies that facilitate access to drug services and minimize health risks.

New Psychoactive Substances (NPS) in 146 Samples Seized in Colombia (2021-2022)

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Introduction: New Psychoactive Substances (NPS) have become a rising phenomenon, showing an increase in the illicit market in different world regions. Therefore, the Anti-Drug Research Chemical Laboratory (LQIA, for its acronym in Spanish) of the Anti-Narcotics Directorate of the National Police has been developing a project to properly establish the chemical identity of seized samples, which are sold in the national illicit drug market, to contribute to the control of NPS in Colombia. Hence, in this work, the chemical composition of the 146 samples seized in 2021-2022 was analyzed by Gas Chromatography coupled with Mass Spectrometry (GC-MS) to identify the common combinations of street drugs in dilute mixtures. Methods: Sample collection: The material used in the study were 146 samples such as blotters strips, crystal or powder, pressed tablets or capsules seized from different cities of Colombia. Sample preparation: An approximately 5.0 gm of each sample was diluted to 5 mL with methanol and then treated with an ultrasonic bath for 5 min. The samples were then filtered by PTFE 0,22 µm filter prior to GC-MS analysis. Instrumentation: The samples were injected into a gas chromatography (Nexis GC-2030, Shimadzu) coupled to a mass spectrometer (model GCMS-QP2020 NX, Shimadzu) system. Data analysis: The identification of unknown compounds was undertaken with GC–MS mass spectrums and utilizing suitable libraries for drug discovery (SWGDRUG, NIST Mass Spectral and Wiley-Mass Spectra of Designer Drugs). Results: Mixtures of drugs, such as Methamphetamine, Phenacetin, Ketamine, Oxycodone, Tramadol, Caffeine, Lidocaine, Nicotine, Mephedrone, Eutylone, Amphetamine, Cocaine, Methadone, N-Ethylpentylone, norpseudoephedrine, MDP2P, DOB, 25I-NBOMe, and MDMA were detected in the samples. Conclusions: Gas chromatography in combination with mass spectrometry (GC-MS) plays an important role in the field of comprehension of new illicit drug trafficking methods in Colombia, which have a high impact in areas such as strengthening of the Early Warning System (SAT by its acronym in Spanish), improving responsiveness against the appearance of new psychoactive substances (NPS), and helping in the identification of new methods to produce illicit drugs and the identification of chemical masking used in the country.

A two-year portrait of novel psychoactive substances findings in Quebec (Canada) (2020–2021)

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Introduction: In 2019, the Laboratoire de sciences judiciaires et de médecine légale (LSJML) implemented a comprehensive process to deal with NPS systematic screening (Garneau et al., Forensic Science International 318 (2021) 110595). A combination of an internal early warning system (EWS) and an analytical method with a dynamic scope allows for thorough toxicology testing of all casework. Methods: Blood and urine samples were extracted by protein precipitation. The diluted supernatant was injected on an LC-MS/MS system. The method, currently targeting 49 NPS, was validated and accredited under ISO 17025 and the Standards Council of Canada norms. Results: Between January 2020 and December 2021, one or more NPS was detected in 943 cases, constituting 6% of the total caseload. Benzodiazepines etizolam (n=389), flubromazolam (n=305) and flualprazolam (n=279) were the most prevalent, so much so that they are now part of the top 10 active drugs encountered in driving under the influence of drugs (DUID)

cases. Results also indicate a rise in novel synthetic opioids (NSO), particularly carfentanil (24 cases) and benzimidazoles (39 isotonitazene and 6 protonitazene cases). Conclusions: NPS findings in the province of Québec follows a distinct pattern from other jurisdictions, with a high prevalence of benzodiazepines (84% of NPS cases), followed by NSO (9%), and an almost complete absence of synthetic cannabinoids and stimulants.

Volatile substances misuse and psychiatric comorbidity: a case report

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Introduction: The recreational use of volatile substance or "inhalants" among young and vulnerable people is a growing trend in Italy. This consists in the voluntary inhalation of a wide variety of Novel Psychoactive Substances (e.g. difluoroethane, butane, propane, ethylacetate) contained in easily available products, such as cleaning sprays, hair sprays, paint/polish removers and many others. Users traditionally seek an altered, euphorized mental state, but may incur in serious consequences such as CNS depression, hypoxia, liver and kidney damage as well as permanent neurological and neuropsychological effects. Methods: We present the case of a 23-year-old male followed by Lodi Mental Health Unit and Lodi Addiction Treatment Unit for behavioral disorders related to inhalants use. Results: In 2017, "I.", a 18-year-old male, was hospitalized in Lodi Psychiatric Ward. "I." was born in Russia and was adopted at the age of 2; since the age of 14 he accessed the Emergency Room a number of time, mainly for psychomotor agitation and aggression related to alcohol misuse; he also disclosed the use of a variety of "traditional" substances and NPS (mainly cannabis, cocaine, MDMA, ketamine), although urine toxicological tests generally resulted negative. He was diagnosed with Cluster B Personality Disorder (with prevalent antisocial / narcissistic traits) and Alcohol Use Disorder. He later disclosed the misuse of volatile substances (mainly with cans / lighter gas containing difluoroethane), for recreational purposes, but also seeking a "dissociative" effect in order self medicate painful childhood memories and experiences. A pharmacological therapy of gabapentin 300mgx3, flurazepam 30mg, delorazepam 1mgx3. At discharge, he started a rehabilitation program with slow gradual improvement from a behavioral point of view, and partial acquisition of awareness of substance misuse; isolated relapses occurred, albeit within a context of improvement in the containment of impulsiveness and dysfunctional personality aspects. Conclusion: Inhalants use is a growing phenomenon among young people in Italy. Although literature on the topic remains scarce, health professionals should be aware of such trend in order to develop effective treatments and to inform young users on health related risks.

