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Interpol review of toxicology 2019–2022

Jack Yuk-ki Cheng, Janesse Wing-sze Hui, Wing-sum Chan, Man-ho So, Yau-hin Hong, Wai-tung Leung, Ka-wai Ku, Hoi-sze Yeung, Kam-moon Lo, Kit-mai Fung, Chi-yuen Ip, Kwok-leung Dao, Bobbie Kwok-keung Cheung *

Government Laboratory, Hong Kong Special Administrative Region of China

1. Introduction

The years of 2019–2022 were extraordinary challenging times, in which COVID-19 had infected and killed millions of people worldwide. Governments struggled to impose lockdown measures to tackle the spread of the virus which had a severe impact on economy, daily life and travel. Emergence of new psychoactive substances (NPS) is, however, never hindered by COVID-19, while the closure of public spaces and "stay-at-home" measures brought new challenges arising from drug markets and drug use. In order to prepare ourselves and face the challenge, forensic scientists never stop to push their limits to detect any traces of NPS in various disciplines, such as drug driving, workplace & court-ordered drug testing and drug facilitated crimes, through the latest instrumentation, novel analytical technique and improved quality assurance.

This review paper summarized the latest development and challenges in forensic toxicology from March 2019 to March 2022. A total of seven topics, including quality assurance, driving under influence, surveillance in workplace, drug facilitated crimes, NPS, advances in technology, interpretation of toxicological results, were reviewed. Researches related to COVID-19 were also reported in driving under influence and NPS.

2. Quality assurance

2.1. Method validation

The method validation guidelines [1] from the Standard Practices for Method Validation in Forensic Toxicology, which was published by the Scientific Working Group on Forensic Toxicology (SWGTOX), were widely used in the field of forensic toxicology to demonstrate that the method performance was adequate for intended use and met specific requirements. In 2019, the American Academy of Forensic Sciences Standards Board revised, prepared and finalized the validation guidelines [2] from SWGTOX to provide minimum standards of practice for validating analytical methods used in the field of forensic toxicology that target specific analytes or analyte classes. However, the validation guidelines were not intended to address method validation in the discipline of breath alcohol testing.

Method validations using liquid chromatography-tandem mass spectrometry (LC-MS/MS) for detection of NPS had been done on various biological matrices including blood, urine and oral fluid [3–9]. The use of LC-MS/MS for analyzing benzodiazepines and hypnotic drugs in blood and/or urine was validated for toxicology analyses [10,11]. The determination of opiates in blood [12] and hair [13] by derivatization of opiates prior to gas chromatography-tandem mass spectrometry (GC-MS/MS) was validated and demonstrated for quantifying analytes at low levels.

A fast and accurate LC-MS/MS method using biphenyl column was validated to quantify 18 antidepressants in oral fluid with a short run time of 5 min [14]. Solid phase extraction (SPE) was used for sample cleanup. The method was validated according to the SWGTOX validation guidelines. The range of linearity for all analytes was 10–1000 ng/mL with limit of detection (LOD) at 10 ng/g.

Behnke et al. [15] presented the validation of a semi-quantitative method using enzyme-linked immunosorbent assay (ELISA) for rapid screening of benzodiazepines in blood and urine specimens. Although the manufacturer recommended the use of oxazepam as the target molecule, the authors changed the target molecule to clonazepam which resulted in increasing the cross-reactivity for the majority of 29 benzodiazepines and improved the ability of the screening method to identify designer benzodiazepines.

A dilute-and-shoot procedure with enzymatic hydrolysis of urine specimens followed by LC-MS/MS was developed and validated for forensic toxicology screening [16]. The method was compared with ELISA on sensitivity, specificity and cost per specimen. The SWGTOX validation guidelines were followed and 52 analytes, including conventional illicit and prescription drug classes, were identified. The LC-MS/MS method was found to have better sensitivity and flexibility than immunoassay in the analysis of newly emerged compounds including NPS. The method was demonstrated to be an ideal alternative to screening urine specimens by ELISA.

* Corresponding author. Government Laboratory, 7/F, Homantin Government Offices, 88 Chung Hau Street, Ho Man Tin, Kowloon, SAR, Hong Kong, China.
E-mail address: kkcheung@govtlab.gov.hk (B.K.-k. Cheung).
URL: http://www.govtlab.gov.hk/ (B.K.-k. Cheung).

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2.2. Quality control

Proficiency testing is commonly used as a core component of quality assurance in testing competency of laboratories. Proficiency testing could be in the forms of declared tests or blind tests. The declared proficiency tests are often labeled as tests and clearly specify the scope of examination. On the other hand, the blind proficiency tests are submitted as real cases and the analysts are not aware that they are being tested. Blind proficiency testing is an important tool to forensic quality assurance program as it can demonstrate quality and provide insight into the errors that occur in a laboratory in everyday casework [17]. As the blind proficiency testing is designed to mitigate observer effects and cognitive biases, routine use of blind proficiency testing could valuably inform jury decision-making at criminal trials [18].

A blind quality control program in blood alcohol analysis was implemented by the Houston Forensic Science Center between 2015 and 2018 [19]. The blind blood samples were analyzed by headspace gas chromatography with dual-flame ionization detectors. Results showed that the blind quality control program could provide multiple opportunities for process improvement and the analytical methods were demonstrated to be reliable, adding confidence to staff's testimony in court.

2.3. Uncertainty of measurement

The measurement uncertainty in quantifying delta-9-tetrahydrocannabinol (THC) in blood using SPE and LC-MS/MS was described [20]. The uncertainty sources, including calibration standards, calibration curve, method precision and sample volume, were quantified. The bottom-up approach was used to determine the measurement uncertainty. The calibrating curve was found to be the major contribution to the overall method uncertainty while sample volume contributed the least. Andersen [21] illustrated the use of pooled calibration data to obtain correspondence between predicted and observed uncertainty in the determination of synthetic cannabinoids in biological specimens using LC-MS/MS.

A bottom-up study to quantify uncertainty of breath alcohol concentration (BrAC) measurements with Intoximeter's EC/IR II instrument was conducted [22]. After an exercise in combined uncertainty source identification, individual input values were either reported from National Institute of Standards and Technology traceable reference materials or quantified using instrument data from 2014 to 2018. From input values, an expanded uncertainty value of 4.58×10^{-3} g/210 L was found that encompassed all identified sources with a 95% confidence interval.

2.4. Result interpretation

The effect of cognitive bias in subjective decision making in forensic science was discussed by Camilleri et al. [23]. A risk-based approach identified 32 cognitive bias risks at a multi-discipline forensic laboratory. A list of possible bias-minimizing strategies was suggested for forensic toxicology laboratories by an intentional survey of toxicologists' experiences using contextual information [24]. In order to mitigate the effect of contextual information on decision-making in forensic toxicology, Hamnett and Dror [25] proposed forensic toxicology laboratories to use a consistent protocol for choosing tests and any variations or case-by-case decisions being properly documented and justified.

3. Driving under influence

3.1. Detection of alcohol

The analyses of ethanol in blood and breath are widely used for the prosecution of driving under the influence of alcohol. Related studies including method of determination, uncertainty of measurement and stability of specimen are summarized below.

3.1.1. Blood alcohol concentration (BAC) detection

The use of capillary blood as an alternative to venous blood, in sample volumes of 100 and 10 μL, for BAC detection with gas chromatography-flame ionization detector was reported [26]. Results showed that venous blood was predominantly detected at higher concentrations than the corresponding capillary samples, with a statistically significant difference. Average differences of 3.38 ± 1.99 mg/100 mL at 100 μL and 4.13 ± 2.42 mg/100 mL at 10 μL were observed, while there was no statistically significant difference between the 100 and 10 μL sample volumes. The study indicated that capillary blood was a viable matrix for alcohol measurement.

3.1.2. Comparison of blood and breath alcohol concentration

Jones and Cowan [27] conducted a controlled drinking study involving male and female healthy volunteers from three ethnic groups to evaluate various factors influencing the blood-breath ratio (BBR). Result indicated that BAC and BrAC were highly correlated. In addition, BBR did not depend on gender or racial group and was lower in subjects with higher breath- and body-temperatures and also decreased with longer exhalation times into the breath-analyzer. Another controlled drinking study was conducted with volunteers dosed to produce peak BAC or BrAC of 0.040–0.080 g/100 mL blood or g/210 L breath [28]. Results from the two measurement methods were highly correlated and, BAC on average was 11.3% greater than BrAC in measured values. It was concluded that BAC and BrAC were both objective evidence of violation of per se limit.

3.1.3. Ethanol stability study

A reanalysis of blood specimens from suspected impaired drivers in Texas was carried out to study the gradual loss of ethanol over time [29]. Results indicated that over an average interval of about 13 months, average change of ethanol concentrations was a loss of 0.006 g/dL, with a maximum loss of 0.023 g/dL and a maximum increase of 0.004 g/dL. No correlation was observed between the net loss and the initial BAC value but the amount of time between analyses did impact the extent of ethanol loss.

Kosecki et al. [30] carried out another ethanol stability study in Arizona. Antemortem (AM) blood drawn for forensic purposes was re-analyzed for ethanol concentration at various times after the blood drawn based on routine case flow and within about 1 year after the first analysis. It was found that ethanol-negative cases remained negative on reanalyses. For the ethanol-positive cases, the range of differences was −0.0197 to 0.0103 g/dL and the average difference was −0.004 g/dL, which was statistically significant at the 0.05 level of significance.

Kosecki et al. [31] also investigated the potential for hemolysis to impact BAC determinations. Paired samples of non-hemolyzed and hemolyzed blood were analyzed for ethanol concentration using headspace gas chromatography with no measured statistical difference detected, suggesting that hemolysis would not impact blood ethanol measurement.

3.2. Detection of drug

Toxicological examination for driving under the influence of drugs (DUID) continues to be a challenge in terms of complexity and variability. In this review, various examination methods and technologies across different biological matrices are described with highlight of drugs of interest. Studies on the suitability of oral fluid as an alternative matrix are also summarized.

3.2.1. Simultaneous examination of multiple analytes in different matrices

3.2.1.1. Blood and urine specimens. A liquid chromatography hyphenated with orbitrap high-resolution mass spectrometry method was developed for quantification of 22 psychoactive substances including

cannabinoids, cocaine and its metabolites, amphetamines, opiates and opioids and the major benzodiazepines and Z-drugs in whole blood with extraction performed by protein precipitation [32]. The trueness, precision, recovery and matrix effect were evaluated with satisfactory results indicating parallel reaction monitoring (PRM) an alternative for quantitative toxicology analysis.

A method was developed for the examination of 127 drugs and metabolites in blood and urine including cannabinoids, amphetamines, cocaine and metabolites, benzodiazepines, Z-drugs, opioids, anticonvulsants, first-generation antihistamines, muscle relaxants, barbiturates, dissociatives and hallucinogens [33]. It was a simple method using protein precipitation followed by filtration extraction and then an 8-min run of LC-MS/MS with limits of detection appropriate for DUID.

A method for the detection of 40 benzodiazepines, zopiclone, zaleplon and zolpidem in blood and urine by SPE with LC-MS/MS method was reported by Sofalvi et al. [34]. Extensive sample preparation included combining osmotic lysing and protein precipitation with methanol/acetonitrile mixture followed by freezing and centrifugation resulting in exceptionally high signal-to-noise ratios. Bias and between-and within-day imprecision for quality controls were all within ±20%.

Two LC-MS/MS methods for the quantitative analysis of opioids, cocaine and their metabolites in biological matrices including blood, urine and tissue were published with two sample preparation techniques, namely protein precipitation and SPE [35]. Accuracy and precision, sensitivity, linearity, matrix effects, recovery, carryover, interferences, dilution integrity and post-extraction stability were evaluated with satisfactory results.

Zhoa et al. [36] developed a method using thermal-assisted carbon fiber ionization mass spectrometry to directly analyze drugs in biological fluid such as urine and blood. Sample preparations were achieved online as precipitated protein on the carbon fiber tip and thermally desorbed by the metal ceramics heater, which reduced matrix effects and improved sensitivity with rapid analyte identification regardless of their physical variations.

A study on cloned enzyme donor immunoassay (CEDIA) cut-offs for drugs of abuse in whole blood was carried out by Pelletti et al. [37]. Semi-quantitative results for blood samples containing cannabinoids, cocaine, amphetamines, opiates and methadone obtained with CEDIA were compared with results from gas chromatography-mass spectrometry (GC-MS). Optimized screening cut-offs obtained were 8.0 ng/mL for THC; 5.5 ng/mL for 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (THC-COOH); 21.1 ng/mL for cocaine; 6.9 ng/mL for benzoylecgonine (BZE); 33.1 ng/mL for opiates; 61.6 ng/mL for amphetamines; 5.0 ng/mL for methadone. It was concluded that CEDIA on whole blood permitted the definition of cut-off values with optimal sensitivity and negative predictive values for all analytes (near to 100%), including very good specificity.

3.2.1.2. Oral fluid specimen. A non-targeted LC-MS/MS method with subsequent compound identification by tandem mass spectral library search was developed for examination of drugs in oral fluid samples [38]. Oral fluid sample underwent SPE and chromatographic separation with liquid chromatography quadrupole-time-of-flight mass spectrometer (LC-QTOF-MS) operated with data-dependent acquisition control. The study demonstrated that compounds with logP values in the range 0.5–5.5 were efficiently detected at low nanograms per milliliter concentrations with true positive and true negative rates of automated library search equal or close to 100%.

A method based on magnetic graphene oxide dispersive solid phase extraction combined with ion mobility spectrometry was first introduced for simultaneous determination of ephedrine, pseudoephedrine, diphenhydramine, promethazine and terfenadine in saliva and urine matrices [39]. The prepared magnetic graphene oxide was characterized by Fourier transform infrared spectroscopy and thermogravimetric analysis which succeeded in building a hitherto unexplored tool for quantifying anti-hypersensitivity drugs in saliva and urine matrices of interest in DUID research field.

3.2.1.3. Hair. An ultra-high-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) method was developed for the determination of 16 drugs and metabolites in hair including cocaine and its metabolites, amphetamines, fenproporex, amfepramone, mazindol, opiates and THC for driving license granting [40]. Sample preparation was a one-step liquid extraction of milled hair followed by incubation and chromatographic separation with a run time of 2.2 min. Assay validation criteria were fulfilled with uncertainty of the measurement demonstrated. The method was successfully applied to 50 hair samples from injured drivers.

3.2.2. Drugs of interest

3.2.2.1. Cannabinoids. As more countries legalized cannabis for recreation use, cannabis continues to be one of the most prevalent drugs in DUID. A publication presented a rapid screening technique of THC and synthetic cannabinoids in urine and oral fluid by paper spray mass spectrometry [41]. Analytes were concentrated and preserved on paper with sesame seed oil for at least 27 days at room temperature and they could be detected even at low concentrations.

Chan-Hosokawa et al. [42] presented a quantitative method to separate Δ^8-and Δ^9-THC isomers and their metabolites in blood. Cannabinoids were extracted from whole blood using liquid-liquid extraction (LLE) and then separated with 2D LC-MS/MS over a run-time of 10 min. This is the first report of a method that successfully quantified these primary cannabinoids in blood where significant concentrations of both Δ^8 and Δ^9 isomers were present.

Understanding cannabinoid profiles of frequent and occasional users and the subsequent impact on detectability with per se driving limits is important to support forensic interpretations and the development of scientifically supported laws. In a recent study, occasional and frequent cannabis users' profiles were compared with the determination of 10 cannabinoids including THC metabolites in blood and oral fluid by LC-MS/MS method for up to 6 h after ad libitum smoking [43]. It was found that THC was detectable for significantly longer duration in both matrices from frequent users. Detection rates between frequent and occasional users at multiple per se cutoffs showed larger differences in blood versus oral fluid.

An atmospheric-pressure chemical ionization GC-MS/MS method for simultaneous determination of Δ^9-THC, 11-hydroxy-Δ^9-tetrahydrocannabinol (THC-OH), 11-nor-9-carboxy-Δ^9-THC, cannabidiol (CBD), cannabidiol acid and cannabigerol in human serum was reported by Gottardo et al. [44]. It was the first report describing the application of APGC source in the field of forensic toxicology including the analysis of DUID cases.

A LC-MS/MS method for examination of 13 cannabinoids, including Δ^8-THC, Δ^9-THC, CBD, Δ^9-tetrahydrocannabinolic acid-A, cannabidiolic acid, THC-OH, THC-COOH, tetrahydrocannabivarin, cannabidivarin, cannabidiorcol, cannabichromene, cannabinol (CBN) and cannabigerol in oral fluid was developed [45]. Baseline separation was achieved in the entire quantitation range between Δ^9-THC and Δ^8-THC.

A review summarized analytical methods for the detection and quantification of cannabinoids in human biological specimens with particular attention to the application of LC-MS or LC-MS/MS [46]. It also provided an overview of the effective and selective methods used for extraction and isolation of cannabinoids from conventional matrices, such as blood, urine and oral fluid and alternative biological matrices, such as hair, cerumen and meconium.

3.2.2.2. New psychoactive substances. The abuse of NPS has been increasing dramatically and poses enormous threats to public health and

big challenges to drug policy. Cheng and Dao [47] reported the detection of a newly emerged drug, deschloro-N-ethyl-ketamine, an analog of ketamine, through forensic drug and toxicological examinations of exhibits from drug seizure cases and blood samples from DUID cases in Hong Kong. A lower blood level with more severe impairment was observed, indicating the higher potency of the drug than ketamine.

Krotulski et al. [48] reported the United States' first identification of APP-BINACA, a synthetic cannabinoid, in blood by LC-QTOF-MS method. Further analysis resulted in the identification of five metabolites, including 4-HO-APP-BINACA and APP-BINACA 3-phenylpropanoic acid, which are biomarkers for recent ingestion of DUID drivers.

A method for the determination of 18 synthetic cathinones and one amphetamine-like compound in urine simultaneously by GC-MS was described by Gerace et al. [49]. Sample preparation was based on liquid-liquid extraction under alkaline condition followed by derivatization with trifluoroacetic anhydride. Separation of 19 analytes was achieved in less than a 10-min run. The method showed good sensitivity, selectivity, and optimal linear response, together with good repeatability and accuracy for quantitative determinations with limits of detection and quantitation ranged from 10 to 30 ng/mL and 30–100 ng/mL, respectively.

The quantification of 11 illicit phenethylamines in oral fluid was reported with supramolecular solvents extraction coupled with LC-MS/MS [50]. With rapid run time and minimal sample preparation, the method could be easily extended to monitor other phenethylamine designer drugs with similar physical-chemical properties for which immunoassay kits were not available.

3.2.2.3. Other drugs of interest. There was an upward trend of fentanyl-related DUID cases in the United States. A quantitative method for the analysis of fentanyl analogs in oral fluid using LC-QTOF-MS was presented [51]. The validated method was sensitive with limits of detection and quantification ranging from 0.5 to 1 ng/mL, with a linear range of 1–100 ng/mL for all analytes, except acetyl fentanyl at 0.5–100 ng/mL. Matrix effects exhibited ionization enhancement for all analytes with intensified enhancement at a low concentration.

Sofalvi et al. [52] reported a method for structural/stereo-isomer and isobar analysis of over 20 fentanyl analogues in whole blood by UPLC-MS/MS with focus on decreasing sample size, lowering limits of detection and quantitation, minimizing ion suppression and resolving chromatographic interferences. Baseline resolution of nine structural/-stereo isomers and one isobar were achieved.

An enantioselective LC-MS/MS method for the detection of amphetamine, norephedrine and 4-hydroxyamphetamine was developed [53]. Forensic serum samples and serum samples from psychiatric inpatients stating their last time of amphetamine consumption were examined. Norephedrine and 4-hydroxyamphetamine were detected more frequently at higher amphetamine concentrations and at lower amphetamine (R)/(S) concentration ratios, possibly indicating recent consumption. The use of amphetamine (R)/(S) ratios and simultaneous detection of metabolites were promising factors that could facilitate estimation of consumption time and current impairment.

Årnes et al. [54] carried out a study to determine the rate of elimination of gamma-hydroxybutyrate (GHB) in blood by analysis of two consecutive blood samples from apprehended drivers with GHB by UPLC-MS/MS. The elimination half-life of GHB in blood samples from apprehended drivers was found longer than expected in comparison with results of controlled dosing studies. Zero-order kinetics seems a more appropriate model for GHB when concentrations are back-calculated and GHB's median zero-order elimination rate was found to be 21 mg/L/h.

Mitragynine, a primary active alkaloid in the leaves of the tropical tree *Mitragyna speciosa*, is increasingly seen in forensic toxicology casework including DUID. To appropriately interpret mitragynine concentrations detected in biological specimens from forensic casework and assess its potential toxicity, a validated LC-MS/MS method together with a short series of case reports was presented, providing examples of apparent adverse events and the associated range of mitragynine concentrations [55].

3.2.3. Suitability of oral fluid for drug testing

There are concerns about the use of oral fluid as an alternative matrix for drug impairment test regarding its accuracy compared to those from blood and urine specimens. A review summarized the scientific literature covering analytical methods and interpretation published over the past two decades for amphetamines, cannabis, cocaine, opioids, and benzodiazepines in oral fluid, including the relative merits and limitations of each matrix [56]. Drug concentrations were reviewed in the context of dosing condition and collection methods. Time of last detection was evaluated against several agencies' cutoffs.

A study of paired oral fluid and blood samples collected from drivers suspected of DUID was conducted to compare detection times of drugs in the two types of samples, which were analyzed by UPLC-MS/MS [57]. It was found that amphetamine, methamphetamine (MA), oxazepam, morphine and 6-monoacetylmorphine (6-MAM) were more prevalent in oral fluid than blood, indicating their relative longer detection time in oral fluid.

The accuracy of predicting THC in blood from oral fluid measurement and factors influencing prediction accuracy were discussed by Romano et al. [58]. 7517 drivers with known laboratory results in both oral fluid and blood were included. The number of true and false positives, true and false negatives, sensitivity, specificity and positive predicted value were determined. It was found that THC measured in oral fluid was a good predictor of that measured in blood, in particular when $THC_{oral\ fluid} > 0$ ng/mL was used to predict being positive for THC in blood ($THC_{blood} > 0$ ng/mL).

A study compared paired oral fluid and urine samples with drug recognition expert observations was reported [59]. Urine samples were screened for cannabinoids, opiates, methamphetamine, cocaine, methadone, phencyclidine, amphetamine, benzodiazepines and oxycodone. Impairment observations were recorded from officers undergoing drug recognition expert certification and oral fluid samples were screened by LC-QTOF-MS. Evaluator opinion of drug class was confirmed in oral fluid 90% of time and in urine 85% of the time in reference to scope of testing by LC–MS methods employed (excludes cannabis and central nervous system depressants). The study indicated that oral fluid might be a viable source for confirming DUID.

3.3. Additives in blood sampling tubes

Studies from decades past determined that adding sodium fluoride to whole blood is necessary to prevent ethanol degradation due to storage at room temperature beyond 14 days (or higher temperatures) and microbial contamination. Statistical comparisons were conducted to determine whether significant differences exist between BAC values obtained from 6-mL gray-top tubes with 0.25% sodium fluoride (NaF) versus 10-mL tubes with 1% NaF [60]. Whole blood was spiked at concentrations of 0.04, 0.08, and 0.15 g/100 mL and aliquoted into 6-mL and 10-mL tube pair at three levels of fill volumes. Tubes were refrigerated or ambient storage and analyzed after 1–30 days, using headspace gas chromatography. Analysis of variance found no significant differences between 6-mL and 10-mL tubes for 0.04 and 0.15 g/100 mL concentrations over 30 days. Paired t-tests of grouped samples found no significant differences between 6-mL and 10-mL tubes at any concentration.

A 10-mL evacuated blood sampling tubes recall incident due to missing of preservative NaF and anticoagulant potassium oxalate aroused concern for possible implications in criminal justice when BACs were interpreted. Rodda et al. [61] reviewed literature related to current practices and stability of ethanol in stored blood samples and concluded that anticoagulant was required to maintain the integrity of whole blood

specimen; and concentrations of ethanol and many other drugs actually decreased during storage without a fluoride preservative. Also, there was no clear consensus regarding the amount of fluoride preservative necessary, if any at all, when blood was taken from living subjects under sterile conditions for typical forensic ethanol analysis.

Wiedfeld et al. [62] carried out comparative analysis of positive tested paired routine plasma/serum samples collected at the same time with device with and without fluoride for the detection of cannabinoids and amphetamines. Samples were measured by LC-MS/MS methods for analytes, including THC, THC-COOH and THC-OH, and results were statistically evaluated. It was found that mean concentrations of cannabinoids were significantly reduced whereas mean amphetamine concentration was significantly higher in fluoride-stabilized blood samples.

3.4. Roadside testing

Roadside testing is one of the strategies to detect and deter drink driving and drug driving. Different parties attempted to study, model and evaluate the impact of such intervention on the drink and drug driving outcomes via literature review [63], modelling set up [64] and survey based on self-report questionnaire [65]. These studies tried to identify an optimal point of traffic enforcement (in the form of roadside testing) to lower alcohol-/drug-related traffic incidents or to create intended rule compliance.

Regarding the technical aspect, Scherer et al. [66] evaluated the analytical reliability of 4 point-of-collection testing devices (the DDS2™, the DOA MultiScreen™, the Dräger Drug Test 5000™ and the Multi-Drug Multi-Line Twist Screen Device™) for the detection of cocaine and cannabinoids using oral fluid samples from Brazilian drivers. In addition, Alhefeiti et al. [67] discussed all the available roadside drug testing devices in the market used by the authorities in the review. These devices were applicable to either saliva, sweat, fingerprint and surfaces. This article could help law enforcement agencies to compare and evaluate all the reliable roadside testing devices in the market.

For the latest development, a rapid response electrochemical biosensor was demonstrated to streamline the testing process through impedimetric measurements [68], rather than affinity biosensors operated as home-kit lateral flow assays in most of the current roadside drug testing devices. The developed sensor was capable of providing a rapid detection time of less than a minute, a lower detection limit of 100 pg/mL and a dynamic range from 100 pg/mL to 100 ng/mL for the detection of THC at varying salivary pH and the sensor could be used as a marijuana roadside DUI test for oral fluid.

3.5. Drug level interpretation

3.5.1. Alcohol-impaired driving

Jones wrote an overview in 2019 [69] to include recent publications on analytical methods of quantitative measurement of ethanol in biological specimens and BAC interpretation in relation to the degree of impairment.

A study conducted in Spain assessed the influence of moderate alcohol intake on binocular vision, vergence system and simulated driving performance by analyzing the interactions between visual deterioration and driving variables [70]. Moderate alcohol consumption (BrAC of 0.40 mg/L) was found to impair binocular visual and simulated driving performances.

Alcohol hangover research is an emerging field. A study examined the consequences of alcohol hangover with a driving simulator contrasting a group of 26 participants with zero residual alcohol next day and another group of 26 participants with residual alcohol undertaking a 20 min commute to work [71]. The pattern of impairment was broadly similar across both groups, indicating that no matter residual alcohol was present, consistent driving impairment was seen. The level of impairment seen was comparable to driving while intoxicated at or above a BAC of 0.05%.

