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Interpol review of toxicology 2016–2019

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ABSTRACT

This review paper covers the forensic-relevant literature in toxicology from 2016 to 2019 as a part of the 19th Interpol International Forensic Science Managers Symposium. The review papers are also available at the Interpol website at: https://www.interpol.int/content/download/14458/file/Interpol%20Review%20.Papers%202019.pdf.

1. Introduction

Forensic toxicology is of paramount importance in a scientific investigation for the involvement of drugs or poisons in cases with medico-legal consequences, usually through analysis of biological specimens. While there are continuous challenges in forensic toxicology, such as the emergence of new psychoactive substances (NPS), the untiring research effort and instrumental development bring continuous improvement in forensic toxicology, enhanced capability and reliability of detecting trace amount of analytes in various specimens, as well as better understanding for drug metabolism and postmortem toxicology interpretations.

This review collected relevant publications in forensic toxicology since last review presented in 2016, covering the progress over the past 3 years from March 2016 to March 2019. The review is divided into 3 parts, namely "***Surveillance in Toxicology***", "***Challenges – Selected Topic of Forensic Interests***" and "***Advances – from Sample to Interpretation***".

The first part "Surveillance in Toxicology" summarized the recent development in quality aspects as "Surveillance in the Laboratory", the research in the area of driving under influence as "Surveillance on the Road", and the workplace and court order drug testing as "Surveillance in Workplace". In the second part, selected topic of Forensic Interests included publications in these three years on the chemical warfare agents, drug facilitated crime, NPS and protein analysis. For the last part of the review, advances in the toxicology analysis were summarized covering the sample preparation, instrumentations, alternative specimens and interpretations of toxicology findings.

2. Surveillance in Toxicology

2.1. Surveillance in laboratory – Accreditation and quality assurance

2.1.1. Accreditation

A new version of ISO/IEC 17025 was published by the International Organization for Standardization (ISO) and the International Electrotechnical Commission (IEC) in 2017 to update its content to better serve the laboratories that use it [1]. After the publication of the new standard, there will be a three-year transition period and accreditation bodies will need to have all laboratories assessed to the new standard by the end of 2020. The new version ISO/IEC 17025:2017 has changed its format significantly and the new standard is now structured into: i) scope; ii) normative references; iii) terms and definitions; iv) general requirements: v) structural requirements; vi) resource requirements; vii) process requirements; and viii) management requirements. The scope has

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been revised to cover all laboratory activities of testing and/or calibration and/or sampling associated with subsequent testing and calibration. The new standard has a strong focus on information technologies to cover the use of computer systems, electronic records and the production of electronic results and reports. The terminology has also been updated and a new section on risk-based thinking is added.

A chapter for accreditation was found in the new book written by Collins [2]. The author discussed the importance of accreditation for forensic science laboratories and explained the underlying cultural and administrative philosophies that assured the highest levels of quality. The chapter covered the requirement of accreditation under ISO/IEC 17025 and the involvement of human resource management in the accreditation process. The laboratories seeking their first award of accreditation will find this chapter especially useful.

2.1.2. Method validation

The American Academy of Forensic Sciences (AAFS) Standards Board published the Standard Practices for Method Validation in Forensic Toxicology in 2017 [3]. The standard was developed to provide guidance on minimum requirements for validating analytical methods in forensic toxicology laboratories. The validation parameters were evaluated for the forensic toxicology methods which were categorized as screening methods, qualitative confirmation/identification methods, or qualitative methods. Examples of validation were illustrated in its Annexes for demonstration.

An overview on the process of developing methods for applications in forensic toxicology was made by Peters *et at* [4]. The important aspect and considerations in the development of analytical methods using hyphenated methods combining the high separation power of chromatography with mass spectrometric techniques for application in forensic toxicology was discussed. There were method validations of using liquid chromatography-tandem mass spectrometry (LC-MS/MS) for the detection of drugs in a variety of biological matrices including blood [5], urine [6], hair, nails [7], meconium [8], and oral fluids [9]. Hess *et at* [10] studied the important practical consideration in the method validation of LC-MS/MS for the quantitation of endogenous substances in the human body. A rapid screening of blood and urine for fentanyl using enzyme-linked immunosorbent assay was validated according to the forensic toxicology guidelines proposed by the Scientific Working Group for Forensic Toxicology (SWGTOX) [11].

2.1.3. Quality control

The recent advancement of forensic toxicology brought by instrumental development has urged the societies of forensic toxicologists to develop high quality standards and guidelines for drugs and poisons in biological specimens [12]. Wilson-Wilde [13] highlighted the importance of the international development of forensic science standards which could be used in the accreditation of forensic laboratories or facilities and in the certification of services. The range of factors that should be considered in implementing best practice forensic toxicology were reviewed by Drummer [14]. These factors include laboratory influence over the collection of specimens, their proper transport and chain-of-custody before arrival in the laboratory. The author made thorough discussion on the importance of properly trained staff to use suitably validated and documented procedures to perform analyses which met the intended purpose in an accredited or suitably quality oriented management system.

The current status of forensic toxicology in the United Kingdom was discussed by Cosbey *et at* [15] with an emphasis on establishing best practice for professional training and development. The author intended to incite discussion within the forensic toxicology society, industry regulators and other government bodies responsible for the administration of justice. The United Kingdom & Ireland Association of Forensic Toxicologists (UKIAFT) revised the UKIAFT laboratory guidelines in 2018 as a result of the changing technical and toxicological environment [16]. These guidelines were intended to assist laboratories engaged in the practice of forensic toxicology in improving quality assurance and achieving future goals.

2.1.4. Uncertainty of measurement

The AAFS Standards Board published the Standard Practices for Measurement Traceability in Forensic Toxicology in 2017 [17]. This standard was developed by the Toxicology Subcommittee of the Organizational Scientific Area Committee to provide minimum requirements for establishing measurement traceability in forensic toxicology laboratories. The ultimate goal was to ensure confidence and reliability in forensic toxicological test results.

Milinković *et at* [18] described the significance of an appropriate assessment of the uncertainty of the measurement results in laboratory medicine to reduce diagnostic uncertainty. Several approaches in deriving proper measurement uncertainty from internal quality control data acquired in clinical laboratories were presented by Ceriotti [19]. Several authors discussed the use of error and uncertainty approaches in medical laboratories [20–22]. The authors opined that although error methods were more practical, uncertainty methods might still be preferred. Kadis [23] highlighted some common mistakes in evaluating the uncertainty from linear calibration in current chromatographic literature. Overestimation of the uncertainty from linear calibration might be caused by double counting the precision contribution to the uncertainty budget.

The uncertainties of the concentration of ethanol for Widmark calculations were revised and improved for both the United States and United Kingdom [24]. The authors recommended the use of Monte Carlo Simulation for the determination of uncertainty of measurement for Widmark calculations. The results in this study allowed forensic practitioners to both calculate and use reference variables in order to improve their calculations of uncertainty when using the Widmark equation for medicolegal purposes. The Toxicology Bureau of the New Mexico Department of Health conducted a study to estimate the uncertainty for blood alcohol concentration (BAC) by headspace-gas chromatography coupled with flame ionization detection (HS-GC-FID) [25] and another study to estimate the uncertainty for the preparation and testing of aqueous ethanol wet-bath simulator solutions which were used to perform calibration adjustments, calibration checks, proficiency testing, and inspection of evidential breath testing instruments [26].

Uncertainty associated with the alcohol concentration of packaged beers in the UK was determined using an industry standard near infra-red analyser [27]. It was found that the standard deviation from the declared % of alcohol by volume was larger than those previously utilized for uncertainty calculations, illustrating the importance of appropriate experimental data for determination of uncertainty in forensic calculations.

An emergency laboratory in Turkey studied the measurement uncertainty of their BAC test, using Synchron Systems Ethanol assay kit by employing an enzymatic rate method on the Beckman-Coulter Olympus AU400 auto analyzer [28]. BAC tests for drivers involved in traffic accidents were retrospectively inspected with the measurement uncertainty calculated according to the Nordtest guidelines. The study obtained an expanded uncertainty of 19.74% which concluded that BAC test results with values close to legal limits should be reported as the obtained ethanol concentration with corresponding measurement uncertainty.

A software application, named Ethanol WorkBook, to evaluate

the measurement uncertainty for BAC by using Visual Basic for Application language and MS Excel® was developed [29]. The program, which was made freely available to the scientific community at request, was able to i) calculate measurement uncertainties and decision limits with different methodologies; ii) assess compliance to specification limits with a guard-band approach; iii) manage quality control data and create control charts for quality control samples; iv) create control maps from real cases data archives; v) provide laboratory reports with graphical outputs for elaborated data and vi) create comprehensive searchable case archives.

The measurement uncertainty of total testosterone analysis using chemiluminescent microparticle immunoassay technology was calculated by Ayyildiz [30]. Two top-down approaches including the single laboratory validation approach and the proficiency testing approach were used to estimate measurement uncertainty of whole blood tacrolimus mass concentration obtained by LC-MS/MS [31]. The study showed that the uncertainty results obtained from the two top-down approaches were quite similar. Either of the two approaches could be used to estimate the measurement uncertainty of whole blood mass concentration tacrolimus values in clinical laboratories.

The bottom-up approach was used to estimate the measurement uncertainty in quantitation of benzoylecgonine and 11-nor-Δ^9-tetrahydrocannabinol-9-carboxylic acid in urine by gas chromatography-mass spectrometry (GC-MS) [32]. The method precision and the preparation of calibrators and samples were found to be the major contributions to measurement uncertainty. The measurement uncertainty for the determination of amphetamines in urine by liquid-phase microextraction and GC-MS was estimated by bottom-up approach [33]. The combined standard uncertainty was determined after identification of sources of uncertainty and quantitation of uncertainty components.

2.2. Surveillance on the road – Driving under the influence

Driving under the influence of alcohol and drugs continues to be a global problem. To combat the issue, numerous resources have been devoted to law enforcement, drug prevalence studies and drug detection. In this review, we summarized studies including surveys on the prevalence of driving under the influence of alcohol and drugs, toxicological examination methodologies, alcohol pharmacokinetics and calculations as well as legal limit establishment and the studies of its effectiveness.

2.2.1. Surveys on alcohol and drugs use among drivers

Surveys on alcohol and drugs on drivers provide valuable information on abuse patterns and trends, which help to establish new examination methods and legal limits as well as preventative measures. Numerous surveys on driving under the influence of alcohol and drugs were conducted worldwide through analyzing data from traffic offences and accidents as well as from roadside testing [34–66]. The surveys revealed that in addition to alcohol, drugs including cannabis, amphetamines and cocaine were frequently taken by the drivers, while polydrug uses were not rare. Moreover, the emergence of new psychoactive substances (NPS) and designer drugs such as cathinone derivatives, synthetic cannabinoids and designer benzodiazepines [67–70] becomes an additional challenge.

2.2.2. Detection of alcohol

Blood and breath are both well recognized sample matrices for the determination of driving under the influence of alcohol. Several studies on these topics were reported.

2.2.2.1. Blood alcohol detection. The presence of other volatile substances can cause interference in ethanol analysis by HS-GC-FID. A method using two chromatographic columns with different polarities to unequivocally identify ethanol in the presence of an interfering volatile anesthetic administered in the hospital was validated in terms of selectivity, limits of detection, limits of quantitation, linearity, repeatability, intermediate precision, accuracy, robustness and carryover [71].

Another study was conducted to estimate BAC levels expected from consuming one or two cans of supersized alcopop, relative to beer [72]. Median weight data from the National Health and Nutrition Examination Survey were used in Matthews and Miller's (1979) BAC estimation formula. It was found that consuming a single supersized alcopop over the course of 2 h could put youth and young adults well over the legal per se driving limit of 0.08 g/dL in the United States, while consuming two cans put them at risk of alcohol poisoning. The estimates showed that supersized alcopop consumers obtained dangerously high BAC levels and the reductions in the alcohol content of supersized alcopops should be an urgent priority for public health policy and law.

2.2.2.2. Breath alcohol detection. An investigation on a passive in-vehicle driver breath alcohol detection system was conducted as part of the work for the Driver Alcohol Detection System for Safety program [73]. It was reported that the detection of alcohol vapor in the proximity of a human subject might have been traced to that subject by means of simultaneous recording of carbon dioxide at the same location. Sensors based on infrared spectroscopy were developed to detect and quantify low concentrations of alcohol and carbon dioxide. The investigation confirmed the feasibility of passive driver breath alcohol detection using the system and further improvement of sensor resolution and system ruggedness was required before the results could be industrialized.

2.2.3. Detection of drugs

Urine, blood and oral fluid are common matrices for analyzing driving under the influence of drugs (DUID). Typical procedures involve screening by various immunoassay methods followed by confirmation and quantitation by gas or liquid chromatography mass spectrometry. Recently, non-invasive matrices such as breath have also been studied.

2.2.3.1. Oral fluid

2.2.3.1.1. Evaluation of on-site oral fluid collection kits and testing devices. The performance of an instrumental oral fluid roadside testing device – Alere DDS®2 was compared with drug recognition expert opinion, oral fluid laboratory-based analysis and routine blood testing by Rohrig et al. [74]. The results showed a good correlation with drug recognition expert observations and the device performance was >80% in all drug categories compared to laboratory-based analytical testing, both in oral fluid and blood. Another project was also conducted to evaluate Alere DDS®2 for use in the field [75]. Oral fluid specimen screened with Alere DDS®2 for six drug categories was found to have the results generally consistent with those of the evidentiary blood specimens.

A study was carried out to compare the results of the Norwegian Mobile Police Service field testing of the drug screening device, Dräger DrugTest (DDT5000), with drug findings in blood and oral fluid samples taken from drivers suspected for DUID [76]. It was found that DDT5000 did not absolutely correctly identify DUID offenders due to fairly large proportions of false-positive or false-negative results compared to drug concentrations in blood. However, it was still a valuable tool in identifying possible DUID offenders.

The performance of two oral fluid collection devices, Quantisal®

and Certus® collectors were evaluated [77]. Four parameters were studied including (i) collected oral fluid volume; (ii) recovery efficiency (iii) drug stability on storage; and (iv) impact of mouth cells present in the collected oral fluid on drug stability with the drug concentrations measured using gas and liquid chromatography mass spectrometry. It was revealed that Quantisal® collector was more reliable than Certus® collector although the practicability of both devices remained to be determined at the roadside.

Another study also compared the on-site results for the DDS®2 to laboratory-based confirmatory assays with respect to detection of drugs of abuse in human subjects [78]. The device demonstrated high sensitivity (>90%), specificity (100%) and accuracy (>97%) when using the manufacturer's reported cut-off concentration during confirmatory testing.

The performances of three rapid oral fluid test devices (DrugWipe® 6S, Ora-Check® and SalivaScreen®) on simultaneous screening for common drugs of abuse including ketamine have been studied [79]. A total of 549 samples were collected in the study. Results showed that the overall specificity and accuracy were satisfactory and met the DUID standard of >80% for all 3 devices but the sensitivity varied. All devices performed poorly for Δ^9-tetrahydrocannabinol (THC). Ora-Check® had the poorest sensitivity among the 3 devices and did not achieve 80% in any of the tests whereas DrugWipe®6S and SalivaScreen® achieved >80% sensitivity in some of the tests.

2.2.3.1.2. Assessment of the suitability of oral fluid as matrix for DUID cases. The effectiveness of using oral fluid during routine traffic stops in DUID cases in conjunction with drug recognition expert officers was evaluated by Veitenheimer et al. [80]. Samples were screened at the roadside using an Alere DDS®2 Mobile Test System and Quantisal™ collection devices were used for laboratory-based screening and confirmation. The usefulness of oral fluid as a DUID specimen was assessed by the results of drug recognition expert observations, alternate specimens like blood and urine, onsite oral fluid screening and laboratory based oral fluid screening and confirmation. It was revealed that oral fluid testing was a viable option both at the roadside and in a laboratory setting.

An ultra performance liquid chromatography tandem-mass spectrometry (UPLC-MS/MS) method was used to quantify cocaine, benzoylecgonine, and other basic drugs in oral fluid [81]. The oral fluid data were compared to plasma concentrations to obtain concentration-time profiles. The sensitivity and accuracy of the Drugwipe5S® were also assessed. The result showed that Drugwipe5S® detected cocaine use until at least 4 h after intake and an accuracy of 75–98% was observed when applying the legal confirmation decision limit of 10 ng/mL in oral fluid. Besides, cocaine concentrations in oral fluid were much higher and detected longer as compared to plasma, when applying the same decision limit.

To examine whether the oral fluid THC test could be used as a valid alternative to the blood THC test, an evaluation of the sensitivity and specificity of the analysis and an estimation of the quantitative relationship between oral fluid THC concentration and blood THC concentration using a correlation analysis and a linear regression on the log-transformed THC concentrations were conducted [82]. Data from drivers who participated in 2013 National Roadside Survey of Alcohol and Drug Use by Drivers and for whom THC testing results from both oral fluid and whole blood samples that available were used. The findings concluded that the oral fluid test was a highly valid method for detecting the presence of THC in the blood but was not an accurate method for estimating blood THC concentration.

2.2.3.1.3. Newly developed examination methods. A robust, sensitive, lateral flow assay was developed to detect recent use via oral fluid testing for THC [83]. The proof-of-concept assay used a fluorescent-based immunoassay detection of polymeric beads, conjugated to antibodies against native THC. The new technique allowed for roadside identification as it provided significantly lower limits of detection and higher precision determination of recent marijuana use without the use of urine or blood sampling. Detection level of 0.01 ng/mL was distinguished from background and the lower limit of quantitation was determined to approach 1 ng/mL.

A LC-MS/MS based targeted oral fluid screening technique that covered a broad range of basic and neutral drugs of abuse was developed [84]. By combining small sample volume, simple extraction procedure, rapid LC-MS/MS analysis and automated data processing, 40 drugs of abuse were separated within 5 min. The method monitored carbon-13 isotopes of 3,4-methylenedioxymethamphetamine (MDMA) and methamphetamine (MA) to reduce detector saturation effects. As a result, large concentrations of these compounds could be confirmed without the need for dilution or re-analysis. The assay was successfully applied for analysis of oral fluid collected as part of law enforcement procedures at the roadside in Victoria, Australia, providing forensic results as well as epidemiological prevalence in the population tested.

2.2.3.2. Blood. In 2013, the National Safety Council's Alcohol Drugs and Impairment Division added zolpidem and carisoprodol and its metabolite meprobamate to the list of Tier 1 drugs that should be tested for in all suspected drug impaired driving and motor vehicle fatality investigations. The validation of an enzyme linked immunosorbent assays for both drugs in whole blood and the utilization of the validated assays to assess their positivity in suspected impaired driving cases were reported [85].

A combined targeted and non-targeted screening approach to authentic DIUD samples was developed and further validated using whole blood samples spiked with 11 low-dose synthetic benzodiazepine analogues [86]. Analytical data were acquired using ultra high performance liquid chromatography coupled with time-of-flight mass spectrometry (UHPLC-TOF-MS) with data-independent acquisition. The approach allowed tentative identification of drugs and metabolites not included in the initial screening.

A broad targeted screening method which covered 467 substances, based on broadband collision-induced dissociation UHPLC-TOF-MS was developed for toxicological screening of whole blood samples [87]. The new method was shown to combine high sensitivity with a very broad scope in toxicological whole blood screening using single injection.

2.2.3.3. Urine. An ultrafast procedure for the simultaneous detection and quantitation of cocaine and its two main metabolites, ecgonine methyl ester and benzoylecgonine, in urine using microextraction by packed sorbent and GC-MS was developed [88]. A fast extraction procedure together with a microwave-assisted derivatization of a small sample volume (200 μL) allowed the quantitation of all analytes in a range of 25–1000 ng/mL.

2.2.3.4. Breath. The detection of drugs of abuse in exhaled breath would be highly desirable as an alternative to blood or urine analysis in situations such as police controls for drugged driving. An overview of the current state of drug detection in breath, including both volatile and non-volatile substances was conducted by Trefz et al. [89]. The detection of the intravenous anesthetic propofol was presented as a detailed example to demonstrate the potential, requirements, pitfalls and limitations of therapeutic drug monitoring by means of breath analysis. A LC-MS/MS method to analyze 28 drugs of abuse in exhaled breath was developed and validated by

Ullah et al. [90]. Excellent results were achieved for all validation parameters including method detection limits down to pg levels for most of the drugs/metabolites.

2.2.4. Alcohol pharmacokinetics and calculations

A study was conducted to investigate the point at which elimination rates turned from zero to first order kinetics at low BAC and the exact elimination rates at the very low BAC intervals in drunk drivers [91]. Two consecutively collected samples from suspected drunk drivers were analyzed by HS-GC-FID. The elimination rates at BAC below 0.25 g/kg was studied, and compared to that in a moderate BAC reference group as well as a high BAC reference group. The study showed that a shift from zero order to first order kinetics occurred when BAC fell below 0.19 g/kg and the mean elimination rate gradually declined from 0.163 g/kg/h to the lowest elimination rate of 0.083 g/kg/h. These results could assist in back-calculations in cases of drunk driving involving low BACs.

Another study for low BAC proposed that the Widmark's equation, which encompassed the one-compartment model with zero-order elimination kinetics but ignored absorption kinetics, might not be applicable to the analysis of low-alcohol dose cases of drink driving because the issue was focused on the absorption phase [92]. Two representative low-alcohol dose cases, which were analyzed using the one-compartment model with first-order absorption and zero-order elimination kinetics, were thought to be more suitable and useful for medicolegal practice than Widmark's formula.

A review which provided a summary of the pharmacokinetic properties of ethanol and the clinical effects of acute intoxication was published by Perry et al. [93]. Concerns regarding the extrapolation of BAC and the implications of impaired memory caused by alcohol-induced blackouts were also discussed.

2.2.5. Legal limits for alcohol and drugs impairing driving ability

Establishing legal limits to unambiguously identify drivers under the influence of alcohol and drugs is challenging, especially for illicit drugs without therapeutic levels.

2.2.5.1. Legal limit establishment. Legal limits for driving under the influence of 20 non-alcohol drugs in blood were introduced in Norway since 2012. The legislation was revised and expanded in 2015 with the introduction of legal limits for 28 non-alcohol drugs. As of 2016 the legislation also regulated the assessment of combined effects of multiple benzodiazepines and opioids. Strand et al. described a methodology for the equivalence tables for concentrations of benzodiazepines/z-hypnotics and opioids implemented in the Norwegian Road Traffic Act [94]. Conversion factors for 14 benzodiazepines/z-hypnotics and two opioids were established to calculate diazepam and morphine equivalents, which in turn might be summarized to assess the overall impairment caused by multiple drugs belonging to either class.