Retrospective 2021 review of NPS in the US and prospective look forward

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Introduction: The novel psychoactive substance (NPS) market in the United States (US) has been very dynamic and diverse over the past decade. Each year, we review our NPS positivity data from many perspectives, including domestic and international legislation, testing capabilities, and improved knowledge of pre-analytical factors such as stability and metabolism. Methods: Toxicological casework reported between January and December 2021 was queried for positivity for synthetic cannabinoid receptor agonists (SCRAs), designer benzodiazepines (DBZD), novel synthetic opioids (NSOs) and synthetic stimulants. Results: In 2021, there were 144 findings of SCRAs reported in 119 blood samples. The major SCRA was MDMB-4en-PINACA (53%), which was added to the scope of testing in June 2021. DBZD positivity increased in 2021, with 3200 DBZD findings in 1926 samples. Etizolam accounted for 63% of results, but flualprazolam, flubromazolam, clonazolam and bromazolam all accounted for >5% each. For NSOs, there were 2973 detections in 2905 samples. para-Fluorofentanyl dominated positivity at 84%, however, that is likely due to infiltration of the illicit fentanyl supply. Non-fentanyl related NSOs (e.g., metonitazene, isotonitazene, brorphine, etc.) comprised 6.7% total. In 2021, there were 235 findings of synthetic stimulants in 231 blood samples. Eutylone was reported in 91% of these cases. Interestingly, pentylone was reported in 4%, and likely present as a metabolite of the emerging stimulant, N,N-dimethylpentylone. Conclusions: There is continued presence of NPS in the US, although markets are constantly shifting. Stakeholders must be vigilant in both current landscape of drugs as well as factors that may prompt changeover; changing positivity will be discussed.

"Benzo-Dope": Exploring Combinations of Novel Synthetic Opioids and Designer Benzodiazepines

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Introduction: Combined use of opioids and benzodiazepines has historically been advised against due to potential for compounding Central Nervous System (CNS) and respiratory depressant effects. Recently, a rise in street opioid exhibits intentionally being mixed with benzodiazepines, colloquially referred to as "benzo-dope", has been observed. In the US and Canada, "benzo-dope" is often etizolam and fentanyl, however there are also new formulations of novel synthetic opioids (NSO) and other designer benzodiazepines (DBZD). This presentation will explore the evolution in concomitant detection of NSO and DBZD in toxicology samples in 2021 and 2022. Methods: Toxicology data acquired by Liquid Chromatography Time of Flight Mass Spectrometry (LC-TOF/MS) was retrospectively examined for the presence of NSO and DBZD. Results: In 2021, 48% of isotonitazene cases (n=54) contained DBZD. Flualprazolam (11.1%), clonazolam/ 8-amino-clonazolam (11.5%), and etizolam (30.8%) were all reported in combination with isotonitazene. In 2021 and 2022, brorphine (n=89), metonitazene (n=513) and N-pyrrolidino etonitazene (n=255) were most often identified with clonazolam/8-amino-clonazolam (47.2%, 55.8%, and 15.7%, respectively). High rates of

incidence for NSO and DBZD continue well into 2022, with 91.6% of brorphine (n=24) and 70.7% of metonitazene (n=65) cases also containing DBZD. Significant geographical distribution differences have been observed, with many cases originating from the midwestern US and Canada. Conclusions: The high prevalence of "benzo-dope" in toxicology samples is of public health concern and can compound adverse events, including death due to combined CNS and respiratory depressant effects and more complex addiction. Toxicological data is an important index on "benzo-dope" use, especially with new NSO and DBZD constantly emerging and changing in popularity.

The European Union Early Warning System: 25 years of monitoring and responding to new drugs in Europe

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Introduction: This year marks the 25th anniversary of the EU Early Warning System (EWS) on new psychoactive substances (NPS), which was the first regional early-warning mechanism set up to monitor and respond to NPS in Europe. Method: Data from event-based surveillance, including law enforcement seizures and serious adverse events, linked to NPS as well as aggregated seizure data reported by 29 national early warning systems in Europe between 2005–2021 was analysed. Results: At the end of 2021, the EMCDDA was monitoring around 880 NPS, 52 of which were first reported in 2021. The number of NPS in circulation remains high, with 350–400 previously reported substances detected every year since 2015. In 2020, 21,200 seizures amounting to 5.1 tonnes of material were reported by the EU Member States. This is the highest quantity seized in a year; 70% of the material (3.3 tonnes) were cathinone powders. The trend towards highly potent substances continues which pose a greater risk of severe poisoning. The market has become highly dynamic and resilient. Conclusion: Over the last 25 years, the new drugs market has undergone significant change, with more novel, potent and toxic substances putting consumers at greater risk. In the past four years alone, the EWS has identified serious harms linked to 16 new substances, which has led to controls at EU-level.

International cooperation to address global public health harms caused by NPS

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Introduction: The international drug control conventions, namely the 1961 Single Convention on Narcotic Drugs and the 1971 Convention on Psychotropic substances are a set of international treaties established by countries to monitor and control the manufacture, trade, and distribution of psychoactive substances. Unlike many national control measures that may permit generic classification of NPS, the international drug control conventions require individual substances to be listed. This is to prevent diversion, abuse, and other harms to health caused by psychoactive substances while ensuring that access to controlled medicines is not inhibited. The World Health Organization (WHO) holds a unique mandate within the international drug control system to advise the drug policymaking body of the UN, the Commission on Narcotic Drugs, of the health effects of NPS and other psychoactive substances assessed by WHO, and subsequently their appropriate level of international control. Methods: The WHO fulfils its mandate to the international drug control treaties through its Expert Committee on Drug Dependence (ECDD), an independent scientific advisory group that evaluates psychoactive substances on their abuse potential, dependence potential, and harms to health. WHO carries out an annual data collection exercise amongst all UN Member States to gather information on specific NPS that have been brought to the attention of WHO with supporting information that these drugs are being clandestinely manufactured and pose a threat to public health. Results: In the past 10 years, more than 75 NPS have been placed under international control based on advice provided by WHO, thereby enabling a coordinated global approach in detecting and reporting NPS that have documented harms to health. Conclusions: The international drug control conventions provide an important mandate to WHO to assess the harms to health caused by NPS and make recommendations about their international regulation to prevent abuse, dependence, deaths due to overdose, and other harms to health while also preventing or minimizing disruption to psychoactive medicines that have proven therapeutic use.