Apart from studying BAC, a study in Korea [72] tried to understand alcohol kinetics and to determine whether an individual is in absorption phase or elimination phase at the time of blood collection by analyzing ethyl glucuronide and ethyl sulfate in blood. It is shown that the ratio of ethyl glucuronide (mg/L)/BAC (g/L) is higher than 1, the individual would be in elimination phase of BAC.

3.5.2. Drug-impaired driving

There were continuous efforts to investigate driving impairment upon intake of drugs, such as benzodiazepines [73–76], zolpidem [73,74,77], buprenorphine [78,79], fentanyl [80], and others [81–85]. As more countries and territories have legalized the medicinal and recreational use of cannabis, numerous studies were found to focus on the effect of cannabis on driving performance [86–93]. Arkell et al. [92] described that THC could impair driving performance and increase crash risk; while there was no evidence that CBD impairs driving. Patients may be tested positive for THC even if they do not feel impaired, and medical cannabis use does not currently exempt patients from mobile (roadside) drug testing and associated legal sanctions in Australia.

Acute cannabis intoxication was demonstrated to impair concentration, reaction time, along with a variety of other necessary driving-related skills [93]. Poor driving performance was observed for non-intoxicated, chronic and heavy recreational cannabis users, while those with earlier onset showed greater impairment [94]. Results of a driving simulator study did not conclusively establish that occasional users exhibited more driving impairment than daily users when both smoke cannabis ad libitum [95]. Nevertheless, a lack of impairment was observed for 18 young adults after consuming “light cannabis” in a 2-h monitoring study, which might be due to the very low concentrations of THC in blood [96]. Another report suggested that the time point after cannabis consumption played an important role regarding driving safety [97]. There was significant increase of driving faults immediately after consumption. No significant increase of driving faults was seen 3 h after consumption, yet after 6 h during the so-called subacute phase. However, an increase of driving faults, even though insignificance, could be noted.

Two case reports documented unusually high concentrations of cocaine [98] and fentanyl [99] in blood of impaired drivers. The exceptionally high concentration of 3000 mg/L of cocaine found in a motorist’s blood (average cocaine concentrations ranging 0.076–0.109 mg/L as stated in this case report) was unusual for an impaired driving case. Investigation revealed that the motorist swallowed cocaine during the traffic stop, which meant a cocaine DUID charge could not be pursued [98]. In the case of fentanyl, a driver with no medical fentanyl administered was found to have a blood fentanyl level of more than 300 ng/mL, which could have been assumed to be fatal if presented on its own [99]. However, the data reported from a national reference laboratory reviewed that there was an increase in higher blood concentrations of fentanyl in DUID cases in recent year. This case served as a reminder that blood toxicology results for opioids should be interpreted with care.

3.6. Legislation & enforcement approaches

Regarding drug-impaired driving laws, Tiscione et al. [100] commented that a more inclusive statutory language such as “any impairing drug” is more appropriate in order to improve safety by removing impaired drivers from the road. In their study over 11 years in Florida, 21% (212 out of 1028) of all drug-positive blood specimens and 47% (711 out of 1527) of all drug-positive urine specimens contained at least one non-controlled drug, often mixed with controlled drugs. Despite documentation of observed impairment with the concurrent identification of impairing drugs, an impaired driving charge could not be supported due to the phrasing of the law in Florida.

In America, there were 2021 updates to the National Safety Council's Alcohol, Drugs and Impairment Division's recommendations for drug testing in DUID cases and motor vehicle fatalities [101]. No changes were made to the Tier I scope, but there were changes to cutoffs of some analytes for blood, urine and oral fluid. It was clarified that the Tier I cutoffs reflect free concentrations, and hydrolysis is recommended but not required. The Tier II scope was expanded to include trazodone and difluoroethane. The consensus panel concluded that urine would not be included in future iterations of recommendations as a recommended matrix.

Strategies to detect cannabis-impaired driving remained a challenge. Many jurisdictions use per se limits to define cannabis-impaired driving. In a stimulated driving study, there were cases illustrating either impairment could be minimal when THC result was positive or impairment could be profound while the THC result was negative [102]. Ginsburg [103] also reviewed two detection methods for cannabis-impaired driving and suggested that general strategies for detecting and preventing impaired driving regardless of the cause would be preferable to establishing specific methods for every situation or substance that could impair driving.

Intervention at different levels to deter impaired driving was evaluated. In Canada, there was a recent shift in impaired driving enforcement from federal criminal proceedings to provincial administrative sanctions. Enacting a package of roadside administrative sanctions such as mandatory provincial administrative license suspensions, vehicle impoundments, monetary penalties, license-reinstatement fees and remedial programs, the impaired driving deaths and injuries had been significantly reduced [104]. The legality of any administrative sanction will likely depend on its severity, the reliability of the test or evidence upon which it is based, and the extent to which the driver has a meaningful opportunity to challenge the decision. In USA, the enforcement strategies, like overservice enforcement, alcohol-impaired driving enforcement (sobriety checkpoints, saturation patrols, open container, overall alcohol-impaired driving enforcement) and retail compliance checks, help to reduce alcohol-impaired driving and related consequences among young people [105–107].

3.7. Back-calculation and hip-flask defense

Jones [108] presented an overview to cover the alcohol pharmacokinetics and respective calculations with examples. Recent approaches to update the Widmark equation were also discussed. Maskell et al. [109] complied information from literatures to evaluate the empirically derived values of distribution volume of ethanol with those derived from various anthropometric equations. Maskell and Cooper [110] attempted to estimate the uncertainty of results as calculated using the Widmark equation and opined an increase in estimated uncertainty when estimated body mass was used rather than measured body mass.

Experimental studies were carried out to assess hip-flask defense. A study investigated how blood and urine ethanol kinetics varied after an initial drinking session of beer and then a subsequent hip-flask drink of three different doses of whiskey [111]. Results supplemented the previous studies mainly based on data from administration of controlled single doses of ethanol. Höiseth et al. [112] further studied the kinetics of ethanol, ethyl glucuronide and ethyl sulfate in blood and urine upon ingestion of two repeated doses of ethanol and investigated the usefulness of different models for assessment of hip-flask defense.

3.8. Driving under influence during COVID-19 pandemic

During the initial stage of the COVID-19 outbreak, lockdown policy was adopted in many countries. A few retrospective studies had been conducted to evaluate the effects of pandemic on the pattern of driving under influence. In Los Angeles, taking into account traffic volume, the odds of encountering an alcohol-intoxicated driver was decreased by approximately 23% during the Safer at Home period [113]. In Romania, there was a sharp decline in the number of drink driving cases in the first six months of the lockdown, with a slow upward trend afterward. This reduction was not associated with statistically significant changes in BrAC or BAC [114]. Chronic excessive alcohol consumption and illicit substance use were more frequently observed in cases in Italy [115], suggesting a possible correlation between the pandemic/lockdown restrictions and an increase in psychoactive substance misuse.

4. Workplace & court-ordered drug testing

To keep drug misuse away from workplace and reduce the chances of accidents under the influence of drugs, workplace drug testing becomes popular. Court-ordered drug testing gives an individual a chance to comply with a legal requirement to develop a drug-free lifestyle. The following sections addressed related issues in these areas.

4.1. Samples validity

4.1.1. Urine

Authenticity of urine samples is always an issue of concerns in urinalysis for workplace drug testing. In order to circumvent the test, one evades the test by substituting his own urine sample with one from a drug-free individual or a "synthetic urine" which is readily available from the market. Moreover, urine sample could be adulterated by simply diluting with water or adding of a chemical.

A study on the effect of common household chemicals (acids, alkalis, oxidizing agents, surfactants) as adulterants on immunochromatographic strips for urine drug screening was conducted by Rajšić et al. [116]. It was found that a lot of the household chemicals would affect the validity of test strips for the detection of amphetamine, MDMA, cocaine, benzodiazepines, THC, morphine, heroin and codeine. Abdelati et al. [117] reviewed the mechanism of action of different adulterants on drug abuse testing in urine samples and discussed the methods of detection of the adulterants.

A case of a tampered urine sample by dilution and a crushed hydrocodone pill as an adulterant [118] was reported. This case highlights the importance of implementation of specimen validity testing, especially samples from pain clinics. Both the Clinical and Laboratory Standards Institute and The National Academy of Clinical Biochemists of the USA have introduced the integrity test of a urine sample including a pH, creatinine and specific gravity tests to ensure specimen validity.

Kyle and Kaur [119] suggested that a typical validity test of urine sample that based on pH, creatinine and specific gravity tests was insufficient to distinguish a synthetic urine substitution. The authors opined 4 markers, caffeine, cotinine, theobromine and urobilin, to be effective for distinguishing non-physiologic specimen.

In addition to substitution with synthetic urine, drug abusers often try to pass drug testing by ingesting different products to "flush out" drugs or adulterating urine samples with various chemicals that would interfere with the analytical process of drug detection. Sofronescu and Zhu [120] reported that a 53 years old woman taking overdose of niacin presented a urine sample for drug testing as a pre-employment requirement with direct evidence of blood niacin concentration. It demonstrated that niacin could be potentially used in an attempt to pass a drug test, despite no objective evidence obtained to confirm the use of niacin as an attempt to circumvent the scheduled urine drug test.

4.1.2. Hair

Hair is another choice of samples for workplace drug testing. It provides a wider time window for detection of drugs comparing to urine. However, hair is subjected to various treatment, such as bleaching, coloring, perming and straightening, which could affect results of drug testing.

Gambier et al. [121] studied the effect of thermal straightening of hair on anhydroecgonine methyl ester (AEME) as well as cocaine and its metabolites. AEME was suggested as a marker in the hair samples of

donors with a history of smoking cocaine base (crack). Increase in concentrations of AEME and BZE and decrease in concentrations of cocaine, norcocaine, ecgonine methyl ester (EME) and cocaethylene were observed in thermal treated hair. Since AEME was found to be produced in the heating process, the authors suggested that AEME being used as a marker of crack smoking history should be used cautiously. The authors also suggested that the ratio of BZE and cocaine (>1) could be used as an indicator of thermic hair treatment.

Elsué and Yegles [122] investigated the effects of bleaching, perming and dyeing treatment on cannabinoids and their metabolites in hair samples. It was found that bleaching and perming reduced all cannabinoids concentration in hair and THC was more affected than THC-COOH, CBN and CBD. Permanent colorings were found having little effects on cannabinoids.

4.2. Detection of drugs

4.2.1. Hair

Vincenti et al. [125] proposed a multiclass method for simultaneous extraction, identification and quantification of sixty drugs of abuse, including both traditional substances and NPS, such as cathinones and synthetic cannabinoids in hair. Both the decontamination step and the extraction of analytes from the inner core of hair samples were carried out by pressurized liquid extraction while the clean-up was performed by dispersive liquid/liquid microextraction, which gave the great advantage of a high enrichment factor.

Matey et al. [126] developed a GC-MS method for detection and quantitation of ketamine and norketamine by derivatization with pentafluoropropionic anhydride. The LOD was determined to be 0.25 ng/mg for ketamine and 0.05 ng/mg for norketamine, which was lower than the unique cut-off suggested by European Workplace Drug Testing Society of ketamine and norketamine at 0.5 ng/mg and 0.1 ng/mg respectively.

In the review period, there were numerous studies on application of LC-MS/MS methods for hair analysis targeting different analytes, such as 16 cathinones {4-fluoromethcathinone, buphedrone, ethcathinone, methcathinone, mephedrone, naphyrone, 4-methylethcathinone (4-MEC), methedrone, alpha-pyrrolidinopentiophenone, alpha-pyrrolidinohexiophenone, methylenedioxypyrovalerone (MDPV), butylone, ethylone, 3,4-dimethylmethcathinone (3,4-DMMC), pentedrone and pentylone} [123], 5-methoxy-*N,N*-diisopropyltrytamine [124], THC-COOH [127], 18 synthetic cannabinoids/metabolites [128], 12 drugs of abuse, including amphetamines, opiates, ketamine, cocaine and their metabolites [129], 19 antipsychotic drugs and metabolites (amisulpride, aripiprazole, chlorpromazine, clotiapine, clozapine, 9-OH-risperidone, olanzapine, pimozine, pimpamperone, quetiapine, risperidone, sertindole, sulpride and tiapride) [130].

4.2.2. Oral fluid

A study was carried out for detection of drugs in oral fluid samples collected by a commercially available device [131]. A urine sample and 2 oral fluid samples were taken together from individuals at workplace. 113 paired oral fluid and urine samples were investigated for the presence of amphetamines, benzodiazepines, opiates and opioids, cocaine and cannabis. There was a good correlation between drugs detected in oral fluid samples and urine sample, but there was a significant difference in concentrations of drugs between the pairs of oral fluid samples. Drugs were found to be stable in the oral fluid samples stored at −20 °C for at least 1 year.

Desrosiers and Huestis [56] conducted a review covering analytical methods and interpretation published over the past two decades for oral fluid examination of amphetamines, cannabis, cocaine, opioids and benzodiazepines. Time of last detected was evaluated against cutoffs suggested by different agencies. A significant correlation between matrices was observed. Since there was a high intra-subject and inter-subject variability, no prediction of blood concentrations from oral fluid concentrations was feasible.

4.2.3. Urine

A LC-MS/MS method for qualitative and quantitative analysis of 73 cathinones and related metabolites in urine was proposed by Fan et al. [132]. The LODs and LOQs for all the analytes were 0.1–0.5 ng/mL and 0.5–1.0 ng/mL respectively. The method was applied to 67 urine samples in which 13 different cathinones were detected from 32 positive samples. Seven different cathinones were found in one case.

Two definitive methods, UPLC-MS/MS and UPLC coupled with hybrid quadrupole time-of-flight mass spectrometer UPLC-MS/TOF, were proposed for the detection of over sixty drugs and metabolites in urine [133]. The two methods based on alternate mass spectrometry technology and column separation could serve a definitive confirmation of a drug detection.

Wang et al. [134] developed an automated online SPE and LC-MS/MS for detection of the metabolites of heroin: morphine, 6-MAM, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). The LODs of the four metabolites were in the range of 1.25–5 ng/mL. The method was then applied to the analysis of urine samples of 20 male heroin abusers. M3G was detected 9–11 days after admission to the drug rehabilitation institute in 40% of heroin users while morphine or M6G was not detected. It was suggested that M3G which had a wider detection window could provide diagnostic information with regard to heroin exposure.

4.3. Interpretation of drug testing results

4.3.1. Hair

There were several studies concerning drugs of abuse in hair of children. Pragst et al. [135] analyzed hair samples from families with drug consuming parents. A total of more than 1300 individuals and 100 families in Germany were being tested. Up to 5 drugs were detected in 95.2% of the family tests with highest occurrence of cocaine (79.7%) and THC (50.2%). The comparison of hair results within families gives a deeper insight in the drug situation.

A study was conducted to analyze the distribution of different cannabinoids in children's hair samples and correlate cannabinoid metabolite levels to the intensity of toxic environmental exposure [136]. It was found that 39% of the children in France could be considered exposed to an intensely toxic environment.

The Society of Hair Testing proposed THC-COOH as a marker to distinguish active cannabis consumption from passive contamination. Casati et al. [137] suggested that 0.5 pg/mg could be used as the cut-off level which was determined by receiver operating characteristics by quantitative analysis of 672 THC-positive hair samples.

The cut-off value of methamphetamine detection for black-hair Chinese populations was studied by Ou et al. [138]. The cut-off value was found to be 0.97 ng/mg by receiver operating characteristics of results of quantitative analysis of 563 hair samples.

A retrospective analysis of drugs of abuse, including amphetamine, methamphetamine, MDMA, MDA, tetrahydrocannabinol, ketamine, norketamine, cocaine, BZE, morphine, 6-acetylmorphine, flunitrazepam and 5-methoxy-*N,N*-diisopropyltrytamine, in Shanghai was done by hair analysis [139]. 5610 cases were examined by LC-MS/MS and concentration distributions of the commonly abused drugs in hair were reported.

Scholz et al. [140] studied the concentration ratio of the hydroxy metabolites of cocaine, hydroxycocaine and hydroxybenzoylecgonine, with respect to cocaine in seized street cocaine samples and in hair samples from different cohorts. Based on these results, a decision workflow was established for the discrimination between cocaine use and external contamination.

Kintz et al. [141] examined hair samples from 8 tramadol abusers and 15 cannabis abusers and concluded that there will be a 3–4 and 6–7 months of delay of the hair yielding negative results with respect to

tramadol and cannabis after discontinuation of their abuse from chronic users.

The concentrations of methamphetamine and amphetamine in 1-cm segments of hair from 10 chronic users were examined by Wang et al. [142]. It was found that amphetamine/methamphetamine ratios increased with the duration of methamphetamine abuse and there was no chiral conversion of methamphetamine or amphetamine in hair matrix.

A method suitable for segmental hair analysis of GHB was presented by Martz et al. [143]. 88 hair samples from volunteers who were not claiming any exposure to GHB were examined and the mean value of 0.673 ng/mg and 0.935 ng/mg were detected in the females and males respectively. It was found that a single dose of 2 g GHB did not cause an increase of GHB in hair compared to his base levels and any significant traceable incapacitation to the volunteer.

4.3.2. Urine

Baeck et al. reported a study where hemp seed products were taken by 32 participants and the cannabinoid levels in urine were analyzed after 7 days and 12 weeks [144]. None of the urine samples were positive for cannabinoids by a COBAS C311 screening and a subsequent GC-MS in the confirmatory test at the cutoff level of 25 ng/mL.

Urine specimens from 11 frequent and 9 occasional cannabis users were analyzed for 11 cannabinoids for 85 h by LC-MS/MS following controlled smoked, vaporized or oral 50.6 mg of THC in a randomized, placebo-controlled, within-subject dosing design [145]. This study provides a scientific database to assess single urine concentrations in cannabis monitoring programs.

Özbunar et al. [146] presented a study that 100 g of poppy seed paste were consumed in breakfast by ten healthy adults over three days and urine samples were collected before and after the breakfast. Positive opiate results were obtained up to 12 h and 48 h after the consumptions with the cut-off value of 2000 and 300 ng/mL respectively.

Cheng and Dao [147] found that the drug positive rates for urinalysis in the selected population group (offenders/probationers who requiring mandatory drug testing) were steady with an average of about 22% in Hong Kong. Single drug user constituted about 80%. Ketamine, methamphetamine and heroin were the three most commonly encountered drugs of abuse.

A study to examine the morphine and codeine contents in the urine of consumers after partaking poppy seed-enriched curry was conducted by Gan et al. [148]. Positive results were obtained from the urine samples which were screened by a test strips with morphine and confirmed by GC-MS at the cut-off value of 300 ng/mL.

The excretion profile of THC-COOH of infrequent cannabis users who used vaporizers for consumption of cannabis was presented by Spindle et al. [149]. Urinary concentrations of THC-COOH were measured at baseline and for 8 h after cannabis administration. THC-COOH concentrations peaked 4–6 h after cannabis administration. Infrequent users of cannabis might excrete relatively low concentrations of THC-COOH following acute inhalation of smoked or vaporized cannabis.

CBD and CBD-dominant products are increasingly popular. Spindle et al. [150] conducted a study characterized the urinary pharmacokinetic profile of 100 mg oral and vaporized CBD as well as vaporized CBD-dominant cannabis. Urinary concentrations of CBD were higher after oral versus vaporized. Concentration peaked at 5 h after oral route and within 1 h after inhaling of vaporized CBD. Acute dosing of pure CBD would not result in a positive urine drug test under current federal workplace drug testing guidelines but those consumed CBD-dominant products could produce positive urine results.

Two cases of false positive MULTIGENT® amphetamine/methamphetamine and MULTIGENT® ecstasy (Abbott®) immunoassays urine screening with the beta-blocker metoprolol were discussed by Leclercq et al. [151]. It was found that metoprolol showed positive results for both amphetamine and MDMA tests at 200 and 150 μg/mL respectively. Metoprolol metabolites cross-reacted with the amphetamines immunoassay only, 2000 μg/mL for α-hydroxymetoprolol and 750 μg/mL for O-demethylmetoprolol.

A retrospective analysis using LC-MS/MS for 500 randomly selected urine samples from probationers in Turkey for synthetic cannabinoids and their metabolites was conducted by Atasoy et al. [152]. 108 samples were found positive for 20 synthetic cannabinoids and their metabolites. The two most detected synthetic cannabinoids were 5F-NPB-22 and (S)-AB-FUBINACA.

4.3.3. Blood

In a study of Spindle et al. [153], 17 healthy adults consumed cannabis brownies containing THC doses of 0–50 mg. The blood and oral fluid specimens were collected at baseline and for 8 h post-brownie ingestion. THC and THC-OH in the blood peaked 1.5–2 h after brownie consumption and returned to baseline within 8 h. THC-COOH and its-glucuronide were at a concentration higher than THC and THC-OH and were often detectable 8 h post-brownie consumption. Detection of THC in oral fluid was immediate and reflect the degree of cannabis deposition in the oral cavity but not levels of THC circulating in the blood.

4.4. Passive and occupational exposure

Hair drug test is useful in documenting patterns of drugs exposure within a certain period in the past rather than recent drug use, in particular it can establish a retrospective calendar of an individual's drug exposure when multi-sectional analyses are performed. However, one commonly encountered issue in hair analysis is the unwanted false-positive results from passive exposure to the drug or environmental contamination. Kintz et al. reported three cases using segmental hair tests to document contamination of drugs from the environment. These included (1) contamination of a powerful hallucinogen N,N-dimethyltryptamine (DMT) in the hair of the partner of a repetitive DMT smoker [154]; (2) contamination of quetiapine, an anti-psychotic drug and propranolol, a β-blocker agent in the hair of a 23-month-old boy of his mother [155]; and (3) a young tennis player failed a doping control when BZE, a cocaine metabolite, was identified in his urine [156]. In these articles, the authors observed that drug concentrations were regularly increased from the proximal to the distal hair end suggesting the older hair (those of the distal part) being for a longer time in contact with the drug and indicating the occurrence of an external contamination. The authors reiterated that a proper interpretation of hair test results was critical and should be done ideally with other information available, such as medical history, witness statements and the available circumstances of the matter.

Hair test can also detect exposure or use of illegal drugs in children. A total of 387 hair samples for commonly applied illegal drugs of children up to 16 years old which were collected between 2014 and 2018 were analyzed for cocaine, cannabinoids, opiates, and amphetamines by LC-MS/MS [157]. Results indicated that utero exposure, breast milk or a close physical contact was a likely source of drug findings in babies. With an increasing age of the child, the risk of being exposed to drugs from drug consuming caregivers or environmental exposure through smoke, dust, or drug residues decreased, whereas the increase of drug concentrations in adolescents' hair, especially of cannabinoids, amphetamines, and cocaine, suggested an accidental or deliberate use of the drug, possibly in addition to a passive exposure.

4.5. Pre-employment and workplace settings, approaches and methodologies

Opioids, both naturally occurring and semisynthetic, are not only commonly prescribed pain medications, but also high potential for misuse and abuse. In order to obtain information regarding opioid trends in general population, Stowe et al. performed a hair analysis, with screening by immunoassays and confirmation by LC-MS/MS, on over

37000 of opioid-positive workplace hair samples containing codeine, morphine, hydrocodone, hydromorphone, oxycodone or oxymorphone [158]. The concentration ranges in workplace hair samples confirmed positive for codeine, morphine, hydrocodone and oxycodone were reported in this study.

The use of two fully automated methods for dried blood spot and dried urine spot in workplace drug testing was reported [159]. The dried cards were first checked in a camera recognition system, spiked with deuterated standards via an in-built spraying module and then directly extracted and transferred online to a LC-MS/MS system. The whole analysis workflow was fully automated without any human interaction required. A method targeting 28 analytes takes 5 min, and it has extended to open up the analysis for more than 1200 drugs within 20 min of sample analysis time.

5. Drug facilitated crimes

5.1. Introduction

Drug facilitated crimes (DFC) have been occurring for over a century. By definition, any criminal activities involving the use of drug(s) to assist a perpetrator to incapacitate a victim in the commission of crime may be classified as "drug facilitated crime". These criminal activities typically involve homicide, robberies, human trafficking, kidnapping and sexual assault [160]. Among these crimes, drug facilitated sexual assault (DFSA) is the one that most concerned. The types of sexual assault usually involve rape, attempted rape and indecent assault. Other types of physical violence such as bodily injury can happen at the same time [161].

5.2. Book chapter and review articles

In the past three years, there were one book chapter and four review articles summarized the recent findings and/or cases related to DFC [160,161,163–165]. LeBeau et al. [160] in the book chapter reviewed the challenges faced by forensic toxicologists and summarized the most common drugs detected in alleged drug-facilitated crimes. Although some of the challenges in DFC were out of the control of toxicologists, forensic laboratories should always improve their analytical methods and/or instruments such that they were sensitive enough to detect the presence of the strong, but often low-dose depressant drugs in DFC. A standard has recently been published by Academy Standards Board and the American National Standards Institute (ANSI) to standardize the required minimum analytical scope and sensitivity for testing of urine in DFC cases [162].

Fiorentin and Logan [163] reviewed 1000 cases of suspected/alleged DFSA in 37 states and 1 territory of the United States. Among those 1000 DFSA cases, 784 cases found positive for one or more intoxicating substances. Not surprisingly, ethanol (309 cases) and cannabinoids (288 cases) were the most commonly detected intoxicating substances. The other drugs commonly detected were amphetamine/methamphetamine (165 cases), cocaine and metabolites (104 cases) and clonazepam and metabolites (76 cases). Cannabinoids and ethanol were the most frequent polydrug combination (69 cases). The authors also indicated the LODs of various intoxicating substances, comparable with the recommended limits by SOFT/UNODC.

Busardò et al. [164] performed a review of toxicological reports from 256 female victims admitted to the Sexual Assaults Centre of Careggi University Hospital in Florence, Italy, between January 2010 and July 2018, and literature search from multidisciplinary databases, including PubMed, PsycINFO and Scopus databases, using the search terms "drug-facilitated sexual assault", "chemical submission", "date rape", "rape drugs" and "drink-spiking". The authors found that most of the research were done in the United States, followed by the United Kingdom and Europe. Australia and Africa each only had one study. The authors also pointed out that there was a serious underestimation for the number of DFSA cases. The low reporting rate may be due to victim's psychological aspect (embarrassment, guilt or perceived responsibility), cultural beliefs, stigmatization and lack of confidence. In conclusion, Busardò et al. suggested two ways to tackle the underestimated issue in DFSA. Firstly, it was necessary to increase the public awareness of DFSA and understand the effects of intoxicating drugs or "date rape drugs". It should also educate the public that the correct way for victim of DFSA was to reach the emergency service for diagnosis and treatment as soon as possible. Secondly, the toxicologist should be provided with the information so that the best biological matrices and analytical strategies could be employed.