The Organization for Economic Cooperation and Development (OECD) International Transport Forum published the Road Safety Annual Report 2017 [95] which provided the most recent road safety data and up-to-date information on road safety measures and strategies for 40 countries including new legal limits for driving under the influence of drink and drugs. The implementation of zero tolerance policy for drink driving in Uruguay in 2016 was also updated.

Looking for reasonable blood cut-offs and realistic analytical values for drugs impairing driving ability, Busardò et al. [96] advocated for achieving a consensus on protocols acceptable both nationally and internationally that included rapid blood collection, reporting the time interval between accident and blood collection, the concentrations of drugs in blood that were more likely related to driving disability, and parameters that were able to guarantee the most reliable analytical concentration and not the lowest one.

2.2.5.2. Effectiveness evaluation on the set legal limits. Studies were conducted to evaluate the effects of a new law introduced in Chile in March 2012 which lowered BAC limit for impaired drivers from 0.1% to 0.08% and BAC limit for driving under the influence of alcohol from 0.05% to 0.03% [97,98]. Data from 2003 to 2014 national databases were studied using a descriptive and a Generalized Linear Models approach, type of Poisson regression, to analyze deaths and injuries in a series of additive Log-Linear Models accounting for the effects of law implementation, month influence, a linear time trend and population exposure. The studies provided a strong evidence of a reduction in traffic injuries related to alcohol following the new law.

Hamnett et al. [99] reported a retrospective study comparing changes in the toxicological findings in deceased drivers and motorcyclists before and after the reduced in legal blood alcohol limit for drivers in both Scotland and New Zealand from 80 to 50 mg/100 mL in December 2014. A year of fatal motor vehicle crashes prior to and following the limit change was examined for both countries. An increase in drug prevalence among fatally injured drivers and motorcyclists was found in Scotland, with the use of all drug groups increasing after the limit change, with the exception of cannabinoids. In New Zealand, a reduction in cases involving drugs only, but increases in the numbers of deceased drivers and motorcyclists positive for alcohol only and co-using alcohol and drugs were found.

In 2013, the National Transportation Safety Board issued a report recommending that United States to lower the illegal BAC limit for driving from 0.08 to 0.05 g/dL. Study on the recommendation included a meta-analysis of qualifying international studies to estimate the range and distribution of the most likely effect size from a reduction to 0.05 BAC or lower, which provided strong evidence of the relationship between lowering BAC limit for driving and the general deterrent effect on alcohol-related crashes [100]. In another study, risk-taking was examined in healthy adults who were tested in a driving simulator following placebo and two doses of alcohol calculated to yield peak BACs of 0.08 g/dL and 0.05 g/dL [101]. The findings provided evidence that reducing legal BAC limit in the United States to 0.05 g/dL would decrease risk-taking among drivers.

The effects of lowering the legal blood alcohol content limit for drivers from 0.05 to 0.03 g/dL and increasing license suspension periods for offenders in Chile were studied by Otero et al. [102]. Data of administrative records were used to direct measures of accidents involving alcohol including fatalities and injuries. Results showed a significant decrease in alcohol-related car accidents and injuries. Complementary analysis of blood samples showed that the law had an effect on BAC of male drivers up to the 90th percentile of BAC distribution.

The prevalence and blood concentrations of drugs for drivers involved in road traffic accidents in the Padova province, Italy and the effects of adopting different concentration cut-off values proposed or applied in other European countries on the number of DUID offences were studied [103]. Blood samples from drivers involved in road traffic accidents in the province from 2014 to 2017 were analyzed and the reduction of cases of driving under the influence of illicit drugs in applying different cut-offs was calculated.

The blood concentration of drugs found in motorists suspected of DUID from 2010 to 2012 in England and Wales were reported by Rooney et al. [104]. The study was carried out as new legislation came into place, setting fixed blood concentration limits for drugs in motorists. The analytical results were compared with the new per se limits to give a reference of drug concentrations prior to the

legislation coming into effect. The result showed that samples containing medicinal and prescription drugs were likely to be detected below the new legal limits, while illicit drugs were typically found in excess of the new specified limits.

To analyze the efficacy of alcohol polices in the new law on road traffic safety, a study was carried out to evaluate inebriated fatally injured drivers (FIDs) according to BAC in a 10-year period (2004–2013) in Autonomous Province of Vojvodina, Republic of Serbia [105]. It was revealed that the highest number of intoxicated FIDs during the period was mildly and completely inebriated. In the 4-year post-policy period (2010–2013), the number of FIDs and average BAC levels of inebriated FIDs did not significantly change, indicative the abolition of a permissible BAC should be considered.

To study the cut-off limits adequacy for driving under the influence in Italy, data from blood tests for alcohol and illicit drugs on drivers involved in road traffic crashes around Milan in 2012–2016 were analyzed and compared with a published random survey on driving under the influence of drugs, alcohol and medicines from the European Community [106]. The result indicated that the 0.5 g/dL BAC cut-off was pertinent whereas the 2 ng/mL and 10 ng/mL cut-off limits for THC and cocaine respectively and/or the pre-analytical procedures for these substances were inadequate. The authors proposed a better standardization of the procedure by shortening the time interval between the request for investigation and blood collection and the adoption of more stringent cut-off limits.

2.3. Surveillance in workplace - Workplace & court-ordered drug testing

2.3.1. Samples validity

2.3.1.1. Urine. Urine authenticity is still a matter of concerns in workplace drug testing. Common tricks for circumventing a positive screening result include dilution of urine, provision of urine-like fluids (artificial urine), and addition of chemicals (such as bleach) into urine. Thus identification of any adulterated urine is a key topic in urine authenticity.

The results of urine specimen validity tests for urinalysis in workplace and court settings in Taiwan over 5 years were reported by Lin et al. [107]. They found that on average, 1.09% and 3.81% urine specimens, submitted from the workplace and court respectively, were tempered (dilute, substituted, or invalid tests). The percentage of dilute, substituted, and invalid urine specimens from the workplace were 89.2%, 6.8%, and 4.1%, respectively and a similar trend was observed in urine specimens from the court (dilution 94.8%, substitution 1.4%, and invalidity specimens 3.8%). Thus, authors suggested that all urine specimens taken for urinalysis from both the workplace and court needed to be tested for validity.

Kim et al. [108] studied whether commercially available synthetic urine (SU) products can be identified by adulteration and on-site SU test strips. Eight SU products were tested by the specimen validity testing (SVT) and all passed and identified as authentic urine. However, all tested SU samples were successfully identified by the on-site SU test strips and five out of eight SU could be identified by physical observation. The authors recommended that direct observation in the collection process was effective to avoid cheating.

A study was conducted to identify new markers for both authentic and synthetic urine samples [109]. Two types of chemicals, benzisothiazolinone (BIT) and ethylene glycols specifically triethylene glycol (E3G) and tetraethylene glycol (E4G), were confirmed as markers of synthetic urine. Either BIT or E3G/E4G was detected in eight commercially available SU samples which all possessed normal creatinine levels in an acceptable pH. Since all SU samples were fortified by creatinine which is a well-known chemical found in urine, the presence of creatinine does not necessarily prove the urine authenticity. Four authentic urine markers, thus, were proposed as uric acid, 3-methylhistidine, normetanephrine and urobilin. 92% from 3827 tested urine samples contained all four markers, and approximately 6% were found to contain uric acid and normetanephrine, but lacking either 3-methylhistidine or urobilin. Those samples were identified as natural samples.

Kluge et al. [110] proposed ten endogenous biomolecules which are commonly identified in authentic urine (phenylacetylglutamine, phenylalanine, tryptophan, propionyl-carnitine, butyryl-carnitine, isovaleryl-carnitine, hexanoyl-carnitine, heptanoyl-carnitine, octanoyl-carnitine and indoleacetylglutamine). The authors defined that a detection of at least six out of ten biomolecules was used to differentiate authentic and suspicious urine samples. A polyglycol pattern (from tetrapropylene glycol to undecapropylene glycol) was also reported as a marker of artificial urine.

Another study indicated that adulterants such as potassium nitrite (KNO_2) altered the endogenous urinary metabolites to become new biomarkers [111]. A high resolution mass spectrometry was used to monitor the concentration changes of common metabolites and those new biomarkers in both untreated and KNO_2 treated urines. Significant concentration changes (greater than 2-fold) were reported. A large number of 5-OH-isourate, for example, was formed by uric acid after KNO_2 treatment. Comparing with the untreated urine, concentrations of some amino acids such as histidine, methylhistidine, di- and tri-methyllysine dropped obviously in the treated samples. The concentration of imidazole lactate, on the other hand, increased due to the breakdown of histidine.

2.3.1.2. Hair. Hair is another matrix commonly collected for workplace drug testing due to its availability. Hair validity is highly sensitive to the external environment. Morini et al. [112] studied the concentration changes of benzodiazepines in hair after a prolonged exposure in swimming pool water. The author freshly prepared chlorinated water in the soaking experiment instead of using real swimming pool water. Six benzodiazepines and metabolites including diazepam, desmethyldiazepam, chlordesmethyldiazepam, desalkylflurazepam, clonazepam, and lormetazepam were monitored in seven hair samples. A control experiment showed that the concentrations of those compounds were stable after being soaked in deionized water up to 30 h. Besides, those which were soaked in chlorinated water for 4 h showed considerable degradation. Experiment showed that diazepam had the greatest loss; its concentration decreased 86% after 30 h soaking. Clonazepam showed the fastest degradation (61% loss in 4 h soaking). In conclusion, the longer the soaking time in chlorinated water, the higher the degradation.

Another study conducted by Ettlinger and Yegles [113] showed the effect of thermal hair straightening on drugs in hair. They monitored 24 hair samples in which 17 samples were positive in cannabis and the rest were positive in cocaine. The hair samples were ironed sequentially 30 times and for 2 s per time. After thermal treatment, the cannabinol and benzoylecgonine contents in all samples significantly increased, and the THC and cocaine in hair were decreased. It therefore suggested that the hair straightening should be taken into consideration for interpretation of hair drug results.

2.3.1.3. Oral fluid. Oral fluid is a biological alternative for urine due to its collection with less privacy concerns and difficult adulteration. Scheidweiler et al. [114] studied the stability of cannabinoids including THC, 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (THC-COOH), Δ^9-tetrahydrocannabivarin (THCV), cannabidiol (CBD), and

cannabigerol (CBG) in oral fluid collected with a specific device. Results within ±20% of baseline concentrations were considered stable after storage at 4 °C for 1, 2, and 3 months. The authors concluded that all analytes were stable for up to 2 months at 4 °C for all participants with positive baseline concentrations.

2.3.2. Detection of drugs

2.3.2.1. Hair. Madry et al. [115] examined the drug extraction efficiencies in hair by several extraction solvent systems. The systems were classified as single and two-step extractions. Three different solvents were tried in the single step extraction including methanol (MeOH), acetonitrile (ACN), and a mixture of ACN and water (1:1 vol by volume (v/v)). In two-step extraction, the solvent used in the first steps was all methanol; four different solvents were subsequently used as the second extraction solvents. They were MeOH, a mixture of MeOH, ACN, and 5mM formate buffer (1:1:2 v/v), a mixture of MeOH and 5mM formate buffer (1:1 v/v), and MeOH acidified with 1.4% hydrochloric acid (v/v). Among different extraction systems, the use of ACN alone showed the least extraction efficiency. On the contrary, the two-step extraction by using methanol plus acidified methanol was most efficient. Different tested solvents gave significantly different extraction yield. The authors, thus, suggested that evaluation of extraction efficiency and recovery by using authentic positive sample in validation protocols was highly recommended. Moreover, the extraction protocols should be harmonized for interpretation of hair testing result in inter-laboratory comparison.

A highly sensitive analytical method was developed for THC-COOH detection in hair by using micropulverized extraction method (MPE) [116]. The method used MPE to analyze the unconjugated THC-COOH, and MPE with hydrolysis to determine the total THC-COOH content including THC-COOH hydrolyzed from conjugated THC-COOH (THC-COOH–glucuronide). In comparison with the conventional extraction by alkaline dissolution of hair, there was no significant difference in the total THC-COOH contents by both methods.

Tassoni et al. [117] described a method for cannabinoids (THC, cannabidiol and cannabinol) detection in hair which was applicable to a limited amount of sample. By using a sample residual from acid hydrolysis, the proposed method had the same efficiency as classic basic hydrolysis. Moreover, this method complied with a standard forensic procedure involving immunoanalysis screening followed by a GC-MS confirmation of positive data. Heinl et al. [118] developed a new workflow for cannabinoids detection in hair which was a comprehensively automated analysis including a sample robot, shaker, centrifuge, solvent evaporator, auto-pipette. The system automatically completed the transfer of solution, digestion of hair, liquid-liquid extraction, extract evaporation, reconstitution, derivatization and GC-MS analysis. This automated analysis with limited manual steps reduced the risk of human errors.

The content of NPS in hair from the attendees of nightclub and disco was studied by Salomone et al. [119]. The authors reported that butylone was the most common NPS. Besides, others drugs including methylone, methoxetamine, 5-(2-aminopropyl)benzofuran (5-APB)/6-(2-aminopropyl)benzofuran (6-APB), alpha-pyrrolidinovalerophenone (α-PVP) and 4-fluoroamphetamine (4-FA) were also detected. Salomone et al. [120] reported another study on the detection of the synthetic opioids including the analogues of fentanyl and non-fentanyl compounds in the hair samples.

Van Elsué et al. [121] determined the concentrations of GHB in the hair samples from non-GHB users and GHB users. The concentrations of GHB in the hair samples from non-GHB users and GHB users were found to be 0.3–2 ng/mg and 6.3–239.6 ng/mg, respectively.

2.3.2.2. Oral fluid. A validated method for the rapid detection of 32 synthetic stimulants and hallucogenic drugs, commonly sold as bath salts, in oral fluid was reported by Williams et al. [9]. The drugs in the oral fluid were detected and quantified by LC-MS/MS. The method provided a comprehensive range of drugs within the class. Another review [122] overviewed practical considerations on applying oral fluid analysis in the context of NPS detection. Authors highlighted the current limitations and addressed options to improve current research and legislative actions.

A study from Miller et al. [123] reported reliability of oral fluid as an alternative to urine. A total of 639 subjects undergoing long-term medication-assisted treatment were recruited in the study. Of the total paired urine and oral fluid tests, approximately 7% were positive and 91% were negative for a drug in both specimen types, resulting in an overall agreement of 98%. The authors affirmed the reliability of oral fluid as an alternative specimen type for compliance testing in this population.

2.3.2.3. Breath. Kintz et al. [124] reported use of exhaled breath which is commonly used in alcohol testing as a source of volatile or semi-volatile substances detection. A sampling device equipped with a filter collected the bio-aerosol particles from exhaled breath. THC was the substance of interest. The concentration from exhaled breath collected up to 6 h after smoking a standard joint of cannabis was compared with that of oral fluid. THC was identified in the exhaled breath up to 6 h after smoking from all four subjects recruited. Their study supported the possibility of using exhaled breath as a new matrix to document exposure to drugs especially for cannabis.

2.3.3. Passive and occupational exposure

A study of passive exposure of ketamine for veterinary physicians (VP) was conducted by Favretto et al. [125]. Ketamine is commonly used by VP as the anaesthesia agent. A total number of 11 VPs, recruited on a voluntary base, had positive results to ketamine in hair. Norketamine was found in all except 3 hair samples; one of them had received hair treatment, and two contained lower ketamine concentration (40 pg/mg). The authors also reported another prospective study of two veterinary postgraduate students starting their practical training in a clinic. Their hairs were obtained before the training and 11 days after the training. The result clearly showed that neither ketamine nor norketamine were detected before their practical training, but both could be found after the training. The authors concluded that the site of ketamine absorption was through skin especially occupationally injured hand contacting with the ketamine solutions and animal body fluids in the clinical activities.

Doran et al. [126] also studied the drugs contamination in police stations. This study indicated that contamination issues were more likely to be focused in higher risk areas where drug exhibits handlings occurred, such as counters and balances in charge areas, and surfaces on drug safes. Majority of detected drugs were found below 40 ng in the alcohol swab. All 64 urine samples collected from volunteers in this study were negative, and trace concentration for cocaine was detected in only 2 of the 11 hair samples without its metabolite benzoylecgonine. Positive hair samples were only obtained from the officers who were in very high risk jobs. Thus, the potential exposure of police officers to drugs was unlikely from their working environments. Similar conclusion by Doran et al. [127] was drawn that no THC was detected in both urine and hair samples from the police officers who were responsible for the seizure and removal of illegally grown cannabis plants.

THC is still one of the most concerned illicit drugs in passive inhalation due to its prevalence and consumption way. Berthet et al. [128] reviewed more than 950 journal articles related to passive

exposure to cannabis. Positive results were observed in all matrices after extremely high passive exposure, but samples from active cannabis user should provide some distinctive features for identification. THC-COOH urinary level should be detected below the positivity threshold used to confirm active cannabis smoking especially after normalization of creatinine level. Also, Low THC and very low THC-COOH concentrations in blood was another sign for passive exposure. No THC-COOH should be detected in hair, oral fluid and sweat/sebum emulsion. If THC-COOH was presented in hair or sweat, it might suggest regular cannabis consumption and recent consumption. It was recommended that any person who has to demonstrate abstinence from cannabis should avoid cannabis smoke in unventilated environments.

Salomone et al. [129] studied the ethanol exposure of medical-health workers by simulating the typical occupational situation of hand disinfection. The authors monitored ethyl glucuronide (EtG) and fatty acid ethyl esters (FAEEs) in hair to differentiate chronic exposure from occasional ethanol intake. The results suggested that a significant dermal absorption and/or inhalation of ethanol occurred in exposure to alcohol-based hand sanitizers. The hand disinfection caused urinary EtG concentrations both higher than the cut-offs normally used for clinical and forensic analyses, but the concentrations of the ethanol metabolites in the keratin matrices were below the cut-offs. Thus, direct biomarkers of alcohol abuse in the keratin matrix were capable of distinguishing between ethanol consumption and incidental exposures.

Nail clippings are believed as a back-up of hair in drug analysis. Similar to hair analysis, differentiating external contamination from drug ingestion is one main aspect of using nails for drug monitoring. Hill et al. [130] studied that an extended washing method, which was developed for hair analysis, was able to decontaminate drugs from nails. However, for the presumptive positive nail samples, the authors failed to demonstrate that the wash method could effectively differentiate contamination from ingestion with nail when applying this extended buffer wash and wash criterion used in hair.

2.3.4. Interpretation of drug testing results

Kulig [131] discussed the interpretation of workplace cannabinoid testing in the United States. The focus on cannabinoid testing appeared to be shifting away from the history of marijuana use to whether or not impairment from THC in the workplace exists. The author reminded that a positive result did not document impairment, or even recent use. A systemic review on working drug testing in Italy was conducted by Rosso et al. [132] and concluded that the number of true positivity at first-level workplace drug testing was low, while the frequency of false positives was relatively high. The author also advised a revision of the Italian legislation on the compulsory workplace drug testing. Ogden et al. [133] reviewed the Australian guidelines for re-licensing drivers or applying safety-sensitive occupation. They proposed that hair testing is reliable and reproducible to demonstrate remission and provide cost-effective monitoring.

Montgomery et al. [134] from FBI laboratory reported a new set of reporting criteria in hair drug analysis to differentiate real cocaine user from individuals passively inhaled or contaminated with cocaine. The two criteria were i) cocaine concentration was identified above 500 pg/mg after a subtraction of five times of any cocaine identified in the last wash of the hair, and ii) two hydroxycocaine metabolites were identified in the hair specimen above 5 pg/mg.

Another study by Wang et al. [135] provided information about deposition of diazepam and its metabolites (nordiazepam, oxazepam, temazepam and others glucuronide conjugates) in hair after single dose of 10 mg of diazepam. The authors studied the different hair samples collected 1-month, 2-month and 10-month after consumption. The samples of both 1-month and 2-month post-exposure showed that nordiazepam content was consistently higher than that of diazepam. Oxazepam, and temazepam could be found in some samples but the glucuronide conjugates were not detected. Both diazepam and nordiazepam were still found in the 10-month post-exposure sample at an extremely low level.

Young children living with their parents who are drug abusers or receiving medication treatment for their drug dependence are one of the concerns in child welfare in many countries. Monitoring the hair of children is commonly used to understand their exposure history. If the children are found positive in drug testing, their parent might have legal consequences such as penalty, removal of the remaining children, or even jail period. Kintz et al. [136] studied the methadone and its metabolites in hair from 4 young children whom three of them were dead and one was admitted to a hospital. Authors mentioned that caution should be taken for concluding a positive result. Hair sample amount was sometimes low for analysis. Children hair was more porous in comparison with adult. It was more subjected to contamination. Also, children hair growing was asynchronous. The detection window was hard to define. Thus, it was very difficult to distinguish a systematic incorporation after ingestion or inhalation from external contamination. Toxicologists had the responsibility to inform all related parties about the limitation.

Another similar study [137] concluded that hair analysis on children less than 29 months old never provided an answer for the discrimination of chronic administration of drugs from an acute poisoning since drugs were detected so quickly all along the strand of the hair. In those children aged over 34 months, hair analysis could allow to identify the chronic or repeated administration of the drugs, like in adults.

A review paper from Salomone et al. [138] mentioned that a consensus of definitive interpretation of NPS consumption by the use of hair analysis was still not reached within scientific community, since the wide range of chemical structures in NPS caused difficulty to speculate about general criteria. The authors highlighted that any findings from NPS hair analysis should be cautiously interpreted.

Solimini et al. [139] published a review article about nails in forensic toxicology. They mentioned using nails to retrospectively investigate drugs or illicit substances had become prevalent in forensic and clinical toxicology as a complementary test, especially for those substances which could be stably accumulated for long periods of time. The authors reviewed how substances were incorporated into nails, and suggested three potential mechanisms of drug incorporation: i) contamination from sweat, ii) incorporation from nail bed and iii) incorporation from germinal matrix. The studies highlighted the importance of standardization and harmonization of the methodologies (either pre-analytical or analytical) for nails analysis and the optimization of sampling as well as the development of proficiency testing programs and the determination of cut-off values.

2.3.5. Court ordered drug testing

Being recognized as a “legal” alternative to cannabis, synthetic cannabinoids (SCs) are commonly consumed because of the presumptive non-detectability in drug tests. Franz et al. [140] mentioned that in Germany, SCs were not included in the scope of drug testing for cases of court-ordered abstinence control and re-granting driving license. Their study showed that certain populations who were under abstinence control programs frequently consumed SCs as a cannabis substitute. They concluded that the analysis for SCs should not be neglected in drug screening programs and the analysis should be carried out by LC-MS/MS analysis

rather than immunochemical assays.