Assessment of structure-activity relationships and biased agonism in a set of (psychedelic) phenethylamine 5-HT2AR agonists

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Introduction: The group of serotonergic psychedelics includes both 'established' substances (e.g. LSD, mescaline, and psilocybin), and more novel derivatives (such as 2C-X, DOx, and 25X-NB(OMe) derivatives). These substances are described to share serotonin 2A receptor (5-HT2AR) activation as their main pharmacological action. Despite their relevance, the molecular mechanisms underlying the psychedelic effects induced by certain 5-HT2AR agonists remain elusive. One of the phenomena hypothesized to be involved is the preferential activation of certain signaling pathways over others, referred to as biased agonism. Methods: This study comparatively monitored the efficiency of a panel of diversely substituted (N-benzyl-derived) phenethylamines, including several psychedelic NPS (2C-X, 25X-NB, and DOx substances), to induce recruitment of β-arrestin2 (βarr2) or miniGαq to the 5-HT2AR, using in vitro bioassays.

Results: All test compounds exhibited agonist properties in the two assays, which allowed for the assessment of their structure-activity relationships and potential biased agonism. Computational analysis revealed that the lipophilicity of the phenethylamines correlated with their efficacy in both the βarr2- and miniGαq-assays, yielding a stronger correlation in the latter assay than in the former. Conclusion: This study has provided novel insights on the structure-activity relationships and biased agonism of a set of diversely substituted phenylalkylamines at the 5-HT2AR.

Fight against emerging drugs in sport: raising the game

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The illicit drug market is in constant evolution and this requires the world of anti-doping to adjust its practices and rules to remain efficient at protecting clean athletes and fair competitions. WADA as the world regulator in anti-doping in sport is at the forefront of the evolution of rules and also of major progress in science to ensure that innovative research is robust to support rules or decisions taken by the anti-doping community. Several recent key evolutions in the drug enforcement in sport domain are to be noted in a context of rapid societal changes and sustained consumption of substances to boost performance in various countries around the world. A global review of such key changes will be presented during this keynote speech at the IXth NPS Conference.

Reducing misdeclaration of NPS

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Novel psychoactive substances(NPS), at present, are globally considering by far the fastest emerging drugs that are spreading in every corner of the universe in the guise of “legal highs” by passing International Drug Control Measures. New psychoactive substances (NPS) are a range of drugs designed to replicate established illicit drugs such as cannabis, cocaine, ecstasy and LSD. International drug traffickers are taking privileges staying at a step ahead of laws of Drug Control Measures of state or territories. Misdeclaration of NPS through shipping containers at seaports, blocking enforcement vigilance, poses globally a continuous threat. Effective control of the shipped materials is a big challenge, according to UNODC, less than two percent of shipping containers are ever screened. Methodology: Drug traffickers are using highly robust and ever-changing concealment methods to smuggle drug from source country to destination areas. To disrupt and dismantle the easy channeling NPS through seaports and monitoring and responding entire activities of export-import dynamics at seaports, the following triangular approaches can be setup for container control profiling measures as dog-squad deployment, sophisticated and hi-tech scanning machine establishment, and data preservations and checking analysis measures. Furthermore, digital payment system of drug money can be checked and monitored creating a high profile watchdog for respective countries or territories. Result: These vigorous measures can highly likely yield noteworthy outcomes cutting out the influx of NPS. Since about ninety percent of global cargo trades are continuing through shipping routes. Though these proposed methods might have some sort of challenges in terms of policy concerned and resource intensive varying country to country. If these measures could adopt with joint collaboration of maximum countries, that would create a dynamic result of stopping the flow of NPS by reducing 60-70% of total NPS trafficking through seaports. Conclusion: As through observation and research of the universe, myriad ways & means are being discovered for the betterment of mankind. In this regard, tremendous research could be taken to unravel mysterious drug menace to make a drug free world for human being as a whole. There might be a desired solution at our door steps.

Different trends in NPS misuse among young people after the COVID-19 lockdown

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Introduction: COVID 19 pandemics has significantly affected drug consumption habits. Our study, carried out in collaboration with local Police Department and addiction services, focused on the city of Terni, the capital of Umbria, which in 2021 was the region with the highest overdose mortality in Italy: more specifically, about 35.6 deaths per million inhabitants among the 15-64 age group of the population against a national average of 8.2 occurred.
During the peak of the pandemic and also after the end of the lockdown Terni remains the epicenter of a cluster of lethal overdoses of young people. We also noticed that since 2017 illegal substances consumption increased by 20%. Methods: we analyzed data provided by the local Police department and addiction services (in particular the Usl2 Umbria Addiction Department). Results: we noticed a trend of general increase in addictions rate (smoking, alcohol, drugs) in particular, over the last two years, among the young population drug consumption increased of 10% (from 59% in 2020 to 69% in 2021). Among the total population of USL2 patients the percentage of under 25 grew from the 8.8% of the total to the 13.04% of the total in 2021. Conclusions: these data show a significant increase of substance misuse expecially among individuals under 25 years that has occurred not only during the pandemic but also after lockdown; this increase involves not only old substances but also NPS misuse, such as cannabinoids, synthetic cathinones and ketamine-like substances. In particular, 50.9% of people aged between 20 and 24 and 37.3% of those under the age of 20 of the UslUmbria2 Addiction Department use illegal drugs: whereas heroin and cocaine represent the mainly widespread substances among people aged between 20 and 24 years, NPS, in particular cannabinoids, remain the first drug consumed in the population under 20 years of age. We are currently cooperating the with law

enforcement agencies and drug services to monitor the phenomenon and design and implement adequate intervention strategies.