Poulsen et al. [165] reviewed the toxicological findings of victims from 162 DFSA cases in New Zealand from December 2015 to 2018. The victim's blood and urine samples were screened for legal drugs and recreational drugs and examined for the alcohol concentration. Alcohol was found to be one of the major facilitators of sexual assault in New Zealand. The higher BAC would result in higher risk of sexual assault. The authors also found that an increase in delay of sampling time would result in a decrease in alcohol concentration. For victims with admitted alcohol use but none was detected, the average sampling time for blood and urine was 14 and 17 h respectively, highlighting the importance of timely sampling for alcohol determination. Furthermore, about 82% of blood alcohol positive samples and about 68% of urine alcohol positive samples were found to contain acetone at about 5–10 mg/L and over 20 mg/L respectively. The authors suggested that victims of sexual assault, who are under extreme physiological and emotional stress, may show a different metabolism of alcohol which favourably increase the production of acetone. For illicit drugs, cannabis was the most commonly encountered, followed by methamphetamine. For medicinal drugs, the most commonly detected drugs were citalopram, fluoxetine and quetiapine, belonging to the antidepressant and antipsychotic class. The high usage of these kinds of medicinal drugs suggested that the victims may have been people of vulnerable personality. Poulsen et al. finally concluded that loss of consent through voluntary alcohol and drug consumption is more common and poses a significantly greater risk to victims than surreptitious drug administration.

Costa et al. [161] reviewed the literature on gender violence and the most common intoxicating substances and drugs, including ketamine, benzodiazepines and gamma-hydroxybutyrate, used to facilitate sexual assault. This review covered the mechanism of action, pharmacokinetics, drug detention times in various human biological matrices (urine, whole blood, plasma, oral fluid and hair) and the appropriate analytical methods and instruments for forensic identification of drugs. The authors opined that toxicologists must interpret their analytical results carefully and presented their findings to the judicial authorities impartially.

5.3. Analytes or cases with interests

Ethanol, being the most commonly detected intoxicating substance in DFC case, was involved in a homicide case as reported by Lancia et al. [166]. In this case report, a drunken man stabbed and killed a 27 y/o man, standing nearby a bar. Toxicological examinations revealed high BAC (280mg/100 mL) for the assailant but no narcotic substances or alcohol for the deceased. The authors concluded that alcohol decreased one's ability to judge and enhanced anger, leading the drunken man to misunderstand of and over-react to other's behaviour. It was suggested that there was necessity to increase the awareness of alcohol-related crime happening close to bars. Bars should also implement some safety practices, such as uses of tempered glass or plastic, to minimize the number of alcohol consumption-related accidents and provide a safer drinking environment.

Apart from those "traditional" intoxicating substances, NPS occupied a significant place in the global drug market and posed a significant risk to health and safety concern. According to the United Nations Office on Drugs and Crime (UNODC), NPS are defined 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" [167]. A recent publication by UNODC highlighted that benzodiazepine-type NPS is a primary NPS threat. About 69% of the 1900 reported NPS cases were related to benzodiazepine-type NPS [168]. Qian et al. [169] reported an anesthesia robbery case involved the use of flualprazolam. In this case report, a 21 y/o female experienced dizziness after drinking tea with a male "netizen" in a teahouse before she woke up in a hotel room with her wallet and cell phone missing. The suspect was later arrested and confessed to adding a liquid from a bottle named 'Lie Yan' to the victim's drinks, which was found to contain flualprazolam. The authors concluded that this case warranted our attentions on more benzodiazepine-type NPS appearing in illegal products.

Among 1100 individual NPS reported, synthetic cannabinoid receptor agonists constituted the second largest group (about 29% of reported NPS) [168]. Aknouche et al. reported a case where SGT-151, a synthetic cannabinoid also known as CUMYL-PEGACLONE, was surreptitiously administrated in a herbal mixture [170]. Two 16 y/o migrants, after having smoked the herbal mixture, presented seizures and then collapsed. Without reference materials of SGT-151's metabolites, the authors prepared the metabolites through human liver microsomes preparation and further characterized them with NMR and LC-High-resolution mass spectrometry (HRMS). SGT-151 and its metabolites were found in the blood samples collected from the two victims and the culprit.

Table 1 summarizes other DFC cases reported in the three-year period covered by this review paper.

5.4. Analytical challenges

One of the biggest challenges in DFC cases is delayed sampling time as victims often hesitate to report the offences [160,161] while detection window for most drugs in blood and urine samples is very short, on the order of hours to a couple of days [171]. If victims report their cases weeks after the incidents, it is almost impossible to detect and correlate whether any drugs are used in the incident. In this scenario, hair specimens are the most informative biological matrices of choice as drugs in hair have longer detection windows [172–174]. Kuwayama et al. reported the use of a two-step hair analysis to estimate the day of drug administration in a DFC case [175]. A woman was fallen asleep and assaulted after consuming a drink offered by an acquaintance. She reported to the police approximately a month later. Toxicological examination of head hair from the victim revealed the presence of zolpidem in the first step of analysis. With her consent, the victim took a cold medicine as an internal temporal marker (ITM) twice at interval of 21 days for the second step of analysis. Hair extracts were prepared by micro-segmental method from a single hair strand collected from the victim two weeks after the second ITM administration. The extracts were analyzed by LC-MS/MS and the distribution of zolpidem and ITMs in the hair was plotted. The day of zolpidem administration could then be estimated, which was consistent with the day of incident as alleged by the victim.

6. New psychoactive substances (NPS)

At the end of 2020, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) was monitoring around 830 NPS [182]. The number of NPS reported keeps rising with a total of 1049 NPS reported to UNODC as of August 25, 2021 [183] and over 1100 NPS in the publication of UNODC in November 2021 [184]. In this regard, an update from EMCDDA has addressed a high-level overview of the situation in Europe to support stakeholders with their ongoing preparedness planning and response activities to the rapid emergence of NPS within the context of the COVID-19 pandemic [185]. Over the last three years, forensic toxicologists and pathologists have worked together to determine the cause of sudden and unexpected death probably related to the use of NPS and numerous researches had been done; these researches with NPS concentrations in biological specimens were summarized in Table 2.

Table 1
Summary of DFC cases in the three-year period covered by this review paper.

Drug	Case history	Analytical findings	Ref.
Tiletamine & zolazepam	A victim lost consciousness and was sexually assaulted after consuming a drink. She reported to the police approximately 16 h later.	Tiletamine, zolazepam, 3 metabolites of tiletamine and 2 metabolites of zolazepam were detected in urine by GC-QTOF-MS.	[176]
Scopolamine	A 51 y/o woman presented a diminished consciousness at home after drinking from a bottle her daughter had brought after attending a party.	Scopolamine was detected in serum [8.4 (1hr), <0.1 (48hr) ng/mL] by LC-MS/MS and urine [62.6 (1hr), 0.2 (30hr), 0.06 (48hr) μg/mL] by GC-MS.	[177]
Flunitrazepam, oxazepam & zolpidem	A 56 y/o female tourist was sexually assaulted by a group of five men after having had an alcoholic drink offered by one of them.	Flunitrazepam, oxazepam and zolpidem were found in hair at 55–67, 32–36 and 0.7–1.06 pg/mg by LC-MS/MS respectively.	[178]
3-methylmeth cathinone (3-MMC) & gamma-hydroxybutyrate (GHB)	A 31 y/o male showed severe impaired consciousness after administration of 3-MMC and GHB during a chemsex party.	3-MMC & GHB were found in blood at 0.177 & 131 μg/mL and in urine at 22 & 2000 μg/mL by LC-MS/MS respectively.	[179]
Bromazepam, lorazepam, mirtazapine & zolpidem	An 11 y/o girl was suspectedly sexually abused by a man several times within the course of a few weeks. The last time happened 4 months prior to hair sampling.	Traces (<0.01 ng/mg) of these drugs were found in the middle segment (3–9 cm) of a strand of hair.	[180]
Zolpidem & alprazolam	A female victim lost consciousness and was sexually assaulted by a suspect after drinking a glass of alcoholic beverage. The case was reported 4 months later.	Zolpidem and alprazolam were detected in hair at average 47 and 0.18 pg/hair strand by LC-MS/MS respectively.	[181]

6.1. Synthetic opioids

Approximately 439 seizures of new opioids were reported to the EU Early Warning System in 2019 [185] and accounted for 14% of the NPS associated fatalities cases reported to UNODC [184]. The number of synthetic opioids newly emerged and associated fatalities may not be as much as the others, but synthetic opioids are still of particular concern of public health [185]. Out-breaks of fentanyl derivatives starting from around 2016 had led to a series of reported intoxication/fatalities [185–192], but a decrease in new fentanyl derivatives was noted for the first time since 2019 [185] when there was a growth in the emergence of new synthetic opioids other than new fentanyls. In 2020, there were 10 new non-controlled synthetic opioids detected for the first time, of which only one was a fentanyl [193]. An increase of reported synthetic opioid overdose deaths was also observed in the US [194]. Isotonitazene and brorphine are two of the newly emerged synthetic opioids

Table 2
Reported NPS concentration in biological specimens between March 2019 and March 2022.

Name of NPS [Reference] Case Information	Analytical methods (Bold) Specimen (conc. in ng/mL or ng/g unless specified)	Other drugs (ng/mL or ng/g unless specified) in blood unless specified
SYNTHETIC OPIOIDS		
Brorphine [203] 61 y/o female, fatal	**LC-MS/MS** cardiac blood (2.0)	ethanol (27 mg/dL), 4-ANPP, gabapentin (6.8 μg/mL), chlorpromazine (82), fentanyl (0.32)
Brorphine [202]	**LC-TOF-MS, LC-MS/MS**	
1. 53 y/o male, fatal, suspected overdose; history of heroin abuse	1. Femoral blood (10), urine (23)	1. Isotonitazene, flualprazolam (50), 4-ANPP, caffeine, cotinine, quinine, codeine (6.6), morphine (66), 6-MAM (1.5), citalopram/escitalopram (76), fentanyl (3.4), norfentanyl (0.36)
2. 60 y/o male, fatal	2. Femoral blood (0.9), urine (0.4)	2. 4-ANPP, caffeine, methadone (160), EDDP (45), morphine (42), bupropion (18), hydroxybupropion (380), duloxetine (520), lamotrigine (6.8 mcg/mL), gabapentin (15 mcg/mL), fentanyl (14), norfentanyl (11), flualprazolam
3. 45 y/o male, fatal. suspected overdose; MOD – accident; COD –toxic effects of multiple drugs	3. Femoral blood (1.0), urine (1.9)	3. Flualprazolam (2.5), 4-ANPP, caffeine, cotinine, tramadol (33), THC (0.62), fentanyl (5.0)
4. 42 y/o male, fatal, suspected overdose; MOD – accident; COD – combined drug toxicity	4. Peripheral blood (1.1), urine (3.3)	4. Flualprazolam, 4-ANPP, caffeine, cotinine, naloxone, diphenhydramine (620), fentanyl (36), norfentanyl (1.4), morphine (110), 6-MAM (7.3)
5. 60 y/o male, fatal, suspected overdose; MOD – accident; COD – combined drug toxicity	5. Peripheral blood (8.1), urine (21)	5. Flualprazolam, cotinine, sertraline (26), desmethylsertraline (110), verapamil (42), diphenhydramine (960), fentanyl (3.1), morphine (79), 6-MAM (2.5)
6. 47 y/o male, fatal, suspected overdose; sudden death; counterfeit pills tested positive for brorphine	6. Femoral blood (2.5)	6. 4-ANPP, naloxone, oxycodone (22), sildenafil (35), *N*-desmethylsildenafil (10), fentanyl (16), norfentanyl (1.1)
7. 39 y/o male, fatal suspected overdose; MOD – accident; COD – combined drug toxicity	7. Peripheral blood (6.7), urine (7.3)	7. Flualprazolam, 4-ANPP (+), caffeine (+), cotinine (+), nicotine (+), alprazolam (14 ng/mL), tramadol (70), gabapentin (10 mcg/mL), diphenhydramine (1200), fentanyl (45 ng/mL), norfentanyl (2.1), codeine (6.5), morphine (290), hydromorphone (4.7)
8. 37 y/o female, fatal, suspected overdose; MOD – accident; COD – combined drug toxicity	8. Peripheral blood (0.7)	8. Flualprazolam, ethanol (138 mg/dL), 4-ANPP (+), cotinine (+), naloxone (+), THC-COOH (85), THC (18), diphenhydramine (110), fentanyl (22)
9. 48 y/o male, fatal, suspected overdose; puncture marks at autopsy; COD – intoxication from brorphine/drugs	9. AM blood (0.6), iliac blood (0.1), urine (0.2)	9. Flualprazolam (5.4), 4-ANPP (+), caffeine (+), naloxone (+), morphine (8.0 ng/mL), diphenhydramine (190), fentanyl (4.7), norfentanyl (1.6), acetyl fentanyl (1.2), clonazolam
10. 47 y/o female, fatal, suspected "heroin" overdose; COD – toxic effects of multiple drugs including brorphine	10. Femoral blood (6.7), urine (2.1)	10. Flualprazolam (13), 4-ANPP (+), cotinine (+), naloxone (+), codeine (7.0 ng/mL), morphine (85), 6-MAM (12), xylazine (170), amphetamine (55), MA (580), fentanyl (190), norfentanyl (5.4), acetyl fentanyl (0.15)
11. 30 y/o female, fatal, suspected overdose; death at hospital; COVID-19 negative	11. AM blood (0.3), urine (1.4)	11. Caffeine (+), naloxone (+), midazolam (20), amphetamine (110), MA (1900), MDA (9.8 ng/mL), MDMA (75), fentanyl (0.37), norfentanyl (0.97)
12. 57 y/o male, fatal, suspected overdose; MOD – accident; COD – combined drug toxicity	12. Peripheral blood (0.5)	12. Flualprazolam, isotonitazene, 4-ANPP (+), cotinine (+), naloxone (+), tramadol (48), diphenhydramine (950), fentanyl (130), norfentanyl (20), acetyl fentanyl (0.10), morphine (21)
13. 54 y/o female, fatal, suspected overdose; pulmonary and cerebral edema	13. Iliac blood (0.1)	13. Flualprazolam, ethanol (19 mg/dL), codeine (21), morphine (290), 6-MAM (34), lamotrigine (0.60 mcg/mL), topiramate (9400 ng/mL), cyclobenzaprine (38), amphetamine (140), MA (730), fentanyl (17)
14. Male, fatal, suspected overdose; MOD – accident; COD – combined drug toxicity	14. Peripheral blood (0.7), urine (negative)	14. Flualprazolam, ethanol (100 mg/dL), 4-ANPP (+), caffeine (+), cotinine (+), naloxone (+), nicotine (+), nordiazepam (130), chlordiazepoxide (66), lorazepam (9.4 ng/mL), THC (0.70), diphenhydramine (53), fentanyl (32)
15. 51 y/o male, fatal, suspected overdose; MOD – accident; COD – combined drug toxicity	15. Peripheral blood (1.1), urine (0.4)	15. Flualprazolam, ethanol (60 mg/dL), 4-ANPP (+), caffeine (+), cotinine (+), naloxone (+), nicotine (+), cocaine (71), BZE (1600), diphenhydramine (98), fentanyl (9.3), norfentanyl (5.6), morphine (19)
16. 49 y/o female, fatal, suspected overdose; COD – combined drug toxicity including brorphine	16. Peripheral blood (3.8), urine (1.8)	16. Flualprazolam, 4-ANPP (+), caffeine (+), naloxone (+), diphenhydramine (260), fentanyl (21), norfentanyl (12), acetyl fentanyl (2.0), morphine (70)
17. 29 y/o male, fatal, suspected overdose; Illicit drugs found at scene; history of drug use; COD – adverse effects of drugs	17. Peripheral blood (1.1), urine (0.8)	17. Flualprazolam (3.6), 4-ANPP (+), caffeine (+), cotinine (+), naloxone (+), nicotine (+), quinine (+), acetaminophen (16 mcg/mL), 7-amino clonazepam (5.2), tramadol (70), diphenhydramine (490), amphetamine (10), MA (42), fentanyl (37), norfentanyl (1.3)
18. 61 y/o male, fatal, suspected overdose; COD – multiple drug intoxication	18. Peripheral blood (0.4), urine (0.2)	18. Ethanol (57 mg/dL), 4-ANPP (+), cotinine (+), naloxone (+), nicotine (+), alprazolam (65), BZE (330 ng/mL), morphine (33), 6-MAM (2.3), gabapentin (9.9 mcg/mL), fentanyl (21), norfentanyl (1.9)
Butonitazene [248]	**LLE - > LC-QQQ-MS**	

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Table 2 (*continued*)

Name of NPS [Reference] Case Information	Analytical methods (Bold) Specimen (conc. in ng/mL or ng/g unless specified)	Other drugs (ng/mL or ng/g unless specified) in blood unless specified
42 y/o male COD: metonitazene intoxication MOD: accident	femoral blood (3.2), serum (2.4), urine (10),	femoral blood: metonitazene (33), *N*-ethyl pentedrone, 5-aminometonitazene *N*-desethylnetonitazene Serum: metonitazene (18), 5-amino metonitazene, *N*-desethyl metonitazene, 4′- hydroxynitazene urine: 4-Hydroxynitazene (9.8), metonitazene (8.4), 5-amino metonitazene, *N*-desethyl metonitazene
Isotonitazene [200]	**UPLC-MS/MS**	
1. Male. Autopsy carried out ~72 h after death	femoral blood (i 2.28 ii 0.59, iii 0.74), cardiac blood (i 1.70, ii 1.13, iii 0.70), urine (i 1.88, ii 3.37, iii 0.19), humor vitreous (i 0.36, ii 0.12, iii 0.65), pericardiac fluid (i 6.7, ii 5.01, iii 2.66), lung (i 0.52, ii 17.9, iii 2.39), liver (i 0.04, ii 0.04, iii 0.02), kidney (i 1.61, ii 1.02, iii 0.67), heart (i 7.74, ii 2.17), brain (i 18.6, ii 2.72, iii 4.45), spleen (i 4.40, ii 3.44, iii 2.62), muscle (i 1.15, iii 1.0), hair (i 75, ii 182, iii 32(0–3 cm)/35(3–6 cm), cerebrospinal fluid(ii 0.88)	(i) diazepam (29), nordiazepam (71), oxazepam (4.8 ng/mL), mefenamic acid (under 5.0 ug/mL), domperidone (6.0) and acetaminophen (4.8 ug/mL)
2. Male. Autopsy carried out ~48 h after death		(ii) lorazepam (12), THC (56), THC-OH (1.8), THC-COOH (6.5) and CBN (2.9)
3. Male. Autopsy carried out ~96 h after death		(iii) ethanol (0.57 g/kg)
Isotonitazene [199]	**LLE - > LC-MS/MS**	
1. 27 y/o female, fatal	1. Blood (1.0)	1. Fentanyl (5.7), norfentanyl (2.4), 4-ANPP (1.4), etizolam (6.2), diazepam (120), nordiazepam (210), oxazepam (22), THC-COOH (64), THC (1.3), caffeine, cotinine, naloxone, acetaminophen, diphenhydramine
2. 27 y/o male, fatal	2. Cardiac blood (1.9), vitreous humor (0.1), urine (2.6)	2. Etizolam (15), caffeine
3. 66- y/o male, MOD: natural due to hypertensive and atherosclerotic cardiovascular disease, and chronic substance abuse as contributory.	3. Peripheral blood (1.5), urine (0.6)	3. Fentanyl (2.9), norfentanyl (1.0), etizolam (13), levetiracetam (14 mcg/mL), diphenhydramine (200), cotinine, quinine
4. 41 y/o male, fatal	4. Subclavian blood (0.9), urine (3.5)	4. Fentanyl (5.8), norfentanyl (0.61), acetyl fentanyl (0.69), 4-ANPP (1.6), morphine-free (12), cocaine (89), BZE (800), Naloxone, tramadol, O-desmethyltramadol, acetaminophen, cotinine, caffeine, levamisole, quinine
5. 53 y/o male, MOD: accident due to combined cocaine, 4-ANPP and U-47700 toxicity	5. Peripheral blood (2.7), urine (4.0)	5. 4-ANPP, BZE (370), U-47700 (0.34), phenacetin, levamisole, diphenhydramine
6. 44 y/o female, fatal	6. Subclavian blood (4.4), urine (0.6)	6. Etizolam (10), hydromorphone-free (3.3), tramadol (670), O-desmethyltramadol (310), amphetamine (65), MA (330), diazepam (150), nordiazepam (330), oxazepam (22), temazepam (20), 7-amino clonazepam (29), doxepin (290), cotinine, flualprazolam
7. 27 y/o male, MOD: accident due to etizolam toxicity	7. Peripheral blood (1.8), urine (2.8)	7. Etizolam (30), THC-COOH (7.7), THC (1.2), diphenhydramine (190), caffeine, cotinine, piperidylthiambutene, cotinine, caffeine, diphenhydramine, quinine
8. 56 y/o female, fatal	8. Iliac blood (0.4)	8. Flualprazolam (4.0), naloxone, hydroxyzine, etizolam, cotinine, caffeine, O-desmethylvenlafaxine, venlafaxine, norfluoxetine, fluoxetine, quetiapine
9. 41 y/o male, fatal	9. Subclavian blood (1.7)	9. Flualprazolam (6.4), caffeine, cotinine
10. 36 y/o male, fatal	10. Blood (0.4)	10. Flualprazolam (9.2), naloxone, alprazolam (10), amphetamine (6.2), MA (5.9), MDA (6.8), MDMA (74), caffeine, cotinine, hydroxybupropion, aripiprazole
11. 48 y/o male, fatal	11. Blood (1.8)	11. Flualprazolam (5.3), caffeine, cotinine
12. 24 y/o male, fatal	12. Cardiac blood (2.2)	12. Flualprazolam (10), THC (1.7), THC-COOH (6.8), caffeine, cotinine, diphenhydramine
13. 40 y/o male, fatal	13. Peripheral blood (2.3)	13. Etizolam (10), hydrocodone (5.3), sertraline (95), desmethylsertraline (170), diphenhydramine (97), hydroxyzine (64), flualprazolam, codeine, methadone, quinine, quetiapine
14. 42 y/o female, fatal	14. Peripheral blood (1.3)	14. Fentanyl (9.0), norfentanyl (12), acetyl fentanyl (0.11), 4-ANPP, morphine-free (72), naloxone, cocaine (290), BZE (2,400), diphenhydramine (340), cotinine, flualprazolam, phencyclidine, tramadol, zolpidem, quinine, quetiapine
15. 28 y/o female, fatal	15. Peripheral blood (3.1)	15. Flualprazolam (6.5), fentanyl (100), norfentanyl (3.9), 4-ANPP, mitragynine (150), morphine-free (62), 6-MAM—Free (3.0), naloxone, cocaine (96), BZE (1,400), sertraline (66), desmethylsertraline (350), diphenhydramine (86), caffeine, cotinine, piperidylthiambutene, benzylfuranylfentanyl, trazodone, mCPP, quinine
16. 35 y/o female, fatal	16. Femoral blood (1.3)	16. Flualprazolam (5.2), BZE (200), THC-OH (1.3), THC-COOH (6.9), THC (1.8), ethanol (76 mg/dL), caffeine, cotinine, cocaethylene

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Table 2 (*continued*)

Name of NPS [Reference] Case Information	Analytical methods (Bold) Specimen (conc. in ng/mL or ng/g unless specified)	Other drugs (ng/mL or ng/g unless specified) in blood unless specified
17. 60 y/o male, fatal	17. Peripheral blood (1.7)	17. Naloxone, cocaine (29), cocaethylene (23), BZE (470), ethanol (53 mg/dL), cotinine, flualprazolam, diphenhydramine, quinine
18. 46 y/o male, fatal	18. Femoral blood (9.5)	18. Fentanyl (3.6), norfentanyl (1.7), 4-ANPP (0.53), tramadol (22), naloxone, diphenhydramine (280), cotinine, flualprazolam, etizolam, tramadol, O-desmethyltramadol, quinine
Metonitazene [248]	**LLE - > LC-QQQ-MS**	
1. 42 y/o male, COD: metonitazene intoxication, MOD: accident	1. Femoral blood (33), serum (18), urine (8.4)	1. Femoral blood: butonitazene (3.2), *N*-ethyl pentedrone, 5-aminometonitazene *N*-desethylnetonitazene Serum: butonitazene (2.4), 5-amino metonitazene, *N*-desethyl metonitazene, 4′- hydroxynitazene urine: 4-hydroxynitazene (9.8), butonitazene (10), 5-amino metonitazene, *N*-desethyl metonitazene
2. 26 y/o male, fatal	2. IVC blood (1.6)	2. Fentanyl (12), norfentanyl (0.66), para-fluorofentanyl, 4-ANPP, 6-MAM (2.7), morphine (43), THC-COOH (20), diphenhydramine (460), caffeine, quinine, ethanol (16 mg/dl)
3. 52 y/o male, COD: metonitazene intoxication, MOD: accident	3. Femoral blood (3.1)	3. 5-Amino metonitazene, caffeine, ethanol (199 mg/dl)
4. 34 y/o male, COD: metonitazene intoxication, MOD: accident	4. Femoral blood (0.52)	4. MA (1400), amphetamine (96), alprazolam (5.0), 7-amino clonazepam (11), diphenhydramine (53), citalopram/escitalopram (420), ethanol (15 mg/dl)
5. 42 y/o male, fatal	5. Femoral blood (8.9), urine (8.0)	5. Femoral blood: fentanyl (17), norfentanyl (3.8), 4-ANPP, caffeine, quinine, 5-amino metonitazene, 4′- hydroxynitazene (1.2) urine: 4′- hydroxynitazene (8.0), *N*-desethyl metonitazene
6. 40 y/o male, fatal	6. Femoral blood (2.3), urine (4.6)	6. Femoral blood:4′- hydroxynitazene, 5-amino metonitazene, fentanyl (5.8), norfentanyl (1.2), acetylfentanyl (0.49), 4-ANPP, MA (29), caffeine, cotinine, venlafaxine (1300), O-desmethylvenlafaxine (390), quinine urine: 4′-hydroxynitazene (1.2), *N*-desethyl metonitazene
7. 44 y/o male, fatal	7. Femoral blood (1.5), urine (4.7)	7. Femoral blood: fentanyl (16), norfentanyl (1.2), 4-ANPP, MA (18), amphetamine (6.6), caffeine, cotinine, xylazine, quinine, ethanol (85 mg/dl), urine: 4′- hydroxynitazene (2.7)
8. 59 y/o male, fatal	8. Peripheral blood (2.4), urine (46)	8. Peripheral blood: 4′- hydroxynitazene (1.4), 5-amino metonitazene, *N*-desethyl metonitazene, fentanyl (33), norfentanyl (10), 4-ANPP, morphine (41), caffeine, cotinine, gabapentin (31 mcg/mL), fluoxetine (85), norfluoxetine (46), quinine urine: 4′- hydroxynitazene (5.3), *N*-desethyl metonitazene
9. 19 y/o male, COD: intoxication by the combined effects of metonitazene, tramadol, and etizolam, MOD: accident	9. Femoral blood (8.7, 7.6)	9. 4′- hydroxynitazene, 5-amino metonitazene, *N*-desethyl metonitazene, *N*-ethyl deschloroketamine, etizolam (6.3), alphahydroxyetizolam (2.3), tramadol (1100), Odesmethyltramadol (270), THC-OH (32), THC-COOH (200), THC (48), caffeine, naloxone
10. 43 y/o male, fatal	10. Femoral blood (6.9), urine (35)	10. Femoral blood: 4′- hydroxynitazene, 5-amino metonitazene, *N*-desethyl metonitazene, caffeine, cotinine urine: 4′- hydroxynitazene (3.5), 5-amino metonitazene, *N*-desethyl metonitazene
11. 47 y/o male, fatal	11. Femoral blood (4.0), vitreous humor (est 0.76)	11. Femoral blood: 5-amino metonitazene, *N*-desethyl metonitazene, fentanyl (41), norfentanyl (2.4), acetylfentanyl (25), 4-ANPP, caffeine, naloxone, diphenhydramine (72), quinine, ethanol (21 mg/dl) vitreous humor: 4′- hydroxynitazene, 5-amino metonitazene, *N*-desethyl metonitazene
12. 27 y/o male, fatal	12. Femoral blood (3.5), urine (19)	12. Femoral blood: 4′- hydroxynitazene, 5-amino metonitazene, *N*-desethyl metonitazene, 8-aminoclonazolam, pyrazolam (14), quinine, caffeine, ethanol (13 mg/dl) urine: 4′- hydroxynitazene (4.6), 5-amino metonitazene, *N*-desethyl metonitazene
13. 35 y/o male, COD: metonitazene intoxication, MOD: accident	13. Iliac blood (5.8), urine (4.0)	13. Iliac blood: 5-amino metonitazene, *N*-desethyl metonitazene, caffeine, cotinine, mirtazapine (37) urine: 4′-hydroxynitazene (28), 5-amino metonitazene, *N*-desethyl metonitazene, *N*,*N*-didesethyl metonitazene
14. 29 y/o female, fatal	14. Femoral blood (13), urine (10)	14. Femoral blood: 4′- hydroxynitazene, 5-amino metonitazene, *N*-desethyl metonitazene, MA (150), amphetamine (32), caffeine, cotinine, naloxone, nicotine urine: 4′- hydroxynitazene (2.1), 5-amino metonitazene, *N*-desethyl metonitazene
15. 47 y/o male, fatal	15. Femoral blood (5.0), heart blood (12), urine (2.1)	15. Femoral blood: 4′- hydroxynitazene, 5-amino metonitazene, *N*-desethyl metonitazene, flunitazene (femoral blood: 2.1, heart blood: 4.8, urine: 0.5), 8-