2.3.6. International guidelines

Brcak et al. [141] overviewed and prepared guidelines for legally defensible workplace drug testing in oral fluid. The guidelines were updated by the European Workplace Drug Testing Society (EWDTS) to establish best practice procedures. In the meantime, individual countries are allowed to operate within the requirements of national customs and legislation. The EWDTS recommended that all European laboratories providing legally defensible workplace drug testing should use these guidelines for accreditation. These guidelines are relevant to laboratory-based testing only.

Crumption and Mitchell [142] summarized the major changes to the Mandatory Guidelines for Federal Workplace Drug Testing Programs (HHS Guidelines) using urine revised by US Department of Health and Human Services effective from October 1, 2017. The HHS Guidelines address all areas of a drug testing program from collection through laboratory testing to medical review officer (MRO) review and verification of results.

3. Challenges – Selected topic of forensic interests

3.1. Challenges – Chemical warfare agent

A chemical warfare agent (CWA) is a chemical substance whose toxic properties are used to kill, injure or incapacitate human beings. CWA are organized into different categories according to the physiological manner (See Table). This section highlights the case study, analysis and medical treatment of selected CWA in the past 3 years.

Class	Example
Nerve agent	VX, Sarin, Soman, NOVICHOKS
Blister agent	Sulfur mustard, Nitrogen mustard, Ethyldichloroarsine
Blood agent	Hydrogen cyanide, Cyanogen chloride
Pulmonary agent	Phosgene, Diphosgene, Chlorine
Harassing agent	Chloroacetophenone, Adamsite

Classification of Chemical Warfare Agents (CWA).

3.1.1. Sulfur mustard (SM)

Known as the “King of Battle Gases”, sulfur mustard (SM), or bis(2-chloroethyl)sulfide, is a potent toxic alkylating agent which first appeared in World War I. Even 3 or 4 decades elapsed, numerous delayed complications among victims are still being reported. Mohammadzadeh Shabestari et al. [143] surveyed the late cardiac complications of SM poisoning in 38 Iranian Veterans who were exposed with SM during the Iraq-Iran War in 1983–1988. These patients suffered from different degrees of tricuspid regurgitation, increased pulmonary artery pressure and non-obstructive or obstructive coronary artery disease. Sezigen et al. [144] described the detailed clinical course of a family of four who suffered from SM attack, including the medical history, initial symptomatology, clinical examination and initial treatment in the first 48 h after exposure. Schmidt et al. [145] closely monitored a patient for over two years who accidently exposed to SM and underwent surgical skin grafting. Isono et al. [146] carried out six regular check-ups between 2006 and 2014 on 44 victims who were poisoned by a mixture of SM and Lewisite. Through a series of tests, diagnosis and questionnaires, they concluded that these patients suffered from cognitive decline, loss in memories and visuospatial abilities and post-traumatic stress disorder.

SM undergoes intramolecular cyclization to form an ethylene episulphonium ion intermediate which then rapidly alkylates a wide variety of electron-rich biological molecules such as proteins and nucleic acids, leading to chromatid aberration and inhibition of DNA, RNA and protein synthesis. After exposing to SM for as shortly as 15 min, several oxidation and hydrolysis products such as sulfur mustard oxide (SMO), thiodiglycol and thiodiglycol oxide are produced. Manandhar et al. [147] reported a quantitative analysis of SMO by GC–CI–MS. The method detection limit was found to be 0.1 μM, with a linear range from 0.5 to 100 μM. On the molecular level, there are several nucleophilic sites in DNA nucleobases that are prone to adduct formation which could serve as long-term biomarkers of exposure. Zubel et al. [148] gave a detailed review on the comparative analysis of published LC-MS/MS-based methods for the detection of SM-induced DNA adducts.

SM has been used for a hundred years, however, the exact pathomechanism is still incompletely understood. There is no specific therapy available so far. Rose et al. [149] analyzed the studies published between 2000 and 2017 on the pathomechanisms and experimental treatments of SM-induced skin lesions with an aim to shed some light on the future treatment. Glucocorticoids and non-steroidal anti-inflammatory drugs (NSAIDS) are recommended treatments. Menacher et al. [150] evaluated the efficacy of dexamethasone, ibuprofen and diclofenac *in vitro*. Two different cell culture models were used, namely monoculture of keratinocytes (HaCaT) and co-culture of keratinocytes (HaCaT) and immunocompetent cells (THP-1). The results reviewed that dexamethasone showed little, but generic protective effect in both monoculture and co-culture; whereas diclofenac showed a more pronounced protective result in co-culture than monoculture, implicative of the ability of diclofenac to modify the immune cells response. On the contrary, ibuprofen strongly amplified apoptosis and necrosis in SM exposed cells, thus should be the least considered treatment. Glutathione has been known to mitigate symptoms of SM poisoning *in vitro* and *in vivo*. Siegert et al. [151] recently reported the mechanistic study of glutathione as a chemical scavenger with microbore LC-ESI-HR-MS/MS.

3.1.2. Nitrogen mustard (NM)

Nitrogen mustard (NM), or tris(2-chloroethyl)amine, is the nitrogen analogue of SM. NM has never been deployed in combat. Because of its toxicity, lipophilicity and stability in acidic environment, it can potentially be used in terrorist attacks.

A phthalein-based method to determine NM was recently reported by Rozsypal and Halamek [152]. NM formed colored adducts with phthalein compounds which were measurable by UV–Vis spectroscopy. The limit of detection was determined to be 10–40 ppm with different phthalein compounds.

Goswami et al. [153] used *ex vivo* rabbit cornea organ culture as a model to study NM-induced corneal injury and for pre-screening of possible therapeutic agents such as dexamethasone, doxycycline and silibinin. The study showed that treatment with 0.2% dexamethasone or 200 nmol doxycycline led to a significant improvement when it was administered up to 2 h after washing NM. Silibinin was found to cause epithelial degradation if it was administered at a higher concentration than 0.01%. It was best prescribed immediately after washout of NM, but showed no effect at later time points.

3.1.3. Tetramethylenedisulfotetramine (TETS)

Tetramethylenedisulfotetramine (TETS) is a highly toxic convulsant and a potent antagonist of γ-aminobutyric acid (GABA). Originally used as an effective rodenticide, it has been banned in many countries due to its toxicity in human. In China, over 14,000 cases of TETS intoxication occurred between 1991 and 2010, and 932 people were reported death [154]. Patocka et al. [155]

summarized the chemical, biochemical, environmental and toxicological data available in the literature.

TETS is conventionally detected and quantified by GC coupled with different detectors such as NPD, FID and MS/MS. However, these methods require laborious work to reduce the matrix effect. Vasylieva et al. [156] recently reported a sensitive immunoassay based method for the quantitation of TETS, which had a performance comparable to the conventional GC methods.

3.1.4. O-ethyl S-2-(N,N-diisopropylamino) ethylmethylphosphonothiolate (VX)

VX is one of the most toxic nerve gases and is stockpiled as a chemical weapon by many countries. Perhaps the most noted case involving VX in recent years was the assassination of Mr. Kim Jong-nam on 13 February 2017. The killing took place at the busy Kuala Lumpur International Airport by two women rubbing Kim's face sequentially within only 7 s. It was certain that the VX was a binary system. Kim complained of eye pain, possibly due to the entrance of VX to his system through his eyes. Shortly after 20 min, he died [157].

Detection of VX agent is difficult, simply because of the rapid enzymatic hydrolysis and the biotransformation products are traceable only within several hours or days. Recent research focuses on biomarkers derived from covalent reactions of VX with proteins which have longer half-life. Kranawetvogl et al. [158] developed a microbore LC-ESI-HR-MS/MS method allowing the investigation of two different classes of adducts of VX with human serum albumin (HSA). Phosphorylated tyrosine residues and novel disulfide adducts at cysteine residues of HSA which were produced by enzymatic cleavage with pronase could be detected simultaneously.

Lee et al. [159] reported a novel sample preparation method to purify VX adducts of albumin and butyrylcholinesterase (BChE). The research group utilized immunomagnetic separation (IMS) and a HiTRAP™ Blue affinity column to isolate VX-BChE and VX-albumin adducts, respectively, from the plasma of rhesus monkeys exposed to nerve agents. The time-concentration and kinetics of these biomarkers *in vivo* up to 8 weeks after exposure were studied in details.

Pralidoxime, atropine and diazepam are used for the immediate treatment of military personnel in order to restore the function of acetylcholinesterase (AChE). The intravenous infusion of asoxime chloride (HI-6) increases the survival rate compared to atropine alone. In the report by Whitmore et al. [160], the research group correlated the pharmacokinetic profile of HI-6 with both its pharmacodynamic action of reactivating nerve agent inhibited AChE and with its efficacy in guinea-pig.

On the other hand, BChE has been studied as a bioscavenger to provide effective post-exposure protection against percutaneous nerve agent. Mann et al. [161] evaluated the efficacy of BChE administration on VX post-exposed guinea pig. On top of atropine, asoxime chloride, avizafone prescription, the guinea pigs were given BChE immediately or 2 h after the appearance of poisoning. Five out of six animals which received BChE at 2 h after showing signs of poisoning survived 48 h later, compared with six out of six which received BChE immediately on signs.

For decontamination, nanosized CeO_2 is a well-known heterogeneous catalyst for the degradation of VX or sarin. Trenque et al. [162] prepared CeO_2 of different shapes such as nanooctahedrons, nanocubes and nanorods by hydrothermal synthesis. The degradation activity as a function of the crystal faces was evaluated *in vitro*, by measuring the degradation kinetics of paraoxon organophosphate in the presence of CeO_2 nanoparticles in aqueous solution.

3.1.5. Sarin

2-Propylmethylphosphonofluoridate (Sarin) is a colorless and odorless liquid which is extremely toxic. Due to the limited stability and high reactivity of sarin, the detection of the intact molecule *in vivo* is not possible. The biological fate of sarin primarily consists of hydrolysis to *O*-isopropyl methylphosphonic acid (IMPA). Additional transformation pathways comprise binding to AChE, BChE, albumin and other less abundant proteins. In a concerted effort by specialized laboratories in the Netherlands and Germany under the arrangement of the Organization for the Prohibition of Chemical Weapons (OPCW), numerous tissues from a deceased female victim were analyzed for an investigation of alleged use of chemical warfare agents [163].

Young and Capacio [164] developed a sensitive GC-MS/MS method for the determination of six nerve agents (tabun, sarin, soman, cyclosarin, VX and Russian VX) and their corresponding breakdown products. The nerve agents were spiked in human serum. Five out of six (except sarin) nerve agents and all six breakdown products were successfully detected. This method could potentially be used as a rapid screening tool in exposure event.

Read et al. [165] fabricated polymethyl[3-(2-hydroxy-4,6-bistrifluoromethyl)phenyl]propyl-siloxane on commercially available GC column as the stationary phase for the retention of nerve agent surrogates. The absorption of these surrogates to the column was improved by one to several orders of magnitude compared to commercial stationary phase.

Paper spray ionization coupled to high resolution quadrupole orbitrap was used in the quantitation of organophosphate simulants and their hydrolysis products in blood and urine [166]. The limits of detection of the hydrolysis products in the negative ion mode was found to range from 0.36 to 1.25 ppb in blood and urine. These detection levels were well below those found in the victims of the Tokyo subway attack of 2–135 ppb.

3.1.6. NOVICHOK

NOVICHOK belong to the organophosphorus nerve agents developed by USSR as a reaction to English/American invention of VX agents. Today, the information on the synthesis, physical-chemical properties, and toxicity of NOVICHOK is still guarded under the designation "top secret". The mode of action of NOVICHOK is the irreversible inhibition of AChE. Once NOVICHOK reaches the bottom of the active site gorge, the nucleophilic attack of the phosphorus atom by the hydroxyl group of serine occurs. This attack is accompanied by a simultaneous departure of fluoride ion and formation of phosphorylated enzyme. Rapid hydrolysis of the oxime bond within the NOVICHOK-AChE adduct results in the aged form of the enzyme. Once it occurs, the enzyme is permanently inactivated and no therapy is available to restore its activity [167,168]. Up to this moment, detection method of NOVICHOK is not available in the literature.

3.2. Challenges – Drug facilitated crime

Drug facilitated crimes (DFC) consist of using drugs to incapacitated the victims. This practice usually results in facilitated robbery and/or most frequently in non-consensual sexual acts. In the last three years, two systemic reviews were undertaken to determine the current global prevalence of drug-facilitated sexual assault (DFSA) in order to identify trends in the toxicology findings in DFSA around the world. Anderson et al. [169] reviewed a total of eight studies (three studies in United States, two studies in the United Kingdom, one study in Canada, one study in France and one study in Australia) that reported the toxicological findings associated with cases of suspected DFSA. Contrary to popular media

reports and public perception, this review indicated that alcohol was the most commonly detected substance in suspected DFSA cases in which the victims aged 16 and above. After alcohol, benzodiazepine was among one of the most commonly detected drugs. This review suggested that alcohol intoxication combined with voluntary drug consumption presented the greatest risk factor for DFSA. In addition, this review also suggested that there was a need to develop policies that encouraged early responders to suspected DFSA to collect detailed information about the individual's licit and illicit drug consumption history in order to assist in providing appropriate and more thorough contextual information. Grela and Gautam et al. [170] reviewed a total of six studies (one study in United States, one study in United Kingdom, one study in Australia, one study in Canada, one study in Norway and one study in N. Ireland). This review discussed the prevalence of drugs used in DFSA in difference countries and went on to explain why the reported drugs might be used in such offences.

In addition to two systemic reviews, there were several studies which reported the toxicological findings of DFC in different countries. A study of 107 victims of DFSA who reported to Victoria Hospital Clinical Forensic Unit in Cape Town, South Africa over a 3-year period from October 2013 to June 2016 was reported [171]. The study showed that alcohol was the most commonly found drug in DFSA cases. Other drugs found in these cases included methamphetamine, methaqualone and diphenhydramine. Bertol et al. [172] reported a study on female patients consulting the Sexual Assault Centre at Careggi University Hospital, Florence, Italy after an allegedly case of sexual abuse. In this study a total of 256 cases were examined between January 2010 and July 2018. Victims were asked to provide their hair sample 3 months after the event to perform segmental hair analysis for retrospective information on the history of drug exposure in the victim. Result of the study indicated that alcohol was the most detected substance (57 cases), followed by cannabis (19 cases), cocaine (15 cases), opiates/methadone (heroin:5; morphine:1; methadone:6), benzodiazepines (13 cases) and amphetamine (2 cases). Regarding GHB, one case has been reported and none NPS has been found. This finding was consistent with the European statistics where alcohol, cannabis and cocaine were the most found drugs of abuse. In Bangladesh, Basher et al. [173] conducted a prospective clinical and toxicological study of 38 patents with acute poisoning who had been admitted to Dhaka Medical College Hospital between October 2008 and December 2008 and suspected to be victims of drug facilitated crimes. Toxicological screening was performed by LC-TOF/MS and LC-MS/MS analysis of the blood samples of 22 of these patients. Examination revealed pharmacological active concentrations of lorazepam in the blood samples of all 22 cases, midazolam in 12 cases; diazepam in 3 cases and nordiazepam in 6 cases. No mortality was observed in the present study. In Hungary, the medical reports of Peterfy Sandor Street Hospital Clinic and Casualty Centre's 408 GHB-intoxication cases (352 patients) were reviewed by Kapitány-Fövény et al. [174]. Majority of the patients were male, in their twenties. GHB was detected in 34.1% and it was solely consumed in 27.7% of all cases. Ethanol (13.73%) was found to be the most frequently co-ingested substance and it was followed by benzodiazepines (1.72%), amphetamines (1.23%), opioid (0.5%), THC (0.5%) and cocaine (0.25%). The frequency of GHB facilitated sexual assaults or acquisitory crimes under the presumed influence of GHB and other concomitantly consumed psychoactive substances were compared between cases of intentional (111 cases) and unintentional (46 cases) GHB intake. They found that there was significant difference in the frequency of sexual assaults and acquisitory crimes between intentional and unintentional GHB intake cases. The finding that GHB facilitated sexual assaults and acquisitory crimes only occurred among cases of unintentional GHB intake suggested that GHB is indeed used as an instrument of criminal offense.

3.2.1. Method development for DFC

In DFC, victims frequently delay or do not report the crime and extended delays in sample collection will lower the probability of drug detection in blood and urine. To address these difficulties encountered in the toxicological analysis of exhibits in connection with DFC, new sensitive method was developed to detected drugs implicated in DFC cases. Recently, method for determination of drugs of abuse, benzodiazepines and new psychoactive drugs in urine was validated by Lee et al. [175]. This method was applied to 126 urine sample of DFSA victims. 29 urine samples were found positive for abused drugs. The most common drug identified is flunitrazepam followed by nimetazepam and ketamine. Some NPS, such as 2C−B, mephedrone, PMA and PMMA were also detected.

The occurrence of DFC is usually confirmed by analyzing biological fluids. Other evidence can also be collected from the crime scene such as medicine bottle and the remains of suspected doped drink. de Paula et al. [176] developed a method using liquid-liquid extraction with low temperature partitioning (LLE-LTP) and paper spray mass spectrometry (PS-MS) to identify and quantify 5 benzodiazepines (diazepam, alprazolam, bromazepam, clonazepam and cloxazolam) in beverages. The quantitation potential of the LLE-LTP/PS-MS methodology was demonstrated by using beer as matrix, diazepam as target analyte and cloxazolam as an internal standard. The recovery and LOD of this method for diazepam were 90% and 0.05 μg/ml respectively.

3.2.2. Hair analysis in DFC

In DFC, it is not rare that the delay between incidents and the sample collection time can exceed several days or weeks. In such situation, hair is generally the only matrix able to establish the involvement of drugs in crime owing to its long detection window. Hair serves as a specimen for identification of past drug exposure. Segmental hair analysis may differentiate a single exposure from chronical use. In the past three years, numerous methods were developed for the detection of drugs in hair specimen. Van Elsué et al. [177] presented a method with solid phase extraction using GC-MS/MS to determine concentration of GHB in hair samples. The author used this method to determine the endogenous level of non-GHB user as well as the hair samples of abstinent, frequent and chronic GHB users. In 20 non-GHB user, a mean endogenous concentration of 1.1 ± 0.6ng/mg hair was found. In GHB-dependent patients, concentrations between 6.3 and 239.6ng/mg hair were found with no correlation between concentration in hair and dose of GHB intake. Kuwayama et al. [178] reported a study on the ability of micro-segmental hair analysis using internal temporal markers (ITMs) to estimate the day of drug ingestion of an over-the-counter sleeping aid. In this study, volunteers were requested to ingest a dose of diphenhydramine, followed by ingestion of two doses of the ITM, chlorpheniramine after 14 days apart. Several hair strands were collected from each subject's scalp several weeks after the second ITM ingestion. The day of diphenhydramine ingestion was estimated from the distance between the regions and the days of ITM ingestion. The error between estimated and actual ingestion day ranged from −0.1 to 1.9 days regardless of subjects and hair collection times. This method may be utilized to determine the specific day of ingestion of other sleeping aids such as sedatives and hypnotics, which are abused in the commission of drug-facilitated crimes.

Wang et al. [179] presented an overview of toxicological investigations that have used hair analysis in DFC cases from 2009 to 2016 in Denmark. Hair samples were used to determine 24 DFC-related drugs and metabolites, including benzodiazepine and other hypnotics, antihistamine, opioid analgesic, antipsychotics,

barbiturates and illicit drugs from DFC cases. A literature review on concentration in the published DFC-related hair cases and on concentrations in hair of these substances after single and multiple doses was included. These cases demonstrated the value of segmental hair analysis in DFCs and facilitated future interpretations of result.

Busardò et al. [180] reported a study on the decay of GHB concentration on a specific segment of a hair strand over a year. Thirteen hair specimens (all the hair shaft) were provided by a woman who was given a dose of about 2g of GHB dissolved in a non-alcoholic drink during a sex-party. The first hair sample was taken about two days after the presumed GHB unconscious intake, the second one 28 days after and then one shaft per month up to 12 months. In the study period, the concentration of GHB in the hair segment corresponding to the intake of GHB decayed from 4.3 ng/mg to 2.1 ng/mg. The ratios between GHB value in the targeted segment and the mean in others progressively decreased month by month (from 5.56 at the first month to 2.84 at the twelfth month) with ratios at the eleventh and twelfth month lower than 3.

Controlled dose studies of drug concentration in hair after administration improves our understanding of interpretation of drug found in hair. Kintz et al. [181] has reported a study on the segmental hair analysis after a single dose of tramadol. Three adult subjects were orally administered a single 50mg dose of the drug. A hair strand was collected after four weeks post administration and stored in an envelop at room temperature until analysis. Tramadol was extracted from 10mg decontaminated (2x5 ml of dichloromethane) cut hair (3 x2 cm segments) in the presence of 10ng of diazepam-d5 used as internal standard. After overnight incubation in 1 ml saturated borate buffer pH 9.5, drug was extracted by 5 ml of a mixture of dichloromethane-isopropanol-n-heptane (50-17-33, v/v). The extract was reconstituted in 50µl of 5mM ammonium formate buffer adjusted at pH 3. The sample was submitted to LC-MS/MS analysis on an Acquity class I UHPLC coupled to a Xevo TQD tandem mass spectrometer (UHPLC-MS/MS). The hair of three volunteers that had ingested a single 50 mg tramadol dose was segmented analyzed and quantified. Tramadol tested positive in the proximal segment of all three subjects at concentration of 34, 70 and 106 pg/mg and was negative in other segments.

3.2.3. DFC - case reports

The DFC cases reported in different countries in the last three years are summarized in the following Table 1:

3.3. Challenges – New psychoactive substances (NPS)

According to the World Report 2018 of United Nations Office on Drugs and Crime (UNODC), a total of 803 NPS were reported in the period 2009–2017 [188]. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) also reported more than 670 NPS by the end of December 2017 [189]. As more and more new NPS emerge, some of the NPS may also disappeared from the market. It was shown that about 60 NPS have disappeared from the drug market since 2013 [190].

With the lack of information of NPS, such as toxicity and metabolism, for the interpretation of NPS concentration, Gerostamoulos et al. [191,192] proposed that the qualitative detection of NPS in casework is not appropriate until more toxicity knowledge is available. In recent years, more case reports which contained valuable information such as the metabolism and post-mortem redistribution on NPS were published. Elliott et al. [193] published a paper on a system that allows the toxicological significance of NPS to be assessed for the purposes of risk assessment. This review focused on some case reports associated with NPS, especially for some fentanyl derivatives, synthetic cathinones and synthetic cannabinoids. Other information that is important for the interpretation of results, such as metabolism, post-mortem redistribution and stability of NPS, were also reviewed.