'Synthetic cannabinoids' and NPS: harnessing the terminological and conceptual naming and classification issues

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Introduction. "Spice" is a "synthetic cannabinoid" and a NPS. CBD obtained in a laboratory is a "synthetic cannabinoid"... but it is not a NPS. "Naloxone" obtained from yeasts qualified as GMOs is a NPS... but is it a "synthetic cannabinoid" is it derives from a natural organism? The confusion, at times juxtaposition, of these two categories (cannabinoid-like NPS, and synthetic cannabinoid) only increases as both the number of cannabinoid compounds known to humans augment, and the methods to obtain them diversify. It is time to discuss the ontological problems with cannabinoids, synthesis, and "unnatural" compounds. Methods. The presentation builds upon a study published in 2020 (doi.org/10.1177/2050324520945797), researched in the context of the assessment of Cannabis and cannabioids by the WHO. The study adopts a philosophical scrutiny to the terms and concepts associated with cannabinoids, aided by Bachelard's metaphysics of chemistry; it reviews a wide range of sources (literature, folk knowledge, archives, pharmacopœias, international legal texts, and elements of pharmacy and pharmacognosy, clinical and herbal medicine nomenclatural frameworks). Generic and Cannabis/cannabinoid-specific nomenclatural frames are compared to determine the extent to which they coincide or conflict, and lessons to be learnt for the classification of cannabinoids. Neologisms are suggested, carefully crafted following lege artis in the field. Results. Cannabinoid-related NPS terminologies are often ambiguous beyond a specific discipline or inconsistent between them. There is insufficient scientific grounds for many terms and concepts used at the policy level. Existing models of cannabinoid classification at times conflict by adopting idiosyncratic, partial, outdated, or utilitarian schemes. Differences in kind between subtypes of the large category "synthetic cannabinoids" need closer consideration, to avoid confusions. Beyond specific scientific disciplines, where complex terminologies have their use and justification (e.g. "synthetic cannabinoid receptor agonist (SCRA)"), the broad group of "synthetic cannabinoids" could be usefully subdivided in distinct subcategories (e.g. differentiating "biosynthesis" between GMO and non-GMO organisms) or using the same subcategories with simpler names (e.g. "neocannabinoid" instead of SCRA). Conclusions. The category "synthetic cannabinoid" is outdated. The naming and policy-making challenges posed by the diversification of types of cannabinoids (in kind, in effects, and in methods of obtention) should start being addressed as early as possible. An update of the terms and concepts we use to designate cannabinoid-like NPS could greatly facilitate the understanding of threats and challenges by the general population, facilitate public health prevention campaigns, and foster sound basis for media and political discussions. This presentation introduces a new bioethical nomenclature that aims to resolve some of the challenges outlined.

Development and application of a border to grave real-time New Zealand integrated Drugs Surveillance System (ESR iDSS)

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Introduction: New drugs including novel psychoactive substances (NPS) are being increasing found in New Zealand (NZ). these substances can cause harm and a system to monitor and track the use of such drugs in NZ in real time was needed. This system will need to be readily accessible by stakeholders such as health professionals and police. Methods: The ESR iDSS was developed to provide real time information on what NPS's are emerging on the NZ market, track their real time use in NZ and monitor their risk and potential harm in our communities. Results: The iDSS is a rapid information sharing tool used within our organisation and also used across other organisations including police, hospitals, ambulance services, mental health services and the Ministry of Health. Information of what drugs, where and when these drugs are found, and which drugs are causing harm is used to develop harm reduction strategies at a community level and to develop a national forecasting strategy. Synthetic cannabinoids are a dominant group of drugs associated with drug-related deaths in NZ. From May 2017 until March 2022 one or more synthetic cannabinoids were detected in 127 deaths where the cause of death was not ascertained after autopsy and in a further six cases with pre-existing heart disease and death following use of synthetic cannabinoids. The cause of death was determined by autopsy in a further 16 cases where synthetic cannabinoids had been used, with hanging being the cause of death in seven of those cases. Conclusions: The ESR iDSS provides real time information of the temporal and geographical trends of each NPS found entering NZ that enables the development of harm reduction strategies at a community level. The use and harm caused by synthetic cannabinoids has changed over the last five years in NZ. Initially AMB-FUBINACA was causing the most harm and was dominant in the upper North Island, and 5F-ADB was also common and was associated with harm in the lower part of the North Island. As time has progressed the change to new synthetic cannabinoids is becoming more rapid and can differ between communities. Most synthetic cannabinoid related deaths are preventable by timely hospital treatment therefore community-based knowledge of drug use is essential to develop appropriate drug harm reduction strategies.

Novel psychoactive substances: laboratory limitation

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Bangladesh in a transit country for drugs produced in the 'Golden Triangle' and the 'Golden Crescent'. There are reports which indicate that heroin is smuggled from India to Bangladesh through the porous Indo-Bangladesh border. Very recently there were seizures of NPS drugs like LSD, DMT, Magic Mushroom, Khat, DOB etc. has been received in Bangladesh by air shipments or by Courier Services. Bangladesh is a signatory to all the three UN Conventions of 1961, 1971 and 1988 as well as the SAARC Convention of Narcotic Drugs and Psychotropic Substances, 1990. In view of its obligations under these conventions and the potential for diversion of NPS drugs and its precursors due to its close proximity to heroin-producing localities in South East Asia, Bangladesh has imposed restrictions on the import of NPS Drugs or their precursors. As of December 2021, the United Nations Office on Drugs and Crime (UNODC) reports 1,124 NPS have been documented in 134 countries and territories. Since NPS are specifically designed to evade legal control based on chemical structure, the UNODC has established the early warning advisory (EWA) on NPS, which shares information on distribution, harm, and drug identification. The emergence of new psychoactive substances (NPS) provides challenges for most forensic toxicology labs. Drug designers use the chemical structure of existing substances and modify one or more functional sites, leaving the rest of the structure intact. This generates a variety of molecules that produce the desired results but circumvent existing drug laws, which are based on the chemical structures of banned substances. NPS drug designers can synthesize and commercialize new substances much faster than forensic labs can develop and validate new analytical test methods to identify and quantitative them in seized samples. It is very much essential to provides forensic labs support on quality assurance, manuals and guidelines, training, and field detection through UNODC lab in Vienna, Austria. These efforts are helping our laboratory finally our nations to find out the screening and identification limitations (qualitative as well as quantitative) which our laboratory are facing main obstacle to the emergences of new psychoactive substances (NPS) as well as Chemicals of similarity to existing controlled substances. As most NPS are not detected in routine drug screening, an extra effort has been made to develop new analytical methods for the detection of these compounds, with several approaches being successfully applied and reported in the literature. The increased traffic of NPS is often related to limited capacity for detecting and monitoring these compounds, which makes essential to explore in detail both conventional and more recent approaches to prospect novel sensing strategies and develop in-the-field sensors able to detect NPS in a time efficient manner, within a wide range of concentrations, in a variety of sample matrices such as biological samples, wastewater, powders, crystals and post-mortem specimens. In this context, our aim is to, the UNODC lab should provide an overview about capacity building to our lab with providing rational guidelines to the identification of NPS and its precursors analytical detection as well as sample preparation techniques so that we can identify qualitatively and quantitatively of NPS and its precursors, which must help our labs as well as our justice judiciary system.