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Table 2 (*continued*)

Name of NPS [Reference] Case Information	Analytical methods (Bold) Specimen (conc. in ng/mL or ng/g unless specified)	Other drugs (ng/mL or ng/g unless specified) in blood unless specified
		aminoclonazolam, flualprazolam, fentanyl (3.0), norfentanyl (0.44), 4-ANPP, THC (0.52), THC-COOH (12), caffeine, cotinine, nicotine, bupropion (300), hydroxybupropion (290), 10-hydroxycarbazepine (9.5 mcg/mL), quetiapine (590), gabapentin (34 mcg/mL) urine: 4′- hydroxynitazene (5.0), 5-amino metonitazene, *N*-desethyl metonitazene
16. 32 y/o male, fatal	16. IVC blood (2.5), urine (2.0)	16. IVC blood: Flunitazene (0.6), fentanyl (6.6), 4-ANPP, caffeine, (0.083 mcg/mL), ziprasidone (10), diphenhydramine (110), quinine, ethanol (170 mg/dl) urine: flunitazene
17. 32 y/o male, fatal	17. Femoral blood (10), urine (28), vitreous humor (est 37)	17. Femoral blood: 5-amino metonitazene, *N*-desethyl metonitazene, fentanyl (3.2), norfentanyl (1.1), 4-ANPP, MA (3900), amphetamine (160), caffeine, cotinine, quinine urine: 4′- hydroxynitazene (10), 5-amino metonitazene, *N*,*N*-didesethyl metonitazene, *N*-desethyl metonitazene vitreous humor: *N*-desethyl metonitazene
18. 53 y/o female, fatal	18. Blood (14)	18. 4′- hydroxynitazene, etizolam (54), parafluorofentanyl (28), 4-ANPP, methadone (130), morphine, (36), caffeine, naloxone, mirtazapine (52)
FENTANILS		
Carfentanil [249]		
1. 31 y/o male, DUID@1007 h sampled@1158 h	1. Blood (8.2)	1. Fentanyl (<1.0), norfentanyl (<1.0), BZE (113), THC-COOH (<5.0)
2. 55 y/o male, DUID@1537 h, sampled@1710 h	2. Blood (1.5)	2. Fentanyl (<1.0), norfentanyl (<1.0), cocaine (324), BZE (359), EME (45)
Carfentanil [250]	**Protein PPT - > LC-MS/MS**	
1. 52 y/o Indian male, fatal	1. Peripheral blood (0.5)	1. Naproxen (2.6 μg/mL), desloratadine (0.001 μg/mL), olopatadine (0.0004 μg/mL), zolpidem (0.01 μg/mL)
2. 25 y/o Indian male, fatal	2. Iliac blood (0.9)	2. Desloratadine (0.004 μg/mL), zolpidem (0.09 μg/mL)
Cyclopropyl fentanyl [251]	**LLE - > GC-MS**	
25 y/o white male, COD: combined effects of alcohol, cocaine, oxycodone and cyclopropyl fentanyl; accident	heart blood (14)	oxycodone total (0.07 μg/mL), oxymorphone total (0.03 μg/mL), BZE (1.2 μg/mL), cocaethylene (0.07 μg/mL), and ethanol (0.036 g%, femoral)
Methoxyacetylfentanyl [252]	**LC-MS/MS**	
COD: Mixed drug intoxication		
1. 33 y/o	1. Femoral blood (52)	1. Pregabalin (9.2 g/g blood)
2. 38 y/o	2. Femoral blood (18)	2. Tramadol (0.06 μg/g), oxycodone (0.03 μg/g), norfludiazepam (1.0 μg/g)
3. 34 y/o	3. Femoral blood (21)	3. Norfludiazepam (0.06 μg/g), and ethanol (0.26 g/dL)
4. 41 y/o	4. AM blood (41)	4. Norfludiazepam (0.82 μg/g)
5. 29 y/o	5. Femoral blood (31)	5. Tramadol (0.44 μg/g), etizolam (NA), balimemazine (0.09 μg/g)
6. 35 y/o	6. Femoral blood (17)	6. Clonazepam (0.01 μg/g), alprazolam (0.007 μg/g), pregabalin (11 μg/g)
COD: acute heart complications		
7. 28 y/o,	7. Femoral blood (25)	7. None
COD: methoxyacetylfentanyl intoxication		
8. 28 y/o	8. Femoral blood (76)	8. None
9. 35 y/o	9. Femoral blood (37)	9. None
10. 30 y/o	10. Femoral blood (51)	10. None
11. 27 y/o	11. Femoral blood (140)	11. None
SYNTHETIC CANNABINOIDS		
ADB-FUBINACA [253]	**LC-MS/MS**	
23 y/o male, fatal	blood (0.08)	*N*-ethyl-hexedrone (285)
ADB-FUBINACA [254]		
17 y/o male, fatal, COD:cannabinoid toxicity	femoral blood (56)	–
5F-ADB [218]	**SPE - > LC-MS/MS**	
COD: acute 5F-ADB Toxicity		
1. 46 y/o white male	1. Peripheral blood (0.01)	1.5F-ADB metabolite 7 (11)
2. 46 y/o white male	2. Central blood (0.17)	2. 5F-ADB metabolite 7 (37)
3. 62 y/o black male	3. Peripheral blood (0.02)	3. 5F-ADB metabolite 7 (2.0)
4. 28 y/o black male	4. Peripheral blood (0.02)	4. 5F-ADB metabolite 7 (23)
5. 56 y/o white male	5. Central blood (2.2)	5. 5F-ADB metabolite 7 (166)
6. 48 y/o male	6. AM- blood (0.12)	6. AM-blood: 5F-ADB metabolite 7 (27)
7. 50 y/o white male	7. Peripheral blood (0.05) central blood (0.31)	7. Peripheral blood: 5F-ADB metabolite 7 (4.6), central blood C: 5F-ADB metabolite 7 (81)
8. 37 y/o white male	8. Peripheral blood (0.03) central blood (0.01)	8. Peripheral blood: 5F-ADB metabolite 7 (34), central blood: 5F-ADB metabolite 7 (64),
9. 48 y/o white male	9. Peripheral blood (0.02) central blood (0.04)	9. Peripheral blood: 5F-ADB metabolite 7 (11), central blood: 5F-ADB metabolite 7 (18)

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Table 2 (*continued*)

Name of NPS [Reference] Case Information	Analytical methods (Bold) Specimen (conc. in ng/mL or ng/g unless specified)	Other drugs (ng/mL or ng/g unless specified) in blood unless specified
10. 62 y/o black male	10. Peripheral blood (0.27) central blood (0.11)	10. Peripheral blood: 5F-ADB metabolite 7 (21), central blood: 5F-ADB metabolite 7 (41)
11. 56 y/o male	11. Peripheral blood (0.15) central blood (0.64)	11. Peripheral blood: 5F-ADB metabolite 7 (4.9), central blood: 5F-ADB metabolite 7 (2.4)
12. 20 y/o male	12. Peripheral blood (0.09) central blood (1.9)	12. Peripheral blood: 5F-ADB metabolite 7 (14), central blood: 5F-ADB metabolite 7 (39)
13. 34 y/o white male COD: 5F-ADB Toxicity	13. Peripheral blood (0.19) central blood (0.11)	13. Peripheral blood: 5F-ADB metabolite 7 (41), central blood: 5F-ADB metabolite 7 (31)
14. 50 y/o white male	14. Peripheral blood (0.77) central blood (0.76)	14. Peripheral blood: 5F-ADB metabolite 7 (12) central blood: 5F-ADB metabolite 7 (6.8)
15. 28 y/o male	15. Central blood (0.21)	15. Central blood: 5F-ADB metabolite 7 (34)
16. 34 y/o male	16. Central blood (0.20)	16. Central blood: 5F-ADB metabolite 7 (78)
17. 54 y/o male	17. Central blood (0.18)	17. Central blood: 5F-ADB metabolite 7 (128)
18. 46 y/o male	18. Central blood (0.07)	18. Central blood: 5F-ADB metabolite 7 (41)
19. 54 y/o male	19. Central blood (0.01)	19. Central blood: 5F-ADB metabolite 7 (<LOQ)
20. 38 y/o male	20. Central blood (0.02)	20. Central blood: 5F-ADB metabolite 7 (7)
21. 29 y/o male	21. Peripheral blood (0.07) central blood (0.10)	21. Peripheral blood: 5F-ADB metabolite 7 (15), central blood: 5F-ADB metabolite 7 (9.8)
22. 54 y/o male	22. AM-serum (0.12)	22. AM-serum: 5F-ADB metabolite 7 (42)
23. 62 y/o male	23. Central blood (0.08)	23. Central blood: 5F-ADB metabolite 7 (80)
24. 56 y/o male	24. Peripheral blood (0.03) central blood (0.23)	24. Peripheral blood: 5F-ADB metabolite 7 (12) central blood: 5F-ADB metabolite 7 (23)
25. 32 y/o male	25. Peripheral blood (0.01) central blood (0.70)	25. Peripheral blood: 5F-ADB metabolite 7 (15) central blood: 5F-ADB metabolite 7 (63)
26. 50 y/o male	26. Peripheral blood (0.05) central blood (0.28)	26. Peripheral blood: 5F-ADB metabolite 7 (14) central blood: 5F-ADB metabolite 7 (35)
27. 53 y/o male	27. Central blood (0.5)	27. Central blood: 5F-ADB metabolite 7 (46)
28. 27 y/o male	28. Central blood (0.08)	28. Central blood: 5F-ADB metabolite 7 (37)
29. 39 y/o black male, COD: multiple drug toxicity	29. Peripheral blood (0.37) central blood (0.37)	29. Peripheral blood: 5F-ADB metabolite 7 (2.4), central blood: 5F-ADB metabolite 7 (2.5), blood: ethanol and cocaine
30. 37 y/o white male, COD: acute poly-drug toxicity	30. Peripheral blood (0.08) central blood (0.15)	30. Peripheral blood: 5F-ADB metabolite 7 (15), central blood: 5F-ADB metabolite 7 (73), blood: cocaine and heroin
31. 44 y/o black male, COD: aspiration associated with 5F-ADB Toxicity, Part II: cardiomegaly, hypertensive	31. Peripheral blood (0.12) central blood (0.01)	31. Peripheral blood: 5F-ADB metabolite 7 (14), central blood: 5F-ADB metabolite 7 (21)
32. 49 y/o black male, COD: acute combined drug toxicity (5F-ADB, MMB-2201, and *N*-ethylpentylone)	32. Peripheral blood (0.56) central blood (0.66)	32. Peripheral blood: 5F-ADB metabolite 7 (10), central blood: 5F-ADB metabolite 7 (10), blood: MMB-2201, and *N*-ethylpentylone
33. 54 y/o male, COD: hemorrhagic stroke due to hypertensive cardiomegaly (990 g), contributing: ADBFUBINACA and 5F-ADB toxicity	33. Central blood (0.07)	33. Central blood: 5F-ADB metabolite 7 (8), ADB-FUBINACA
34. 52 y/o male, COD: ADB-FUBINACA and 5F-ADB toxicity; contributing: hypertensive and atherosclerotic heart disease	34. Central blood (0.03)	34. Central blood: 5F-ADB metabolite 7 (12)
35. 40 y/o male, COD: 5F-ADB and ABCHMINACA toxicity	35. Central blood (0.05)	35. Central blood: 5F-ADB metabolite 7 (38), ADB-FUBINACA
4F-MDMB-BINACA [255]	**SPE - > LC-QTOF-MS**	
1. 64 y/o male, COD: acute heart failure as severe pathological heart damage.	1. Femoral blood (0.48)	1. 5F-MDMB-PICA (0.14), mirtazapine (1900), tramadol (970), O-desmethyltramadol (100), piritramide (8.8), doxepine (60)
2. 50 y/o male, COD: polytrauma from the fall	2. Serum (6.6)	2. 5F-MDMB-PICA (7.0), THC (12), THC-OH (1.8), THC-COOH (21), amphetamine (460), nordiazepam (22), alcohol (0.25%)
3. 22 y/o male, property damage	3. Serum (60 min after incident), (0.25)	3. 5F-MDMB-PICA (0.26), THC (1.3), THC-OH (1.2), THC-COOH (28), amphetamine (17), alcohol (2.1%)
4. 19 y/o male, resisting enforcement officers	4. Serum (50 min after incident), (1.62)	4. 5F-MDMB-PICA (0.14), THC (0.6), THC-COOH (21), alprazolam (86), doxylamine, cetirizine, alcohol (2.1%)
5F-MDMB-PICA [256]	**LC-MS/MS**	
1. 47 y/o male, COD: diabetic ketoacidosis	1. Femoral blood (0.28)	1. 0.45 part per thousand of acetone, BHB at >1000 μg/g
2. 49 y/o male, COD: ketoacidosis possibly with a contribution from his drug use	2. Femoral blood (0.32)	2. 0.13 part per thousand of acetone, BHB at >1000 μg/g
5F-MDMB-PICA [255]	**SPE - > LC-QTOF-MS**	
1. 64 y/o male, COD: acute heart failure due to pathological heart damage.	1. Femoral blood (0.14)	1. 4F-MDMB-BINACA (0.48), mirtazapine (1900), tramadol (970), O-desmethyltramadol (100), piritramide (8.8), doxepine (60)
2. 33 y/o female, COD: drowning	2. Femoral blood (1.7)	2. 5F-Cumyl-P7AICA (<0.1), 5F-Cumyl-PICA (<0.1)
3. 50 y/o male, COD: fall from height	3. Serum (7.0)	3. 4F-MDMB-BINACA (6.6), THC (12), THC-OH (1.8), THC-COOH (21), amphetamine (460), nordiazepam (22), ethanol (0.25%)
4. 38 y/o male, Traffic accident	4. Serum (0.89)	4. 4F-MDMB-BINACA, THC (0.6), THC-OH (0.3), THC-COOH (6), ethanol (1.7%). Serum was taken 150 min after the incident.

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Table 2 (*continued*)

Name of NPS [Reference] Case Information	Analytical methods (Bold) Specimen (conc. in ng/mL or ng/g unless specified)	Other drugs (ng/mL or ng/g unless specified) in blood unless specified
5. 29 y/o male, DUID	5. Serum (16)	5. None. Serum was taken 50 min after incident.
6. 22 y/o male, DUID	6. Serum (2.4)	6. None. Serum was taken 85 min after incident.
7. 26 y/o male, DUID	7. Serum (0.54)	7. None. Serum was taken 75 min after incident.
8. 20 y/o male	8. Serum (0.11)	8. THC (5.6), THC-OH (9.8), THC-COOH (140), ethanol (2.0%) Serum was taken 90 min after incident.
9. 22 y/o male, property damage	9. Serum (0.26)	9. 4F-MDMB-BINACA (0.25), THC (1.3), THC-OH (1.2), THC-COOH (28), amphetamine (17), ethanol (2.1%). Serum was taken 60 min after incident.
10. 29 y/o male, resisting officers	10. Serum (2.5)	10. Ethanol (2.3%). Serum was taken 50 min after incident.
11. 19 y/o male, resisting officers	11. Serum (0.14)	11. 4F-MDMB-BINACA (1.62), THC (0.6), THC-COOH (21), alprazolam (86), doxylamine, Cetirizine, ethanol (2.1%). Serum was taken 50 min after incident).
5F-PB22 ethyl ester (metab olite of 5F-PB),2) [257]	**LLE - > LC-HRMS**	
22 y/o male	femoral blood (~0.4),	ethanol (212 mg/100 mL)
Designer Benzodiazepines		
Clonazolam [258]	**LLE - > LC-MS/MS**	–
26 y/o woman, non-fatal	blood (0.077, 0.015, 0.009) [4, 8, 12 h after ingestion]	
Diclazepam [75]	**UPLC-MS/MS**	
All DUID		
1. 25–29 y/o, moderately impaired	1. Blood (0.061)	1. Ethanol (0.053)
2. 35–39 y/o, considerably impaired	2. Blood (0.048)	2. -
3. 30–34 y/o, moderately impaired	3. Blood (0.045)	3. Ethanol (0.084)
4. 20–24 y/o, mildly impaired	4. Blood (0.035)	4. Lorazepam (0.014)
5. 25–29 y/o, considerably impaired	5. Blood (0.035)	5. THC (0.0011)
6. 20–24 y/o, moderately impaired	6. Blood (0.032)	6. -
7. 30–34 y/o, not impaired	7. Blood (0.032)	7. Lorazepam (0.012)
8. <20 y/o, moderately impaired	8. Blood (0.019)	8. -
9. 45–49 y/o, moderately impaired	9. Blood (0.016)	9. Lorazepam (0.063)
10. 30–34 y/o, considerably impaired	10. Blood (0.014)	10. -
11. 50–54 y/o, moderately impaired	11. Blood (0.011)	11. Nitrazepam (0.017)
12. 20–24 y/o, not impaired	12. Blood (0.0089)	12. -
13. 30–34 y/o, not impaired	13. Blood (0.0077)	13. -
14. 20–24 y/o, mildly impaired	14. Blood (0.0077)	14. THC (0.0007)
15. 35–39 y/o, not impaired	15. Blood (0.0054)	15. -
16. 20–24 y/o, mildly impaired	16. Blood (0.0051)	16. -
Diclazepam [259]	**QuEChERS and ITSP-SPE - >**	delorazepam (DE), lormetazepam (LT), lorazepam (LO), pyrazolam (PY),
27 y/o man.	**UPLC-MS/MS**	3-fluorophenmetrazine (3FP), 2-fluoroamphetamine (2FA)
COD: positional asphyxia promoted by poly-drug intoxication by arising from designer benzodiazepines and the presence of synthetic stimulants	femoral blood (1),	femoral blood: DE (100), LT (6), LO (22), PY (28), 3FP (10). 2FA (~89), methiopropamine (~2.2), amphetamine (~21)
	heart blood (1),	heart blood: DE (250), LT (4) LO (22), PY (28), 3FP (9)
	pericardial fluid (1)	pericardial fluid: DE (130), LT (1), LO (19), PY (11), 3FP (16)
	cerebrospinal fluid (4),	cerebrospinal fluid: DE (110), LT (5), LO (55), PY (~45), 3FP (13)
	urine (1),	urine: DE (570), LT (~810), LO (~820), PY (500), 3FP (120), 2-luorophenmetrazine (120), 2FA (≫500), methiopropamine (~16), amphetamine (75), diphenhydramine (~340)
	bile (27),	bile: DE, LT (130), LO (330), PR (340), 3FP (190)
	brain (23),	brain: DE (470), LT (20), LO (150), PY (100), 3FP (76)
	liver (34),	liver: DE (640), LT (65), LO (260), PY (92), 3FP (160)
	lung (21),	lung: DE (340). LT (15), LO (34), PY (98), 3FP (89)
	kidney (45),	kidney: DE (580), LT (28), LO (62), PY (160), 3FP (94)
	muscle (19),	muscle: DE (430), LT (45), LO (160), PY (88), 3FP (56)
	stomach content (16)	stomach content: DE (210), PY (380), 3FP (84)
Etizolam [260]	**LC-MS/MS, LC-QTOF-MS**	
1. 43 y/o male, fatal	1. AM blood (14), femoral blood (8.8)	1. AM blood: fentanyl (3.2), methadone (60), carbamazepine (1200), flualprazolam, acetaminophen (910) femoral blood: fentanyl (15), methadone (280), carbamazepine, flualprazolam, acetaminophen, diphenhydramine (traces), naloxone (276)
2. 26 y/o male, fatal	2. AM blood (34), femoral blood (180)	2. AM blood: fentanyl (7.6), THC (2.6), THC-COOH (57), THC-OH, valproic acid (20 mg/L), bisoprolol femoral blood: fentanyl (>800), diphenhydramine (150), flual-prazolam, naloxone (traces), THC (1.6, heart blood), THC-COOH, THC-OH, valproic acid (29 mg/L), bisoprolol
Etizolam [261]	**LC-MS/MS**	
1. 51 y/o male, COD: complications of chronic ethanolism, with a contributing factor of hypertension and a natural manner.	1. Cardiac blood (29), urine (2)	1. Cardiac blood: ethanol (0.02), EDDP, methadone, mirtazapine, norfentanyl, oxycodone, oxymorphine urine: EDDP, gabapentin, methadone, mirtazapine, norfentanyl oxycodone, oxymorphone, trazodone

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Table 2 (*continued*)

Name of NPS [Reference] Case Information	Analytical methods (Bold) Specimen (conc. in ng/mL or ng/g unless specified)	Other drugs (ng/mL or ng/g unless specified) in blood unless specified
2. 29 y/o male, COD: polydrug toxicity in an accidental manner	2. Cardiac blood (45), urine (13)	2. Cardiac blood: fentanyl (6), ethanol (0.23), α-hydroxyalprazolam, alprazolam (228), chlordiazepoxide, nordiazepam, norfentanyl urine: fentanyl, α-hydroxyalprazolam, alprazolam (238), doxylamine, nordiazepam, norfentanyl
3. 27 y/o woman, COD: polydrug toxicity of fentanyl, cocaine and ethanol with a contributing factor of MA presence in an accidental manner.	3. Peripheral blood (237), cardiac blood (813), vitreous humor (2921)	3. Peripheral blood: fentanyl (21), ethanol (0.12) alprazolam (282), BZE, cocaine (302), diphenhydramine, MA, nordiazepam, norfentanyl cardiac blood: fentanyl, acetaminophen, alprazolam (1830), BZE, cocaethylene, cocaine, diphenhydramine, doxylamine, MA Vitreous humor: fentanyl, acetaminophen, α-hydroxyalprazolam, alprazolam (5213), BZE, cocaethylene, cocaine, diphenhydramine, doxylamine, MA, nordiazepam, norfentanyl
4. 34 y/o male, COD: mixed drug intoxication in an accidental manner	4. Peripheral blood (9), cardiac blood (<5)	4. Peripheral blood: ethanol (0.23), 6-MAM (11), citalopram, codeine, diphenhydramine, morphine (185), desalkylflurazepam, nordiazepam cardiac blood: 6-MAM, citalopram, codeine, diphenhydramine, hydrocodone, morphine, desalkylflurazepam, nordiazepam
5. 36 y/o man, COD: acute polydrug toxicity in an accidental manner.	5. Peripheral blood (10), urine (8)	5. Peripheral blood: fentanyl (31), alprazolam (27), amphetamine, EDDP, methadone, MA (1212), norfentanyl urine: 7-aminoclonazepam, α-hydroxyalprazolam, alprazolam, flubromazolam
6. 30 y/o man, COD: acute heroin toxicity in an accidental manner	6. Peripheral blood (25), urine (13)	6. Peripheral blood: 6-MAM, alprazolam, codeine (17), THC-COOH, THC-OH, THC, diphenhydramine, morphine (219) urine: 6-MAM, codeine, THC-COOH, diphenhydramine, morphine
7. 28 y/o man, COD: acute mixed drug toxicity in an accidental manner.	7. Peripheral blood (15), cardiac blood (15), urine (20)	7. Peripheral blood: fentanyl, 7-aminoclonazepam, acetaminophen, α-hydroxyalprazolam, alprazolam (179), chlorpheniramine, diazepam, doxepin, MA, nordiazepam cardiac blood: fentanyl, 7-aminoclonazepam, α-hydroxyalprazolam, alprazolam (235), amphetamine, chlorpheniramine, diazepam, doxepin, MA, nordiazepam, promethazine, temazepam urine: fentanyl, 7-aminoclonazepam, acetaminophen, α-hydroxyalprazolam, alprazolam amphetamine, BZE, chlorpheniramine, diazepam, doxepin, hydrocodone, MA, nordiazepam, norfentanyl promethazine, temazepam
8. 30 y/o man, COD: combined toxicity of fentanyl, cocaine and MA in an accidental manner with hypertrophic heart disease as a main contributor.	8. Peripheral blood (6), urine (<5)	8. Peripheral blood: fentanyl (5), alprazolam, amphetamine, BZE, cocaethylene, cocaine (43), THC-COOH, THC, MA (246), norfentanyl urine: fentanyl, α-hydroxyalprazolam, alprazolam, amphetamine, BZE, cocaethylene, cocaine, THC-COOH, MA, nor-fentanyl
9. 61 y/o man, COD: combined toxicity of fentanyl and morphine with contributing factors of atherosclerotic heart disease and hepatic cirrhosis due to hepatitis C in an accidental manner.	9. Cardiac blood (22), urine (26), vitreous humor (<5)	9. Cardiac blood: fentanyl (13), THC-COOH, gabapentin, morphine, norfentanyl urine: fentanyl, THC-COOH, gabapentin, morphine, norfentanyl vitreous humor: fentanyl, morphine, norfentanyl
10. 30 y/o man, COD: acute mixed drug intoxication of fentanyl, benzodiazepines and ethanol in an undetermined manner.	10. Peripheral blood (187), cardiac blood (214), urine (64), vitreous humor (33)	10. Peripheral blood: fentanyl (17), ethanol (0.02), alprazolam, amphetamine, delorazepam, flualprazolam, flubromazolam (619), lorazepam, MA, norfentanyl cardiac blood: fentanyl, amphetamine, delorazepam, flualprazolam, flubromazolam (878), lorazepam, MA, norfentanyl urine: fentanyl, 7-aminoclonazepam, alprazolam, amphetamine, delorazepam, flualprazolam, flubromazolam (552), lorazepam, MA, norfentanyl vitreous humor: fentanyl, ethanol (0.03), alprazolam, amphetamine, delorazepam, flualprazolam, flubromazolam, MA, norfentanyl
Etizolam [75]	**UPLC-MS/MS**	
1. 25–29 y/o, mildly impaired)	1. Blood (0.21)	1. -
2. <20 y/o, mildly impaired)	2. Blood (0.12)	2. Tramadol (0.071)
3. 40–44 y/o, DUID (obvious impaired)	3. Blood (0.11)	3. -
Etizolam [76]	**Protein PPT - > LC-MS/MS**	
1. 37 y/o male, DUID	1. Blood (40) (elapsed time: 2 h)	1. Amphetamine (<50)
2. 20 y/o female, DUID	2. Blood (88) (elapsed time: 1.75)	2. THC (11)
3. 35 y/o male, DUID	3. Blood (330) (elapsed (time: 3.5)	3. MA (<50), amphetamine (<50)
Etizolam [225]	–	
1. 39 y/o female, fatal, COD: acute polydrug intoxication	1. Central blood (13.2)	1. Flualprazolam (48.0), fentanyl (14), THC (3.7), THC-OH (15.1), THC-COOH, acetaminophen, caffeine, norfentanyl
2. 26 y/o female, fatal, COD: acute fentanyl and MDMA intoxication	2. Central blood (2.6)	2. Acetaminophen (815), alprazolam (82.0), amphetamine (92.1), cyclobenzaprine (83.3), ephedrine (21.5), flualprazolam (11.1), fentanyl (7.5), MDMA (1110), MDA (88.0), MA (1070), 4–ANPP, caffeine, diazepam,