3.3.1. Fentanyl derivatives

Fentanyl is a synthetic opioid 50–100 times more potent than morphine [194]. Fentanyl-adulterated heroin was found in recent years, which may lead to unexpected fentanyl intoxication and deaths [188,195–199]. In recent years, there have been an increase in opioid overdose deaths [200–208]. Several fentanyl analogues such as sufentanil, remifentanil, alfentanil and carfentanil, have been approved for veterinary use on large animals. Fentanils first emerged on the illicit drug market in the United States of America in 1979 [209] and more fentanyl analogous emerged in recent years. Between years 2012–2016, 17 fentanils were reported to UNODC EWA [201]. A total of 28 new fentanils were reported to EMCDDA since 2009 [189]. More than 250 deaths involved new fentanils were reported in Europe [189]. Drummer has reviewed on fatalities caused by novel opioids including fentanils [210].

3.3.1.1. Furanylfentanyl. Furanylfentanyl is a recently emerged fentanyl derivative. Its potency is reported to be 50–100 times higher than morphine [211]. The risk assessment report on furanylfentanyl published by EMCDDA reported 11 acute intoxication and 23 deaths associated with furanylfentanyl. Furanylfentanyl was reported to be the cause of or to have contributed to death in 10 of the 23 death cases, in which, furanylfentanyl was found to be the only substance detected in 2 of the cases [212]. O'Donnell et al. [213] reported that furanylfentanyl associated with 3.5% (182 out of 5152) of the opioid overdose death reported in 10 states participating in CDC's Enhanced State Opioid Overdose Surveillance (ESOOS) program in July–December 2016. Daniulaityte et al. [203] also reported 87 out of 281 overdose deaths related to fentanyl and its analogue involved furanylfentanyl. The chemistry, synthesis, prevalence, metabolism, pharmacology, toxicology, legal status and analytical methods in biological specimens of furanylfentanyl were reviewed by Misailidi et al. [211]. The following table (Table 2) is a summary of furanylfentanyl associated death cases in recent years in which the concentration ranged from 0.38 to 8.7 ng/mL.

3.3.1.2. Carfentanil. Carfentanil is one of the most potent fentanyl analogues, of which the potency is estimated to be 10,000 times of that of morphine [194]. It is the most common fentanyl analogue involved in drug overdose deaths in Ohio in 2017 [217]. During July 2016–June 2017, 1,236 (11.2%) out of 11,045 opioid overdose deaths were tested positive for carfentanil in 10 states including Ohio in US [218]. Tiscione and Alford [219] also reported a significant increase in the detection of carfentanil in blood in DUID cases from 5% of cases in 2016 to 38% of cases in 2017 in Palm Beach County, FL, USA. 262 carfentanil associated fatalities were reported by Shanks and Behonick [220] with concentration of carfentanil in blood ranged from 10.2 to 2000 ng/L. A series of carfentanil associated deaths was also reported in UK [221,222]. Shoff et al. [223] reported some qualitative death cases associated with carfentanil. EMCDDA also published a joint report [224] and a report on the risk assessment of carfentanil [225]. The table (Table 3) below summarizes death cases associated with carfentanil which are not listed in the EMCDDA risk assessment:

3.3.1.3. Ocfentanil. Ocfentanil is a derivative of fentanyl developed in the early 1990s with an attempt to obtain an analgesic opioid. But it has not been approved for medical use [229]. Ocfentanil was reported to be an adulterant in heroin [230]. Several fatal cases associated with ocfentanil were reported in recent years [229,231–234]. Misailidi et al. [235] reviewed also the cases of

Table 1
Summary of DFC case reports in the last three years.

Drug [Ref.]	Case history	Analytical method	Findings
Chloroform [182]	26 years old woman declared that her partner get her to sleep with chloroform previous night.	HS-G-MS	Chloroform in blood at 580μg/L
Cathinones & doxylamine [183]	44-year-old man was sexually assaulted by two men after a party. Hair was sampled 15 days later.	LC-MS/MS	Hair: (0–1cm) 4-methylethcathinone:3pg/mg methylenedioxypyrovalerone:5pg/mg Doxylamine:9pg/mg
Quetiapine [184]	Teenage girl was sexually abused by a man who was met at a bar. She went to the home of the man & drank an alcoholic beverage provided by the man, fell asleep afterwards. Hair sample was taken after 6 months.	UHPLC-TOF-MS UPLC-MS/MS	Blood:0.007mg/kg Urine:0.19mg/l Hair: (7–9cm) 0.11ng/mg (0–7cm) not detected
Scopolamine [185]	53-year old man was found dead at home, lying in his bed in prone position.	GC-MS HPLC-DAD LC-MS/MS	Heart blood:0.30mg/ml Femoral blood: 0.0048mg/L Stomach content:20mg/kg Additional toxicology findings: citalopram Heart blood:0.47mg/ml Femoral blood: 0.66mg/L Stomach content: Not detected
Scopolamine [185]	Victim met the suspect in a cafe and went to victim's home after together after having dinner. After drinking the whiskey, victim only remembered that he had been scaring off the visitor.	GC-MS GC-FID HPLC-DAD LC-MS/MS	Urine: detected Hair: (0–3cm)0.2–0.8ng/mg (3–4cm) not detected Additional toxicology findings: Urine: amphetamine, morphine codeine, paracetamol, ethanol
Scopolamine [185]	Victim acquainted the suspect through a gay dating site. On the day of the incidence, the suspect came to victim's home and they have dinner together. Victim lost consciousness afterwards.	GC-MS HPLC-DAD LC-MS/MS	Serum:0.00035mg/L Urine: detected
Xylazine [186]	4-year old boy was sent to hospital by his godfather in an unconscious state. Investigations revealed that the godfather had injected xylazine to the boy, possibly in preparation for a share bath.	GC-MS	Serum:0.053 mg/L Urine:~0.63mg/L
Xylazine [187]	73-year-old woman was sent to the emergency department after being found unconscious at the hospital cafeteria. She recalled that after drinking a bottle of water given by a stranger, she felt dizzy & sleepy	GC-MS LC-MS/MS	Gastric content: detected Serum: Not detected
Xylazine [187]	A 71-year-old woman was found drowsy in the outpatient lounge of a hospital.	LC-MS/MS	Serum:0.057μg/ml Urine:0.294μg/ml
Xylazine [187]	A 76-year-old man was found drowsy in the outpatient lounge of a hospital.	LC-MS/MS	Urine:0.533μg/ml

Table 2
Summary of furanylfentanyl associated death cases in recent years.

Subject Age/ Sex [Ref.]	Autopsy finidng/ Cause of death	Furanylfentayl conc. In blood (ng/mL or ng/g)	Other findings
26/M [214]	Intoxication	1.00	THC, mirtazapine*, pregabalin, buprenorphine*, clonazepam*
36/M [214]	Intoxication	2.74	Pregabalin
37/M [214]	Intoxication	0.90	Carbamazepine, venlafaxine, alimemazine, promethazine*, methylphenidate, ritalinic acid, paracetamol, pregabalin, amphetamine, 7-amino-clonazepam
26/M [214]	Intoxication	0.41	–
26/M [214]	Intoxication	0.74	Carbamazepine, pregabalin, gabapentin, norbuprenorphine, fentanyl, alimemazine*, alprazolam, diazepam, methylphenidate, ritalinic acid
27/M [214]	Intoxication	1.1	–
24/M [214]	Intoxication	0.38	Fentanyl
53/F [215]	coronary artery atherosclerosis & hepatic cirrhosis	8.7[1] 5.5[2]	Fentanyl*, 6-acetylmorphine*,4-ANPP, nicotine, diphenhydramine
23/M [216]	acute toxicity of furanylfentanyl	1.9[3] 2.8[4]	4-ANPP

Remarks: * and metabolite.
Specimens: [1]Heart blood; [2]Fermoral blood; [3]Peripheral blood; [4]Cardiac blood.

ocfentanil. Some of the data was summarized in a UNODC published manual [236].

3.3.1.4. Methoxyacetylfentanyl. Methoxyacetylfentanyl is a fentanyl analogue structurally related to ocfentanil. It has been available in Europe since at least November 2016 [237,238]. The risk assessment report on methoxyacetylfentanyl by EMCDDA mentioned a total of 13 deaths reported to EMCDDA. Methoxyacetylfentanyl was quantified in nine of the cases and the concentration of methoxyacetylfentanyl in blood ranged from 18 to 550 ng/mL [237]. Mardal et al. [239] also reported three methoxyacetylfentanyl related deaths, the methoxyacetylfentanyl concentration ranged from 0.022 to 0.056 mg/kg. Fogarty et al. [240] reported some methoxyacetylfentanyl associated fatal cases in which the concentration ranged from 0.21 to 39.9 ng/mL (n = 11; mean: 17.7 ng/mL; median: 15.1 ng/mL).

3.3.1.5. Cyclopropylfentanyl. Cyclopropylfentanyl has been

Table 3
Summary of death cases associated with carfentanil.

Subject Age/Sex, [Ref]	Case Nature	Carfentanil conc. in blood (ng/mL)	Other findings
40/M [221]	Death	3.3[1]	6-AM*, methadone, cannabinoids*, cocaine* (COC), olanzapine, tramadol, mirtazapine, diazepam, paracetamol (PAR)
36/M [221]	Death	0.80[1]	6-AM*, methadone, COC*, 7-aminonitrazepam, 7-aminoclonazepam, trazodone, nortripytline, diazepam, ibuprofen, cannabinoids, clozapine
36/M [221]	Death	0.22[1]	6-AM*, cannabinoids, clozapine
44/F [221]	Death	0.82[1]	6-AM*, dihydrocodine, COC, mebeverine, diazepam,
29/M [221]	Death	0.24[1]	6-AM*, ketamine*, amphetamine, alprazolam
37/M [221]	Death	0.50[1] 1.05[2] 0.57[3]	Noscapine, cannabinoids, PAR, sertraline
31/F [221]	Death	0.66[1]	Morphine* (MOR), methadone, COC, amitriptyline
21/M [226]	Suicidal	92	norcarfentanil in blood at 0.532 ng/mL
44/- [227]	Drug overdose	5.1	EtOH, MOR, diphenhydramine (Diphen), methadone
35/- [227]	Drug overdose	6.0	diphenhydramine
34/- [227]	Drug overdose	9.3	MOR
36/- [227]	Drug overdose	7.6	Positive result in urine only
27/- [227]	Drug overdose	2.7[4]	Positive result in urine only
33/- [227]	Drug overdose	5.82	MOR, diphenhydramine
37/- [227]	Drug overdose	2.72[4]	EtOH, MOR, Diphen, metoprolol, chloroquine
24–/– [227]	Drug overdose	1.0	Alcohol, Diphen, nordiazepam
25/- [227]	Drug overdose	0.2	–
67/- [227]	Drug overdose	0.3	Diphen
45/- [227]	Drug overdose	Traces[4]	7-aminocloazepam
37/- [227]	Drug overdose	0.7	Bromazepam
38/- [227]	Drug overdose	4.35[4]	No positive result in blood
35/- [227]	Drug overdose	Traces[4]	EtOH
26/- [227]	Drug overdose	0.3	MOR, Diphen
34/M [228]	–	1.3[5]	Furanylfentanyl (0.34), fentanyl (6), MOR, hydromorphone
25/M [228]	–	0.12[5]	–

Remarks: * metabolite also reported.
Specimens: [1]Femoral blood; [2]Aorta; [3]Right ventricle; [4]Urine with concentration in blood not reported; [5]Heart blood.

available in the European Union since June 2017 [241]. Cyclopropylfentanyl and crotonylfentanyl are structural isomers having the same molecular formula. They show different UV spectra but identical mass-spectral fragmentation pattern in UHPLC–QTOF [242]. The risk assessment report by EMCDDA mentioned a total of 78 deaths, which occurred between June 2017 and December 2017, related to cyclopropylfentanyl. The concentration of cyclopropylfentanyl reported in 77 of the quantified cases ranged from 1.1 to 270 ng/g [243]. Fagiola et al. [244] reported 5 postmortem (PM) cases associated with cyclopropylfentanyl, in which its concentration in cardiac blood ranged from 5.6 to 82 ng/mL. Fogarty et al. [240] reported a series of cyclopropylfentanyl related death, with cyclopropylfentanyl concentration ranged from 1.4 to 43.3 ng/mL (n = 32; mean: 15.2 ng/mL; media: 12.3 ng/mL). Brede et al. [245]reported a fatal case of a 27 year-old male with cyclopropylfentanyl concentrations in blood and urine of 0.029 and 0.61 μg/mL, respectively. Brockbals et al. [246] studied a fatal case involving cyclopropylfentanyl and observed a significant PM concentration increases of cyclopropylfentanyl in femoral blood 18 h after the first sampling, which indicated a relevant potential for postmortem redistribution (PMR) and the finding was supported by a central-to-peripheral blood concentration ratio (C/P-ratio) of 2.6.

3.3.1.6. Acetyl fentanyl. Acetyl fentanyl is a non-prescription fentanyl analogue which is 15 times more potent than morphine and is not approved for medical use [247]. It emerged in the market in 2013 [248]. The joint report published by EMCDDA mentioned 32 deaths associated with acetyl fentanyl [249]. Some previously reported acetyl fentanyl related cases were summarized in a UNODC published manual [236]. Avedschmidt et al. summarized the acetyl fentanyl-related deaths, together with the study of acetyl fentanyl associated cases in their office. The author concluded that the lower acetyl fentanyl concentrations in peripheral blood are most likely an artifact in the manufacture of the consumed illicit fentanyl [247]. 41 overdose deaths associated with acetyl fentanyl reported in multiple countries of the southwestern region of the state of Pennsylvania were summarized by Dwyer et al. [250]. Zawilska [251] also summarized several acetyl fentanyl related fatal cases.

3.3.1.7. Acrylfentanyl. Acrylfentanyl, also called acryloylfentanyl, is a fentanyl analogue of 170 times more potent than morphine firstly described in 1981 [252,253]. The risk assessment report of EMCDDA on acrylfentanyl mentioned that there were a total of 47 deaths associated with acrylfentanyl and that acrylfentanyl was the cause of death or likely to have contribution to death in at least 40 of the death cases [209]. Ujváry et al. [254] also published a review on acrylfentanyl. The following table (Table 4) shows a summary of some reported cases associated with acrylfentanyl (AF):

3.3.2. Synthetic cannabinoids (SCs)

Synthetic cannabinoids (SCs) are substances that work in a similar way to THC [189]. SCs have been available on the recreational drug market since 2004 [257]. They constitute the largest category among all NPS reported to UNODC. The number of SCs reported increased from 32 in year 2009 to 251 by the end of 2017 [190,258].

3.3.2.1. MDMB-CHMICA. MDMB-CHMICA, also called MMB–CHMINACA (methyl 2-(1-(cyclohexylmethyl)-1H-indole-3-carboxamido)-3,3-dimethylbutanoate) is a SC first detected in seizures in 2014 [259]. A temporary scheduling order to control MDMB-CHMICA was imposed on April 10, 2017 DEA [260]. A study of Haden et al. [261] observed a limited reduction in the availability of MDMB-CHMICA from internet-based suppliers after the UK Government implemented the Psychoactive Substances Act in May 2016 to control the NPS production and supply of many drugs including NPS. EMCDDA published a joint report [262] and a report on the risk assessment [263] of MDMB-CHMICA. A total of 29 deaths associated with MDMB-CHMICA were reported and among the 12 death cases, MDMB-CHMICA was reported either as the cause of death or likely to have contributed to death. A report from the Swedish STRIDA project described 9 intoxication cases involving MDMB-CHMICA. The patients of the reported cases were aged 23–62 (median 34) years with MDMB-CHMICA concentration ranged from less than LLOQ (LOD = 0.6 ng/mL; LLOQ = 1.25 ng/mL) to 86.4 ng/mL [264]. Gaunitz et al. [265] summarized also published MDMB-CHMICA associated fatal and non-fatal acute intoxication cases, MDMB-CHMICA concentration of fatal intoxication/autopsy cases ranged from <0.2 ng/mL (in post-mortem blood) to 5.6 ng/mL (in ante-mortem blood). Gaunitz et al. reported the post-mortem distribution of MDMB-CHMICA in a case of a 27-year-old-man. The authors also summarized some previously published MDMB-CHMICA fatal and non-fatal intoxication cases. The metabolites studies of MDMB-CHMICA after microsomal incubation [265] and by detection in human urine sample [266] were also reported.

Table 4
Summary of some reported cases associated with acrylfentanyl (AF).

Subject Age/ Sex [Ref.]	Case Nature	Sampling time (after admission)	AF conc. in blood (ng/mL)	Other findings
29/M [255]	Non-fatal intoxication	2h	1.3[1]	-*
35/M [255]	Non-fatal intoxication	6.5h	0.6[1]	-*
51/M [255]	Non-fatal intoxication	1.5h	0.7[1]	-*
29/M [255]	Non-fatal intoxication	1.5h	1.0[1]	-*
23/M [255]	Non-fatal intoxication	–	2.1[1]	-*
27/M [255]	Non-fatal intoxication	14h	0.7[1]	NPP*, flunitrazolam*, oxazepam*, temazepam*
38/M [255]	Non-fatal intoxication	–	0.8[1]	4Cl-a-PVP*, ephylone*, amphetamine*
19/F [255]	Non-fatal intoxication	2h	1.3[1]	EtG*
23/M [256]	Death (AF toxicity)	–	0.3[2]	Ibuprofen, nicotine[#], MA[#,*], THC-COOH*, fentanyl[#,*]
43/M [256]	Death (AF & hydrocodone toxicity)	–	0.95[2]	Caffeine, naloxone, hydrocodone (11ng/mL), Nicotine*, ethanol*, dihydrocodeine[#,*]
26/M [256]	Death (AF, furanylfentanyl toxicity)	–	0.32[2]	Furanylfentanyl (0.95ng/mL), naloxone, nicotine[#], MOR*, hydromorphone*
25/M [207]	Death (AF intoxication)	–	0.02	–
48/M [207]	Death (accidental AF intoxication)	–	0.31	mirtazapine[#], citalopram[#], pregabalin, Ritalin, methylphenidate, (+) N-etylnorhexe-dron.
22/M [207]	Death (accidental AF intoxication)	–	0.78	7-aminoclonazepam, nordazepam
45/M [207]	Death (intentional AF intoxication with fluoxetine)	–	2.9	bupropion[#], quetiapine, fluoxetine[#], zopiclone, dihydropropiomazin, diazepam, nordazepam,
35/M [207]	Death (intentional AF intoxication)	–	0.01	EtOH (0.46%)
26/F [220]	Death (carfentanil intoxication)	–	234[3]	THC-COOH, topirmate, buprenorphine*, norfentanyl*, MOR*
38/M [220]	Death (carfentanil toxicity)	–	221[4]	MOR*, codeine*. Hydromorphone*, norfentanyl*
36/F [220]	Death (carfentanil toxicity)	–	107[4]	THC[#], nordiazepam[#,*] , norfentanyl*, morphine*, hydromoprhine*
33/F [220]	Death (mixed drug toxicity)	–	145[3]	MOR, THC[#], morphine*, codeine*
25/M [220]	Death (COC & carfentanil intoxication)	–	241[5]	Benzoylecgonine (54.3μg/L), naloxone, caffeine, norfentanyl*
44/F [220]	Death (carfentanil intoxication)	–	105[4]	Cotinine
28/M [220]	Death (acute carfentanil intoxication)	–	23.3[3]	THC-COOH
38-/M [220]	Death (acute carfentanil toxicity)	–	30.1[6]	MOR*, hydromorphine*, fentanyl*,[#]
44/M [220]	Death (multi-drug intoxication)	–	114[4]	Furanylfentanyl (0.61μg/L), alprazolam, THC[#], codeine, buprenorphine, phenytoin, quetiapin, naloxone, cotinine
50/M [220]	Death (Fentanyl and carfentanil toxicity)	–	617[6]	Fentanyl (2.9μg/L)
27/M [220]	Death (carfentanil toxicity)	–	529[4]	THC-COOH
62/F [220]	Death (fentanyl & carfentanil toxicity)	–	45.7[4]	Fentanyl (1.1μg/L)
39/M [220]	Death (mixed drug intoxication)	–	10.4[4]	EtOH (1.54g/L), amitriptyline, nicotine[#]

Remark: * in urine; [#]and metabolite.
Specimens: [1]Serum; [2]Peripheral blood; [3]Iliac blood; [4]Femoral blood; [5]Heart blood; [6]Subclavian blood.

3.3.2.2. 5F-MDMB-PINACA and 5F-MDMB-PICA. 5F-MDMB-PINACA (methyl 2-{[1-(5-fluoropentyl)-1H-indazole-3-carbonyl]amino}-3,3-dimethylbutanoate) and 5F-MDMB-PICA (methyl N-{[1-(5-fluoropentyl)-1H-indol-3-yl]carbonyl}-3-methylvalinate) are indole or indazole-based SCs emerged recently. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) published a joint report [267] and report on the risk assessment of 5F-MDMB-PINACA [268]. 35 acute intoxication and 28 death with confirmed exposure to 5F-MDMB-PINACA were reported. 5F-MDMB-PINACA was found to be the cause of death or likely to have contributed to the death in at least 20 of the death cases [268]. Mogler et al. [269] reported the detection of 12 phase I metabolites of 5F-MDMB-PICA in human urine samples. The authors also demonstrated the application of immunochemical assays (homogeneous enzyme immunoassays (HEIA™) SC-1, SC-2, and SC-3 [Immunalysis, Pomona, CA, USA]) were not capable of detecting 5F-MDMB-PCA in urine [269].