Philippine Angel's trumpet: exploring a non-regulated psychoactive plant

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Angel's trumpet plants are native to South America but became naturalized in some tropical areas in Asia. In the Philippines, angel's trumpet is referred to as "talampunay" or "katsubong" depending on the geographical location. Locally, it is commonly cultivated for ornamental purposes because of its attractive trumpet-shaped flowers. The said plant substance is also considered by several indigenous cultures as essential traditional medicine, and is used during religious ceremonies and rituals. However, there is an impending threat on this introduced species since recreational usage reports, alongside with poisoning incidents among Filipinos, are significantly observed through the years. This is mainly attributed to its psychoactive contents namely scopolamine and hyoscyamine. An exploratory study to acquire preliminary data on existing angel's trumpet plants in the Philippines was carried out, in order to have an overview about its metabolite profile and species level identities. This undertaking is beneficial to drug policy makers, as angel's trumpet including its psychoactive contents are still not locally controlled. Suspected angel's trumpets were collected in selected regions of the Philippines. Plant samples specifically leaves, flowers, and twigs needed for chemical analysis, were prepared and analyzed using Gas Chromatograph-Mass Spectrometer (GC-MS). Meanwhile, DNA analysis was performed at the University of the Philippines-Philippine Genome Center (UP-PGC), to determine the species level identities of claimed to be angel's trumpet plants in the wild. DNA were extracted from leaf samples using extraction kit, following its manufacturer's protocol. The top 3 basic local alignment search tool (BLAST) results for the sequenced DNA samples were considered for the plant species identification process. Results revealed that samples collected in Apayao, Benguet, Nueva Vizcaya, Bataan, Cavite, Laguna, and Cotabato, were confirmed to be trumpet plants based on botanical and chemical examination. On the other note, samples from Antipolo, Rizal and Talisay, Negros Occidental yielded negative indications that they are trumpet plants. All confirmed angel's trumpet plants were sampled in high altitude areas. While marker psychoactive alkaloid specifically scopolamine was detected in confirmed trumpet plant samples, however detection of hyoscyamine vary among plant parts tested. Importantly, variation in scopolamine contents seem to differ in terms of plant parts examined. Other plant metabolites such as useful fatty acids and vitamin E, were detected in the said samples. Samples subjected to DNA barcoding were likely to be Brugmansia candida. Angel's trumpet appears to be widely distributed in the wild, specifically in high altitude areas of the Philippines. Although organized survey regarding the plant's usages was not included in the exploration, it was evident that locals are highly aware about its worrying threats. Thus, it is also important to document local perceptions on angel's trumpet, as this will give holistic data and guide policy makers in their potential regulatory evaluation. Importantly, preliminary data indicates that there are other important natural products that can be isolated in the said

psychoactive plant, which can be utilized in various applications. Therefore, non-traditional policies that will allow isolation of other plant metabolites from both illicit and non-regulated substances that can be used for other important applications, can be reviewed. If this will be pursued, investigating whether some environmental factors play a vital role in the concentration of psychoactive alkaloids and other plant metabolites of angel's trumpet, will be of great significance to be researched as well.

New psychoactive substance situation in the Philippines: an emerging challenge of drugs of abuse

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In the Philippines, the proliferation of illicit drugs has been very alarming due to its adverse social, health and economic impacts, therefore forcing the government to wage a war against millions of drug personalities. Methamphetamine is by far the most widespread dangerous drug in the country, also accompanied by significant seizures of marijuana, ecstasy and cocaine. However, the emergence of New Psychoactive Substances (NPS) amplify the existing global drug concerns and demonstrates a tremendous challenge to various drug law enforcement agencies, of which Philippines is not an exemption. Substances under NPS category gained popularity among drug syndicates because clandestine chemists modify the chemical structures of controlled drugs to synthesize novel drugs of same effects to avoid drug law violations. Alarmingly, not all NPS are synthetic in nature, as plant-based sources of NPS are also rampant among users because of its natural availability. This review will discuss the present NPS situation in the Philippines which consists of drug forensic analysis to detect locally reported NPS, using both traditional and modern analytical techniques. Forensic chemists have a vital role in detecting NPS by providing valuable analysis reports required to assist law makers in crafting regulation policies to include such emerging substances under legal control, since majority of the NPS are not listed in any United Nations Drug Conventions. Also, this report will cover the NPS challenges not only on forensic laboratories, but also on drug operatives and legislators as well. Lastly, this report intends to alert international counterparts on the NPS trends and patterns in the country, and suggest suitable preventive and control measures in the future.