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Table 2 (*continued*)

Name of NPS [Reference] Case Information	Analytical methods (Bold) Specimen (conc. in ng/mL or ng/g unless specified)	Other drugs (ng/mL or ng/g unless specified) in blood unless specified
		nordiazepam, norfentanyl, *N*-desmethylcyclobenzaprine, temazepam-glucuronide
3. 24 y/o male, fatal, COD: acute fentanyl, flualprazolam, etizolam intoxication	3. Central blood (62.3)	3. BZE (165), flualprazolam (13.8), fentanyl (1.8), THC (2.4), THC-COOH (41.2), 4-ANPP, caffeine, norfentanyl
Etizolam [262]	**UPLC-HRMS**	
1. 39 y/o male. COD: mixed-drug toxicity	1. Unpreserved femoral blood (4)	1. Flubromazolam (70), ethanol (24 mg/100 mL), quetiapine (15), diazepam (68), nordiazepam (365), temazepam (6), oxazepam (22), morphine (free) (1076), morphine (total) (1149), 6-MAM, codeine (free) (289), mirtazapine (121), cocaine (184), BZE (525), cocaethylene (22)
2. 49 y/o male, COD: mixed-drug toxicity	2. Unpreserved femoral blood (1.5)	2. Flubromazolam (33), pregabaline (38.1 mg/L), diazepam (89), nordiazepam (575), temazepam (5), oxazepam (13), methadone (685), EDDP (100), mirtazapine (12), morphine (free) (44), morphine (total) (73), 6-MAM, codeine (free) (18)
Etizolam [199]	**LLE - > LC-MS/MS**	
1. 27 y/o female, fatal	1. Blood (6.2)	1. Fentanyl (5.7), norfentanyl (2.4), 4-ANPP (1.4), Isotonitazene (1.0), diazepam (120), nordiazepam (210), oxazepam (22), THC-COOH (64), THC (1.3), caffeine, cotinine, naloxone, acetaminophen, diphenhydramine
2. 27 y/o male, fatal	2. Cardiac blood (15)	2. Isotonitazene (1.9), caffeine
3. 66- y/o male, MOD: natural due to hypertensive and atherosclerotic cardiovascular disease; chronic substance abuse noted as contributory.	3. Peripheral blood (13)	3. Fentanyl (2.9), norfentanyl (1.0), Isotonitazene (1.5), levetiracetam (14 mcg/mL), diphenhydramine (200), cotinine, quinine
4. 44 y/o female, fatal	4. Peripheral blood (10)	4. Isotonitazene (4.4), hydromorphone-free (3.3), tramadol (670), O-desmethyltramadol (310), amphetamine (65), MA (330), diazepam (150), nordiazepam (330), oxazepam (22), temazepam (20), 7-amino clonazepam (29), doxepin (290), cotinine, flualprazolam
5. 27 y/o male, MOD: accident due to etizolam toxicity.	5. Peripheral blood (30)	5. Isotonitazene (1.8), THC-COOH (7.7), THC (1.2), diphenhydramine (190), caffeine, cotinine, piperidylthiambutene, cotinine, caffeine, diphenhydramine, quinine urine: piperidylthiambutene
6. 40 y/o male, fatal	6. Peripheral blood (10)	6. Isotonitazene (2.3), hydrocodone (5.3), sertraline (95), desmethylsertraline (170), diphenhydramine (97), hydroxyzine (64), flualprazolam, codeine, methadone, quinine, quetiapine
Flualprazolam [75]	**UPLC-MS/MS**	
35-39 y/o, DUID (considerably impaired)	blood (0.015)	tramadol (0.065)
Flualprazolam [263]	**LC-MS/MS**	Additional information
1. 20 y/o white female, DUID	1. Blood (12)	1. Incident: 0240 h, sample collect: 0348 h
2. 22 y/o white male, DUID	2. Blood (18)	2. Incident: 1917h, sample collect: 2051h
3. 27 y/o mixed race female, DUID	3. Blood (9.3)	3. Incident: 2346 h, sample collect: 0053 h
4. 22 y/o black female, DUID	4. Blood (16)	4. Incident: 2110 h, sample collect: 2240 h
5. 29 y/o white male, DUID	5. Blood (5.5)	5. Incident: 2120 h, sample collect: 2324 h-
6. 25 y/o white male, DUID	6. Blood (26)	6. Incident: 1145 h, sample collect: 1337 h
7. 18 y/o white male, DUID	7. Blood (12)	7. Incident: 2034h, sample collect: 2237 h
8. 35- y/o hispanic male, DUID	8. Blood (5.9)	8. Incident:1307 h, sample collect: 1532 h; oxandrolone
9. 24 y/o white male, DUID	9. Blood (10)	9. Incident: 1812h, sample collect: 1921h MA (32)
10. 18 y/o black male, DUID	10. Blood (7.0)	10. Incident: 1713 h, sample collect: 1821h
Flualprazolam [225]	**NA**	
1. 39 y/o female, fatal, COD: acute polydrug intoxication	1. Central blood (48.0)	1. Etizolam (13.2), fentanyl (14), THC (3.7), THC-OH (15.1), THC-COOH
2. 29 y/o male, fatal, COD: acute polydrug intoxication	2. Central blood (4.85), urine (4.07), brain (23.7), liver (37.1)	2. BZE (517), fentanyl (5.1), 4-ANPP, caffeine, EME, norfentanyl, sildenafil
3. 24 y/o male, fatal, COD: fentanyl intoxication	3. Central blood (4.82), urine (4.71), brain (13.5), liver (24.6)	3. Fentanyl (9.5), THC (5.0), THC-OH (2.3), THC-COOH (44.4), 4-ANPP, caffeine, norfentanyl
4. 18 y/o male, fatal, COD: gunshot wounds	4. Central blood (8.36), urine (10.1), brain (22.1), liver (77.2)	4. THC (8.4), THC-OH (2.6), THC-COOH (29.3), caffeine, levamisole
5. 21 y/o male, fatal, COD: acute polydrug intoxication	5. Central blood (46.3), urine (30.9), vitreous humor (12.0), brain (58.0), liver (156), gastric contents (0.47 mg)	5. BZE (58.1), ethanol (0.011% w/v), acetaldehyde, caffeine, paroxetine
6. 25 y/o male, fatal, COD: acute polydrug intoxication	6. Central blood (10.3), urine (5.43), brain (21.2), liver (49.8)	6. Ethanol (0.020% w/v), fentanyl (29.8), MDMA (700), MDA (78), morphine (20.3), oxycodone (46.0), 4-ANPP, acetaldehyde, caffeine norfentanyl, noroxycodone
7. 41 y/o male, fatal, COD: Combined effects of methadone, morphine, alprazolam, and flualprazolam	7. Central blood (47.7), urine (25.7), vitreous humor (10.4), brain (53.4), liver (146), gastric contents (0.50 mg)	7. Acetaminophen (940), alprazolam (64.7), EDDP (81.4), gabapentin (12100), morphine (18.5), methadone (1680), duloxetine, EMDP, quetiapine, norquetiapine, caffeine
8. 26 y/o female, fatal, COD: acute fentanyl and MDMA intoxication	8. Central blood (11.1), urine (5.3), brain (20.1), liver (41.9), gastric contents (0.03 mg)	8. Acetaminophen (815), alprazolam (82.0), amphetamine (92.1), cyclobenzaprine (83.3), ephedrine (21.5), etizolam (2.6), fentanyl (7.5), MDMA (1110), MDA (88.0), MA (1070), 4–ANPP, caffeine, diazepam, nordiazepam,

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Table 2 (*continued*)

Name of NPS [Reference] Case Information	Analytical methods (Bold) Specimen (conc. in ng/mL or ng/g unless specified)	Other drugs (ng/mL or ng/g unless specified) in blood unless specified
		norfentanyl, *N*-desmethylcyclobenzaprine, temazepam-glucuronide
9. 24 y/o male, fatal, COD: acute ecstasy, meth, cocaine, fentanyl, ketamine, and flualprazolam	9. Central blood (9.33), urine (36.12), brain (9.99), liver (42.2), gastric contents (0.02 mg)	9. BZE (1810), cocaine (48.1), fentanyl (20.3), ketamine (131), MDMA (79), MA (2280), THC-COOH (7.8), 4-ANPP, amphetamine, AEME, caffeine, EME, levamisole, norfentanyl, norketamine, sildenafil
10. 36 y/o male, fatal, COD: acute polydrug intoxication	10. Central blood (7.13), brain (8.44), liver (25.5)	10. BZE (542), cocaine (47.8), fentanyl (71.5), morphine (11.3), 4-ANPP, caffeine, EME, norbuprenorphine, norfentanyl
11. 22 y/o male, fatal, COD: acute polydrug intoxication	11. Central blood (8.47), brain (12.0), liver (43.4), gastric contents (0.05 mg)	11. Acetaminophen (970), fentanyl (23.5), caffeine, fluoxetine, norfentanyl, norfluoxetine
12. 22 y/o male, fatal, COD: acute polydrug intoxication	12. Central blood (15.6), brain (15.6), liver (44.3), gastric contents (0.07 mg)	12. Acetaminophen (1160), codeine (10.9), fentanyl (38.7), gabapentin (1120), hydroxyzine (31.6), methorphan (331), promethazine (98), THC (3.2), THC-OH (2.4), THC-COOH (46.5), 1-(4-chlorobenzhydryl)- piperazine, -4-ANPP, caffeine, cetirizine, dextrorphan/levorphanol, -mirtazapine, *N*–desmethylmirtazapine, norfentanyl, norquetiapine
13. 34 y/o male, fatal, COD: acute polydrug intoxication	13. Central blood (22.9), urine (16.8), brain (27.8), liver (103), gastric contents (2.5 mg)	13. Ethanol (0.033% w/v), gabapentin (6390), ketamine (402), oxycodone (1100), THC (6.8), THC-OH (1.7), THC-COOH (18.4), acetaldehyde, oxymorphone, duloxetine, norketamine, noroxycodone
14. 25 y/o male, fatal, COD: acute intoxication of cocaine, fentanyl, and cocaethylene	14. Central blood (9.13), urine (4.8), brain (11.2), liver (33.5), gastric contents (0.02 mg)	14. BZE (242), cocaethylene (44.1), cocaine (19.4), ethanol (0.160% w/v), fentanyl (7.9), acetaldehyde, EME, norfentanyl
15. 28 y/o male, fatal, COD: acute polydrug intoxication	15. Central blood (9.59), urine (6.41), brain (4.69), liver (13.6)	15. Alprazolam (11.9), fentanyl (17.1), norfentanyl, 4-ANPP
16. 19 y/o female, fatal, COD: acute polydrug intoxication	16. Brain (12.1), liver (17.8)	16. Fentanyl (14.2), THC (9.5), THC-OH (8.6), THC-COOH (163), norfentanyl, caffeine
17. 36 y/o male, fatal, COD: acute polydrug intoxication	17. Brain (3.99), liver (14.9)	17. Cannabidiol (10.9), fentanyl (7.7), morphine (23.8), 6-MAM, Naloxone, caffeine
18. 24 y/o male, fatal, COD: acute fentanyl, flualprazolam, etizolam intoxication	18. Central blood (13.8), urine (5.74), brain (16.8), liver (56.6), gastric contents (0.04 mg)	18. BZE (165), etizolam (62.3), fentanyl (1.8), THC (2.4), THC-COOH (41.2), 4-ANPP, caffeine, norfentanyl
19. 62 y/o male, fatal, COD: acute fentanyl intoxication	19. Central blood (4.24), brain (4.36), liver (15.0)	19. Acetaminophen (980), alprazolam (20.0), BZE (242), THC (1.6), THC-COOH (11.6), doxylamine (94.3), fentanyl (16.8), hydrocodone (49.9), caffeine, Fluoxetine, THC-OH, norfentanyl, norfluoxetine, norhydrocodone
20. 27 y/o male, fatal, COD: cardiomegaly	20. Central blood (5.00), brain (23.0), liver (20.7)	20. -
21. 20 y/o male, fatal, COD: acute fentanyl intoxication	21. Central blood (4.43), brain (18.9), liver (22.9), gastric contents (0.2 mg)	21. Fentanyl (8.0), norfentanyl
22. 30 y/o male, fatal, COD: acute fentanyl, alprazolam, flualprazolam, and hydrocodone intoxication	22. Central blood (12.9), urine (13.7), vitreous humor (4.03), brain (32.8), liver (66.7)	22. Acetaminophen (746), alprazolam (112), fentanyl (14.0), hydrocodone (55.6), 4-ANPP, norfentanyl, norhydrocodone
23. 25 y/o male, fatal, COD: acute fentanyl intoxication	23. Central blood (28.3), urine (35.8), vitreous humor (6.98), brain (69.3), liver (69.3), gastric contents (0.02 mg)	23. Acetaminophen (3130), baclofen (742), BZE (3420), cocaine (203), fentanyl (24.4), gabapentin (31100), MA (104), 4-ANPP, 7-aminoclonazepam, amphetamine, EME, norfentanyl
24. 30 y/o male, fatal, COD: acute poly drug intoxication: hydrocodone, norhydrocodone, dihydrocodeine, flualprazolam, pheniramine, acetaminophen, and ethanol	24. Central blood (27), urine (9.84), vitreous humor (5.11), brain (51.5), liver (44.1), gastric contents (0.33 mg)	24. Acetaminophen (32900), ethanol (0.142% w/v), hydrocodone (608), acetaldehyde, albuterol, caffeine, dihydrocodeine, norhydrocodone, Pheniramine
Flualprazolam [224	**LC-QTOF-MS**	
1. 16 y/o male, non-fatal intoxication	1. Urine (19.4), blood (14.6)	1. -
2. 16 y/o female, non-fatal intoxication	2. Urine (3.0)	2. -
Flualprazolam [226]	**LLE - > LC-MS/MS**	
1.Male, fatal	1.Blood (2.1)	1.Fentanyl, morphine, BZE and THC
2.53 y/o male, fatal, suspected drug overdose	2.Blood (2.1)	2.Fentanyl, cocaine, methadone and gabapentin
3.32 y/o male, suspected overdose; found breathing strangely; history of drug use, alcohol use and depression; known to buy Xanax® from friends	3.Blood (2.2)	3.Mitragynine, cyclobenzaprine, hydroxyzine, THC, gabapentin and BZE
4.22 y/o male, fatal, history of alcohol and drug use	4.Blood (3.2)	4.Ethanol (0.173%) and desmethylloperamide
5.36 y/o male, fatal	5.Blood (3.6)	5.MA and amphetamine
6.29 y/o male, fatal, suspected overdose; history of drug use; found lying in yard of drug house	6.Blood (4.1)	6.Isotonitazene, MA and amphetamine
7.49 y/o male, fatal	7.Blood (4.5)	7.BZE
8.35 y/o female, MOD: accident; suspected overdose; history of drug/alcohol use; autopsy found cerebral edema and mild pulmonary edema	8.Blood (5.2)	8.Isotonitazene (presumptive), ethanol (0.076%), BZE and THC
9.38 y/o male, fatal, suspected overdose	9.Blood (6.2)	9.Isotonitazene, fentanyl, MA, amphetamine and hydroxyzine
10.19 y/o male, MOD: accident; COD: blunt impacts of torso and extremities	10.Blood (6.4)	10.THC, BZE, ethanol (0.029%) and COHb 5%
11.23 y/o female, fatal, mixed drug intoxication	11.Blood (9.9)	11.Fentanyl, 4-ANPP, BZE, THC, MA and amphetamine

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Table 2 (*continued*)

Name of NPS [Reference] Case Information	Analytical methods (Bold) Specimen (conc. in ng/mL or ng/g unless specified)	Other drugs (ng/mL or ng/g unless specified) in blood unless specified
12.23 y/o male, fatal, found apneic and pulseless at home; drug use previous evening; drug of choice Xanax®	12.Blood (15)	12.Fentanyl and 4-ANPP
13.33 y/o male, died by gunshot	13.Blood (22)	13.Alprazolam
14.21 y/o male, fatal, suspected overdose	14.Blood (29)	14.Fentanyl, THC, MA and amphetamine
15.36 y/o male, fatal, history of hypertension; known heavy drinker and recreational Xanax® user; history of depression and suicidal intentions	15.Blood (63)	15.Methadone
16.40 y/o male, fatal,	16.Blood (95)	16.Methadone, diphenhydramine, cocaine and ethanol (0.012%)
17.21 y/o male, fatal	17.Blood (96)	17.Isotonitazene, diazepam and THC
18.42 y/o male, MOD: natural	18.Blood (110)	18.Fentanyl, 4-ANPP, diazepam, cocaethylene, BZE, THC and ethanol (0.131%)
19.33 y/o male, MOD: homicide; stab wound to heart	19.Blood (520)	19.Fentanyl, alprazolam, cocaine, methadone, 6-MAM and morphine
20.Female	20.Blood (620)	20.Fentanyl, 4-ANPP, loperamide and ethanol (0.011%)
21.31 y/o male, DUID	21.Blood (4.4)	21.THC-COOH and levetiracetam
22.22 y/o male, DUID	22.Blood (8.3)	22.Ethanol (0.095%)
23.31 y/o male, DUID	23.Blood (8.9)	23.Alprazolam, etizolam, delorazepam, norbuprenorphine and THC
24.51 y/o male, DUID, Percocet® use	24.Blood (10)	24.Oxycodone and Oxymorphone
25.47 y/o male, DUID, impairment from methadone and opiates	25.Blood (11)	25.Carfentanil, fentanyl, cocaine and methadone
26.24 y/o male, DUID	26.Blood (13)	26.No other reported findings
27.30 y/o male, DUID	27.Blood (39)	27.Mitragynine and BZE
28.20 y/o male, DUID	28.Blood (46)	28.Ethanol (0.029%)
29.40 y/o male, DUID	29.Blood (46)	29.Bupropion
30.20 y/o male, DUID, suspected alcohol, cannabis and MA use	30.Blood (65)	30.THC
31.26 y/o male, DUID, suspected Xanax® use	31.Blood (68)	31.Methadone and etizolam
***Flualprazolam* [199]**	**LLE - > LC-MS/MS**	
1. 56 y/o female, fatal	1. Iliac blood (4.0)	1. Isotonitazene (0.4), naloxone, hydroxyzine, etizolam, cotinine, caffeine, O-desmethylvenlafaxine, venlafaxine, norfluoxetine, fluoxetine, quetiapine
2. 41 y/o male, fatal	2. Subclavian blood (6.4)	2. Isotonitazene (1.7), caffeine, cotinine
3. 36 y/o male, fatal	3. Blood (9.2)	3. Isotonitazene (0.4), naloxone, alprazolam (10), amphetamine (6.2), MA (5.9), MDA (6.8), MDMA (74), caffeine, cotinine, hydroxybupropion, aripiprazole
4. 48 y/o male, fatal	4. Blood (5.3)	4. Isotonitazene (1.8), caffeine, cotinine
5. 24 y/o male, fatal	5. Cardiac blood (10)	5. Isotonitazene (2.2), THC (1.7), THC-COOH (6.8), caffeine, cotinine, diphenhydramine
6. 28 y/o female, fatal	6. Peripheral blood (6.5)	6. Isotonitazene (3.1), fentanyl (100), norfentanyl (3.9), 4-ANPP, mitragynine (150), morphine-free (62), 6-MAM—-Free (3.0), naloxone, cocaine (96), BZE (1,400), sertraline (66), desmethylsertraline (350), diphenhydramine (86), caffeine, cotinine, piperidylthiambutene, benzylfur-anylfentanyl, trazodone, mCPP, quinine
7. 35 y/o female, fatal	7. Femoral blood (5.2)	7. Isotonitazene (1.3), BZE (200), THC-OH (1.3), THC-COOH (6.9), THC (1.8), ethanol (76 mg/dL), caffeine, cotinine, cocaethylene
***Flubromazolam* [76]**	**Protein PPT - > LC-MS/MS** # sampled taken after	
1. 17 y/o male, DUID	1. Blood #1.5 h (17)	1. THC (6.1)
2. 18 y/o male, DUID	2. Blood # 1.25 h (18)	2. THC (2.2)
3. 21 y/o male, DUID	3. Blood # 1 h (19)	3. BZE (348), THC (1.5)
4. 17 y/o female, DUID	4. Blood # 2.75 h (14)	4. Ethanol (0.014g%)
5. 19 y/o female, DUID	5. Blood # 2.5 h (21)	5. Cocaine (<50), BZE (749)
6. 19 y/o male, DUID	6. Blood # 1.75 h (7)	6. Oxycodone (<25), clonazepam (17), 7-aminoclonazepam (26), THC (27)
7. 22 y/o female, DUID	7. Blood # 1.5 h (12)	7. THC (2.9)
8. 35 y/o female, DUID	8. Blood # 1.5 h (31)	8. THC (4.1)
9. 21 y/o male, DUID	9. Blood # 2.25 (8.2)	9. BZE (356), THC (1.0)
***Flubromazolam* [75]** 20-24 y/o, DUID (not impaired)	**UPLC-MS/MS** blood (0.0070)	amphetamine (0.040)
***Flubromazolam* [262]** 32 y/o male, COD: chronic effects of alcohol	**UPLC-HRMS** Unpreserved femoral blood (8)	ethanol (104mg/100 mL), amphetamine (12), propranolol (4), THC (11.2), buprenorphine (0.8)
***Flubromazolam* [262]**	**UPLC-HRMS**	
1. 39 y/o male, COD: mixed-drug toxicity	1. Unpreserved femoral blood (70)	1. Etizolam (4), ethanol (24 mg/100 mL), quetiapine (15), diazepam (68), nordiazepam (365), temazepam (6), oxazepam (22), morphine (free) (1076), morphine (total) (1149), 6-MAM, codeine (free) (289), mirtazapine (121), cocaine (184), BZE (525), cocaethylene (22)
2. 46 y/o male, COD: heroin toxicity	2. Unpreserved femoral blood (16)	

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Table 2 (*continued*)