3.3.2.3. Other reported synthetic cannabinoids cases. Besides the SCs mentioned above, there are some more intoxication cases of other SCs reported in recent years. For example, Adamowicz et al. [270] reviewed 39 cases of UR-144 associated cases, with UR-144 concentrations ranged from trace amount (LOD: 0.15 ng/mL; LOQ: 0.5 ng/mL) to 17 ng/mL (mean 636 ng/mL, median 1.6 ng/mL). Halter et al. [271] reported 27 fatal and non-fatal intoxication associated with Cumyl-PEGACLONE. Among that, a total of 6 deaths cases were reported with the Cumyl-PEGACLONE concentration in blood (femoral vein) ranged from 0.12 to 0.84 ng/mL. And the non-fatal intoxication cases with Cumyl-PEGACLONE concentration ranged from 0.14 to 13 ng/mL. Joint report and report on risk assessment of AB-CHMINACA, ABD-CHMINACA and CUMYL-4CN-BINACA [272–277]. Other reported cases related with SCs were summarized in the table (Table 5) below:

3.3.3. Synthetic cathinones

Synthetic cathinones are cathinone derivatives structurally related to a psychoactive alkaloid found in khat plants. According to the world report of UNODC 2018, there are 148 synthetic cathinones reported by the end of 2017 [258]. The legal status, chemistry, patterns of use, prevalence, biological effects, pharmacokinetics, toxicity and factors affecting stimulant/toxicological effects of 3-methylmethcathinone (3-MMC or metaphedrone) were reviewed by Ferreira et al. [282]. The 3-MMC concentration in deaths and non-fatal intoxication cases related to 3-MMC was also listed. Majchrzak et al. [283] reviewed on the newest cathinone derivatives NPS. The chiral resolution and enantioselectivity of synthetic cathinones were also reviewed by Silva et al. [284]. Stability of synthetic cathinones in blood [285], urine [286,287] and oral fluid [288] were also reported.

Pyrovalerone derivatives type synthetic cathinones such as MPDV, α-PVP, α-PBP, α-PHP and α-PHPP have caused numerous reported deaths [289–296]. The detection and effect of MDPV (3,4-methylanedioxypyrovalerone) and α-PVP (α-pyrrolidinopentiophenone) on human were reviewed by Karila et al. [289]. Richman et al. [297] published a review on α-PVP. Metabolism, dosage, toxicity, reported fatalities and DUID cases of several pyrovalerone type cathinones were reviewed by Zawilska et al. [298]. Franzén et al. [295] reported several acute intoxications cases involving α-PBP, the α-PBP concentrations were found ranged 2.0–13,200 ng/mL in urine and 2.0–440 ng/mL in serum. Fujita et al. [299] reported an autopsy case involving α-PHP. The deceased was a 27/- man and the toxicokinetics of α-PHP in the PM specimen was also studied, the half-life $T_{1/2}$ α-PHP of was determined to be 37 h. Majchrzak et al. [300] reported a α-propylaminopentiophenone (N-PP) related fatal, which believed to be the first N-PP cases reported to the authors' knowledge. There are also several studies on effect of structural changes for pyrovalerone derivatives [290,301,302].

More cases report on different type of synthetic cathinones such as 4-chloromethcathinone (4-CMC) [303], dibutylone (bk-DMBDB), butylone (metabolite of dibutylone) [304] were reported during the past few years. A series of fatal and non-fatal intoxication cases associated with ephylone were reported by Costa et al. [305], Krotulski et al. [306], Ikeji et al. [307] and Thirakul et al. [308]. Ephylone, also known as n-ethylnorpentylone or n-ethylpentylone is a synthetic cathinones structurally related to methylone and was first described by Boehringer Pharmaceuticals in the 1960s [305]. A temporary scheduling order to control ephylone was imposed on August 31, 2018 until August 31, 2020 by the Drug Enforcement Administration (DEA) [309]. The following two tables (Table 6 & Table 7) summarize fatal and non-fatal intoxication cases associated with ephylone:

3.3.4. Arylcyclohexylamines class NPS

3-MeO-PCP (3-Methoxyphencyclidine) is one of the methoxylated analogues of phencyclidine (PCP) that reaches the MPS market in recent years. Metabolisms of 3-MeO-PCP and 3-MeO-PCPy were studied by Michely et al. [310]. Several fatal and non-fatal cases related to 3-MeO-PCP were related during the past three years. Below (Table 8 and Table 9) are the summary of the cases reviewed.

3.3.5. Ketamine derivatives

2-oxo-PCE (N-Ethyldeschloroketamine) is an arylcyclohexylamines class NPS first synthesized in 1962 as a short-acting phencyclidine derivative [318]. Tang et al. [319] reported 3 out of 56 cases of 2-oxo-PCE associated acute poisoning intoxication in

Table 5
Summary of SCs related case reports.

Subjects Age/Sex [Ref]	SCs	Conc. in blood (ng/mL)	Other findings Conc. in ng/mL (unless specified)
Mid-20/M [278]	5-APB	860[1]	Ethanol, THC (0.0024mg/L)
53/M [279]	5F-ADB	0.19±0.04[2]	Diphenidine (12 ± 2.6)
27/- mean [265]	MDMB-CHMICA	1.7[1]	Amphetamine (1050), MDMA (275), MDA(22), THC(9.3), THC-OH(0.9), THC-COOH(65)
25/M [280]	5F-PB-22	0.37[1]	BAC (2.6g/kg), AB-CHMINACA, 5F-AKB-48
28/M [280]	AB-CHMINACA	~4.1*[,1]	BAC (1.45 g/kg)
41/M [280]	5F-ADB		
14/M [280]	AB-CHMINACA	8.2[3]	–
17/M [281]	UR-144	12.3[3]	–
	XLR-11	1.3[3]	
	JWH-022	3[3]	

Remarks: *value above highest calibrator.
Specimens: [1]Femoral blood; [2]Right heart blood; [3]Subclavian blood.

Table 6
Fatal cases associated with ephylone.

Subject Age/Sex [Ref.]	Case Nature	Ephylone conc. in blood (ng/mL)	Other findings
32/M [304]	–	170	–
-/M [305]	Alleged "Molly" use	50,000	Dibutylone
35/M [305]	Homicide	833	Butylone, midazolam, THC
-/M [305]	–	790	Pentylone, dibutylone, butylone
28/M [305]	Suspected drug overdose	600	–
49/M [305]	Suspected drug overdose	550	Dibutylone, 4-chloro-α-PVP
-/M [305]	–	540	Dibutylone
-/M [305]	Possible drug overdose	430	–
-/M [305]	–	358	–
-/M [305]	Following vehicular crash	210	Pentylone
-/F [305]	Homicide	160	–
31/M [305]	Suicide, gunshot wound	150	–
47/M [305]	Suspected drug overdose	90	Carfentanil
53/M [305]	–	86	U-47700, U-49900. THFF, Acrylfentanyl, 4-ANPP
-/F [305]	Suspected drug overdose	38	dibutylone, butylone, FIBF
25/M [305]	–	24	Alprazolam, THC
-/M [305]	Suspected drug overdose	18.4	Furanylfentanyl, 4-ANPP, cocaine, THC
-/M [305]		12	–

Table 7
Non-fatal cases associated with ephylone.

Subject Age/Sex [Ref.]	Case nature	Ephylone conc. (ng/mL)	Other findings
18/M [304]	Intoxication	7[1]	–
19/M [304]	Intoxication	19[1]	MDMA, caffeine, cotinine, alcohol
35/M [304]	Intoxication	149[1]	–
26/M [304]	Intoxication	61[1]	–
23/M [305]	DUID	87[2]	–
40/M [305]	DUID	41[2]	Fentanyl*
Male [305]	DUID	34.3[2]	–
36/M [305]	DUID	23[2]	MA*
32/M [305]	DUID	21[2]	Clonazepam

Specimens: [1]Serum; [2]Blood. *Remarks: metabolite also reported.

Table 8
Fatal cases related to 3-MeO-PCP.

Subject Age/Sex [Ref.]	3-MeO-PCP conc. in blood (ng/mL)	Other toxicological findings
29/M [311]	139 ± 41	Diphenhydramine, amphetamine
21/M [312]	3200	Ethanol, bupropion, delorazepam, mitragynine, paroxetine
58/M [312]	630	methamphetamine
39/F* [313]	63	Alcohol, diazepam, nordiazepam, cocaine[#]
27/M [314]	380	–
21/M** [314]	180	Burprenorphine and metabolite, 5-MeO-MiPT
27/M [314]	230	Methadone, diazepam[#], pregabalin, MA, buprenorphine[#]
29/M** [314]	120	Nordiazepam, pregabalin, flubromazolam, AB-FUBINACA, THJ-018, buprenorphine[#], methylphenidate[#]
32/M [314]	60	Oxycodone, amphetamine, flubromazolam, MT-45, 4-MeO-PCP, THJ-018, THC
27/M [314]	50	Tramadol, alprazolam, fentanyl, amphetamine
20/F [314]	80	Tramadol[#]

Remarks: * for Homicide case; ** for Suicidal case; [#] for metabolite also reported.

Table 9
Non-fatal intoxication related to 3-MeO-PCP.

Subject Age/Sex [Ref.]	3-MeO-PCP concentration in blood (ng/mL)	Sampling time
19/M [314]	140	Upon arrival
	80	2.5 h from arrival
	60	5 h from arrival
	40	17 h from arrival
19/M [315]	350	Upon arrival
21/M [315]	180.1	Upon arrival
37/M [316]	49	Upon arrival (2 h after drug ingestion)
40/M [316]	66	–
27/M [317]	131	0.2 h from arrival
	90	3 h from arrival

Hong Kong between October and November 2017. A fatal case involving 2-oxo-PCE was reported by Theofel et al. [320].

3.3.6. Stability of NPS

Factors that affect the interpretation of results include ionization suppression and enhancement [321], post-mortem redistribution and also the stability of drugs. For example, 4-chloromethcathinone (4-CMC) was found to be highly unstable at 4 °C with concentration dropped by 65% 3 days after measurement [322]. 25I–NBOMe (4-iodo-2,5-dimethoxy-N-[(2-methoxyphenyl) methyl]-benzeneethanamine) was found to be relatively unstable among different NBOMe, and concentration dropped more than 40% at RT [323]. Hence, understanding the stability of drugs in biological specimens could be essential for the results interpretation. The below tables (Tables 10–12) listed the recent studies on stability of NPS in biological specimens:

3.3.7. Post-mortem redistribution

Sampling site and time for post-mortem specimens may affect the analytical results due to post-mortem redistribution of drugs. For example, significant increase in postmortem concentration of cyclopropylfentanyl was observed in femoral blood during 18 h after first sampling [246]. Time-dependent postmortem redistribution was also observed for butyrfentanyl and its metabolites at time of sample collection 9 h and 28 h after death [332]. While post-mortem redistribution was not observed in case of MDAI (5,6-methylenedioxy-2-aminoindane) and 2-MAPB (1-(benzofuran-2-yl)-N-methylpropan-2-amine) in peripheral and heart blood sampled at 11 h and 29 h after death [333]. Glicksberg et al. [334] investigated postmortem redistribution of nine synthetic cathinones, including α-PVP, ethylone, methylone, butylone, MDPV, methedrone, pentylone, 4-MEC, and MDPBP. Concheiro et al. [252] reviewed the postmortem concentrations in different biological samples, as well as the metabolism of some synthetic opioids. Some of the postmortem redistribution (PMR) data are summarized in the tables (Tables 13–17) below:

3.3.8. Studies on metabolism of NPS

The metabolism studies of NPS are necessary for a better detection of analytes. There were a large amount of publications on metabolism of NPS, especially for SCs in recent 3 years. Urine could provide a longer detection period but metabolites of SCs instead of the parent SCs are usually detected in urine [349]. However, a better understanding the metabolism of NPS may provide more information to prevent incorrect interpretation. For example, 6 of the metabolites of 5F-CUMYL-PEGACLONE were also identified metabolites for CUMYL-PEGACLONE [349]. Diao et al. [350] has reviewed on the metabolism of SCs. The below table (Tables 18–22) listed reported metabolism of the NPS and the study approach, the metabolites were mainly analyzed by LC-HR-MS and LC-tandem-MS.

3.3.9. Immunoassay

Immunoassays provide an inexpensive, sensitive and rapid screening for drugs in biological samples. However, not all NPSs can be detected by immunoassay methods. For example, CUMYL-PEGACLONE shown no positive results in 15 CUMYL-PEGACLONE positive authentic urine samples analyzed by the ready-to-use homogeneous enzyme immunoassays (HEIA®) Synthetic Cannabinoids-1, Synthetic Cannabinoids-2, and Synthetic Cannabinoids-3 (Immunalysis, Pomona, CA, USA) when cut-offs recommended by manufacturer were applied [366]. Nieddu et al. [393] described the cross-reactivity profiles of 30 new amphetamine designer drugs in whole blood, urine and oral fluid, using the Neogen® (Amphetamine Specific and Methamphetamine/MDMA assays) drug tests and it was found that only a few of the analyzed compounds exhibited a measurable cross-reactivity in whole blood or oral fluid and no compound showed an absorbance significantly greater than the positive control, even at concentrations up to 10,000 ng/mL for urine matrix.

The cross-reactivity of 13 designer benzodiazepines in the CEDIA, EMIT II Plus, HEIA, and KIMS II immunoassays were studied by Pettersson Bergstrand et al. [392].

Several studies on the immunoassay cross reactivity of fentanils were listed in the table (Table 23) below:

3.4. Challenges - Protein of forensic interest

With the continuous development of biopharmaceuticals, peptides and proteins drugs have gained increasing attentions. The methodologies for protein or peptide analysis in bio-matrices emerge. In the past three years, reviews on the analysis of protein by LC with superficially porous particles (SSP) [395], MS [394], and LC-MS [396] have focused on the use of these techniques to tackle the technical challenges for protein analysis, especially analysis of proteins in bio-matrices. The application of LC-MS/MS for analysis of therapeutic peptides in rat plasma for pharmacokinetic study have also been reported [397,398]. The analysis of proteins and peptides in bio-matrices of selected forensic applications will be discussed below.

3.4.1. Protein in doping control

In doping control, a group of small peptides which can be used to improve performance in sports are included in the prohibited list

Table 10
Stability studies of Synthetic cathinones.

Analytes	Matrix	Ref.
Pentylone, butylone, mephedrone and benzedrone	DBS & whole blood	[329]
Methcathinone, 3-FMC, 4-fluoromethcathinone (4-FMC, flephedrone), methylone, ethcathinone, ethylone, methedrone, buphedrone, butylone, mephedrone, eutylone, 4-methylethcathinone (4-MEC), MDPBP, pentedrone, pentylone, 3,4-dimethylmethcathinone (3,4-DMMC), α-PVP, 4-ethylmethcathinone (4-EMC), 4-methyl-a-pyrrolidinobutiophenone (MPBP), MDPV, pyrovalerone, and naphyrone	Authentic urine	[287]
Methcathinone, 3-FMC, 4-FMC, methylone, ethcathinone, ethylone, methedrone, buphedrone, butylone, mephedrone, eutylone, 4-MEC, MDPBP, pentedrone, pentylone, 3,4-DMMC, α-PVP, 4-EMC, MPBP, MDPV, pyrovalerone and naphyrone	Urine	[286]
3-FMC, 3,4-DMMC, 4-EMC, 4-FMC, 4-MEC, Buphedrone, Ethcathinone, Mephedrone, Methcathinone, Methedrone, Pentedrone, Butylone, Ethylone, Eutylone, Methylone, Pentylone, MPBP, Naphyrone, α-PVP, Pyrovalerone, MDPBP, MDPV	Blood	[285]
4-CMC, 4-FMC, α-PBP, dibutylone, dimethylone, ethylone, eutylone, mephedrone, mephedrone-D3, methedrone, methylone, MDPV, 3,4-MDPBP, MPBP, naphyrone, n-ethylbuphedrone (NEB), pentedrone and pentylone	Blood & urine	[330]
Cathinone, methcathinone, buphedrone, mephedrone, 4-methylethcathinone, MDPV, methylone, naphyrone, α-PVP and Nethylcathinone	Preserved oral fluid (Quantisal™)	[288]

Table 11
Stability studies of SC (synthetic cannabinoids) and fentanils.

Analytes	Matrix	Ref.
XLR-11, UR-144, AB-Pinaca and AB-Fubinaca	Whole blood	[326]
SDB-006-N-phenyl-analogue, AB FUBINACA/AB FUBINACA 3 Isomer, UR-144, ADB CHMICA, Mepirapim, MAB-CHMINACA, SDB 006, MA-CHMINACA, XLR-11, MAM-2201, FAB-144, 5-fluoro NNEI9, 5-fluoro SDB 006, 5-fluoro NNEI 2-naphtyl Isomer, A-834735, 5-fluoro MN 18, THJ-018, NM 2201, M − 144, 5-fluoro PCN, ADBICA, 5-fluoro SDB 005, MMB-018, 5-fluoro PB-22, ADB-PINACA, 5-fluoro NPB-22, AMB, F2201, 5-fluoro ABICA, 5 fluoro ADB, 5-fluoro AB PINACA, Cumyl THPINACA, Cumyl Pica, FUB JWH 018, AB-001, 3-CAF, FUB-144, ADB-FUBINACA, XLR12, STS-135, AB-005-azepane Isomer, FUB-AMB, AB-005, 5-fluoro AKB-48, A-796260, MDMB-CHMICA, NNEI, MDMB-CHMINACA, AB-CHMINACA, MO-CHMINACA, MN-018, EAM-2201, SDB-005, 5-chloro NNEI, THJ, EG 018, PB-22, Cl-2201, NPB-22, FDU NNEI, THJ2201, FDU-PB-22, AM-2201 benzimidazole analogue, PX-1, MMB-2201, MAM2201 N(5chloropentyl) analogue d5, 5-fluoro ADB PINACA, FUB-PB-22, 5 fluoro ADB PINACA 2-Isomer, PX-2, 5 fluoro 2 ADB PINACA 2 Isomer, MDMB-FUBINACA, 5-fluoro AMB, FUB NPB 22, 5-chloro AB-PINACA, AKB-48 N-(4fluorobenyzyl) analogue, APICA, APP CHMINACA, 5 fluoro Cumyl Pica, EG2201, 5-fluoro JWH018 adamantyl analogue, APP FUBINACA, AB FUBINACA 2 Isomer, MN-25	Serum	[327]
Fentanyl type: Butyryl Fentanyl, MT-45, AH-7921, 2-Furanylfentanyl, para-Fluorofentanyl, ortho-Fluorofentanyl, para-Fluorobutyryl Fentanyl, 4-Methoxybutyrylfentanyl, 4-ANPP, alpha-Methylfentanyl, 4-Methylphenethyl acetylfentanyl, U-47700*, U-50488*, Acrylfentanyl, Valerylfentanyl, Carfentanil, beta-Hydroxythiofentanyl	Blood, serum/plasma & urine	[324]
Furanylfentanyl, Ocfentanil, Acetylfentanyl, Butyrfentanyl	Whole blood	[325]

Table 12
Stability studies of NBOMes and Synthetic Piperazines.

Analytes	Matrix	Ref.
Phenylethylamine derivatives - NBOMes: 25C-, 25H-, 25I-, 25B-, 25G-, 25D- and 25E-NBOMe 25B-, 25C-, 25D-, 25E-, 25G-, 25H- and 25I−NBOMe	DBS Whole blood	[328] [323]
Synthetic Piperazines 1-benzylpiperazine (BZP), 1-(4-fluorobenzyl)-piperazine (FBZP), 1-(4-methylbenzyl)-piperazine (MBZP), 1-(4-methoxyphenyl)-piperazine (MeOPP), 1-(para-fluorophenyl)-piperazine (pFPP), 1-(3-chlorophenyl)-piperazine (mCPP), 1-(3-trifluoromethylphenyl)-piperazine (TFMPP) and 2,3-dichlorophenylpiperazine (DCPP)	Human whole blood	[331]

by the World Anti-doping Agency (WADA). Growth hormone releasing peptides (GHRPs), gonadotropin releasing hormones (GnRHs), vasopressin analogues, and agonists of growth hormone secretagogue receptors (GHSRs) are known examples of small peptides used for performance enhancing. LC-HRMS method for detection of the aforesaid peptides in urine was reported [399], in which DMSO was used as mobile phase additive to enhance ESI of peptides and proteins. The enhanced sensitivity by DMSO allowed a simple sample preparation, 2-fold dilution of urine, while achieved the detection of 36 small peptides and related metabolites with LOD between 50 and 1000 pg/mL. Analysis of bioactive peptides such as GHRPs and desmoporessin, in human urine by LC-MS and solid-phase extraction on weak cation-exchange microelution 96-well plates was also reported [400]. Similar approach using LC-QTOF was used in the determination of 25 doping-related peptides and 3 metabolites, including GHRPs, GnRHs and anti-diuretic hormones [401]. Some other LC-MS methods reported focused on the analysis for growth hormone (GH) administration markers such as insulin-like growth factor in human plasma [402] and its synthetic analogues such as Long R3-IGFI in human plasma [403]; procollagen III amino-terminal propeptide (P-III-NP) in human serum [404]; monitoring 22KDa-GH in serum [405]; four different GHRHs and respective metabolites in human plasma [406]; 8 proteins biomarker related to recombinant GH administration in samples from athletes [407]; and 3 recombinant GHs in equine plasma [408].

Human chronic ganodotropin (hCG) stimulates testosterone production, which can be used to normalize the suppressed testosterone level in males with prolonged intake of anabolic steroid, and hence it is also in WADA list of prohibited substances. Butch et al. [409] studied the reference threshold of intact hCG in human urine for detecting male athletes that doped with hCG using immunoaffinity extraction LC-MS/MS method. The study also included the alpha and beta heterodimer of hCG (hCGα and hCGβ). The same group furthered their study and compared the concentration of hCG, hCGα, hCGβ and core fragment of hCGβ (hCGβcf) in male urine by immunoassay and LC-MS/MS [410]. The study indicated that the intact hCG immunoassay slightly overestimated the hCG level compared to LC-MS/MS method, however, the immunoassay method was capable of detecting the case of hCG use. The metabolisms of GnRH and its synthetic analogues were also studied using LC-MS/MS method [411]. LC-MS analysis for other performance enhancing protein or peptdies, such as mitochondrial derived peptide MOTS-c in plasma [412], Activin receptor competitors including Sotatercept and Lusparercept in serum [413]; erythropoietin Fc (EPO-c) in biological specimens [414] were also reported. Most of the aforesaid methods adopted the immunoaffinity extraction for sample preparation followed by LC-MS analysis, some also include digestion by trypsin prior to LC-MS analysis. Etanercept, a protein-base medication for rheumatoid arthritis treatment, was rumored to be used in horse racing in North America. Guan et al. [415] studied Etanercept in equine plasma adopted immunoaffinity extraction followed by digestion. The analyte was reduced and alkylated, and digested by trypsin prior to LC-MS analysis. The presence of etanercept was confirmed by BLAST and SEQUEST searches. They further adopted the methodology for the detection of α-Cobratoxin (α-Cbtx) in equine plasma [416]. α-Cbtx is a toxin in Cobra venom, with strong analgesic effect and may be misused in sports such as horse racing. Analysis of α-Cbtx in equine plasma was also achieved by split-free nano-LC- HRMS method with LOD down to 50pg/mL [417].