Epidemiology of emerging novel psychoactive substances in the United States using pooled medical examiner records

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Introduction: Novel psychoactive substances (NPS) are identified through early warning systems; however, their absence from national data means that their prevalence in the illicit drug supply often remains poorly understood for years after their discovery. Detailed medical examiner records can potentially provide this information. Methods: We pooled medical examiner records from 2019 through 2022 (as available) from four U.S. states (Connecticut, North Carolina, Minnesota, Wyoming) and 21 U.S. counties that together comprise 17% of the U.S. population and represent all four Census Regions. We used t-tests (alpha-level 0.05) and chi-square tests to analyze demographic and substance characteristics for deaths involving any of the 38 NPS listed in the United Nation Office on Drugs and Crime (UNODC) 2021 report. Results: Across 50,598 deaths that involved at least one drug or medication, 2,683 (5.3%) involved at least one NPS mentioned in the UNODC report. Twenty-three of the 38 NPS were identified in at least one jurisdiction. The jurisdiction with the largest share of NPS deaths was Cook County, Illinois (n=997), followed by Connecticut (n=329), North Carolina (n=321), Minnesota (n=304), Lorain County, Ohio (n=135); Maricopa County, Arizona (n=103). Significant correlates of NPS involvement included male sex (74% versus 72% of non-NPS deaths, p=0.02); younger age (average age 40 versus 46 for non-NPS deaths, $p<0.0001$). Black or African Americans and whites comprised significantly higher proportions of NPS deaths compared to drug deaths not involving NPS, while the opposite was observed for American Indian or Alaska Native, Asian, and Hispanic or Latin Americans. Fentanyl was co-involved in 85% of NPS deaths compared to 43% of non-NPS deaths ($p<0.001$). Compared to non-NPS deaths, NPS deaths were more likely to involve heroin or cocaine and less likely to involve methamphetamine or alcohol (all $p<0.001$). Conclusions: Medical examiner records provide a feasible method to estimate the spread and prevalence of NPS. Epidemiologically, NPS deaths differ from drug-related deaths not involving NPS in several key ways that may inform both surveillance of the illicit drug-supply and prevention interventions targeting the most affected communities.

Laboratory and instrumental indicators of cardiac disorders in people with NPS addiction

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Introduction: The high prevalence of new psychoactive substances (NPS) and their cardiovascular toxicity are a growing concern among physicians. Case reports of acute cardiotoxic effects of NPS are common in the literature. But the issue of clinical manifestations of beyond acute NPS intoxication remains poorly understood. The aim of the study was to investigate laboratory and instrumental indicators of cardiac manifestations beyond acute NPS intoxication. Methods: We conducted a cross-sectional study of 61 drug dependent patients: 33 NPS users (synthetic stimulants like mephedrone and alpha-PVP) and 28 non-NPS users. We assessed subjects' complaints, blood pressure, pulse, glucose levels, as well as ECG and echocardiographic parameters. Results: Groups differed in age: 29,06+ 5,08 years among NPS users versus 34,32+10,29 among NPS nonusers; and length of drug use: 4,02+4,06 years versus 12,44+9,25 respectively. Cardiac complaints were more likely to be reported by NPS users: 75,8% versus 50%. Tachycardia and a

feeling of lack of air prevailed among the complaints. Blood pressure and heart rate indicators were in relevant values. Groups also differed in blood glucose levels: 4,5+0,64 mmol/l versus 5,2+1,13 mmol/l. Blockade of the right branch of the bundle of His on ECG was more common in the group of NPS users: 21,2% versus 3,6%. The pulmonary artery pressure gradient also prevailed on echocardiography in the group of NPS users: 3,09+0,92 mmHg versus 2,61+0,84 mmHg. Conclusions: Laboratory and instrumental indicators of cardiac manifestations outside of acute NPS intoxication revealed a number of findings that warrant further investigation of this problem of toxicological cardiology.

Increased neuronal differentiation of NG108-15 cells promoted by the synthetic cannabinoid AMB-FUBINACA is associated with decreased DNA methylation

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Introduction: The use of synthetic cannabinoids (SCs) represents a major threat to adolescents and young adults (SCs' main consumers), as the developing brain in these individuals and/or their offspring makes them especially vulnerable to SC-elicited effects and to the onset of neurodevelopment perturbations. Here, we assessed the in vitro impact of a commonly used SC, AMB-FUBINACA (AMB), on the neurodifferentiation of NG108-15 neuroblastoma x glioma cells, while addressing whether AMB-induced changes in global DNA methylation were associated with this SC effects on neurogenesis. Methods: NG108-15 cell neurodifferentiation was induced in serum-starved (1% FBS) medium supplemented with retinoic acid and forskolin. Neurite outgrowth was analyzed by measuring the differentiation ratios (number of newly formed neurites/total cell number) and total neurite length after adding AMB once (at day 0) or every 24h for 3 days. Global DNA methylation was assessed using a commercially available colorimetric kit, in 3 distinct exposure settings: A) one-time addition at the start of differentiation (t0), sample collection on day 3 (t3); B) one-time addition at t3, sample collection on day 6 (t6); C) additions at t0 and t3, sample collection at t6. AMB was tested at 1pM, 1nM, and 1μM. In a set of experiments, 500nM SR141716A, a selective cannabinoid type 1 receptor (CB1R) antagonist, was added 20 minutes prior to AMB addition to assess CB1R's involvement in the affected parameters. Results: AMB increased differentiation ratios (1.6-1.8-fold) and total neurite length (1.7-2.5-fold), compared to the control, at all tested concentrations, with no differences between single and multiple additions. Such effects were CB1R activation-dependent, as pre-incubation with SR141716A reset differentiation ratios to control levels. Interestingly, this AMB-induced neurodifferentiation was associated with a decrease in global DNA methylation, noted in treatments B (1pM), and C (1μM). Preliminary data showed that AMB's epigenetic action was not prevented by pre-incubation with SR141716A. Conclusions: AMB enhanced NG108-15 cell neurodifferentiation in a CB1-dependent manner. This occurred concomitantly with decreased global DNA methylation, though different mechanisms seemed to underlie these effects. Our data also suggest that AMB's epigenetic impact occurs at a later stage of differentiation, as no changes in DNA methylation were noted in treatment A. Further research is thus required to better understand the potential mechanisms involved in AMB-induced disruption of neurogenesis, and whether they may be regulated by AMB's epigenetic action.