Name of NPS [Reference] Case Information	Analytical methods (Bold) Specimen (conc. in ng/mL or ng/g unless specified)	Other drugs (ng/mL or ng/g unless specified) in blood unless specified
		2. Levetiracetam (6.7), phenytoin (4.3), morphine (free) (341), morphine (total) (431), 6-MAM, codeine (free) (28).
3. 49 y/o male, COD: mixed-drug toxicity	3. Unpreserved femoral blood (33)	3. Etizolam (1.5), pregabaline (38.1), diazepam (89), nordiazepam (575), temazepam (5), oxazepam (13), methadone (685), EDDP (100), mirtazapine (12), morphine (free) (44), morphine (total) (73), 6-MAM, co-deine (free) (18)
4. 32 y/o male, COD: chronic effects of alcohol	4. Unpreserved femoral blood (8)	4. Ethanol (104mg/100 mL), amphetamine (12), propranolol (4), THC (11.2), buprenorphine (0.8)
Flubromazolam [261]	**LC-MS/MS**	peripheral blood; fentanyl (17), ethanol (0.02), alprazolam, amphetamine, delorazepam, flualprazolam, etizolam (187), lorazepam, MA, norfentanyl
30 y/o man, COD: acute mixed drug intoxication of fentanyl, benzodiazepines and ethanol in an undetermined manner.	peripheral blood (619), cardiac blood (878), urine (552)	cardiac blood; fentanyl, amphetamine, delorazepam, flualprazolam, etizolam (214), lorazepam, MA, norfentanyl urine; fentanyl, 7-aminoclonazepam, alprazolam, amphetamine, delorazepam, flualprazolam, etizolam (64), lorazepam, MA, norfentanyl
Phenazepam [75]	**UPLC-MS/MS**	
1. 20–24 y/o (mild impaired)	1. Blood (0.26)	1. THC (0.0007)
2. 20–24 y/o, DUID (mild impaired)	2. Blood (0.17)	2. -
3. <20 y/o, DUID (not impaired)	3. Blood (0.12)	3. -
4. 40–44 y/o, DUID (mildly impaired)	4. Blood (0.012)	4. -
Pyrazolam [259]	**QuEChERS and ITSP-SPE - > UPLC-MS/MS**	Refer to Diclazepam
27 y/o man, COD: positional asphyxia promoted by poly-drug intoxication by arising from designer benzodiazepines and the presence of synthetic stimulants	femoral blood (28), heart blood (28), pericardial fluid (11), cerebrospinal fluid (~45), urine (500), bile (340), brain (100), liver (92), lung (98), kidney (160), muscle (88), stomach content (380)	
Pyrazolam [248]	**LLE - > LC-QQQ-MS**	4′- hydroxynitazene, 5-amino metonitazene, *N*-desethyl metonitazene, 8-aminoclonazolam, metonitazene (3.5), quinine, caffeine, ethanol (13 mg/dl)
27 y/o male, fatal	femoral blood (14)	
SYNTHETIC CATHINONES		
Alpha-pyrrolidinoisohexanophenone (α- PiHP) 264]	**LLE - > LC-MS/MS**	urine: 4-chloromethcathinone (1477), *N*-ethylhexedrone (1351), BZE (30)
18 y/o man, died due to acute circulatory and respiratory failure; specimen was collected as tissue homogenate* or bloody fluid**	blood (69), urine (2072), bile (341), liver* (7), liver** (33), kidney* (78), kidney** (194), stomach *(478), intestine* (115), intestine** (185), lung* (213), lung** (448), brain* (230)	bile: 4-CMC (41), *N*-ethylhexedrone (34) lung: *N*-ethylhexedrone (3) brain: *N*-ethylhexedrone (5)
Alpha-Pyrrolidinohexanophenone (α-PHP) [265]	**Protein PPT > LC-MS/MS**	
	#time period between observed failure symptoms/incident and blood sampling:	
1. 35 y/o male, offence: aggravated theft	1. Plasma (47) # 3.0 h	1. α-PVT (124), α-PVP (1.4), α-PHpP (1.2), Bupropion (1.6), methadone (110), diazepam (180), nordazepam (90), oxazepam (4.8), temazepam (11), lorazepam (95)
2. 31 y/o male, offence: violation of the narcotics law (NPS)	2. Plasma (1.0) # 0.0/4 months	2. MDPHP (5.93), α-PVT (128), tramadol (170), pregabalin (4700)
3. 26 y/o female, sexual assault (victim)	3. Plasma (18) # 0.0/2.8 h	3. α-PVT (231), MDPHP (1.10), levomethadone (210), lorazepam (74), diazepam (10), nordazepam (42), clonazepam (6.0), pregabalin (10000), THC (2.1), THC-OH (1.1), THC-COOH (67)
4. 44 y/o male, offence: violation of the narcotics law,	4. Plasma (4.6) #0.0 h/5 months	4. α-PVT (0.90), MDPHP (1.44), buprenorphine (0.29), norbuprenorphine (traces)
5. 33 y/o male, offence: obstructing police officers, theft, assault, attempted bodily harm	5. Plasma (16) #0.9 h	5. α-PVT (9.86), levomethadone (160), diazepam (180), nordazepam (320), oxazepam (16), Temazepam (7.4), lorazepam (36), THC (1.6), THC-OH (0.58), THC-COOH (48)
6. 28 y/o male, offence: grievous bodily harm	6. Plasma (128) # 0.0/4.8 h	6. α-PVT (19.6), MDPHP (34.8), morphine (3.2), codeine (3.2), levomethadone (28), diazepam (270), nordazepam (660), oxazepam (39), Temazepam (16), lorazepam (100)
7. 48 y/o male, offence: aggravated theft	7. Plasma (8.4) # 2.4 h	7. α-PVT (23.9), α-PHpP (2.3), levomethadone (96), lorazepam (55), nordazepam (10), THC-COOH (4.3)
8. 32 y/o male, offence: robbery	8. Plasma (10) # 0.0/5.3 h	8. MDPHP (35.1), α-PVT (31.4), morphine (6.0), codeine (6.9), Racemic methadone (640), diazepam (730), nordazepam (1000), oxazepam (57), Temazepam (49)
9. 37 y/o male, offence: robbery	9. Plasma (4.8) # 2.0 h	9. α-PVT (34.2), 6-MAM (10), morphine (61), codeine (6.5)
Alpha-pyrrolidinoheptiophenone (α-PHpP, PV8 or α-PEP) [265]	**Protein PPT - > LC-MS/MS**	
	#time period between observed failure symptoms/incident and blood sampling:	
1. 40 y/o male, offence: DUID	1. Plasma (2.0) # 1.6 h	1. α-PVT (7.55), 2-fluoroamphetmaine (33), mitragynine (110), tilidine (2.2), nortilidine (1.0), THC (7.4), THC-OH (1.9), THC-COOH (42)

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Table 2 (*continued*)

Name of NPS [Reference] Case Information	Analytical methods (Bold) Specimen (conc. in ng/mL or ng/g unless specified)	Other drugs (ng/mL or ng/g unless specified) in blood unless specified
2. 39 y/o male, offence: grievous bodily harm	2. Plasma (6.5) # 3.1 h	2. α-PVT (8.18), levomethadone (120), diazepam (540), nordiazepam (210), oxazepam (6.1), temazepam (18), clonazepam (4.0), pregabalin (4400), THC (0.61), THC-COOH (6.7), ethanol (0.10% in whole
3. 48 y/o male, offence: violation of the narcotics law	3. Plasma (15) #0.0 h/4–13 months	3. α-PVT (8.95), methoxyphenidine (2.8), diazepam (440), nordiazepam (270), oxazepam (14), temazepam (22), clonazepam (20), bromazepam (8.7), THC (0.27), THC-COOH (13), ethanol (0.38% in whole blood)
4. 48 y/o male, offence: aggravated theft	4. Plasma (2.3) # 2.4 h	4. α-PHP (8.4), α-PVT (23.9), levomethadone (96), lorazepam (55), nordazepam (10), THC-COOH (4.3)
5. 33 y/o male, offence: grievous bodily harm	5. Plasma (2.9) # 0.0/7–9 h	5. α-PVT (35.4), codeine (30), morphine (2.0), lorazepam (10), THC (0.29), THC-COOH (7.8), etoricoxib (450)
6. 40 y/o female, offence: theft, obstructing police officers, bodily harm	6. Plasma (1.5) # 0.0/52 h	6. α-PVT (118), levomethadone (31), lorazepam (23), diazepam (5.6), nordazepam (26), pregabalin (1500)
7. 30 y/o male. DUID (cyclist)	7. Plasma (1.5) # 2.4 h	7. MDPV (9.0), α-PVT (170), 3-MMC (8.1), buprenorphine (0.66), norbuprenorphine (0.40), ethanol 0.40‰ (in whole blood),
Alpha-Pyrrolidinopentiothiophenone (α-PVT) [265]	**Protein PPT - > LC-MS/MS** #time period between observed failure symptoms/incident and blood sampling:	
1. 44 y/o male, offence: violation of the narcotics law	1. Plasma (0.90) # 0.0 h/5 months	1. α-PHP (4.6), MDPHP (1.44), buprenorphine (0.29), norbuprenorphine (traces)
2. 40 y/o male, offence: attempted robbery	2. Plasma (3.86) # 3.5 h	2. MDPHP (2.10), levomethadone (280), pregabalin (11000), ethanol (0.23% in whole blood)
3. 38- y/o male, offence: obstructing police officers	3. Plasma (4.64) # 5.3 h	3. BZE (2.0), EME (0.78), Bupropion (35), morphine (22), fentanyl (2.4), norfentanyl (1.8), diazepam (1100), nordiazepam (870), oxazepam (70), temazepam (81), lorazepam (170), alprazolam (37), pregabalin (17000), gabapentin (58), THC (3.0), THC-OH (1.2), THC-COOH (24), ethanol (0.52% in whole blood)
4. 34 y/o male, offence: violation of the narcotics law	4. Plasma (5.04) # 3.5 h	4. Cocaine (17), BZE (140), EME (11), morphine (2.1), codeine (0.85), gabapentin (120), pregabalin (760)
5. 35 y/o male, offence: bodily harm	5. Plasma (6.82) # 2.5 h	5. Ethanol (1.7% in whole blood)
6. 40 y/o male, offence: DUID	6. Plasma (7.55) # 1.6 h	6. α-PHpP (2.0), 2-fluoroamphetmaine (33), mitragynine (110), tilidine (2.2), nortilidine (1.0), THC (7.4), THC-OH (1.9), THC-COOH (42)
7. 39 y/o male, offence: grievous bodily harm	7. Plasma (8.18) # 3.1 h	7. α-PHpP (6.5), levomethadone (120), diazepam (540), nordiazepam (210), oxazepam (6.1), temazepam (18), clonazepam (4.0), pregabalin (4400), THC (0.61), THC-COOH (6.7), ethanol (0.10% in whole)
8. 31 y/o male, offence: dangerous interference with rail traffic, robbery	8. Plasma (8.25) # 2.6 h	8. BZE (110), EME (8.3), morphine (33), codeine (6.2)
9. 48- y/o male, offence: violation of the narcotics law	9. Plasma (8.95) #0.0 h/4–13 months	9. α-PHpP (15), methoxyphenidine (2.8), diazepam (440), nordiazepam (270), oxazepam (14), temazepam (22), clonazepam (20), bromazepam (8.7), THC (0.27), THC-COOH (13), ethanol (0.38%)
10. 35 y/o male, offence: grievous bodily harm, coercion	10. Plasma (9.18) #0.0 h/3.0 h	10. MDPHP (18.8), buprenorphine (1.3), norbuprenorphine (0.69), diazepam (780), nordiazepam (230), oxazepam (11), temazepam (23), clonazepam (39), zolpidem (4.1), zopiclone (0.24)
11. 33 y/o male, offence: obstructing police officers, theft, assault, attempted bodily harm	11. Plasma (9.86) #0.9 h	11. α-PHP (16), levomethadone (160), diazepam (180), nordazepam (320), oxazepam (16), temazepam (7.4), lorazepam (36), THC (1.6), THC-OH (0.58), THC-COOH (48)
12. 30 y/o male. DUID	12. Plasma (11.3) # 2.0 h	12. Buprenorphine (1.5), norbuprenorphine (1.5), pregabalin (3000), ethanol 1.74‰ (in whole blood)
13. 29 y/o male, offence: bodily harm, obstructing police officers. violation of narcotic law	13. Plasma (13.2) #2.3 h	13. Amphetamine (190), lorazepam (51), diazepam (19), nordazepam (17), temazepam (2.8), THC-COOH (1.3)
14. 54 y/o male, offence: violation of the narcotics law	14. Plasma (16.4) # 0.0/4 months-2 years	14. MDPHP (41.9), α-PHP (0.9), fentanyl (13), norfentanyl (9.1)
15. 28 y/o male, offence: robbery	15. Plasma (18.6) #5.2 h	15. Diazepam (490), nordazepam (130), temazepam (8.4), oxazepam (3.7), lorazepam (19), ethanol 0.11‰ (in whole blood)
16. 28 y/o male, offence: grievous bodily harm	16. Plasma (19.6) # 0.0/4.8 h	16. α-PHP (128), MDPHP (34.8), morphine (3.2), codeine (3.2), levomethadone (28), diazepam (270), nordazepam (660), oxazepam (39), temazepam (16), lorazepam (100)
17. 39 y/o male, offence: bodily harm, obstructing police officers	17. Plasma (20.7) #1.7 h	17. Methoxphenidine (4.8), levomethadone (110), lorazepam (97), diazepam (10), nordazepam (54), pregabalin (5500), THC (0.8), THC-OH (0.26), THC-COOH (13), ethanol 1.15‰ (in whole blood)
18. 48 y/o male, offence: aggravated theft	18. Plasma (23.9) # 2.4 h	18. α-PHP (8.4), α-PHpP (2.3), levomethadone (96), lorazepam (55), nordazepam (10), THC-COOH (4.3)
19. 39 y/o male, offence: obstructing police officers	19. Plasma (24.7) #0.2 h	19. Nordoxepine (5.0), ethanol 1.42‰ (in whole blood)
20. 32 y/o male, offence: robbery	20. Plasma (31.4) # 0.0/5.3 h	

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Table 2 (*continued*)

Name of NPS [Reference] Case Information	Analytical methods (Bold) Specimen (conc. in ng/mL or ng/g unless specified)	Other drugs (ng/mL or ng/g unless specified) in blood unless specified
		20. MDPHP (35.1), α-PHP (10), morphine (6.0), codeine (6.9), Racemic methadone (640), diazepam (730), nordazepam (1000), oxazepam (57), temazepam (49)
21. 37 y/o male, offence: robbery	21. Plasma (34.2) # 2.0 h	21. α-PHP (4.8), 6-MAM (10), morphine (61), codeine (6.5)
22. 33 y/o male, offence: grievous bodily harm	22. Plasma (35.4) # 0.0/7–9 h	22. α-PHpP (2.9), codeine (30), morphine (2.0), lorazepam (10), THC (0.29), THC-COOH (7.8), Etoricoxib (450)
23. 45 y/o male, offence: aggravated theft	23. Plasma (35.7) # 4.7 h	23. Buprenorphine (0.03), norbuprenorphine (0.04)
24. 31 y/o male, Offence: Theft	24. Plasma (38.2) # 3.0 h	24. Levomethadone (62), diazepam (600), nordazepam (490), oxazepam (410), temazepam (100), lorazepam (71), clonazepam (2.9), Trimipramine (5.1), THC (0.26), THC-COOH (6.0)
25. 37 y/o male, Bodily harm (victim)	25. Plasma (38.2) # 19 h	25. Morphine (3.7), codeine (1.3), buprenorphine (0.5), norbuprenorphine (0.6), ethanol 0.58‰ (in whole blood)
26. 41 y/o male, Offence: Bodily harm, obstructing police officers	26. Plasma (38.9) # 3.8 h	26. Levomethadone (43), diazepam (1000), nordazepam (120), temazepam (34), lorazepam (19), Amitriptyline (5.6), Nortriptyline (11)
27. 34 y/o male, Offence: Violation of the narcotics law	27. Plasma (40.6) # 2.3 h	27. Cocaine (0.46), BZE (110), EME (8.8), morphine (62), codeine (10), levomethadone (490), diazepam (110), nordazepam (130), oxazepam (15), temazepam (13), alprazolam (7.7), lorazepam (4.9), Sertraline (31), mirtazapine (13), pregabalin (5200), THC (0.87), THC-OH (0.46), THC-COOH (10)
28. 33 y/o male, Sexual assault (victim)	28. Plasma (41.7) # 1.1 h	28. Buprenorphine (1.4), norbuprenorphine (1.6), tramadol (1400), diazepam (110), nordazepam (81), oxazepam (2000), temazepam (13), Lormetazepam (35), lorazepam (30), Venlafaxine (280), (Es-),citalopram (23), THC-COOH (10)
29. 34 y/o male, DUID	29. Plasma (48.5) # 1.6 h	29. ritalinic acid (25), lorazepam (25), pregabalin (2100), ethanol 0.98‰ (in whole blood)
30. 49 y/o male, offence: bodily harm	30. Plasma (57.6) # 4.2 h	30. Morphine (15), codeine (6.6)
31. 38 y/o male, offence: violation of the narcotics law, trespass	31. Plasma (72.3) #4.9 h	31. MDPHP (29.3) clonazepam (12)
32. 41 y/o male. DUID	32. Plasma (83.8) # 2.2 h	32. 6-MAM (0.13), morphine (14), codeine (4.0), buprenorphine (0.76), norbuprenorphine (0.31), lorazepam (61), diazepam (3.4), nordazepam (10), pregabalin (2100)
33. 34 y/o male. DUID (caused accident)	33. Plasma (99.4) # 1.6 h	33. 4-MEC (3.1), levomethadone (150), lorazepam (14), mirtazapine (7.6), ethanol 0.70‰ (in whole blood)
34. 31 y/o male, offence: theft	34. Plasma (99.8) #3.9 h	34. Morphine (46), codeine (10), levomethadone (250), diazepam (510), nordazepam (290), oxazepam (13), temazepam (30), clonazepam (8.4), Carbamazepine (150)
35. 33 y/o female, grievous bodily harm (victim)	35. Plasma (103) #3.8 h	35. Diazepam (160), nordazepam (140), oxazepam (6.8), temazepam (12), lorazepam (32), Trazodone (28), THC (0.16), THC-COOH (6.3),
36. 40 y/o female, offence: theft, obstructing police officers, bodily harm	36. Plasma (118) # 0.0/52 h	36. α-PHpP (1.5), levomethadone (31), lorazepam (23), diazepam (5.6), nordazepam (26), pregabalin (1500)
37. 35 y/o male, offence: aggravated theft	37. Plasma (124) # 3.0 h	37. α-PHP (47), α-PVP (1.4), α-PHpP (1.2), Bupropion (1.6), methadone (110), diazepam (180), nordazepam (90), oxazepam (4.8), temazepam (11), lorazepam (95)
38. 31 y/o male, offence: violation of the narcotics law (NPS)	38. Plasma (128) # 0.0/4 months	38. MDPHP (5.93), α-PHP (1.0), tramadol (170), pregabalin (4700)
39. 30 y/o male, DUID (cyclist)	39. Plasma (170) # 2.4 h	39. MDPV (9.0), α-PHpP (1.5), 3-MMC (8.1), buprenorphine (0.66), norbuprenorphine (0.40), ethanol 0.40‰ (in whole blood)
40. 34 y/o male, offence: grievous bodily harm	40. Plasma (191) # 3.2 h	40. Midazolam (36), Ketamine (91) (probably application within medical treatment after the incident)
41. 26 y/o female, sexual assault (victim)	41. Plasma (# 0.0/2.8 h 231)	41. α-PHP (18), MDPHP (1.10), levomethadone (210), lorazepam (74), diazepam (10), nordazepam (42), clonazepam (6.0), pregabalin (10000), THC (2.1), THC-OH (1.1), THC-COOH (67)
42. 34 y/o male, DUID	42. Plasma (254) #0.6 h	42. Levomethadone (170), diazepam (110), nordazepam (42), oxazepam (3.1), temazepam (7.5), lorazepam (25)
43. 34 y/o male, offence: threat, coercion, bodily harm, obstructing police officers	43. Plasma (286) # 4.3 h	43. Tramadol (490), nordazepam (20), diazepam (trace amount)
44. 31 y/o female, offence: violation of the narcotics law (NPS)	44. Plasma (306) # 0.0/4 months	44. MDPHP (10.5), BZE (0.89), morphine (5.5), codeine (2.3), Racemic methadone (350), fentanyl (4.2), norfentanyl (0.67), tramadol (37), O-demethyltramadol (4.4), lorazepam (3.5), pregabalin (23000)
N-ethyl-hexedrone [253] 23 y/o male, fatal	**GC-MS (HFBA-derivatized)** blood (285)	ADB-FUBINACA (0.08)
N-Ethylhexedrone [266] 21 y/o man, fatal	**LLE - > LC-MS/MS** femoral blood (145)	amphetamine (12), THC-COOH (<5),

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Table 2 (*continued*)

Name of NPS [Reference] Case Information	Analytical methods (Bold) Specimen (conc. in ng/mL or ng/g unless specified)	Other drugs (ng/mL or ng/g unless specified) in blood unless specified
MDPHP [265]	**Protein PPT - > LC-MS/MS** #time period between observed failure symptoms/incident and blood sampling:	
1. 44 y/o male, offence: violation of the narcotics law	1. Plasma (1.44) # 0.0 h/5months	1. α-PHP (4.6), α-PVT (0.90), buprenorphine (0.29), norbuprenorphine (traces)
2. 40 y/o male, offence: attempted robbery	2. Plasma (2.10) # 3.5 h	2. α-PVT (3.86), levomethadone (280), pregabalin (11000), ethanol (0.23% in whole blood)
3. 35 y/o male, offence: grievous bodily harm, coercion	3. Plasma (18.8) #0.0 h/3.0 h	3. α-PVT (9.18), buprenorphine (1.3), norbuprenorphine (0.69), diazepam (780), nordiazepam (230), oxazepam (11), temazepam (23), clonazepam (39), zolpidem (4.1), zopiclone (0.24)
4. 54 y/o mal, offence: violation of the narcotics law	4. Plasma (41.9) # 0.0/4 months-2 years	4. α-PVT (16.4), α-PHP (0.9), fentanyl (13), norfentanyl (9.1)
5. 28 y/o male, offence: grievous bodily harm	5. Plasma (34.8) # 0.0/4.8 h	5. α-PHP (128), α-PVT (19.6, morphine (3.2), codeine (3.2), levomethadone (28), diazepam (270), nordazepam (660), oxazepam (39), temazepam (16), lorazepam (100)
6. 32 y/o male. offence: robbery	6. Plasma (35.1) # 0.0/5.3 h	6. α-PVT (31.4), α-PHP (10), morphine (6.0), codeine (6.9), Racemic methadone (640), diazepam (730), nordazepam (1000), oxazepam (57), temazepam (49)
7. 38 y/o male. offence: violation of the narcotics law, trespass	7. Plasma (29.3) #4.9 h	7. α-PVT (72.3) clonazepam (12)
8. 31 y/o male. offence: violation of the narcotics law (NPS)	8. Plasma (5.93) # 0.0 h/4 months	8. α-PVT (128), α-PHP (1.0), tramadol (170), pregabalin (4700)
9. 26 y/o female. Sexual assault (victim)	9. Plasma (1.10) # 0.0/2.8 h	9. α-PHP (18), α-PVT (231), levomethadone (210), lorazepam (74), diazepam (10), nordazepam (42), clonazepam (6.0), pregabalin (10000), THC (2.1), THC-OH (1.1), THC-COOH (67)
10. 31 y/o female. offence: violation of the narcotics law (NPS)	10. Plasma (10.5) # 0.0/4 months	10. α-PVT (306), BZE (0.89), morphine (5.5), Codeine (2.3), racemic methadone (350), fentanyl (4.2), norfentanyl (0.67), tramadol (37), O-Demethyltramadol (4.4), lorazepam (3.5), pregabalin (23000)
4-Methylethcathinone (4-MEC) [267] 35 y/o man autopsy finding: no natural disease or injury which could have caused, contributed to, or accelerated death was identified	**LLE - > GC-MS/MS** peripheral blood (14.6) cardiac blood (43.4) right vitreous humor (2.9) left vitreous humor (4.4) bile (43.5) gastric content (28.2) urine (619)	central blood: hydroxyzine (160),
4-Methylethcathinone (4-MEC) [233] 40 y/o male, chemsex COD and MOD: compatible with intoxication by drugs consumed in the hours immediately prior to the death	**LLE - > derivatized - >** GCMS peripheral blood (15.5) central blood (10.6) urine (20)	peripheral blood: GHB (150.8 μg/mL) central blood: GHB (115.4 μg/mL) urine: GHB (5800 μg/mL)
4-Methylethcathinone (4-MEC) [265] 34 y/o male. DUID (caused accident) # 1.6 h	**Protein PPT - > LC-MS/MS** plasma (3.1)	α-PVT (99.4), levomethadone (150), lorazepam (14), mirtazapine (7.6), ethanol 0.70‰ (in whole blood)
3-methylmethatinone (3-MMC) [268] 19 y/o female, excluded any other causes of death, and recognized intoxicant poisoning as the COD	**LLE - > LC-PDA-MS** blood (800), vitreous humor (150), total stomach contents (5.5 mg)	–
3-methylmethatinone (3-MMC) [179] 31 y/o man, chemsex/slamex, non-fatal intoxication	**Protein PPT - > LC- MS/MS** blood (177) urine (22,000)	blood: GHB (131 mg/L) urine: GHB (2000 mg/L)
4-methylpentedrone [232] 57 y/o white male, chemsex COD: fatal intoxication mainly involving 4-MPD along with cocaine, sildenafil, bromazepam and nevirapine.	**SPE - > GC-MS/MS** peripheral blood (1285), cardiac blood (1128), left vitreous humor (734), right vitreous humor (875), bile (1187), urine (>10,000)	cocaine (66, femoral blood), BZE (2084, femoral blood), EME (262, femoral blood), nevirapine, sildenafil (<1), bromazepam (140)
Mephedrone [229] 56 y/o male, chemsex, fatal intoxication	**LC-MS/MS** central blood (1.0), peripheral blood (0.8), urine (2.0), bile (1.1)	–
AMPHETAMINE TYPE ***2-fluoroamphetmaine*** [265] 40 y/o male, offence: DUID	**Protein PPT - > LC- MS/MS** plasma (33)	α-PVT (7.55), α-PHpP (2.0), mitragynine (110), tilidine (2.2), nortilidine (1.0), THC (7.4), THC-OH (1.9), THC-COOH (42)
4-fluoroamphetamine [269] 29 y/o man	**LC-MS/MS and LC-HRMS** blood (184) # 17 h	

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Table 2 (*continued*)

Name of NPS [Reference] Case Information	Analytical methods (Bold) Specimen (conc. in ng/mL or ng/g unless specified)	Other drugs (ng/mL or ng/g unless specified) in blood unless specified
# sampling time after consumption	blood (4.1) #61 h urine (1635) #61 h hair (315 pg/mg) #103 h	
Threo-4-fluoromethylphenidate (4F-MPH) [270] 25 y/o white male, fatal	**LC-MS/MS, Immunoassay,GC-NPD-MS LC–Ion Trap-MS^n, GC-NPD-MS, LC–Ion Trap-MS^n**	
	femoral vein blood [0.017 (grey top #1), 0.019 (grey top #2), 0.012 (red top), 0.049 (purple top)] urine (detected)	femoral vein blood: MA, codeine, morphine, papaverine, diphenhydramine, 3-MeO-PCP urine: Cannabinoids, MA, amphetamine, morphine, 6-MAM, codeine, norcodeine, naproxen, diphenhydramine, 3-MeO-PCP
	gastric contents (273g), 0.795 mg total	gastric contents: MA, amphetamine, 6-MAM, codeine, acetylcodeine, naproxen, diphenhydramine
3-fluorophenmetrazine [259] 27- y/o man. COD: positional asphyxia promoted by poly-drug intoxication by arising from designer benzodiazepines and the presence of synthetic stimulants	**QuEChERS and ITSP-SPE - > UPLC-MS/MS** femoral blood (10), heart blood (9), pericardial fluid (16), cerebrospinal fluid (13), urine (120), bile (190), brain (76), liver (160), lung (89), kidney (94), muscle (56), stomach content (84)	Refer to Diclazepam
OTHERS i) ***2-fluoro-deschloroketamine (2F-DCK)*** ii) ***3-methoxyeticyclidine (3-MeO-PCP)*** iii) ***5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT)*** [271] 42 y/o Caucasian man, fatal	**LC-MS/MS,** peripheral blood [i) 1780, ii) 90, iii) 52] urine [i) 6106, ii) 6305, iii) 2190] bile [i) 12200, ii) 3500, iii) 1740] vitreous humor [i) 1500, ii) 66, iii) 155] hair [i) 4410, 4860, 5080, 4330 pg/mg, ii) 1610, 3600, 3410, 3610 pg/ml, iii) 1990, 3030, 3160, 3390 pg/ml]	peripheral blood: THC, THC-COOH, THC-OH, amphetamine, BZE, EME, levamisole urine: THC-COOH, amphetamine, cocaine, BZE, EME, levamisole, lorazepam bile: amphetamine, BZE, EME, lorazepam vitreous humor: cocaine, BZE, EME, levamisole Hair: THC, amphetamine, BZE, EME, levamisole, diphenidine, etizolam, flualprazolam, 4F-MDMB-BINACA, X-APB 3-FPM, cannabidiol, CBN, benzocaine, quetiapine, loxapine (and metabolites), acetaminophen, tramadol (and metabolites), clozapine diazepam (and metabolites),
3-methoxyphencyclidine (3-MeO-PCP) 272] mid-thirties male, fatal	**SPE - > UPLC-MS/MS** serum (est 123), femoral whole blood (est 152)	GHB (~10 mg/L), amphetamine (85),
Methoxphenidine (methoxydiphenidine, 2-MeO-diphenidine, MXP) [265] 39 y/o male. offence: bodily harm, obstructing police officers	**LLE - > HPLC-DAD** Plasma (4.8); time period between observed failure symptoms/incident and blood sampling:1.7 h	α-PVT (20.7), levomethadone (110), lorazepam (97), diazepam (10), nordazepam (54), pregabalin (5500), THC (0.8), THC-OH (0.26), THC-COOH (13), ethanol 1.15‰ (in whole blood)
Methoxphenidine (methoxydiphenidine, 2-MeO-diphenidine, MXP) [231] 55 y/o man, chemsex COD: stabbing homicide	**LC-MS/MS** femoral blood (606) urine (1066) hair (13 ng/mg of hair)	femoral blood: Lidocaine (traces) urine: 3-MMC (238), oxazepam (750), valsartan (traces), lidocaine (traces), Hair 3-MMC: <0.25 ng/mg of hair; diphenidine: <0.25 ng/mg of hair, cocaine, BZE, lidocaine, quetiapine, zopiclone
25B–NBOMe [254] 19 y/o Chinese male, fatal COD: 25B–NBOMe toxicity	– peripheral (femoral), blood (10)	

Note: years old (y/o); Cause of Death (COD); Manner of Death (MOD).

consecutively dominated the US NPS opioid market in 2019 and 2020 [195].