3.4.2. Insulin

Insulin which is a hormone comprising two peptide chains

Table 13
Summary of PRM data for Synthetic cathinones.

Specimens	Concentration in ng/mL or ng/g unless specified									Ref.
	Blood	Urine	Liver	Brain	Gastric contents	Kidney	Lung	Vitreous	Others	
α-PHP	15.3	5.6	3.5	4.7	Detect	7.9	71.1	–	1.2[8]; 83.8[9]; 23.6[10]; 1078.0 pg/mg[11]	[335]
α-PVP	174	401	190	292	606	122	–	–	–	[291]
α-PVP**	4[1]; 3[5]	–	8	ND	ND	4	ND	–	positive[8]; ND[12]	[336]
PV8	260^	110^	20^	–	–	10^	–	–	–	[337]
PV8	70^	130^	40^	–	–	40^	–	–	–	[337]
N-PP*	3200^	–	5900^	2300^	–	5400^	–	4400^	–	[300]
Butylone	6[3]; 8[4]	934	116	–	–	–	–	–	–	[334]
Ethylone	872[3]; 780[4]	214	170	–	–	–	–	–	–	[334]
Ethylone	1270[3]	8740	857	–	–	–	–	–	–	[334]
Ethylone	10[4]; 5[5]	273	–	–	–	–	–	–	–	[334]
Ethylone	4[3]; 6[4]	958	–	–	–	–	–	–	–	[334]
Ethylone	19[1];19[6]	150	<60	–	–	–	–	–	–	[334]
Ethylone	298[1]; 2740[3]	–	–	–	–	–	–	–	–	[334]
Ethylone	193[3]; 69[1]	>20,0000	116	–	–	–	–	–	–	[334]
Ethylone	146[3]; 59[4]	32	–	–	–	–	–	–	–	[334]
Ethylone	262[1]	–	5200	–	6830	–	–	279	–	[334]
4-MEC**	8[5];34[5]	–	36	47	–	29	27	–	27[12]	[336]
4-MEC**	97[1]; 150[5]	–	75	138	77	43	200	–	901[8]; 162[12]	[336]
MDPV	80[3]; 80[1]	5210	–	–	–	–	–	–	–	[334]
MDPV	10[3]; 35[4]	–	–	–	–	–	–	–	–	[334]
MDPV	6[1];: 6[5]	166	–	–	19	–	–	5	–	[292]
MDPV**	3[5]; 11[5]	–	16	8	–	15	11	–	48[8]; 8[12]	[336]
MDPV**	396[1]; 426[5]	–	1073	478	1050	1202	802	–	978[8]; 722[12]	[336]
4-methoxy PV8	960[5]; 389[1]	245	–	–	550	–	–	–	–	[336]

Remarks.
ND = not detectable.
*N-PP (α-propylaminopentiophenone): intraday result presented.
** result with exaction method utilizing QuEChERS.
^ Original unit not in ng/mL or ng/g.
Blood: 1. Femoral; 2. Peripheral; 3. Aorta; 4. Iliac vein/vena cava; 5. Heart/Cardiac/Pericardial fluid; 6. Central.
Other specimens: 8. Bile; 9. Spleen; 10. Heart; 11. Hair; 12. Muscle.

Table 14
Summary of PRM data for Synthetic Cannabinoids.

Specimens	Concentration in ng/mL or ng/g unless specified								Ref.
	Blood	Urine	Liver	Brain	Gastric contents	Kidney	Lung	Others	
Synthetic Cannabinoids									
MDMB-CHMICA	2.1[5]; 1.7[1]	0.01	2.6	5.5	2.4	3.8	2.6	1.2[12]	[265]
AB-FUBINACA	Detect[1,5a,5b]	–	0.046^	–	–	0.0217^	0.124^	–	[338]
AB-PINACA	0.0126^[1]; 0.0196^[5a]; 0.0206^[5b]	–	0.169^	–	–	0.138^	0.355^	–	[338]
Mepirapim	593[5]; 567[1]	527	–	–	–	–	–	–	[339]
Mepirapim	587[5]; 554[1]	309	6300	2740 *; 2690**; 3300[#]; 1710[##]	–	5410	2720	3120[10]; 2400[13]; 1580[14]; 3610[9]; 792[12]	[340]
EAM-2001	0.0566^[1]; 0.0287^[5a]; 0.031^[5b]	–	0.126^	–	–	0.120^	0.348^	–	[338]

Remarks: ^ Original unit not in ng/mL or ng/g.
Blood: 1. Femoral; 2. Pericardial fluid; 3. Aorta; 4. Iliac vein/vena cava; 5. Heart/Cardiac (5a: right heart; 5b: left heart); 6. Central.
Other specimens: 8. Bile; 9. Spleen; 10. Heart/Myocardium; 11. Hair; 12. Muscle; 13. Pancreas; 14. Adrenal gland.
Brain: * Cerebrum; ** Cerebellum; # Pons; ## Medulla oblongata.

namely, A and B chains, have been involved in many forensic cases. Investigation of homicidal inulin overdose is challenging because of difficulty in toxicology analysis for insulin, as well as the rapid degradation of insulin in PM samples. In a report of four post-mortem cases, the skin tissue of the injection sites was analyzed by chemiluminescene immunoassay [418]. A rapid detection of C-peptide of insulin in human urine was also developed with the use of double-antibody sandwich ELISA [419]. Other than immunoassay, LC-HRMS was used to detect insulin, proinsulin and C-peptide in human plasma [420]. The method utilized immunoaffinity extraction of insulin from plasma, followed by orbitrap mass spectrometry analysis with full scan and data dependent MS^2 experiments, achieving the limit of detection down to about 0.05ng/mL.

Table 15
Summary of PRM data for Fentanils.

Specimens	Concentration in ng/mL or ng/g unless specified									Ref.
	Blood	Urine	Liver	Brain	Gastric contents	Kidney	Lung	Vitreous	Others	
Acetyl fentanyl	21[2]; 95[5]	8	160	200	28,000	–	–	68	330[8]	[341]
Acetyl fentanyl	285[5] ; 192[1]	3420	1,100	620	–	–	–	–	–	[342]
Acetyl fentanyl	210[5] ; 255[1]	2720	–	–	–	–	–	140	–	[342]
Acetyl fentanyl	7.2[5]; 2.2[1]	–	–	–	–	–	–	1.3	–	[215]
Acetyl fentanyl	155[5]; 125[1]	126	–	–	–	–	–	–	–	[339]
Acetyl fentanyl	212[5]; 170[1]	169	416	649*; 688**; 821[#]; 489[##]	–	1140	448	–	1180[10]; 987[13]; 481[14]; 1150[9]; 281[12]	[340]
Acetyl fentanyl	239[5]; 153±2[1]	240	–	–	880	–	–	–	–	[343]
4-ANPP	4.3[2]; 5.8[5]	Detect	>40	–	-ve	–	–	<0.20	–	[216]
Butyryl fentanyl	99[2] 220[5]	64	41	93	590	–	–	32	260[8]	[341]
Butyryl fentanyl	3.7[2]; 9.2[5]	2	39	63	4,000	–	–	9.8	49[8]	[341]
Carfentanil	92	2.8	–	–	–	–	–	23	–	[226]
Norcarfentanil:	0.532							0.300		
Carfentanil	1.9[5]; 0.36[1]	–	–	–	–	–	–	–	–	[215]
Furanylfentanyl	1.9[2]; 2.8[5]	Detect	-ve	–	55,000	–	–	<0.20	–	[216]
Furanylfentanyl	8.7[5]; 5.5[1]	–	–	–	–	–	–	30	–	[215]
3-methylfentanyl	2.6[5]; 1.7[1]	–	–	–	–	–	–	0.65	–	[215]
Ocfentanil	15.3[1(EDTA)] ;23.3[5(EDTA)] ; 21.9[5]	6.0	31.2	37.9	17.1	51.2	–	12.5	13.7[8]	[229]
Ocfentanil	36.4[1]; 49.8[5]	67.9	106	72	–	75.5	108	–	365[8]	[231]
Ocfentanil	9.1[1(fluoride)] ; 7.5[1(heparin)] ; 27.9[5]	480	–	–	–	–	–	–	360ng[15]	[231]
Ocfentanil	3.7[2]; 3.9[5]	–	–	–	2.5	–	–	2.0	8.4[8]	[233]

Remakrs: ^ Original unit not in ng/mL or ng/g.
Blood: 1. Femoral; 2. Peripheral; 3. Aorta; 4. Iliac vein/vena cava; 5. Heart/Cardiac/Pericardial fluid; 6. Central.
Other specimens: 8. Bile; 9. Spleen; 10. Heart/Myocardium; 11. Hair; 12. Muscle; 13. Pancreas; 14. Adrenal gland; 15 Nasal swab.
Brain: * Cerebrum; ** Cerebellum; [#] Pons; [##] Medulla oblongata.

Table 16
Summary of PRM data for Synthetic Opioids.

Specimens	Concentration in ng/mL or ng/g unless specified								
	Blood	Urine	Liver	Brain	Gastric contents	Kidney	Lung	Vitreous	Ref.
U-47700	190[2]; 340[6]	360	1700	–	Trace (<1mg)	–	–	170	[344]
U-47700	525[1]; 1347[5]	1393	4.3	0.97	–	2.7	3.2	–	[345]
U-47700	819[1]; 1043[5]	1848	3.1	1.1	–	1.4	2.4	–	[345]
U-47700	260^[5]; 400^[1]	4600^	280^	380^	–	–	–	19^	[346]

Remarks: ^ Original unit not in ng/mL or ng/g.
Blood: 1. Femoral; 2. Peripheral; 3. Aorta; 4. Iliac vein/vena cava; 5. Heart/Cardiac/Pericardial fluid; 6. Central.

Table 17
Summary of PRM data for Designer Benzodiazepine and others.

Specimens	Concentration in ng/mL or ng/g unless specified								
	Blood	Urine	Liver	Brain	Gastric contents	Kidney	Lung	Others	Ref.
Designer Benzodiazepine									
Flubromazolam	8^[1]	58^	58^	51^	–	–	–	14^[12]	[347]
Flubromazolam	4.4^[1]	–	17^	43^	–	–	–	13^[12]	[347]
3-Fluorophenmetrazine	2400^[1] 2600^[6]	–	–	–	–	–	–	–	[348]
Others:									
MXE**	2[5c]; 7[5d]	–	8	5	58	16	7	35[8]; 6[12]	[336]
MXE**	295[1]; 698[5d]	–	974	408	1391	846	554	777[8]; 440[12]	[336]
3-MeO-PCP	63[1]	94	–	–	–	–	–	64[8]; 731[11]*pg/mg; 893[11]** pg/mg; 846[11#]pg/mg	[313]

Remarks: ^ Original unit not in ng/mL or ng/g.
Blood: 1. Femoral; 2. Peripheral; 3. Aorta; 4. Iliac vein/vena cava; 5. Heart/Cardiac/Pericardial fluid; (5c: heart; 5d: Pericardial fluid); 6. Central.
Other specimens: 8. Bile; 9. Spleen; 10. Heart/Myocardium; 11. Hair; 12. Muscle; 13. Pancreas; 14. Adrenal gland; 15 Nasal swab.
Hair: *0–2cm:; **2–4cm; [#] 4–6cm.

Table 18
Metabolism study of Synthetic Cannabinoids.

Compound	Study approach	Ref.
3,5-AB-CHMFUPPYCA	Pooled human liver microsomes (pHLM)	[351]
ADB-FUBINACA	Authentic human urine	[352]
ADB-FUBINACA	HLM	[353]
4′N−5F-ADB	Rat and human urine, pooled human S9	[354]
AM-694	Human urine (clinical casework)	[355]
AM-2201	Human urine (clinical casework)	[355]
AMB-CHMICA	Pooled rat and human hepatocytes	[356]
APINAC (AKB-57,	Rat urine samples	[357]
ACBL(N)-018)	Rat liver microsomes and blood sample of rats administered	[358]
BB-22	Urine and/or serum specimens	[359]
	Human hepatocytes	[360]
5F-ADB	HLM	[361]
5C-AKB48	Pooled human hepatocytes and rat Hepatocytes	[356]
CUMYL-PICA	Rat and HLM	[362]
CUMYL-PINACA	pHLM	[363]
	pHLM and human urine	[364]
5F-CUMYL-PINACA	pHLM and human urine	[364]
CUMYL-4CN−B7AICA	pHLM	[363]
CUMYL-4CN-BINACA	pHLM	[363]
5F-CUMYL-P7AICA	Authentic human urine, pHLM	[365]
		[363]
CUMYL-PEGACLONE	pHLM and human authentic urine samples	[366]
5F-CUMYL-PEGACLONE	pHLM and human urine	[349]
5F-CUMYL-PICA	Rat and HLM	[362]
5F−CUMYL-PINACA	pHLM	[363]
CUMYL-4CN-BINACA	Authentic urine samples and HLM	[367]
EG-018	Human hepatocytes	[368]
	Authentic human urine	[369]
EG-2201	Authentic human urine	[369]
JWH-007	Human urine (clinical casework)	[355]
JWH-019	Human urine (clinical casework)	[355]
JWH-203	Human urine (clinical casework)	[355]
JWH-307	Human urine (clinical casework)	[355]
MAM-2201	Human urine (clinical casework)	[355]
	HLM; human, mouse, and rat hepatocytes	[370]
MDMB-CHMCZCA	Authentic human urine	[369]
MDMB-CHMICA	Authentic human urine and serum	[266]
MDMB-FUBINACA	Authentic human urine specimens	[352]
MN-18	Pooled rat and HLM and hepatocytes	[371]
NM-2201 (CBL-2201)	Human hepatocytes and authentic human urine specimens	[372]
NNEI	Pooled rat and HLM and hepatocytes	[371]
5F-PY-PICA	Pooled HLM and hepatocytes, suspended and sandwich-cultured rat hepatocytes	[373]
SDB-006	Human hepatocytes	[374]
5Cl-THJ-018	Human urine	[375]
UR-144	Human urine (clinical casework)	[355]
XLR-11	Human urine (clinical casework)	[355]

Table 19
Metabolism study of Fentanils.

Compound	Study approach	Ref.
Acetylfentanyl	Human-induced pluripotent stem cell-derived hepatocytes	[378]
	hepatocytes isolated from a liver-humanized mouse (PXB-cells)	[379]
	Pooled human hepatocytes, authentic human urine samples from autopsy cases	[380]
Acrylfentanyl	Pooled human hepatocytes, authentic human urine samples from autopsy cases	[380]
Butyrfentanyl	HLM and recombinant cytochrome P450 enzymes (CYP)	[381]
Fentanyl	Human-induced pluripotent stem cell-derived hepatocytes hepatocytes isolated from a liver-humanized mouse (PXB-cells)	[378]
		[379]
4-fluoro-isobutyrylfentanyl	Pooled human hepatocytes, authentic human urine samples from autopsy cases	[380]
Furanylfentanyl	Pooled human hepatocytes, authentic human urine samples from autopsy cases	[380]
Methoxyacetylfentanyl	Pooled human hepatocytes	[239]
Ocfentanyl	HLM	[233]

3.4.3. *Botulism toxins*

Botulism is a life-threatening neuroparalytic disease caused by botulism toxins, which is a closely monitored in Europe [421,422]. Botulism can be foodborne, with the diagnosis confirmed by identification of botulinum neurotoxin (BoNT) in patient's stomach or intestinal contents, vomit or feces, in blood in the hyper-acute stage or in the ingested food [423]. Recently, cosmetic injection of BoNT has swept the world, and a clinical analysis of 86 botulism cases caused by cosmetic injection of BoNT was reported [424]. The current standard test for BoNT is the mouse bioassay (MBA) with immunoassay is a common alternative. A Rapid detection of BoN-Tusing a sinlge-molecule array assay was developed for the

Table 20
Metabolism study of Synthetic Cathinones.

Compound	Study approach	Ref.
Dibutylone	HLMs (HLM)	[304]
α-PBP	pHLM or pooled human liver S9 fraction (pS9)	[376]
α-PHP	pHLM or pS9	[376]
	Urine	[302]
α-PHPP	Urine	[302]
α-PEP/PV8	pHLM or pS9	[376]
α-POP/PV9	pHLM or pS9	[376]
α-PVP	Urine	[377]
α-PVT	pHLM or pS9	[376]

quantitative analysis of BoNT serotype A1, the most common serotype with the limit of detection down to 200 fg/mL for serum accomplished in about an hour [425]. Another handy tool for detection of active BoNT Type A in human serum by a gold nanoparticle-based lateral flow test was reported [426] which only required 1 μL of serum samples. With the advance MS technology, detection of BoNT type A in biological specimens was reported with the use of MALDI-TOF mass spectrometry [427]. Prior to the mass spectrometry, the toxin in biological matrices was first immune-captured by antibodies immobilized on streptavidin beads, and then subjected to a cleavage reaction to generate a cleavage product

Table 21
Metabolism study of Designer benzodiazepines.

Compound	Study approach	Ref.
Clonazolam	pHLM or 13 different human UDP-glucuronyltransferases (UGTs)	[382]
Deschloroetizolam	pHLM or 13 different human UDP-glucuronyltransferases (UGTs)	[382]
Etizolam	pHLM or 13 different human UDP-glucuronyltransferases (UGTs)	[382]
Flubromazolam	pHLM or 13 different human UDP-glucuronyltransferases (UGTs)	[382]
	Authentic urine and serum	[383]
Flunitrazolam	pHLM or 13 different human UDP-glucuronyltransferases (UGTs)	[382]
Metizolam	pHLM or 13 different human UDP-glucuronyltransferases (UGTs)	[382]
Nifoxipam	pHLM or 13 different human UDP-glucuronyltransferases (UGTs)	[382]
Nitrazolam	pHLM or 13 different human UDP-glucuronyltransferases (UGTs)	[382]
Pyrazolam	pHLM or 13 different human UDP-glucuronyltransferases (UGTs)	[382]

Table 22
Metabolism study of Others.

Compound	Study approach	Ref.
Phencyclidine type:		
3-MeO-PCP	pHLM and rat urine	[310]
3-Methoxyrolicyclidine (3-MeO-PCPy)	pHLM and rat urine	[310]
Phenethylamine type:		
4-EA-NBOMe	Rat urine and pS9	[384]
25C–NBOMe	Human hepatocytes, mice urine and authentic human urine	[385]
25I–NBOMe	Human hepatocytes, mice urine and authentic human urine	[385]
Typtamine derivatives:		
5-fluoro-DALT	Rat urine and pooledHLM	[386]
7-methyl-DALT	Rat urine and pooledHLM	[386]
5,6-methylenedioxy-DALT	Rat urine and pooledHLM	[386]
5-MeO-2-Me-ALCHT	pHLM and cytosols and rat urine	[387]
5-MeO-2-Me-DALT	pHLM and cytosols and rat urine	[387]
5-MeO-2-Me-DIPT	pHLM and cytosols and rat urine	[387]
Synthetic Opioids:		
U-4770	HLM and authentic human urine	[388]
U-49900	HLM and authentic human urine	[388]

Table 23
Studies on the immunoassay cross reactivity of fentails

Target analysts	Immunoassay kits	Ref.
Fentanyls type:		
acetylfentanyl, acrylfentanyl, butyrfentanyl, 4-chloroisobutyrfentanyl, 4-fluorobutyrfentanyl, 4-fluorofentanyl, 4-fluoroisobutyrfentnyl, isobutyrfentanyl, methoxyacetylfentanyl, or tetrahydrofuranfentanyl, 4-methoxybutyrfentanyl and 2-fluorofentanyl	Thermo DRI® Fentanyl Enzyme, Immunoassay, the ARK™ Fentanyl Assay homogeneous enzyme immunoassay, and the Immunalysis® Fentanyl Urine SEFRIA™ Drug Screening Kit	[389]
2-fluorofentanyl, acetylfentanyl, acrylfentanyl, carfentanil, cyclopropylfentanyl, tetrahydrofuranylfentanyl, furanylfentanyl, ocfentanil, valerylfentanyl	Fentanyl direct ELISA kit (Immunalysis KI-218-IMM) on a Freedom EVOlyzer 150 system	[390]
Norfentanyl, acetyl fentanyl, 4-anilino-N-phenethylpiperidine, beta-hydroxythiofentanyl, butyryl fentanyl and furanylfentanyl	Neogen® Fentanyl ready-to-use enzyme-linked immunosorbent assay kit	[11]
4-ANPP, acetylfentanyl, butyrylfentanyl, furanylfentanyl, isobutyrylfentanyl, valerylfentanyl, norfentanyl, (+)-cis-3-methylfentanyl, carfentanil, alfentanil, norcarfentanil, remifentanil, sufentanil	Fentanyl ELISAPlate (FE 3505) and Carfentanil/Remifentanil ELISA Plate (CFE10185)(from Randox Laboratories Ltd.); Fentanyl Group Kit (131519) and Fentanil Group Forensic Kit (1000519) (from Neogen); Fentanyl ELISA Kit (218-0096) (from Immunalysis)	[391]

of peptide substrate for detection of toxin activity. In another article, a MALDI-TOF MS method with similar approach was directly compared with the MBA and validated [428].

3.4.4. Cardiac Troponins in the PM cases

With development in proteomics, the search for disease-specific biomarkers for diagnostic or clinical applications gained significant attention. The advancements in mass spectrometry (MS), LC-MS and protein microarray technology and other protein profiling methodologies have accelerated the discovery of disease-specific biomarkers. A review described commonly used proteomic technologies for biomarker discovery and the most popular approaches for diagnosis with biomarkers [429]. Troponin I is known to be one of the most commonly used biomarker for diagnosis of myocardial damage or cardiac dysfunction. A review discussed the different isoforms of cardiac-specific troponin, covering the current situation, advance and prospect of analytical platform for routine Troponin I analysis for diagnosis [430]. The review also discussed the procedures, pros and cons, as well as applications of the two main MS-based proteomics approaches: to-down for intact protein and bottom-up for peptide analysis after proteolytic digestion. The possible use of troponin I as biomarkers in postmortem diagnosis of cardiac failure is well known in the forensic setting. Troponin T and NT-proBNP (N-terminal pro-B-type natriuretic peptide) may also be useful alternatives to Troponin I. The usefulness of troponins and natriuretic peptides as indicators of fatal damage to heart in cases of severe sepsis and septic shock without concomitant underlying coronary syndromes was evaluated by comparing data postmortem cases of sepsis-related fatalities and a control group [431]. The use of cardiac troponins and NT-proBNP in postmortem diagnosis of heart disease was evaluated, including the sampling site, PM interval, and the influence of cardiopulmonary resuscitation (CPR), by a study of 24 PM cases of ischemic heart disease (IHD) and 24 control cases [432]. High-sensitive cardiac troponin T (hs-TnT) is used in clinical practice for diagnosis of myocardial ischemia, and its potential for PM assessment was also evaluated with 85 autopsy data [433]. The influence of CPR attempts on PM hs-TnT was also investigated. Both studies determined the peptides level by immunoassay technique, however, no significant correlations could be established. Therefore more studies in this area were required. Alternative to immunoassay, quantitation of cardiac troponin I in human plasma using immunoaffinity enrichment strategy and isotope dilution LC-MS/MS was reported [434]. This served as a first step for preparation of matrix-based reference materials and potential harmonization for analysis of Troponin I in human plasma.