Effects of the synthetic cannabinoid ADB-FUBINACA on the neurodifferentiation of primary hippocampal neurons

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Introduction: The use of synthetic cannabinoids (SCs), a group of New Psychoactive Substances (NPSs) that mimic with higher potency the effects of Δ9-tetrahydrocannabinol (Δ9-THC), by adolescents and young adults is especially alarming due to the possible onset of neurodevelopmental disorders (e.g., psychoses) in these individuals or their offspring. Here, we assessed the impact of the commonly used SC ADB-FUBINACA on the differentiation and maturation of primary hippocampal neurons (PHN), and ascertained whether this SC modulates astrocyte activation during such processes, as astrocytes play a key role in the neuronal network formation and provide neuronal support during neurogenesis. Methods: PHN isolated from Wistar rat embryos at embryonic days 18-19 were exposed to ADB-FUBINACA at human-relevant, non-cytotoxic concentrations (1pM–1μM) after 24h in culture and every 4 days in vitro (DIV) up to 21 DIV. A solvent control (0.02% DMSO) was also tested. Neuronal differentiation and maturation were assessed by immunocytochemistry at 3, 7, 14 and 21 DIV by determining the percentage of cells labeled for Tuj 1 (neuron-specific beta-tubulin III; immature neurons) and MAP2 (microtubule-associated protein 2; mature neurons), relatively to the total number of cells. Astrocyte number and activation were expressed as the percentage of cells positive for GFAP (glial fibrillary acidic protein) labeling and by the relative fluorescence intensity of GFAP per cell, respectively. Results: ADB-FUBINACA increased the percentage of Tuj-1-positive cells after 3 DIV in about 11% and 14%, at 1nM and 1μM, respectively, and about 11% at 1 pM, at 7 DIV. This indicates a stimulation of PHN differentiation. In contrast, at 21 DIV there was a marked decrease in the percentage of Tuj-1 positive cells (40-65%) for all concentrations tested in relation to control. At 14 DIV, MAP-2 labeling decreased by 20% for 1μM and increased by 17% for 1pM (no significant changes observed at other timepoints). Moreover, 1pM and 1μM ADB-FUBINACA decreased the number of GFAP-positive cells at 7 DIV by about 11% and 7%, respectively, relative to the control ($p<0.01$), and by about 20%, at 1 pM ($p<0.05$), at 21 DIV. In addition, astrocyte activation was increased about 2-fold by 1 nM ADB-FUBINACA at 7 DIV ($p<0.05$) and about 2.5-fold at 1 μM at 21 DIV. Conclusions: Overall, our data suggest that ADB-FUBINACA increased the differentiation of PHN, but compromised the maturation of newly formed

neurons. Notably, this SC-mediated neurodifferentiation was also accompanied by early astrocyte activation. Considering the importance of astrocyte activation to neurodifferentiation, further research is required to ascertain whether this ADB-FUBINACA-mediated modulation of astrocyte function is associated with its impact on neurogenesis.

Kratom use among people who use other substances: A critical review of published evidence from Southeast Asia

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Introduction: In Southeast Asia, kratom has been reported as a co-occurring substance of use, a substitute for opioid drugs, or a remedy for problems resulting from the use of other substances. This review article identifies relevant studies through a systematic review of published research from Southeast Asia. Methods: A search of published articles was conducted through ScienceDirect, Scopus, PubMed, and Google Scholar. Identified studies were summarized and evaluated on their methodological rigor and strength of presented evidence. The studies were further categorized into levels of methodological rigor and the strength of evidence, and the study findings were summarized. Results: Eight original research articles reporting on kratom use by people in Southeast Asia who also use other substances were identified. Studies categorized as having high level of methodological rigor and providing strong evidentiary support reported on kratom being used as substitute for opioid substances, for self-treatment of opioid use disorder and opioid withdrawal symptoms, and to alleviate adverse psychological symptoms related to other substance use or discontinuation of substance use. Conclusions: Despite the reported curative properties, kratom's efficacy in reducing consumption of opioids and other substances, as opioid substitute, or as an opioid-withdrawal aid requires further rigorous research.

The reporting desk for new drugs; a unique system to monitor drug market dynamics and to verify signs of new psychoactive substances use in the Netherlands

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Introduction: In order to monitor drug market dynamics and to verify signs of new psychoactive substance (NPS) use, it is key to have access to local data from different sources. In 2012, the Reporting Desk for New Drugs was established in order to collect data on production, trade and consumption of NPS in the Netherlands. Methods: Data triangulation is used to monitor NPS market dynamics. The Customs Laboratory, the Netherlands Forensic Institute (NFI) and the Drugs Information and Monitoring System (DIMS) provide twice a year analytical data of NPS that have been seized or submitted to a drug checking service. Results: Most NPS are being detected for the first time by the Customs Laboratory. Data from DIMS shows that only a subset of NPS are being detected in consumer samples. Signs of use of NPS in the Netherlands can be confirmed by comparing data with information from the Monitor Drug-related Incidents, Dutch Poisons Information Centre and online discussion boards. Conclusions: The Reporting Desk for New Drugs has been acknowledged as a valuable asset for policy makers, specifically to assess risks associated with NPS use. A key element is the access to data from both forensic laboratories and drug checking services. This has proven to be invaluable in verifying signals of NPS use.

Pharmacological evaluation and forensic case series of N-pyrrolidino etonitazene (etonitazepyne), a newly emerging 2-benzylbenzimidazole 'nitazene' synthetic opioid

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Introduction: New synthetic opioids continue to emerge on recreational drug markets worldwide. Here, we pharmacologically characterize a novel cyclic etonitazene analogue, called N-pyrrolidino etonitazene/'etonitazepyne'. A series of analytically confirmed fatalities is described to complement preclinical findings. Methods: N-pyrrolidino etonitazene was pharmacologically characterized via radioligand binding assays and a μ-opioid receptor (MOR) activation (β-arrestin2 recruitment) assay. Antinociceptive, cataleptic, and thermic effects were evaluated after s.c. administration to Sprague Dawley rats. Twenty-one overdose fatalities associated with N-pyrrolidino etonitazene were summarized in terms of case history, demographic information and analytical findings. Results: N-pyrrolidino etonitazene has high affinity and selectivity for MOR (Ki=4.09 nM). The drug further displayed high potency (EC50=0.348 nM), similar to etonitazene (EC50=0.360 nM). In rats, N-pyrrolidino etonitazene induced opioid-like antinociceptive, cataleptic, and thermic effects. Its potency in the hot-plate test (ED50=0.0017 mg/kg) was tenfold greater than that of fentanyl (ED50=0.0209 mg/kg). In 21 overdose fatalities associated with N-pyrrolidino etonitazene, low blood concentrations were found (median=2.2 ng/mL), commonly in the context of polysubstance use. N-Pyrrolidino etonitazene was reported as a cause of death in at least two cases, demonstrating toxicity in humans. Conclusions: We demonstrate that N-pyrrolidino etonitazene is an extremely potent MOR agonist that likely presents high risk to users.