6.1.1. Isotonitazene

Isotonitazene, belonging to the benzimidazole group of synthetic opioids, was first synthesized in mid- 1950s, and has been available in the European drug market since at least April 2019 [185,196–198]. EMCDDA has published initial report [196], technical report [197] and risk assessment report [198] of this compound in April, June and November 2021, respectively. In a report of 18 fatal cases associated with isotonitazene, the average isotonitazene concentration in blood was found to be 2.2 ± 2.1 ng/mL (median 1.75 ng/mL, range 0.4–9.5 ng/mL), while that of the urine was 2.4 ± 1.4 ng/mL (median 2.7 ng/mL, range 0.6–4.0 ng/mL). It was also suggested that *N*-desethyl-isotonitazene and *N*-desethyl-O-desalkyl-isotonitazene are the most appropriate metabolite biomarkers in urine, while 5-amino-isotonitazene was identified in most blood samples [199]. Three fatal intoxication cases associated with isotonitazene in Switzerland were reported with isotonitazene concentration in femoral whole blood at 0.59–2.28 ng/mL and that in cardiac whole blood at 0.70–1.7 ng/mL. The quantification results in other specimens including urine, vitreous humor, pericardiac fluid, lungs, liver, kidney, heart, brain, spleen, muscle, cerebrospinal fluid and hair were also reported [200]. Details of findings were also included in Table 2.

6.1.2. Brorphine

Brorphine is another new synthetic opioid urging concern after isotonitazene. It is a μ-opioid receptor agonist first synthesized in 2018 and first report to UNODC Early Warning Advisory (EWA) in July 2019 [195, 201]. In a report of 20 authentic forensic cases with brorphine detected,

the average concentration of brorphine in blood was determined to be 2.5 ± 3.1 ng/mL (median: 1.1 ng/mL, range: 0.1–10 ng/mL), while that in urine was 4.6 ± 7.6 ng/mL (median: 1.6 ng/mL, range: 0.2–23 ng/mL) [202]. Brorphine concentration in a reported death of a 61 y/o female was found to be 2.0 ng/mL [203]. An *in vivo* and *in vitro* metabolism study of brorphine using urine samples from real forensic cases and pooled human liver microsomes (pHLM), respectively suggested three *in vivo* metabolites as biomarkers for the detection of brorphine consumption [204].

6.2. Synthetic cannabinoids

Synthetic cannabinoids were first appeared in the European drug market in around 2006 [185]. They are one of the predominant NPS seizures reported to the EU Early Warning System [185] and the second largest group of NPS reported to UNODC EWA up to November 2021 [184]. Synthetic cannabinoids could be adulterated to CBD, heroin, THC e-liquids or other illicit drugs [205–208]. The most identified synthetic cannabinoid reported in US in 2020 was MDMB-4en-PINACA [194]. Initial report [212], technical report [213], risk assessment [214] of MDMB-4en-PINACA were published by EMCDDA on November 2020, December 2020 and March 2021, respectively. Detections of more than one synthetic cannabinoid in toxicology caseworks were observed. For example, 4F-MDMB-BINACA was commonly found in conjunction with 5F-MDMB-PICA (n = 12, 41%), another emergent synthetic cannabinoid and close variant of 5F-MDMB-PINACA (5F-ADB). 4F-MDMB-BINACA was found in combination with APP-BINACA in four cases [215].

6.2.1. 4F-MDMB-BICA (4F-MDMB-BUTICA)

4F-MDMB-BICA is a synthetic cannabinoid which first appeared in Belgium in March 2020 and the World Health Organization has released a 4F-MDMB-BICA critical review report in September 2021 [216]. EMCDDA has released initial report [209], technical report [210] and risk assessment [211] of 4F-MDMB-BICA in November 2020, December 2020 and March 2021, respectively.

6.2.2. 5F-ADB (5F-MDMB-PINACA)

Quite a large number of 5-fluoro-ADB (5F-ADB) cases, including fatalities and impaired driving, were reported in these few years [217–221]. Yeter and Öztürk [219] have reported 70 fatal cases with only 5F-ADB detected. 5F-ADB and its methyl ester hydrolysis metabolite were detected in the blood at concentrations ranged from 0.10 to 1.55 ng/mL (mean: 0.40 ng/mL) and 0.15–23.4 ng/mL (mean: 2.69 ng/mL), respectively. 5F-ADB methyl ester metabolite was detected in 35 urine samples of the cases with concentrations ranged from 0.28 to 72.2 ng/mL (mean: 9.02 ng/mL). In an impaired driving case associated with 5F-ADB reported by McCain et al. [217], 5F-ADB metabolite 7 (Cayman Chemical) (Fig. 1) was detected in the blood at a level of 26.37 ng/mL while the parent drug 5F-ADB was not detected. In a report of 43 fatalities involving 5F-ADB, only 5F-ADB metabolite 7 instead of the parent drug was detected in some of the cases while the cause of death was acute 5F-ADB toxicity [218], indicating that 5F-ADB metabolite 7 is a biomarker for the detection of 5F-ADB consumption.

6.3. Designer benzodiazepines

As of February 28, 2021, the EMCDDA was monitoring 30 new benzodiazepines through the EU Early Warning System [222]. Flualprazolam together with etizolam and flubromazolam accounted for 64% of all the identified NPS in the toxicology cases reported to UNODC between 2019 and April 2020 [201]. Among 48% of postmortem cases reported to UNODC of which benzodiazepine-type NPS were identified, etizolam, flualprazolam, flubromazolam and phenazepam were assessed to have either contributed to or been the cause of death [201].

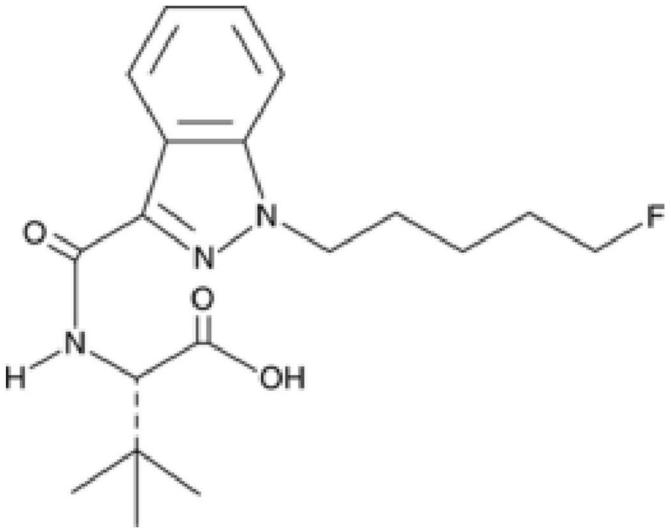

Fig. 1. 5-fluoro ADB metabolite 7.

6.3.1. Flualprazolam

Flualprazolam was the 19th most frequently reported drug by 2020 [184,194]. The World Health Organization has released a Critical Review Report of Flualprazolam [223]. An outbreak of flualprazolam among adolescents was also reported. [224]. In an investigation of flualprazolam distribution in 24 postmortem samples, the liver-to-central blood ratio, urine-to-central blood ratio, brain-to-central blood ratio and vitreous humor-to-central blood ratio for flualprazolam were found to be 0.88, 1.4, 3.1 and 0.47, respectively [225]. 197 forensic investigation cases, including postmortem cases and drug impaired driving cases, associated with flualprazolam were reported. The flualprazolam concentration in blood ranged from 2.0 to 620 ng/mL (mean: 20 ng/mL, standard deviation: 63 ng/mL) for postmortem cases (n = 167), while that of DUID cases ranged from 4.4 to 68 ng/mL (mean: 22 ng/mL, standard deviation: 18 ng/mL) [226].

6.4. Synthetic cathinones

Synthetic cathinones, as well as synthetic cannabinoids, are predominant categories of NPS seizures, and the two together accounted for 62% of all NPS seizures reported in 2018 [185]. In December 2021, EMCDDA released initial reports of two synthetic cathinones, 3-chloromethcathinone [227] and 3-methylmethcathinone (3-MMC) [228]. Several intoxications related to synthetic cathinones, including mephedrone [229,230], 3-MMC [179,231], 4-methylpentedrone [232] and 4-MEC [233] in chemsex were reported in recent years. Adamowicz [234] reviewed blood concentrations of some synthetic cathinones from fatal and non-fatal cases. Maida et al. [235] reviewed synthetic cathinone-related fatalities (such as N-ethylpentylone, N-ethylhexedrone, 3-MMC, 4-CMC, etc) from 2017 to 2019. Soares et al. [236] also published a review on synthetic cathinones.

6.5. Stability of NPS

Pharmacological knowledge of NPS is essential for successful detection of NPS in biological specimens and interpretation of toxicological results. It may happen that parent drugs are unstable and only present in body for a short period of time. For example, MMB-FUBINACA (FUB-AMB), 5F-MDMB-PICA and 5F-ADB (5F-MDMB-PINACA) are unstable in blood at either room temperature or refrigerated. Their respective butanoic acid metabolites, however, were determined to be stable in blood at all storage conditions (room temperature, refrigerated and in freezer) [237].

Storage temperature and sample concentration are factors that affect

the stability of some NPS. Long-term stability (over 36-week period) of novel synthetic opioids, including AH-7921, U-47700, U-49900, U-50488, MT-45, W-15, and W-18, in blood at various temperatures was studied and it was found that blood samples with synthetic opioids, particularly at low concentrations, should be stored refrigerated or frozen, when possible, in order to preserve analyte stability [238]. Long-term stability study of 13 fentanyl analogs in blood [3-methylfentanyl, 4-ANPP, 4-fluoroisobutyrylfentanyl (4-FIBF), acetylfentanyl, acrylfentanyl, butyrylfentanyl, carfentanil, cyclopropylfentanyl, fentanyl, furanylfentanyl, methoxyacetylfentanyl, *p*-fluorofentanyl and valerylfentanyl] under various temperature conditions (−20 °C, 4 °C, ~25 °C and 35 °C) for 9 months using a validated LC-QTOF-MS method concluded that fentanyl analogs were stable for 9 months under room and refrigerated temperatures, except for acrylfentanyl. It was suggested that samples should be stored frozen and analyzed within 1 month in case of acrylfentanyl overdose [239].

Storage media may also be important especially for unstable NPS. Aldubayyan et al. [240] had reviewed stability of synthetic cathinones and/or metabolites in various human biological samples and concluded that samples probably containing synthetic cathinones should be stored at −20 °C or lower with appropriate preservatives, such as NaF and acidic condition. An investigation of stability of some common drugs of abuse and NPS, including mephedrone and 5F-AKB48, in oral fluid suggested that samples should be stabilized with M3 Reagent Buffer® for storage at room temperature for up to 2 weeks, or at 4 or −20 °C for up to a year [241]. A stability study for of 1-propionyl-LSD (1P-LSD) in urine and serum recommended that the urine and serum samples should be stored at −20 °C and NaF should be added to serum samples to prevent enzymatic hydrolysis to LSD [242].

In addition to the stability of NPS in preserved blood and urine, the stability of 3 synthetic cathinones (mephedrone, MDPV and α-PVP) in methanol and acetonitrile was also investigated. It was noted that the 3 synthetic cathinones were unstable in methanol under refrigerator conditions [243]. As a result, the selection of solvent and storage condition for standard solutions should also be concerned.

6.6. Metabolite identification

Some NPS are unstable in biological specimens or even in solvents. Analysis of NPS metabolites is an alternative to obtain critical toxicological findings. Different NPS might share a common metabolite; for example, AB-FUBINACA and AMB-FUBINACA have a common hydrolysis metabolite [244]. Investigation of NPS metabolic pattern is hence important in order to choose suitable metabolites as markers for NPS analysis. *In vitro* study was usually done by pooled human liver S9 fraction (pHLS9), pHLM or liver microsomes of animals such as pig, while *in vivo* study was done by animals (such as rat and pig) after administration of drug or self-administration by human. Diao and Huestis [245] reviewed and evaluated metabolic patterns of synthetic cannabinoids and devised a practical strategy to select optimal urinary marker metabolites for synthetic cannabinoids. Table 3 shown a summary of metabolites studies reported in the three-year period covered by this paper.

6.7. NPS isomers

Enantiomers of NPS could have different biological and toxicological activities. A study on elimination half-lives of (R)- and (S)-4-fluoroamphetamine found that the serum half-life of (R)-4-FA is significantly longer than that of (S)-4-FA and has a linear relationship, making it possible to assess the time since ingestion from the (R)/(S)-concentration ratio [246].

Cyclopropylfentanyl and crotonylfentanyl are structural isomers having same molecular mass and fragmentation patterns. UPLC chromatographic separation of the two compounds by ethyl siloxane/silica hybrid (BEH) C18 (2.1 · 100 mm, 1.7 mm), Kinetex biphenyl (2.1 · 100

Table 3
Summary of NPS metabolites studies in the three-year period covered by this review paper.

NPS	Method	Ref.
SYNTHETIC OPIOIDS		
Brorphine	pHLM and forensic urine samples	[204]
U-51754	pHLS9 faction and rat urine after oral administration	[273]
U-47931E	pHLS9 and rat urine after oral administration	[273]
U-48800	pHLS9 incubation Isozymes incubation (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A5) rat urine after oral administration	[274]
FENTANILS		
Acetylfentanyl	Cryopreserved hepatocyte incubation and urine samples	[275]
Acrylfentanyl	Cryopreserved hepatocyte incubation and urine samples	[275]
Cyclopropylfentanyl	human liver microsomes incubation, authentic human blood	[276]
Cyclopropylfentanyl	Cryopreserved hepatocyte incubation and urine samples	[275]
O-, M − & P-fluorofentanyl	Human hepatocytes incubation and authentic human urine	[277]
4-fluoro-furanylfentanyl	Mouse hepatocytes incubation and urine	[278]
Isobutyrylfentanyl	Cryopreserved hepatocyte incubation and urine samples	[275]
Isobutyrylfentanyl	Mouse hepatocytes incubation and urine	[278]
4F-isobutyrylfentanyl	Cryopreserved hepatocyte incubation and urine samples	[275]
Methoxyacetylfentanyl	pHLS9 and rat urine after oral administration	[273]
Tetrahydrofuranylfentanyl	Fresh human hepatocytes	[279]
SYNTHETIC CANNABINOIDS		
A-796260	pHLM incubation or isozyme incubations	[280]
ADAMANTYL-THPINACA	pHLM incubation	[281]
ADB-BUTINACA	Cryopreserved pooled primary human hepatocyte incubations and forensic toxicology blood and urine samples	[282]
ADB-4en-PINACA	Cryopreserved pooled primary human hepatocyte incubations and forensic toxicology blood and urine samples	[282]
APP-CHMINACA (PX-3)	Incubation of human liver microsomes	[283]
5F-ADB	Incubation of human liver microsomes and authentic forensic human blood	[284]
5F-ADB	pHLM incubation, authentic blood and urine samples	[285]
Cumyl-CBMICA	pHLM incubation and human urine (tested positive)	[286]
Cumyl-CBMINACA	pHLM incubation and human urine (tested positive)	[286]
Cumyl–CH–MEGACLONE	pHLM incubation and authentic urine samples	[287]
5F-Cumyl-PINACA	pHLM incubation and human urine after self-administration	[208]
5F-CUMYL-PEGACLONE	pHLM incubation and human urine	[288]
CUMYL-THPINACA	pHLM incubation	[280
JWH-200	pHLM incubation or isozyme incubations	[280]
4F-MDMB-BICA	pHLM incubation, human urine and blood samples	[289]
5F-MDMB-PICA	Human hepatocytes incubation and authentic urine (autopsy case)	[256]
5F-MDMB-PICA	Human hair from suspected 5F-MDMB-PICA user	[290]
5F-MDMB-PICA	LC-Q Exactive HF MS of human urine, serum and pubic hair	[291]

(*continued on next page*)

Table 3 (*continued*)

NPS	Method	Ref.
5F-MDMB-PINACA	Human hepatocytes incubation and authentic urine (DUID case)	[256
MDMB-4en-PINACA	Human hepatocyte Incubation, human Liver Microsome Incubation, authentic blood, hydrolyzed urine and non-hydrolyzed urine	[292]
MDMB-4en-PINACA	pHLM incubation and authentic blood and urine samples	[293]
MDMB-CHMINACA	Incubation of human liver microsomes	[294]
MDMB-CHMINACA	Zebrafish and human liver microsomes	[295]
4F-MDMB-BINACA	LC-QTOF analysis of blood and urine positive cases	[215]
4F-MDMB-BINACA	pHLM incubation and authentic urine	[296]
MMB022	Incubation of human liver microsomes	[297]
5F-EMB-PINACA	pHLM incubation or isozyme incubations	[280]
5F-AB-P7AICA	pHLM incubation and self-administration (serum and urine)	[298]
QMPCB	pHLS9, recombinant human monooxygenases, three recombinant human carboxylesterases, and pHLM incubation	[299]
QMPSB	pHLS9, recombinant human monooxygenases, three recombinant human carboxylesterases, and pHLM incubation	[299]
SYNTHETIC CATHINONES		
Buphedrone	Mice (male CD-1) urine	[300]
N-ethylhexedrone	Mice (male CD-1) urine	[300]
4-Methyl-α-ethylaminopentiophenone	pHLM	[301]
4-Methylpentedrone	pHLM	[301]
AMPHETAMINES		
4-fluoroamphetamine	Human urine sample collected up to 12 h after oral ingestion of two doses (100 and 150 mg of 4-FA)	[302]
Methamnetamine	Human liver microsomes and flavin-containing monooxygenase	[303]
OTHERS		
3-HO-PCP	Pooled human hepatocytes incubation and authentic samples (blood, urine and brain)	[304]
1-acetyl-LSD (ALD-52)	pHLS9, CYP inhibitors (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A5), rat urine	[305]
1-propionyl-LSD (1P-LSD)	pHLS9, CYP inhibitors (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A5), rat urine	[305]
1-butyryl-LSD (1B-LSD)	pHLS9, CYP inhibitors (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A5), rat urine	[305]
N^6-ethyl-nor-LSD (ETH-LAD)	pHLS9, CYP inhibitors (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A5), rat urine	[305]
1-propionyl-N^6-ethyl-nor-LSD (1P-ETH-LAD)	pHLS9, CYP inhibitors (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A5), rat urine	[305]
N^6-allyl-nor-LSD (AL-LAD)	pHLS9, CYP inhibitors (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A5), rat urine	[305]
N-ethyl-N-cyclopropyl lysergamide (ECPLA)	pHLS9, CYP inhibitors (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A5), rat urine	[305]
(2′S,4′S)-lysergic acid 2,4-dimethylazetidide (LSZ)	pHLS9, CYP inhibitors (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A5), rat urine	[305]
lysergic acid morpholide (LSM-775)	pHLS9, CYP inhibitors (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A5), rat urine	[305]
25CN–NBOMe	Rat urine, human liver microsomes, and *C. elegans* culture medium samples	[306]
2C-EFLY	Rat urine, pS9 incubation, CYP isoenzyme (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4, or 3A5) or 0.25 mg protein/mL FMO3	[307]
2C-EF-FLY	Rat urine, pS9 incubation, CYP isoenzyme (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4, or 3A5) or 0.25 mg protein/mL FMO3	[307]
2C-T-7-FLY	Rat urine, pS9 incubation, CYP isoenzyme (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4, or 3A5) or 0.25 mg protein/mL FMO3	[307]

mm, 1.7 mm) and high strength silica T3 C18 column (2.1 ·100 mm, 1.8 mm) followed by QTOF-MS analysis was performed. An optimized 10-min gradient profile for the two compounds was developed with BEH C18 column. In addition, major metabolites after incubation of cyclopropylfentanyl and crotonylfentanyl with human liver microsomes were also identified and it was suggested that the two compounds can be distinguished by the identification of their main metabolites [247].

7. Advances in technology

7.1. Mass spectrometry (MS)

MS has been a powerful analytical technique with a wide range of forensic application in the past decade. While GC/MS continues to be the forensic standard for toxicology, LC-MS as well as high-resolution MS (HRMS), such as LC-TOF-MS, LC-QTOF-MS and LC-Orbitrap, are well established as important technique particularly for very low-level analysis (pg/mL). In addition, HRMS enables presumptive identification of unknowns without the need to match MS library or comparison against known standards, which is ideal for broad spectrum toxicological screening and searching for metabolites of novel drugs.

7.2. LC-MS/MS

Hyphenated tandem mass-spectrometry, especially in combination with liquid chromatography, has become a routine in clinical and toxicology laboratory and is often irreplaceable by alternative technologies. Seger et al. [308] reviewed and illustrated the development of LC-MS/MS technology in the past decade (2009–2019), its application in diagnostics, current standing and future directions of the field. A study by Zhu et al. [309] demonstrated one powerful feature of LC-MS/MS technique in the capability of multi-targeted analysis, which allowed simultaneous quantification of 38 psychotropic drugs and relevant metabolites in blood. The method was fully validated with dilution integrity being evaluated to cover the therapeutic and toxic blood concentration range of the target compounds. Rago et al. [310] developed a rapid method for semi-quantitation of 327 drugs in blood with automated data processing capable of analyzing a large number of samples on a daily basis for a comprehensive range of drugs of abuse and NPS. Recent trends were noted on the association of NPS to other common drugs of abuse by consumers. In this concern, Trana et al. [3] developed and validated a comprehensive screening method to quantify a broad range of NPS, classic illicit drugs and the relevant metabolites by LC-MS/MS analysis in blood, urine and oral fluid. With limited

published data regarding the quantification of designer benzodiazepines in forensic cases, Mei et al. [7] developed a method for their determinations in biological samples utilizing LC-MS/MS technique. Applications of LC-MS/MS in toxicological screening and quantitation of synthetic cathinones and other drugs of abuse from cases of mixed poisoning [311], NPS [312] and cannabinoids including THC, CBD and their major metabolites [313] were also reported. Farley et al. [314] reported a method using protein precipitation followed by filtration extraction with an 8-min run time of LC-MS/MS technique for 127 DUID target drugs and a comprehensive ASB/ANSI validation was performed. A review by Nicolaou et al. [46] was published in the light of the growing trend of cannabinoid analysis by LC-MS/MS detection. The review provided an overview of analytical methods used for extraction and isolation of cannabinoids from both conventional and alternative biological matrices.

7.3. Ultra-high performance liquid chromatography MS/MS (UPLC-MS/MS)

With the advance of UPLC technology which enhances speed, resolution and sensitivity, there has been an upward trend for toxicologists to adopt UPLC-MS/MS in developing new high-throughput analytical methods. Rathod et al. [316] reviewed and presented applications of UPLC-MS/MS method for determinations of drugs in bulk and plasma. Mardal et al. [317] described and optimized a UPLC-QTOF-MS screening workflow to allow a comprehensive toxicological evaluation, while also restricted and levelled data analysis to fit in a clinical setting. Orfanidis et al. [318] developed a UPLC-MS/MS method for comprehensive screening and quantification of 84 drugs from various classes including drugs of abuse and pharmaceuticals that are frequently involved in forensic and clinical intoxication in blood in a single run of less than 20 min after sample clean-up by microscale QuEChERS. UPLC-MS/MS technique was also used by Cunha et al. [4] to detect 104 NPS and other drugs of abuse in oral fluid samples with a total run time of 13.5 min. The method was successfully applied to monitor NPS consumption at college parties and electronic music festivals. Similar methods by UPLC-MS for the detection of phenethylamine-type NPS drugs [319], designer benzodiazepines [320] in whole blood, and common drugs of abuse [321] in hair were developed.

7.4. High-resolution mass spectrometry (HRMS)

LC-MS/MS is widely used for toxicological analysis of targeted analytes but not for unknown substances. HRMS approaches are amenable to non-targeted screening and retrospective data analysis. For the last three years, there was tremendous growth in the number of publications on HRMS as screening protocol due to their much higher selectivity and robustness. Using LC-QTOF-MS, Stephenson et al. [322] developed a screening method for whole blood, capable of detecting a comprehensive group of more than 200 drugs at a very low concentration level (LOI ~2 μg/L) for most analytes; and the authors also employed an automated data processing feature using Trace Finder software which reduced processing time. Kleis et al. [323] also developed a sensitive method for a qualitative untargeted screening for approximately 500 NPS, including synthetic cannabinoids (SCs), stimulants, hallucinogens and benzodiazepines after two-step SPE with C18 material; and the authors also examined the resulting extracts separately to determine substance distribution. Other researchers in the field also performed screening of gabapentinoids [324] and pesticide residues [325] in biological specimens.

In another study, Polettini et al. [326] demonstrated a novel approach by application of chemoinformatics for untargeted screening of synthetic cannabinoids and in particular, as a tool for identifying/discriminating isomers, and investigated the potential of predicting retention behaviour under reversed-phase LC conditions. Polettini et al. [327] further presented a computational approach for predicting HR-MS^2 spectrum to increase process efficiency, and they explored a different method from the most currently adopted approach for untargeted identification of unknown. Cannaert et al. [328] also demonstrated the ability of LC-QTOF-MS to perform identification and full characterization of a novel non-fentanyl opioid.

Non-targeted screening is a more comprehensive approach that potentially does not limit the list of analytes but is considered to be more computationally intensive. Identification criteria using HRMS approaches may include retention time, accurate mass, isotope patterns/spacing, product ion spectra and library searching. In regard of this, an online mass spectral database for LC-HRMS named HighResNPS.com containing 5400 entries (as of March 2022) with contributions from laboratories worldwide was created. This crowd-sourced database can be used for direct searches on compound names and exact mass of precursors and/or fragment ions, and is useful in presumptively identifying NPS without a reference standard and improve performance of non-targeted approaches. Cüpper et al. [329] presented a screening method for NPS using UPLC-QTOF/MS and this online mass spectral database (HighResNPS.com).