4. Advances – from Sample to Interpretation

4.1. Advances – Sample preparation

Sample preparation plays a crucial role in toxicological analysis because it represents an estimate of 80% of the whole process. Even with the best instrument, a poor sample preparation likely results in unsatisfactory analytical result. A good sample preparation should be able to retain and concentrate the analytes of interest to an extent suitable for instrumental analysis and at the same time eliminate or reduce the matrix interference. García-Repetto [435] surveyed the sample preparation for pesticide analysis in forensic toxicology laboratories. The author carried out database searching on pesticide extraction from human samples and concluded that liquid-liquid extraction (LLE), solid-phase extraction (SPE) and solid-phase microextraction (SPME) remained the three most used extraction methods. These traditional methods suffer from drawbacks such as laborious procedure and large consumption of organic solvents.

4.1.1. Dried blood spot (DBS)

DBS is a sampling technique that involves collection of a low volume of blood by puncturing the fingertip or heel using sterile disposable lancet in the filter paper. Alternatively, the volume of blood can be made precise by using a micropipette. DBS has been used for highly diverse applications, such as newborn screening, therapeutic drug monitoring (TDM) as well as toxicology. Velghe et al. [436] published an article on DBS, focus on the use of DBS in the fields of toxicology and TDM. Compared to whole blood collection technique, DBS is less invasive, easier to store and transport. Because it is a dry matrix, it reduces the enzymatic activities and microbial degradation of compounds, which extend the storage lifetime of more labile compounds such as cocaine and opiates. In recent years, more forensic laboratories published on the method validation for determination of cocaine and its metabolites [437–439]. Sadler Simões et al. [440] further extended the scope to include opiates, cocaine, amphetamines and some of their metabolites in a single determination. DBS approach has been studied for organophosphorus insecticides [441] and paraquat determination [442].

4.1.2. Supported liquid extraction (SLE)

SLE is an analogue of the traditional LLE approach where the aqueous phase is coated onto a large surface area material such as diatomaceous earth held in the cartridge. Automated online extraction can minimize tedious work. Valen et al. [443] reported a high-throughput UPLC tandem mass spectrometry for the determination of 21 drugs in oral fluid (OF) using fully automated online SLE extraction system. Similarly, Kristoffersen et al. [444] incorporated fully automated online SLE extraction system for the extraction of opiates, benzodiazepines, amphetamine and derivatives? from whole blood sample in cases involving Driving Under the Influence of Drugs (DUID).

4.1.3. Disposable pipette extraction (DPX)

DPX is a dispersive micro SPE that enables rapid extraction of analytes from liquid solutions by means of the loosely contained sorbent placed inside a pipette tip. Sample is drawn into the pipette tip directly where it gains contact with the solid phase. Air is drawn into the pipette tip to allow efficient dispersion of the sample with the sorbent. After equilibrium, the sorbent is washed with an organic solvent. The analyte is eluted by another organic solvent. Nowadays, DPX can be fully automated and coupled with GC-MS or LC-MS for injection [445]. Commercially acquired pipette tip for extraction was utilized in the determination of Cannabinoids and metabolites [446] and pesticides [447] in human urine. Recently, Zhang et al. [448] synthesized a novel three-dimensional ionic liquid-ferrite functionalized graphene oxide nanocomposite and successfully applied it to the extraction of 16 polycyclic aromatic hydrocarbon (PAHs) in human blood sample.

4.1.4. Phospholipid removal

Phospholipids are major components of cell membranes. These compounds are problematic to forensic analysts particularly when they are not the analytes of interest. Phospholipids are strongly retained on hydrophobic columns, and cause significant ionization suppression in the mass spectrometer [449]. In recent years, many forensic laboratories incorporated phospholipid removal plates in the sample preparation to reduce the matrix effect due to the endogenous phospholipids without sacrificing analyte signals. Sensitive determination of peramivir [450], cannabinoids [451], anticoagulant rodenticides [452], insecticides and pesticides [453] were reported. While phospholipids were undesirable in these

publications, Casati et al. [454] worked on the determination of phosphatidylethanols which served as the alcohol biomarkers. The phospholipids were retained in the phospholipid removal plates. After washing the matrix, the phospholipids were eluted with 1% ammonia in 2-propanol solution.

4.1.5. QuEChERS

Originally developed for multi-residue pesticides analysis in fruits and vegetables in 2003, this extraction has recently been utilized in forensic analyses. QuEChERS is an acronym for Quick, Easy, Cheap, Effective, Rugged and Safe. The extraction process is divided into two steps: the salting out assisted liquid-liquid extraction (SALLE) and clean-up of the organic extract using dispersive solid phase. Using this extraction method, Srivastava et al. [455] reported the simultaneous determination of 31 multi-class (organophosphates, organochlorines, and synthetic pyrethroids) pesticide residues in human plasma. Similar work by Lehmann et al. [456] whose research group used QuEChERS extraction for the simulataneous determination quantification of 37 multi-class pesticides in human hair. Alves et al. [457] made the first report on the extraction and determination of two antidepressants, fluoxetine and clomipramine, and their metabolites in human urine. QuEChERS extraction were found applicable in human whole blood and serum for the determination of THC and its metabolites [458], antipsychotic and antidepressant drugs [459], pesticides, abuse drugs, prescription drugs and metabolites [460].

4.1.6. Microextraction

Microextraction is an extraction technique where the volume of the extraction solvent is very small compared to that of the sample. Depending on the extraction phase, it is categorized into solid-based method and liquid-based methods. Solid phase microextraction (SPME), microextraction by packed sorbent (MEPS) and stir-bar sorptive extraction (SBSE) belong to the solid-based method. On the other hand, hollow fiber liquid-liquid microextraction (HFLLME), electomembrane extraction (EME) and dispersive liquid-liquid microextraction (DLLME) belong to the liquid phase microextraction (LPME).

4.1.6.1. Solid phase microextraction (SPME). SPME is an extraction technique which resembles a syringe. The needle of the syringe is the fiber coated with an extraction phase of polydimethylsiloxane (PDMS), polyacrylate (PA), carbowax/polyethylene glycol fiber (CW/PEG) or carbowax/template resin (CW/TPR). SPME integrates sampling, preconcentration, removal of matrix and introduction of extracts into one step, thereby greatly simplifying the sample preparation procedure. Owing to the advantages of rapidness, simplicity, being solvent free and easy automation, SPME has been extensively used for the analysis of biological, forensic, environmental, clinical, food, and pharmaceutical samples. In forensic toxicology, Waters et al. [461] used head-space solid phase microextraction (HS-SPME) to quantify 24 compounds including aliphatic and aromatic volatile hydrocarbons from blood of cadavers in fire-related cases. SPME can also be coupled with 2D GC/HRTOF-MS for profiling volatile organic compounds in postmortem (PM) blood [462]. Human scent is a form of trace evidence collected for biometric individualization. The Individual Odour Hypothesis assumes that everyone has a unique scent due to the variation of genetics, diets, metabolism and environmental factor. A procedure based on HS-SPME coupled with GC-MS has been developed for the determination of common used drugs in sweat of drivers stopped during roadside controls [463]. Recently, a novel selective multi-walled carbon nanotubes/ionic liquid based on imidazolium was synthesized and successfully coated on the SPME fiber for the extraction of methamphetamine and methylenedioxymethamphetamine in human urine [464]. Not only being coupled with GC-MS, in-tube SPME-LC tandem mass spectrometry has been reported in the determination of nicotine and cotinine in hair [465].

4.1.6.2. Microextraction by packed sorbent (MEPS). MEPS is a miniaturized version of SPE in which a packed sorbent cartridge is mounted at the needle of the syringe. Common sorbent materials include reversed phases (C_2, C_8, C_{18}), normal phases (silica), mixed mode (C_8/SCX) and ion exchange resin. With MEPS, the sample size can be as little as 10 μL. Besides, the sorbent material in MEPS can be reused for multiple extractions if cleaned properly. MEPS has been employed in the extraction of NPS in oral fluid [466,467], abuse drugs [468], THC and its metabolites in human plasma [469], cocaine and its metabolites in urine [88] and organopesticides in blood [470].

4.1.6.3. Stir-bar sorptive extraction (SBSE). SBSE is a microextraction technique where a stir bar is coated with an extraction phase of polydimethylsiloxane (PDMS). After stirring for some time to achieve equilibrium of the analytes between the PDMS sorbent and the sample matrix, the adsorbed compounds are thermally desorbed for GC-MS analysis or desorbed with a solvent for LC system. SBSE has been widely applied in the environmental and food analysis. Only a handful examples of forensic analysis using SBSE as extraction method are found in the literature. Determination of dimethyl trisulfide in rabbit blood [471], Ghrelin hormone (aka. hunger hormone) [472], losartan and valsartan in human plasma [473] were reported by different research groups. The aforementioned examples made use of commercially available stir bars. On the contrary, novel stir bars on which surface modification had been applied to improve the extraction efficiency were reported. Wang et al. [474] reported a method to chemically modify the inert surface of polyether ether ketone (PEEK) jacket of metal stir bar with polar benzoic acid followed by immobilization of metal organic framework consisting of aluminum-based Materials of Institute Lavoisier-68 (MIL-68). The MIL-68@PEEK-based SBSE device was used to determine three parabens in cosmetics and rabbit plasma. Grau et al. [475] prepared a magnetic composite made of $CoFe_2O_4$ magnetic nanoparticles (MNPs) embedded into a mixed-mode weak anion exchange polymer (Strata™-X-AW) (i.e., $CoFe_2O_4$-Strata™-X-AW) as the sorbent material in SBSE to extract traces of triphenyl and diphenyl phosphate in urine of nail polish users. This novel approach combined the principles of stir bar sorptive extraction (SBSE) and dispersive solid-phase extraction (DSPE), in such a way at low stirring rate the magnetic material remained onto the surface of the stir bar like in SBSE, whereas at high stirring rate the material was completely dispersed into the donor solution like in DSPE.

4.1.6.4. Hollow fiber liquid phase microextraction (HF-LPME). HF-LPME system is a syringe device with a porous polypropylene hollow fiber for immobilization of extraction solvent in the pores of the hollow fibers. There are two different modes, namely, two-phase and three-phase HF-LPME. In the two-phase HF-LPME, the analytes of interest migrate from the sample matrix (donor phase) to the extraction solvent (acceptor phase), which is an organic solvent within the hollow tube lumen; whereas in the three-phase system, an additional thin layer of organic phase is sandwiched between the two aqueous donor and acceptor phases. The three-phase HF-LPME works well with drugs with ionizable functional groups. For basic drugs, the pH at the donor phase should be alkaline to keep the analytes unionized for the efficient extraction into the thin layer of organic solvent in the hollow tube. The pH of the acceptor phase inside the hollow tube lumen should be made

acidic to back-extract the analytes of interest. Using the two-phase or three-phase HF-LPME as the extraction system, determination of benzodiazepine drugs [476], bisphenol A and other plasticizer metabolites [477], quercetin [478], proton pump inhibitor drugs [479], anticancer drugs [480], ezetimibe and simvastatin [481] in biological samples were reported.

4.1.6.5. Dispersive liquid-liquid microextraction (DLLME). DLLME is performed by adding a small volume of the immiscible extraction solvent to the sample. Both phases are mixed thoroughly in order to obtain a fine dispersion which maximize the contact surface between the extraction solvent and the sample containing the analytes. The extraction solvent can be organic solvent or ionic liquid, which is a liquid ionic salt with a melting point typically lower than 100 °C. Eventually both phases are separated by centrifugation. On the other hand, the extraction solvent can be solidified at low temperature. The extraction solvent is collected and analyzed. Much work has been reported using this extraction technique. Selected examples include DLLME of benzodiazepines and benzodiazepine-like hypnotics [482], recreational drugs [483], cocaine's major adulterants (caffeine, levamisole, lidocaine, phenacetin, diltiazem, and hydroxyzine) [484], stimulants [485], trizole fungicides [486], abuse drugs and NPS [487] in human blood and urine.

4.1.6.6. Electromembrane extraction (EME). Electromembrane extraction was introduced in 2006 as a totally new microextraction method for charged analytes in aqueous samples. Unlike all the above extraction methods which rely on mass transfer between phases, electromembrane extraction is based on electrokinetic migration of the analytes through a supported liquid membrane and into an acceptor solution under an influence of electric potential. The supported liquid membrane is an organic solvent immobilized in the pores of the porous membranes. Since analytes must pass through the supported liquid membrane (SLM), the chemical and physical properties of the organic solvent is critical to the extraction process [488]. Drouin et al. [489] investigated as many as 22 organic solvents to evaluate the extraction efficiency of 45 polar basic metabolites. From the study, 2-nitrophenyl pentyl ether (NPPE) appeared to be the most efficient SLM. EME has been applied for the extraction of benzodiazepines [490], propylthiouracil [491] and zolpidem [492]. Interestingly, Vårdal et al. [493] looked into ways for phospholipid cleanup in human plasma sample. With optimized conditions, no trace of phospholipids was detected in any of the acceptor solutions, whereas the non-polar basic drugs, polar basic drugs and non-polar acidic drugs were extracted with recoveries up to 50%.

4.2. Advances – Instrumentations

4.2.1. Mass spectrometry overview

Mass spectrometry is the most important technique in forensic toxicology analysis. Publications on multi-drugs toxicology analysis by hyphenated tandem Mass spectrometry (MS/MS), especially LC-MS/MS have predominated for decades. An article on the extended role of MS in drug testing [494] gave an introduction to the application of MS in therapeutic drug monitoring (TDM) and toxicology, the implementation and quality assurance, with emphasis of the advances and recent trends such as HRMS. High-resolution mass spectrometry (HRMS) has gained popularity in toxicology with its increased availability. Mogollón et al. [495] summarized the MS methods for the identification and drugs of abuse in various biological fluids and tissues, focusing on the most commonly used methodologies, including GC-MS, LC-MS and other direct techniques, such as direct analysis in real time (DART), paper spray (PS) and laser diode thermal desorption (LDTD). In conclusion, the authors opined that MS coupled with chromatography are more preferred techniques for screening analysis, while the direct techniques with MS are more likely for target analysis or qualitative analysis. A review by Maurer [496] on mass spectrometry in toxicology covered GC, LC, matrix-assisted laser desorption ionization (MALDI) coupled to quardrupole (Q), ion trap (IT), time-of-flight (TOF), or Obitrap (OT) mass analyzers. Meyer and Maurer [497] reviewed and compared the use LC coupled to low- and high-resolution MS for screening of NPS in biological matrices, and opined that the low-resolution MS might remain the standard for the next couple of years at least for easy-to-use quantitative screening procedures. Maurer and Meyer [498] further published a review on the use of HRMS in toxicology covering areas, such as drug metabolism studies, screening and quantification for detection of drugs and poisons for forensic toxicology. The review concluded that with very high identification power together with comparable easy development of qualitative and quantitative methods, HRMS would gain much more attraction when cheaper equipment and user-friendly software packages available in the market.

4.2.2. HRMS

4.2.2.1. HRMS – Screening protocol. A comprehensive screening procedure for drugs and poison is an essential task in analytical toxicology. Systematic toxicological analysis (STA) by a technique or a combination of techniques with large reference libraries have been adopted. The coverage of STA relies on the coverage of reference libraries. The challenge of continuous NPS proliferation had accelerated need for non-targeted screening protocols. In a review by Pasin et al. [499] on the use of HRMS for the analysis of NPS, the research group gave an overview of the current state of non-targeted screening strategies with HRMS, covering sample preparation procedures, data acquisition, instrumental analysis and data processing techniques. In data processing techniques, targeted, suspect and non-target screening were discussed. The author further gave an overview of two different approaches of non-targeted screening, namely, top-down and bottom-up. Pasin et al. [500] also reported the characterization of phenethylamines analogues using HRMS bottom-up approach for non-targeted screening, and identified that common product ions and neutral losses could be monitored using basic data processing techniques such as product ion searching and neutral loss filtering (NLF). For non-targeted screening analysis, data processing is considered as the bottleneck, McEachran et al. [501] described the openly available workflow for the generation and linking of about 700,000 MS-ready structures as well as download, search and export capabilities to serve structure identification using HRMS. In this article, the importance of the "MS-ready" structural representation for HRMS was demonstrated with several examples. The use of HRMS coupled with paper spray for drug screening was also discussed by McKenna and coworkers [502]. This approach served as an alternative for rapid drug screening, in which the biological fluid was simply spotted onto a paper substrate. Upon the application of a spray solvent and an electric potential, extraction and ionization occur directly from the paper without need for additional sample preparation for the HRMS analysis. HRMS proves to be a versatile technical for screening, it allows retrospective screening of data in couple studies [503–505].

4.2.2.2. HRMS - QTOF for screening. QTOF is becoming more prevalent as screening tools in toxicology laboratories, and there are numerous publications on the screening protocol using LC-QTOF in the review period. Grapp et al. [506] reported a systematic forensic toxicology analysis in serum by LC-QTOF-MS, and compared the

results with GC-MS. It was found that LC-QTOF-MS procedure was superior to GC-MS in screening, as more drugs were identified as compared to GC-MS (335 versus 141). However, detection of analytes with nonpolar and volatile nature is privileged to GC-MS. Bidny and co-workers [507] published their validated method for the screening of more than 185 drugs and metabolites in blood by LC-QTOF-MS, while simultaneously quantifying more than 90 drugs. Similarly, Partridge et al. [508] published their screening method covering 320 forensically significant compounds in blood by LC-QTOF-MS. Both articles shared their methodology and validation data. Liu et al. [509] established a MS spectral database by UHPLC-QTOF-MS, including over a thousand compounds of interests. It could serve as an effective protocol for general unknown screening using the established database. The effectiveness of the database and protocol was evaluated through analysis of external proficiency tests and PM samples. A short communication by Colby et al. [6] discussed the optimization and validation of HRMS data analysis parameter for the screening method by LC-QTOF-MS with data-dependent acquisition of product ion spectra. Colby et al. [510] later reported a suspect screening for detecting drugs in biological samples using LC-QTOF-MS with data-dependent acquisition. In their work, they demonstrated that retention time was not required for drug identification, using accurate mass, isotope pattern and product ion library matching would be sufficient for identification. The use of LC-QTOF-MS with data-dependent acquisition for screening drugs in urine samples in forensic casework was also studied and compared to an established GC-MS procedure [511]. Data-independent acquisition in LC-QTOF-MS was a choice for untargeted screening. Mollerup et al. [86] reported a method for targeted and non-targeted drug screening in blood also using UHPLC-QTOF-MS with data-independent acquisition and shared their targeted and non-targeted screening workflow. Data-independent acquisition in LC-QTOF been applied to screening for fentanyl analogues in biological samples [242,512], urine drug screening [513].

4.2.2.3. HRMS - Orbitrap technology for screening. The orbitrap based mass spectrometer was first made commercially available in 2005, and has attracted research interests in applying them for screening of drugs in clinical and forensic toxicology. Helfer et al. [514] reported a comprehensive screening for drugs and their metabolites in blood and plasma by LC-HRMS using orbitrap technology, with a target screening for about 700 relevant compounds, as well as data-dependent acquisition for unknowns. Allard et al. [515] reported the use of orbitrap technique for untargeted toxicological screening with the application of molecular networking. In the study, this approach was applied to three real cases, and the study illustrated that molecular networking can be useful complement to conventional approaches for untargeted screening interpretation, for example for xenobiotics identification or NPS metabolism elucidation. There are also other studies using orbitrap technology for screening of 228 drugs and poisons in human blood [516], screening of drugs of abuse in biological fluid [517], and screening of rodenticides in blood [518].

4.2.2.4. HRMS - Metabolism studies and metabolomics. Over the past few years, interests in metabolomics have increased in forensic toxicology. LC-HRMS has been widely used for metabolism studies, especially for NPS, such as N,*N*-diallytryptamine (DALT) derivatives or tryptamine-derived NPS [386,387], NBOMe derivatives [384,385,519], synthetic cannabinoids [520], designer benzodiazepines [521], new PCP analogues [522] and new NPS of NBOMes (3,4-dimethoxyamphetamine and 4-methylmethamphetamine) [523]. The feasibility of LC-HRMS metabolomics for untargeted diagnostic screening in clinical toxicology was studied by Rochat et al. [524]. Another article by Boxler et al. [525] has discussed several analytical issues for the use of UHPLC-QTOF for untargeted metabolomics studies including: a) two different approaches on "blind matrix" for calibration samples; b) comparison of two different HPLC columns; and c) different acquisition modes, including the TOF-MS, information dependent data acquisition (IDA) and sequential window acquisition of all theoretical fragment-ion spectra (SWATH). In their study, all the modes performed equally in metabolite quantification, while TOF-MS being more sensitive, it lacked MS/MS spectra. IDA and SWATH provided MS/MS spectra, with IDA showed good spectra match, and SWATH gave better detection rate. However, SWATH was incompatible with many important software tools in metabolomics. In additional to the analytical considerations, the quality aspect is also important. A review by Dudzik et al. [526] on quality assurance procedures for mass spectrometry had considered sources of variation, discussed the methodologies to minimize them, strategies for monitoring and improvement the quality of results. This served as an overview with tools for monitoring, controlling and improving the reliability of findings by implementation of good experimental quality practices in the untargeted metabolomics study.

4.2.2.5. HRMS - Doping control. In the battle against doping with new performance-enhancing drugs continuously emerge from pharmaceutical industries and black markets, a non-target screening approach by LC-HRMS will be a very useful tactic. A screening method for doping compounds with GC-EI-hybrid quadrupole orbitrap mass spectrometry was reported [527]. In this study, the analysis on exogenous anabolic steroids with a simple 4-step sample preparation including an enzymatic hydrolysis, liquid-liquid extraction, evaporation and trimethylsilation was described. The author also discussed their initial findings of using a full-scan selected ion monitoring-tander mass spectrometry (SIM-MS/MS) approach as a way to obtain lower detection limits than the reported method using full-scan mode. LC-HRMS/MS has been applied in other reported method for anabolic and androgenic steroids and analogues in horse hair [528,529], in human whole blood and hair [530], and also in steroid profiling in serum [531].