A decade of NPS control - a success story?

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The emergence of large numbers of structurally diverse new psychoactive substances (NPS) with a range of pharmacological effects continue to pose challenges to national and international control efforts as well as to laboratory identification. Currently, approximately 1,145 individual NPS have been reported to the UNODC Early Warning Advisory by 137 countries and territories. In the past decades, the international scheduling of drugs was characterized by long periods of inactivity. However, the emergence of NPS triggered the full use of the scheduling provisions in 2014, when the global dimension of the problem became more apparent. In January 2014, the United Kingdom submitted a notification on mephedrone to the Secretary-General of the United Nations which led to the provisional control of mephedrone, the first-ever in modern times, while the scheduling request was under consideration. In 2015 mephedrone and nine other NPS were placed under international control. In the meantime, 71 substances have been placed under international control. The presentation looks at UNODC's work in prioritizing the most harmful, prevalent, and persistent NPS and shows examples from NPS emergence to international control.

Forensic toxicological analysis of pregabalin from urine using FTIR-ATR

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Pregabalin available in the market under the brand name Lyrica is a known medicine for the treatment of fibromyalgia, convulsions, and anxiety. Several cases of pregabalin abuse have been reported which has raised the concern for law enforcement agencies. The present study focuses on the toxicological analysis of pregabalin. The drug was spiked into the biological matrix and analyzed thereafter. Solid-phase extraction was used for efficient separation of drug from urine. Subsequently, the extract was detected with the help of Nicolet is20 FTIR-ATR. Principal component analysis was performed using Minitab software. The method employed presents a reliable tool for the analysis of pregabalin from a biological matrix such as urine.

First identification, chemical analysis and pharmacological characterisation of N-piperidinyl etonitazene (etonitazepipne), a recent addition to the 2-benzylbenzimidazole opioid subclass

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Introduction: N-piperidinyl etonitazene/'etonitazepipne' represents one of the newest additions to the rapidly expanding class of 2-benzylbenzmidazole/'nitazene' opioids. Following its first identification in an online-sourced powder and in biological samples from a patient seeking detoxification assistance, this report details its first in-depth chemical analysis and pharmacological characterization. Methods: An online-sourced powder was analyzed via LC-HRMS, GC-MS, UHPLC-DAD and FT-IR. An activity-based bioassay (monitoring activation of the μ-opioid receptor (MOR)) was used to detect N-piperidinyl etonitazene in serum and urine. In vitro characterization encompassed radioligand binding assays and a MOR-β-arrestin2 activation assay. Pharmacodynamic effects were evaluated in male Sprague Dawley rats. Results: Analysis of the powder led to the unequivocal identification of N-piperidinyl etonitazene. We further report its first activity-based detection and analytical identification/quantification in serum (1.21 ng/mL) and urine (0.51 ng/mL). N-piperidinyl etonitazene is a highly potent (EC50=2.49 nM) and efficacious (Emax=183% versus hydromorphone) MOR agonist with a high affinity (Ki=14.3 nM). In rats, N-piperidinyl etonitazene induces opioid-like antinociceptive, cataleptic, and thermic effects, its potency in the hot-plate assay (ED50=0.0205 mg/kg) being comparable to that of fentanyl (ED50=0.0209 mg/kg). Conclusions: Being a highly active MOR agonist, our data indicate that misuse of N-piperidinyl etonitazene is of great concern to public health.

Understanding the reasons why prisoners use NPS whilst in custody and the need for suitable regulatory approaches

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HM Prison Parc in Swansea (UK) has been running a Psychoactive Substances Rapid Response service for the past four years, where every individual who uses NPS or is found with NPS is seen by the substance misuse team. During this presentation we will share the outcome derived from a set of brief interventions which was implemented to address three primary research questions: 1. Which motivations do prison residents report as their primary motivation to use PS? 2. In line with the RNR principles (Andrews et. al, 1990), what motivations are reported by frequent PS users who require the most intensive interventions? 3. Can PS users who will go onto have multiple incidents be identified after first use? (So that early interventions can be offered). Finally, we will draw some conclusion on the importance of novel policy responses in custodial settings.

Using emergency department drug surveillance (EDDS) data to describe and monitor drug exposure trends in ED patients

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Introduction: EDDS was launched by the Center for Substance Abuse Research (CESAR) to show national trends in the drugs that persons seeking treatment at emergency departments (EDs) have tested positive for and to discover drugs that are not included in participating hospital's limited drug screens. EDDS is currently being launched in 33 hospitals. Methods: EDDS obtains quarterly de-identified exports of urinalysis results in each hospital's electronic health records (EHRs) and provides each hospital the opportunity to submit annually up to 150 de-identified urine specimens which EDDS retests for approximately 500 drugs. Results: In 2021, amphetamines were the most prevalent drugs detected in the EHRs in hospitals from Denver CO, Portland OR, and Salt Lake City UT, and cocaine was the most prevalent drug found in the hospital in Newark NJ. These drugs reached 4-10 year highs in 2021. In four hospitals (excluding NJ), the EDDS retesting found amphetamines in 62%-76% of specimens the hospital indicated had tested positive for any drug in their routine test panels. Conclusions: EDDS identified considerable geographic variation in exposure of ED patients to drugs such as opiates and stimulants. There were also frequent poly-substance positives in specimens positive for stimulants.