Bergström et al. [330] established the first method for comprehensive screening of common drugs of abuse including NPS in oral fluid by LC-HRMS, and published the largest dataset on the detection of drugs of abuse in oral fluid. The authors successfully replaced immunoassay of urine in their clinical laboratory by the described method, demonstrated its robustness and greatly improved the identification and treatment of drug addiction. Natural product poisoning cases can be chronic or acute, and is common in clinical toxicology cases. Luo et al. [331] reported the establishment of an LC–HRMS spectral library consisting of 95 natural products commonly implicated in poisoning and a validated LC–HRMS method to identify natural products in urine and serum samples for real cases.

With the increasing challenges of toxic screening in suicides, poisoning and accident cases, Pan et al. [332] developed a sensitive and high-throughput screening method for toxicological analysis of 288 drugs and poisons in blood samples simultaneously, using Orbitrap technology with GC-HRMS of which the data were analyzed by Trace Finder software. The group also created an in-house database library containing information for 647 compounds on RT, base and confirmatory peaks. This method was demonstrated to be robust in real cases with good match to the in-house library.

7.5. Comparative analyses involving LC-MS/MS and immunoassay

Traditionally, toxicological screening of alternative specimens such as hair, nails, oral fluid and sweat is usually performed by immunoassays. With recent rapid advancement of chromatography hyphenated with MS, researchers had developed analytical methods to replace immunoassays with the merit of specificity, highly sensitive, high throughput and, in some cases, lower running cost than immunoassays. Kennedy et al. [333] presented a comparative analysis of LC-QTOF-MS and ELISA immunoassay for the detection of opioids in 968 blood samples. This study verified the capability of LC-QTOF-MS to detect opioids at low concentrations. Similar comparison study for 42 drugs including drugs of abuse in blood was also presented by Swanson et al. [334]. On the contrary, Puzyrenko et al. [335] revealed immunoassays having a greater sensitivity for non-classical benzodiazepine drugs than targeted LC–MS/MS. The authors evaluated the risk of falsely ruling out designer benzodiazepines based on traditional screening LC-MS/MS method, and illustrated that the result was not a consequence of analytical instrumental sensitivity but rather due to antibody cross-reactivity with untargeted or unknown drugs with a similar structure to the target. Kahl et al. [16] developed and validated a LC-MS/MS technique to screen 52 drugs and their metabolites in urine. The authors further evaluated the toxicological results and made cost comparisons between the LC-MS/MS and ELISA methodologies with authentic urine specimens from suspected DUID and drug facilitated

crime cases, and concluded that the former was an ideal alternative to screening urine specimens.

7.6. Metabolism studies and metabolomics

Metabolomics, which is the profiling of metabolites in biological samples, has attracted much research interests in forensic toxicology. Owing to high potency and rapid metabolism of NPS and synthetic cannabinoids, analysis of their main metabolites is critical and becomes routine. Xu et al. [295] developed a method to identify metabolic pathway and major metabolites of a synthetic cannabinoid MDMB-CHMINACA in human liver. Using a similar approach, the metabolic profiles of synthetic cannabinoids 5F-MDMB-PICA (5F-MDMB-2201) [336], 4F-MDMB-BICA [289] and ADB-BUTINACA [337], methoxetamine [338], tryptamine-derived NPS [339] and ortho-, meta- and para-fluorofentanyl [277], in biological samples were also investigated.

7.7. Extraction/sample treatment techniques

Careful consideration of sample preparation in toxicological analysis is necessary due to the high complexity of matrices and the low concentration of analytes. An optimum choice of technique enhances selectivity and sensitivity and reduces matrix interference. A review paper by Jones [340] summarized sample pre-treatments, sample preparations and their applications in forensic toxicology. Kanu [341] presented a review article on an array of sample preparation techniques combined with HPLC, and discussed the principles/concepts and recent developments in biomedical, forensics, and environmental/industrial hygiene and applications of each sample preparation technique. Esteve-Turrillas et al. [342] also conducted a review on different sample preparation strategies for the determination of psychoactive substances in biological fluids by chromatographic methods.

7.8. Solid-phase extraction (SPE)

SPE remains one of the most common and preferred sample extraction techniques in forensic toxicology. Selected examples using SPE including analysis of common drugs and metabolites [343], benzo drug and Z-drugs [34], antipsychotic drugs and metabolites [344] and drugs of abuse [345] present in a range of biological matrices were published in the review period. Wagner and Moses [35] compared two sample preparation techniques, protein precipitation and SPE, for the analysis of cocaine and opioids in biological samples using LC-MS/MS, and found both techniques having the pros and cons. The developed methods required less sample volume and combined four analytical techniques into one method, which significantly impacted laboratory productivity. Carbon nanotubes (CNTs) are useful for extracting chemical compounds and the formation of CNTs with carboxylic acid functional group makes them having strong interaction forces with cationizable analytes. CNT can also be gathered using an external magnet by forming complex with iron oxide magnetic nanoparticles (MNPs). Based on these features, carboxylic acid functionalized multi-walled CNTs (COOH-MWCNTs) have been used as extraction sorbents. In a study by Moon et al. [346], COOH-MWCNTs with MNPs were subjected to magnetic solid-phase extraction (mSPE) in order to extract the targeted substances from human plasma samples. The authors optimized the conditions and the performance of mSPE was compared with liquid-liquid extraction (LLE) method using ethyl acetate.

7.9. Solid-phase micro extraction (SPME)

SPME is an effective extraction method used for volatile and/or semi-volatile analytes, partitioned between the stationary phase coated on a fiber and the aqueous phase or the headspace (HS) phase. It had been proven an important technique for treatment of biological samples with advantages with respect to traditional extraction techniques. Giovanni and Marchetti [347] conducted a review on SPME applications in forensic context. The review was conducted in a systematic approach according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. Shin et al. [348] focused on HS-SPME-GC/MS technique to perform chiral analysis of selegiline metabolites, L-methamphetamine and L-amphetamine in urine samples, so as to differentiate medical selegiline users from illicit MA abusers. Bastiani et al. [349] optimized SPME conditions and validated ethyl palmitate assay in hair to evaluate chronic ethanol drinking behaviour in real cases. Lizot et al. [350] applied commercially available biocompatible SPME fiber tips C18 for extraction of cocaine and metabolites in human plasma. Molecularly imprinted polymers (MIP) are synthetic polymers that are capable of selectively extracting a target analyte or class of analytes. Unlike SPE columns, which are one-time use, MIP materials can be reused for multiple extractions. Milder and Halquist [351] summarised the growing trend of MIP synthesis and their application in the areas of forensic and clinical toxicology for their potential use on sample preparation.

7.10. Microextraction in a packed syringe (MEPS)

Use of microextraction-based approaches has gained considerable popularity, mainly due to the great simplicity, cost-benefit and environmental sustainability. Ahmad et al. [352] reviewed advantages and future trends on application of microextraction-based techniques for screening of controlled drugs. Analytical procedures for the determination of synthetic cannabinoids in saliva are traditionally based on LLE or SPE, followed by chromatographic analysis coupled to MS detectors. MEPS, being a miniaturization of the conventional SPE packed bed cartridges, offers many advantages including small volumes of samples and solvents required, the capability for automation and a lower cost compared to conventional SPE. Sorribes-Soriano et al. [353] developed a method for the determination of five third-generation synthetic cannabinoid in oral fluid based on MEPS extraction and GC/MS analysis. Rosado et al. [354] developed an analytical method using MEPS to determine methadone and EDDP in hair samples by GC-MS/MS. The MEPS procedure was optimized, and the method was fully validated. The result showed great recoveries, high sensitivity, low carry over and low cost. Prata et al. [355] described a validated method for the determination of opiates in blood samples by GC–MS/MS with sample preparation by MEPS and this is the first report on such analysis. Simultaneous determination of nine synthetic fentanyl opioids in urine with semi-automated MEPS and LC-MS/MS was developed by Cunha et al. [356]. The extraction procedure requires only 10 min per sample and the LOQ was sufficiently low for clinical and forensic toxicology testing.

7.11. Other microextraction based techniques

Homogeneous liquid-liquid microextraction (HLLME) is an extraction technique developed within the last decade, and it involves dispersion of fine droplets of extraction solvent in an aqueous sample. Scheid et al. [357] developed a method for the determination of substituted phenethylamines in postmortem blood samples based on HLLME with switchable hydrophilicity solvent as extraction phase coupled to LC-MS/MS. Similar study for the determination of antidepressants in pericardial fluid by dispersive LLME [358] and warfarin in biological samples by air-assisted LLME [359] were developed. Li et al. [360] presented the use of hollow fiber-based solid-phase microextraction for extraction of antipsychotics from human whole blood and urine for UPLC-MS/MS. The proposed method was compared with traditional extraction techniques and the authors concluded the former is a reliable alternative. A method for the determination of cocaine and its metabolites in urine samples based on hollow-fiber renewal liquid membrane extraction and LC-QTOF-MS analysis was also reported

[361].

7.12. Disposable pipette extraction (DPX)

The principle of DPX is based on a dynamic mixture between matrix and sorbent which allows rapid and effective extraction of analytes and provides vigorous clean-up of samples. In a recent review paper, Carasek et al. [362] presented concepts, applications, the pros and cons, future trends and growth paths of DPX. Bordin et al. [363] published the first report on DPX extraction for the detection of drugs of abuse in sweat analysis, and presented the investigation of stimulant psychoactive substances on urine and sweat samples from real cases of professional athletes using DPX tips followed by GC/MS detection. This method explored the potential of sweat as a complementary matrix to urine for the analysis of illicit drugs.

7.13. QuEChERS

QuEChERS, originally developed for analysis of multi-residue pesticides in fruits and vegetables, produces cleaner extracts than LLE and is environmental friendly due to low solvent consumption. It involves two main steps, which are an extraction assisted by salting out and a clean-up by dispersive solid-phase extraction. Regarding drug analysis with chromatography techniques, QuEChERS is good at reducing matrix effect and ion suppression. Degreef et al. [364] optimized sample preparation methods by comparing different protein precipitation, LLE, SPE and mini-QuEChERS protocols, for quantification of 52 benzodiazepines and Z-drugs in plasma. Rodrigues et al. [365] developed and validated a modified micro-QuEChERS and LC-MS/MS assay to quantify 28 psychotropic drugs in blood. Using a similar approach, Campêlo et al. [366] optimized QuEChERS extraction from design of experiment for the determination and quantification of 20 antidepressants in postmortem blood samples. QuEChERS extraction and LC-MS/MS analysis were found applicable to sample preparation of liver tissues for the determination of fentanyl and metabolites [367], fentanyl analogs [368] and heroin [369] as well as breast milk for the determination of cannabinoids [370]. A new and effective clean-up approach by QuEChERS for high lipids samples such as stomach content was also presented by Peres et al. [371] to analyze pesticides and drugs in forensic cases.

7.14. Dried blood spots

Dried blood spot (DBS) is a microsampling technique which involves the collection of blood samples on absorbent paper. The DBS is then punched from the DBS card for analysis. Advantages of DBS sampling technique include minimal requirement of blood sample, reduced chance of sample adulteration, easy handling and high potential for automation. The early DBS technique used a fixed area of DBS for subsequent analysis. As the spreading area of a blood spot on absorbent paper varies with hematocrit (HCT) value of the blood sample, quantitative drug testing using DBS sampling is subject to HCT bias. Strategies to overcome HCT bias include introduction of internal standard and fixed-volume DBS sampling. Luginbühl et al. [372] developed an automated system to measure HCT of samples to correct the analytical results. Applications of DBS sampling technique on analysis of a variety of drugs have been published. Velghe et al. [373] developed a LC-MS/MS method coupled with automated DBS extraction system for the determination and quantification of certain anti-epileptic drugs in DBS samples. Tagwerker et al. [374] performed analysis of DBS as an alternative to urine samples for the detection of various medications and drugs of abuse. In a study of synthetic cathinones, Wang et al. [375] demonstrated the potential of DBS as a reliable specimen of choice for the control of novel NPS.

8. Interpretation of toxicological results

Detection and quantitation of drugs and poisons in biological specimens denote the initial stage of analytical toxicology. Subsequent interpretation of analytical results requires comprehensive understanding of circumstances of case background and knowledge in both pharmacokinetics and pharmacology. Wille and Elliott [315] had reviewed the challenges in forensic toxicology in particular, both analytically and interpretatively, in relation to an increase in potential drugs of interest. Interpretation of toxicological results could be affected and complicated by various factors, such as postmortem redistribution, drug stabilities and drug interactions. The following section gives an overview of recent researches related to interpretation of toxicological results.

8.1. Postmortem redistribution

Postmortem redistribution describes changes in drug concentrations in body after death. An extensive study on postmortem redistribution of several classes of drugs including antidepressants, antipsychotics, benzodiazepines, cardiovascular drugs, amphetamines and opioids were reported [376]. The study demonstrated that the median postmortem/antemortem ratios for all antidepressants were >1, indicative of their significant postmortem redistribution. On the contrary, the median postmortem/antemortem ratios for most benzodiazepines were <1, suggesting minor changes in benzodiazepines concentrations in the postmortem period. Although the study showed some drug-dependent trends in postmortem redistribution, there were no significant variations for most drugs.

Drummer et al. studied the time-dependent changes in THC level in postmortem period [377]. It was found that THC concentration increased in the early postmortem period after admission to mortuary, followed by a decrease in concentration when the blood was collected some days after autopsy. Such changes could have been attributed to a release of drug into blood in the early period after death followed by a redistribution phase. On the other hand, Hoffman et al. reported the impact of sample preservation on postmortem concentration of THC and THC-COOH [378]. It was demonstrated that concentrations of THC were higher in specimens preserved by sodium fluoride and potassium oxalate. The authors also reported that the median central blood-to-peripheral blood ratios for THC and THCA were 1.1 and 1.3 respectively, indicative of slight postmortem redistribution of THC and THCA.

Fentanyl has been receiving increasing attention worldwide owing to its related intoxication and deaths. Andresen-Streichert et al. [379] carried out a study in terminal cancer patients with transdermal fentanyl applications and found that postmortem blood concentrations of fentanyl and its metabolite, norfentanyl, both increased rapidly after death. Postmortem fentanyl concentrations differed significantly from those in antemortem specimens 6–8 h after death. In addition, a case report on a fatal intoxication related to furanyl fentanyl has been evaluated by Morini et al. [380]. The heart blood concentration of furanyl fentanyl was found to be 4 times higher than that of femoral blood, indicative of an extensive postmortem redistribution. The furanyl fentanyl level determined in the cerebrospinal fluid was similar to that in femoral blood, suggesting that cerebrospinal fluid could be an alternative biological specimen for analysis.

Postmortem redistribution of antidepressants and antipsychotic drugs has also received considerable attention because of their involvement in overdose deaths. Steuer et al. [381] evaluated the postmortem redistribution of 20 widely used antidepressants and neuroleptics in 37 deceased and found most of these drugs showing significant time-dependent concentration changes, indicative of the occurrence of postmortem redistribution. The authors proposed a passive diffusion process of the drugs from muscle-to-femoral blood, liver-to-heart blood and lung-to-heart blood.

Potential postmortem redistribution of quetiapine and its metabolites, including norquetiapine and 7-hydroxyquetiapine, has also been reported [382]. The study showed that quetiapine would undergo a significant postmortem redistribution, while norquetiapine and 7-hydroxyquetiapine were less affected by postmortem redistribution. Since norquetiapine could be detected in blood at relatively high concentrations, it was suggested that quantitation of both quetiapine and norquetiapine could provide a better interpretation of potential intoxication with quetiapine. Another study by Breivik et al. reported simultaneous postmortem concentrations of quetiapine in heart blood, femoral blood, brain, muscle and liver tissue [383]. Due to postmortem redistribution and hepatic accumulation, liver tissue was shown to have the highest concentrations of quetiapine, while femoral blood was the lowest.

Moretti et al. [384] published a case report on a fatal intoxication by fluvoxamine and evaluated fluvoxamine concentrations in various postmortem specimens, including femoral blood, heart blood, urine and bile. The heart/femoral ratio of the drug was determined to be 1.86, indicating a significant postmortem redistribution.

8.2. Drug stabilities

Understanding stability of drugs in biological specimens is crucial to interpretation of toxicological findings. Drug stability may depend on chemical structure, sample matrix and storage conditions. In order to preserve the authenticity of a sample, toxicologists should choose a proper storage condition with due care. The stability of THC, THC-OH, THCA, CBN and CBD in antemortem and postmortem blood under refrigerated and frozen conditions was studied by Meneses et al. [385]. The samples were analyzed in triplicate 12 times over a 6-month period. It was found that the cannabinoids in the antemortem blood had a higher stability in the refrigerated condition than in the frozen condition, while the frozen condition was more suitable for postmortem blood.

Jurado et al. [386] evaluated the stability of cocaine and its metabolites (BZE, EME and benzoylecgonine ethyl ester) in blood and urine under the influence of various parameters including storage time, temperature, preservative (for blood sample) and pH (for urine samples). The four compounds were found stable in frozen conditions for one year, but they degraded quickly on storage at 4 °C. Their stabilities were found to be higher on preservation with NaF. The four compounds in urine were stable in frozen conditions regardless of the pH of the samples, but their stabilities dropped significantly when the pH increased from 4 to 8 at 4 °C.

Interpretation of GHB level in postmortem biological specimens has been found challenging due to the possible postmortem generation of GHB. Storage conditions and specimen types for GHB analysis were evaluated by Andresen-Streichert et al. [387]. NaF was shown to be significant in minimizing GHB generation. At both 4 °C and 20 °C, GHB in venous blood and heart blood increased significantly but that in urine increased slightly. On the contrary, GHB in cerebrospinal fluid and vitreous humor was relatively stable.

8.3. Alternative specimens

Blood and urine are the most common specimens for toxicological analysis, but any other biological specimens with various matrices could be chosen as alternatives. Wiart et al. [388] had demonstrated toxicological investigation of skeletonized bodies using hair, bones and nails. In this section, various alternative specimens, including meconium, breast milk oral fluid, cerumen, sweat and oral fluid, and their feasibility in toxicological examination will be discussed.

8.3.1. Perinatal/neonatal history

8.3.1.1. Meconium. Meconium is introduced as one of the possible neonatal matrices for toxicological analysis of newborn cases. López-Rabuñal et al. [389,390] demonstrated a LC-MS/MS method to identify 28 antidepressants, benzodiazepines and their metabolites in small amount of meconium sample (0.25 ± 0.02 g). The samples were homogenized in methanol and followed by SPE. The authors applied the validated method with LOD at 1–20 ng/g to real neonatal meconium specimens and remarked that sample storage involving several freeze/thaw cycles might alter stabilities of some metabolites.

8.3.1.2. Breast milk. Medication and drug consumption during perinatal period will affect neonate. Taking marijuana comes to be trendy in US and European after its medical use was legalized. In order to compensate underreporting marijuana-taking during gestation, breast milk was utilized as a specimen for revealing toxicological perinatal history. Ramnarine et al. [370] presented a UPLC-MS/MS method to determine CBD, CBN and THC in breast milk. Saponification with hydrochloric acid was done so as to separate lipid in breast milk, following by QuEChERS extraction method. This method was shown to be robust and reliable.

8.3.2. Take as much as you can

8.3.2.1. Hair. Hair specimens are distinctive from blood and urine samples in term of detecting different incidence period and ideal for retaining short half-life drugs. Endogenous GHB always complicates the measurement of exogenous GHB. In addition to cut-off concentrations of 5 and 10 μg/mL to differentiate between endogenous and exogenous GHB established in blood and urine, Strickland et al. [394] studied hair samples from 214 donors to evaluate the cut-off concentration in hair. Millar et al. [395] demonstrated the application of a synthetic hair matrix without detectable endogenous GHB for control samples in hair analysis. Millar et al. [396] later presented the largest endogenous GHB hair population study and suggested the bootstrap estimated range of 0.16–5.47 ng/mg. Martz et al. [143] also conducted similar study and concluded average levels of endogenous GHB in hair were below 3 ng/mg.

Hair samples are used for analysis of indirect or irregular drug exposure of marijuana smoke. Claudet et al. [136] examined hair samples from 41 children admitted to a tertiary paediatric emergency unit for the presence of THC and THC-COOH by LC-MS/MS and revealed that 13 children could be considered exposed to an intensely toxic environment with marijuana smoke. In another study, THC-COOH was found in hair up to 5–6 months after cessation of cannabis abuse [141]. Hair samples were also used for the determination of 18 synthetic cannabinoids and 41 of their metabolites in human hair using LC-MS/MS [128].

With the advance of instrumentation techniques, improved methods were reported in determination of drugs of abuse in hair samples [129,138,139,157]. Other researchers examined hair samples for detecting propranolol, quetiapine and norquetiapine [155], NPS [174,312,336], methadone [354] antidepressants [397,398] and aripiprazole [397].

8.3.2.2. Nail. Nail is another keratin matric specimen which can provide long toxicological history of an individual. Kuwayama et al. [399] first developed a method to measure the three-dimensional distribution of drugs in nails by LC-MS/MS. Pichini et al. [400] developed an analytical method using UPLC–MS-MS to examine nails for common drugs of abuse, including cocaine, BZE, cocaethylene, THC, amphetamine, methamphetamine, MDMA, MDA, ketamine, norketamine, mephedrone, methylone, 4-methyletcathinone, methcathinone, GHB and γ-butyrolactone with concentrations ranged from 0.1 to 690 ng/mg; this study also compared drug content in nail against hair from the same individual. An interesting case on bromazepam intoxication in an infant

was reported by Pelissier-Alicot et al. [401]; 4 pg/mg of bromazepam was detected in the nail of the infant, providing critical information for the case. The authors remarked that nail analysis can replace hair analysis when hair is not available, as is frequent in this age group.

8.3.2.3. Cerumen (Earwax). Like hair and nail, cerumen has a long detection window but it is less prone to contamination. In addition, cerumen also compensates the problem of delaying the detection window in hair and nail samples as Meier et al. [393] successfully detected 4-fluoroamphetamine in cerumen even immediately after a single drug ingestion. Nicolaou et al. [402] also achieved to detect THC and its derivatives in cerumen using UPLC–MS-MS.

8.3.2.4. Sweat. Sweat can be acquired non-invasively with minimal risk of pathogen transmission. Tavares et al. [403] reported the first investigation of use of sweat for the examination of harmine, harmaline and N,N-dimethyltryptamine in ayahuasca users. Linear quantitation was achieved at a range of 20–1500 ng/patch with LOD at 10–15 ng/patch for all analytes. Other study of sweat as althernative sample for analysis of stimulants was reported by Bordin et al. [363].

8.3.2.5. Oral fluid. Oral fluid is a relatively clean alternative sample, and in some procedures, almost no considerable sample manipulation is required, e.g. dilute-and-shoot method [66,391,392,404]. Similar to conventional specimen analysis by chromatographic technique, sufficient amount of clean/drug free oral fluid is required for quality control samples, but it is not as readily available as blood and urine. Gavrilović et al. [405] fabricated artificial oral fluid and showed comparable physical properties to the human oral fluid. Besides spitting, Shin et al. [14], Wang et al. [406] and Desharnais et al. [407] had adopted oral collection devices in their studies of 18 antidepressants, diazepam/metabolites and 97 analytes (most prevalent in DUID) in oral fluid respectively. The collected samples were examined by LC-MS/MS and recovery of analytes was discussed. Accioni et al. [50] presented a method applying hexanol-based supramolecular solvents for sample treatment and extraction of NPS in oral fluid before analysis by LC-MS/MS and confirmed the ability of supramolecular solvent based method for reducing matric effect.

Point-of-collection testing (POCT) is another popular concept introduced to toxicological examination of oral fluid, especially for on-site drug driving investigation. Two POCT devices, Dräger DrugTest® 5000 (DT5000) and DrugWipe® 5 s (DW5s), were compared with results of THC examination obtained from LC-MS/MS analysis [408]. LOD of THC of DT5000 and DW5s can only achieve at 10 ng/mL while that of LC-MS/MS is 1 ng/mL. Confirmatory test by LC-MS/MS analysis was suggested due to the limited sensitivity of both POCT devices. Scherer et al. [66] also studied other POCT devices for common drugs of abuse analysis. They concluded that the performance of the devices was acceptable only if suitable cut-off values were set.

8.3.3. Last-ditch effort

8.3.3.1. Brain. Brain is an anatomically secluded specimen and less affected by postmortem redistribution due to the presence of Blood-Brain Barrier (BBB). BBB is able to guard substance exchange according to physiochemical properties of drugs. Nedahl et al. [409] examined both blood and brain specimens for four analgesics, including codeine, oxycodone, tramadol, fentanyl by LC-MS/MS. The brain-blood ratios among the 210 pairs of autopsy specimens were compared with positive correlations. However, the brain–blood ratio for codeine was significantly higher in cases involving heroin use than in cases where codeine has been administered. Chesser et al. [410] had investigated a number of synthetic opioids in brain and compared results in blood and vitreous humour of the corresponding deceased. In general, concentrations of synthetic opioid in brain are significantly higher than those in blood and vitreous humour. The authors suggested brain tissue and vitreous humour to be viable alternative for determination of synthetic opioids in place of blood. Brain tissues are probably the last resource for toxicological analysis for exhumed bodies. Bolte et al. [411] obtained specimens from over a hundred exhumation for 9 years of burial and successfully detected 14 of 16 administered drugs in brain and liver tissue.

8.3.3.2. Bone (marrow). Bone is found despite bodies extremely putrefied, especially bone marrow protected inside the bone. Mancini et al. [412] ground marrow-containing bone for enzymatic hydrolysis and examined the extracts for 7 benzodiazepines by GC-MS. Samples were chosen from corpses with positive results of benzodiazepines in blood, and benzodiazepines were confirmed in 60% of the bone samples, indicating that the validated method is suitable for routine bone analysis. Giordano et al. [413] developed a method using accelerated solvent extraction for automatized sample preparation and extracts analyzed by orbitrap MS-HPLC. Positive results were obtained in 6 of 7 cases, including psychoactive drugs, analgesic, benzodiazepines and cannabinoid metabolites for bone tissues after over 23 years of postmortem interval. Vandenbosch et al. [414,415] presented two studies to demonstrate the efficacy to detect drugs in bone and bone marrow and concluded the potential forensic value of them as an alternative matrix.

8.3.3.3. Dental calculus. Dental calculus is composed of various apatite and calcium phosphates and easily found in oral cavity. Compared to bone and brain, dental calculus is relatively accessible and is a feasible antemortem sample. However, it is mainly used for archaeological human remains studies but not common for forensic investigation. Sørensen et al. [416] quantified 67 drugs and metabolites, such as heroin, methadone, fentanyl, in dental calculus using UPLC-MS/MS. It was found that whenever analytes were in blood samples, they could be also detected in the corresponding dental calculus samples. The drug concentrations were even higher in the dental calculus than in the blood for over half of the cases.

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