4.2.3. Imagining mass spectrometry (IMS)

Advances in imagining mass spectrometry by direct and/or ambient mass spectrometry approaches have given an impetus for its applications in various areas, including toxicology. A review article by Karlsson and Hanrieder [532] presented an overview of IMS, with particular focus on MALDI IMS, and its use in drug development and toxicology in general. It discussed the principles and modalities of IMS, sample preparation and applications. An article by Steuer et al. [533] also reviewed the instrumental setup and sample preparation of IMS applications, with discussion of their pros and cons and future perspectives. In forensic toxicology, there have been increasing interests in IMS for the analysis of hair samples, as it provides more accurate and visual chronological information in single hair analysis. Flinders and co-workers published research articles [534,535] in the analysis of drugs of abuse in hair by IMS. In the articles, the sample preparation and the instrumental parameters, such as spatial resolution, raster speed and sample orientation have been discussed. Most of the IMS studies on hair analysis used MALDI-MS, such as the mapping of cannabinoids in single hair [536], characterization of synthetic cannabinoid isomers in single hair [537], olanzapines with esculetin as matrix [538], analysis of methamphetamine with umbelliferone as a matrix [539], and the study of zolpidem distribution in hair after a single administration [540]. Instead of MALDI, another ionization technique, DART (direct analysis in real time) was used in

IMS study in forensic hair analysis [541]. In this work, four different mass analyzers, including an orbitrap, a quadrupole orbitrap, a triple quadrupole, and a quadrupole time-of-flight (QTOF) were critically compared. The use of travelling wave ion mobility (TWIM) for isobaric ions separation was also evaluated. The author concluded that the use of triple quadrupole gave highest sensitivity, while HRMS was found to be more specific. In the experiment, it was found that a mass resolution of at least 30,000 FWHM was required to differentiate THC from the isobaric interference from hair matrix, even with the selectivity enhancement by TWIM. Therefore, the quadrupole orbitrap instruments or QTOF at high-resolution mode could be the choice for cases like analysis of THC in hair with endogenous isobaric interferences.

4.3. Advances – Alternative specimens

Toxicology analysis commonly involves blood or urine. There has been continuous interest in alternative matrices for toxicology because each matrix has unique properties that provides advantages for certain applications. Palmer and Krasowski [542] studied four different matrices including meconium, cord tissue, hair and oral fluid, and gave an overview of the utility, advantages and limitations of these matrices. When traditional samples, blood or urine, were unavailable for toxicology analysis, alternative specimens, such as organs or even skeletal remains would be used. Brain and vitreous humor (VH) have been studied for their potential as better options with less endogenous interference. Specimens with easy collection, like oral fluid and sweat were considered to be convenient choices of sample for drug exposure monitoring. With the interest in drug exposure history, specimens like hair and nails, will be a choice for analysis, while meconium or umbilical cord tissues reveal prenatal history. In this section, except oral fluid which have been covered in the first chapter, the aforementioned applications of various matrices were discussed.

4.3.1. Last resort – Organs to skeletal remains

In forensic cases, it is not uncommon that traditional samples such as blood or urine are not available, soft tissues matrices such as liver, kidney, lung and spleen are common samples for toxicology analysis. However, investigations which focus on the spleen and bile are relatively infrequent. Palmiere et al. [543] reviewed the use of spleen in forensic applications, including histology, radiological (PM computed tomography), morphological, toxicological microbiological and genetic investigations. A review [544] on the toxicological significance of PM drug concentrations in bile studies found that the drug levels in bile and blood are generally poorly correlated. However, due to the relative higher drug level in bile compared to blood, bile may allow qualitative identification of drugs present.

In skeletonized cases, soft tissue matrices are no longer available, skeletal matrices including bone or teeth may be the last resort. In a review article [545] about the current state and future directions of skeleton toxicology, a model for the *in vivo* incorporation of drugs of forensic interest into bone tissue is proposed. This model is based on the principles of ion exchange, adsorption and substitution. A special focus on its potential application in chemical weapon nerve agent detection was also discussed.

Other than the mechanism of drug in corporation in bone, there have been study in the distribution of drugs in bone [546]. In this research, the distribution of clomipramine, citalopram, midazolam and metabolites in skeletal tissue of chronically dosed rats was investigated by a fully validated method using LC-MS/MS. It was found that midazolam and its metabolite could not be detected, while clomipramine, citalopram and their metabolites were detectable in bone. Midazolam which was undetectable implied that drugs with pKa values under physiological pH were poorly or not incorporated in bone tissue. Among bone types studied, they found skeletal tissue concentration ranged from 1.1 to 587.8 ng/g, while humerus showed the highest drug levels. In the study, comparison of drug levels in the same bone type between different rats showed high variance, while the drugs to metabolite ratio in the sampled bones was in close concordance to the ratio seen in blood within a rat. From this, the authors suggested the drugs to metabolite ratio in skeletal tissue may be more useful than absolute found concentration.

With levels of drugs detected in bone at level of ng/g, the analysis of drugs in bone is also a challenge. In the instrumentation aspect of skeletal toxicology, a validated method was developed by Orfanidis et al. [547], where samples were extracted with methanol followed by stirring and ultra-sonication. The extract, after filtration, evaporation and reconstitution was analyzed on a reversed-phase column (C18) in gradient elution in the detection and quantitation protocol using UPLC-MS/MS.

An alternative method, employing methanolic microwave assisted extraction (MAE) followed by clean-up by solid-phase extraction (SPE) and detection by GC-MS, in the analysis of dextromethorphan and dextrorphan in skeletal remains of rats was reported by Morrison et al. [548]. Drug levels at different decomposition microclimates (rat skeletons decomposed in a shaded forest microenvironment and rocky substrate exposed to direct sunlight) were compared and no significant difference was observed. Cornthwaite et al. [549] also reported the use of UHPLC-QTOF-MS in the semi-quantitative detection of tramadol, dextromethorphan and metabolites. Methadone, EDDP and EMDP could be detected in highest concentrations in bone marrow using a similar protocol [550].

Other than MS, Raman spectroscopy is a favorable technique for examination of bone, as it is non-destructive and requires a minute sample size. However, biomolecules which exhibit strong intrinsic fluorescence could potentially mask the Raman spectrum and affect the results. Chikhani et al. [551] found that scraping the bone sample could resolve fluorescence better than chemical bleaching, while preserving the sample in a state closest to its original form was apparently beneficial in forensic investigation.

The determination of drugs of abuse in human teeth was accomplished with the use of GC-MS. Pulverized samples of dental material can be subjected to acid hydrolysis to detect opiates, cocaine and their metabolites, whereas basic extraction of these dental material could lead us to the detection of cannabis product (Δ^9-tetrahydrocannabinol, cannabidiol and cannabinol) by GC-MS. The extraction techniques employed yielded recovery at over 74% and LOD of 0.02–0.03 ng/mg and LOQ of 0.05 ng/mg for all the analytes [552].

A case with bone as the only available material for toxicology analysis was reported [553]. With a validated UPLC-MS/MS method, alprazolam and zolpidem were detected in bone, which were in accordance with the deceased's medical record.

4.3.2. Protected samples –VH, IOF & brain

Vitreous humor (VH) is encountered in toxicology analysis routinely for ethyl alcohol analysis. It actually is a more reliable specimen for toxicology tests. Markowska et al. [554] discussed specific applications of VH for biochemical and toxicological test. VH is one of the most well-preserved biological specimens for PM analysis due to the ease of sampling, low endogenous interference and low metabolic activity. Active and passive transport through blood-retina barrier of drugs into VH render the drugs levels in VH more correlated to blood than urine. Methylenedioxyamphetamine derivatives such as MDA, MDMA, MDEA, were detected using a validated method by liquid-liquid extraction (LLE) followed by GC-

EI-MS. The three targets were found to be stable with storage at −20 °C for 5 weeks [555]. Heroin has an extremely short half-life and is immediately converted to 6-acetylmorphine (6-AM) and subsequently morphine, which can be detected in psoas muscle and lateral vastus muscle in comparable concentrations as that in peripheral blood and cardiac blood. In muscle, 6-AM was often not detected, whereas urine and vitreous humor would serve as a better specimen for its qualitative detection [556]. A comparison of stability of endogenous GHB in VH against peripheral blood in dead bodies also demonstrated that VH was a useful matrix for the determination of PM GHB level [557].

Intraosseous fluid (IOF) in the bone has good blood supplies. A study by Rodda suggested that IOF might have similar advantages to vitreous humor in terms of its suitability for toxicological examination as they were both isolated compartments that was less susceptible to PM redistribution (PMR) and bacterial contamination than peripheral or central blood. Comparable ELISA drug screening results between IOF and central/cardiac blood specimens could be obtained with more than 96% correlation. However, drug classes, such as oxycodone and its metabolites (OXY), tricyclic antidepressants (TCA) and cannabinoids (THC), were not deemed positive when they were detected positive in cardiac blood, possibly due to their lipophilicity and conjugation [558].

Similarly, as an anatomically secluded organ, the post mortem brain is protected to some extents from the diffusion of drugs from other tissues. In a study where the adverse effects of adulterants of cocaine on central nervous and cardiac systems were investigated, ten PM brain samples taken from cocaine users were examined for cocaine and its adulterants e.g. benzoylecgonine (BE), ecgonine methyl ester (EME), diltiazem (DIL), hydroxyzine (HYD), levamisole (LEV), cetirizine (CET), lidocaine (LID), phenacetin (PHE) and procaine (PRO) [559]. DIL, PRO, CET were not detected in any brain sample. However, LEV and HYD were detected in brain samples at concentrations up to 426 ng/g and 242 ng/g respectively. LID, a common anesthetic used in medical treatment, was detected in brain samples at low concentrations up to 154 ng/g. In conclusion, it was confirmed that some of adulterants of cocaine could pass through the blood-brain barrier and potentially enhanced the toxicity of cocaine, therefore, the interpretation of cocaine related deaths could include the assessment of its adulterants in addition to the drug itself to give further insight into death inquiry.

For interpretation of toxicology findings in brain, there have been studies in establishing the correlation of drug levels in blood and brain. The reference brain and blood concentrations of a range of antipsychotic drugs and benzodiazepines in PM cases were investigated. Among 40 forensic autopsy cases, the concentrations of olanzapine in brain exceeded those in blood for all cases, a correlation coefficient (R^2) of 0.87 was found between blood and brain concentrations [560]. A new generation of antidepressants which are less toxic than the tricyclic antidepressants, such as citalopram, duloxetine, mirtazapine and sertraline, were examined with their correlations between brain blood concentrations with R^2 between 0.67 and 0.91 [561]. PM Brain-Blood Ratios of Amphetamine (AMP), Cocaine, Ephedrine (Eph), MDMA and Methylphenidate (MPD) were also studied with R^2 in range of 0.58–0.92 [562]. The brain blood ratio of alprazolam, bromazepam, chlordiazepoxide (ClDP), diazepam, and the metabolites desmethyldiazepam (DMdiazapem), oxazepam and temazepam in PM femoral blood and brain tissues were studied with R^2 ranging from 0.51 to 0.95 [563]. The ratio of brain to blood drug concentration for the aforesaid drugs were summarized as below (Table 24), which can be served as reference values for evaluating PM cases:

The case category (Cat.) are divided as Cat. A: the drug was the sole cause of death; Cat. B: the drug contributed to the cause of death; Cat. C: with drugs was not related to the cause of death.

Table 24
Summary for ratio of brain to blood drug concentrations.

Drugs	Cat.	Brain-blood ratio				N	Ref
		Median	Mean (SD)	10–90%	Range		
Olanzapine	A	–	2.7	–	1.8–3.6	2	[560]
Olanzapine	B	2.1	2.1(0.73)	1.2–3.0	1.0–3.9	17	[560]
Olanzapine	C	3.4	3.9(2.4)	1.1–6.7	0.72–10.4	21	[560]
Citalopram	A	–	–	–	3.0	1	[561]
Citalopram	B	3.0	3.2(0.9)	–	1.9–4.7	9	[561]
Citalopram	C	4.1	4.0(1.1)	2.5–5.3	1.4–5.9	25	[561]
Sertraline	A	–	–	–	3.2	1	[561]
Sertraline	B	7.6	7.8(2.9)	–	3.5–12.6	5	[561]
Sertraline	C	7.7	9.1(2.7)	6.7–14.2	6.7–14.2	14	[561]
Mirtazapine	B		1.9	–	1.5–2.3	2	[561]
Mirtazapine	C	1.5	1.9(0.9)	1.2–2.9	1.0–4.7	24	[561]
Duloxetine	A	–	–	–	11.7	1	[561]
Duloxetine	B	–	9.0(2.9)	–	5.0–11.7	3	[561]
Duloxetine	C	9.4	11.6(5.9)	–	5.9–21.6	6	[561]
Cocaine	A	2.3	2.3(1.5_)	–	0.2–4.2	6	[562]
Cocaine	B	3.2	2.8(1.5)	–	0.7–4.8	8	[562]
Cocaine	C	1.9	2.4(1.7)	0.87–4.8	0.2–7.0	44	[562]
AMP	A	1.9	–	–	0.35–3.3	3	[562]
AMP	B	2.0	2.5(1.4)	–	0.9–4.7	10	[562]
AMP	C	3.2	3.3(0.85)	2.3–4.5	2.0–5.0	23	[562]
Ephedrine	C	2.3	4.0(6.5)	1.1–6.2	0.6–30	19	[562]
MDMA	B	2.1	3.3(1.3)	–	1.9–5.1	4	[562]
MDMA	C	3.3	3.1(1.4)	–	0.92–5.0	5	[562]
MPD	B	–	–	–	4.6	1	[562]
MPD	C	2.3	2.5(0.92)	–	0.92–3.8	9	[562]
Alprazolam	B	–	2.21	–	1.95–2.48	2	[563]
Alprazolam	C	2.21	2.54	1.65–3.78	1.61–4.78	12	[563]
Bromazepam	B	1.31	1.42	–	1.00–1.97	7	[563]
Bromazepam	C	1.43	1.48	0.95–1.99	0.9–3.06	21	[563]
ClDP	B	1.68	1.59	–	0.87–2.21	3	[563]
ClDP	C	1.13	1.32	0.76–2.34	0.74–2.91	10	[563]
Diazepam	B	–	–	–	1.64	1	[563]
Diazepam	C	1.35	1.70	0.59–2.77	0.37–10.73	38	[563]
DMdiazepam	B	0.92	0.96	–	0.44–1.53	3	[563]
DMdiazepam	C	2.27	2.56	1.22–4.14	0.51–6.38	54	[563]
Temazepam	C	1.30	1.31	0.51–2.35	0.42–2.42	27	[563]
Oxazepam	C	1.88	2.09	1.1–3.42	0.90–4.19	49	[563]

In a study where 221 PM samples were collected for the comparison of GHB level in brain (frontal lobe) and blood (femoral vein) by Thomsen et al. [564], it was found that PM generation of GHB was much lower in brain than in peripheral blood, and hence analysis of GHB in brain provided an improved capability to identify exogenous source of GHB. However, evaluation of decomposition level was pertinent since endogenous levels of GHB in brain could be extremely high in cases where advanced decomposition had taken place at the time of autopsy. The authors recommended a cut-off concentration for brain tissue of 10mg/kg in cases with limited decomposition.

4.3.3. Matrices for drug history – Hair, nail & earwax; placenta & meconium

4.3.3.1. Hair. Hair analysis has become prevalent in recent years [134,565–567], one main pitfalls of hair analysis is the possibility of external contaminations from sweat or other chemicals/drugs. The differentiation between systemic exposure and external contamination continues to be one of the limitations of hair testing for drugs [568].

A recent report on a novel contactless decontamination of THC from the surface of human hair using an 1-ethanol-3-methyl tetrafluoroborate, which was an ionic liquid, demonstrated a 13-h extraction at 100 °C with 96% decontamination efficiency [569].

There have been reports on the detection of ethyl glucuronide, abused drugs and other prescribed benzodiazepines, antidepressants, antipsychotic drugs with the use of UPLC HRMS or QTOF [570–574].

Analysis of hair can establish drug intake profile over a period of months to years, complementing the drug intake information to give a more comprehensive picture [575], e.g. to determine whether psychiatric patients are receiving a stable intake of antipsychotics. UPLC-MS/MS analysis can be used in the detection and examination of quetiapine in hair [576]. A significant positive correlation was observed between estimated daily dosage of quetiapine and average concentration in hair of natural hair colour. On the contrary no correlation was established with the dyed/bleached hair samples. This study highlighted hair treatments should be taken into account when hair was used as the target specimen for toxicological examinations. In another study, natural hair colour of rats were examined to determine the incorporation of NPS including 25B-, 25C- and 25I− NBOMe. It was found that incorporation of these drugs was better in black hair than white hair of rats [577].

The detection of exogenous gamma-hydroxybutyric acid (GHB) has always been problematic as it is endogenous and no reference values of endogenous GHB in hair have been reported until recently. In a study with 150 hair samples, the baseline level of GHB in hair was detected in the range of 0.27–2.84 ng/mg and that the concentration of GHB in male hair was significantly higher than that in females [578]. A single exogenous intake of GHB could be detected in hair using GC-MS/MS [579], providing supplementary information in crimes like drug-facilitated sexual assault (DFSA) when blood and urine provide narrow ($t_{1/2}$ = 30 min) detection window for detection of GHB [580,581].

In the evaluation of adherence to treatment of alcohol dependent patients, hair ethylglucuronide (ethanol metabolite, EtG) or baclofen quantitation could be used as monitoring markers to assess patient's compliance or abstinence and alcohol consumption behavior [582]. However, washout effect by chlorinated water (e.g. swimmers) could lead to a significant decrease of EtG concentrations in hair, thus lifestyle and habit could play a role in such monitoring using hair analysis [583,584].

Hair analysis is also used in the detection of synthetic androgenic steroid, e.g. androstenedione, stanozolol, cyionate and clostebol etc., in the monitoring of the use of performance-enhancing drug in sports competition. Previous studies showed a positive result in urine analysis in cases of single or unintentional intake of clostebol. This could be overcome by the detection of clostebol acetate in hair to distinguish long term administration of steroid [530,585].

4.3.3.2. Nail. Nail can be used for the determination of chronic intake of drugs prior death or a back-up for hair analysis when hair is unavailable. A review [139] on the use of nails in forensic toxicology focused on the investigation of drug incorporation mechanism and the drug detection in nails. The studies pointed out the importance of standardization and harmonization of methodologies for nails analysis, as well as the determination of cut-off values. Another article discussed the role of nail analysis for drugs in workplace testing [130] in order to distinguish whether drugs present is from ingestion or contamination.

In a study done by Kuwayama et al. [586], the concentration of hair and toenails were collected at intervals up to 12 months from healthy live subjects. It was found that acidic compounds were not detected in any nail samples. In comparison with hair, the concentration of basic drugs in hair were higher than those in nail, which could be attributed to the affinity of basic compounds to melanin, which was abundant in hair. On the contrary, neutral or weakly acidic compounds, such as allyl isopropyl acetylurea and acetaminophen, were detected more frequently in nails than in hair segments. Chlorpheniramine (CP) and desmethylchlorpheniramine (DCP) were detected in nails 12 months after administration. Another method for the quantitation of methadone, and its metabolites: 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) and 2-ethyl-5-methyl-3,3-diphenylpyrrolidine (EMDP) in nails [587] were reported with recovery ranging from 82% to 98%.

4.3.3.3. Earwax. Cerumen, a mixture of squalene, cholesterol esters, wax esters, triacylglycerols, ceramides, and cholesterol sulfate, is secreted by sebaceous glands located in the cartilaginous outer third of the external auditory canal. It contains a high level of keratin and thus can be grouped with hair and nail as having a similar keratinized matrix. A pioneering study on quantitation of 12 neuropsychotic drugs, including clozapine, carbamazepine, lamotrigine, clonazepam, phenytoin and phenobarbital etc., in cerumen using LC-MS/MS after straightforward fast extraction with methanol, followed by vortex and centrifugation have been reported [588]. Earwax can serve as a diagnostic biological secretion due to its non-invasive sampling procedure. Moreover, it is less prone to contamination by ambient air or by cosmetic as the ear canal is protected from external environment. Earwax can probably provide information on past drug use (a few months back) as well as recent use.

The concentrations of common drugs of abuse in earwax, blood, urine and hair were compared in a study by Meier et al. [589]. Opiates, amphetamines and derivatives, cocaines, methadone, diazepam and derivatives were detected in cerumen. In some cases, drugs that could only be detected in urine were also found in the corresponding cerumen sample. Drug detectability in cerumen exceeds the time range of blood as well as urine but not as long as hair. Current obstacle is that detections of opiates and cannabinoids have yet to be optimized. Another challenge is to get sufficient sample as the current reported techniques require at least 10mg of sample.

4.3.3.4. Umbilical cord tissue and meconium for prenatal drug history. Sometimes it is desirable to investigate *in utero* exposure to drugs in order to identify any short- or long-term health problems of babies. Umbilical cord tissue and meconium are always choices for neonatal toxicology testing, and there was an article on the comparison of these matrices [590]. Colby [591] also compared the use of umbilical cord tissue and meconium for the confirmation of in-utero drug exposure. In comparison of different sensitivities of drug detection, it was found that meconium gave greater sensitivity for drugs studied. Wu et al. [592] developed a validated LC-MS method for the simultaneous determination of Δ^9-tetrahydrocannabinol (THC), 11-nor-9-carboxy-Δ^9-THC (THC-COOH), 11-hydroxy-Δ^9-THC (11-OH-THC) and cannabinol (CBN) in umbilical cord tissue. Another study of detection *in utero* cannabis exposure by umbilical cord analysis was also reported using LC-MS/MS with dual ionization source [593]. Active and passive tobacco exposure during pregnancy could lead to complications in the health of the new born. Nicotine, cotinine and hydroxycotinine (OH-cotinine) were detectable in placenta and umbilical cords by LC-MS/MS using a HILIC analytical column; these findings were confirmed by hair analysis for the same target analytes [594].

4.4. Advances – Interpretations

The interpretation of toxicology findings in various matrices has been covered in the above sections, such as the implication of drugs in various biological matrices and the significance of drug levels inside certain matrix by studies of their correlation with drug levels in blood. There have been studies on specific drug in various biological specimens to evaluate interpretation values. A case report on fatal zolpidem poisoning by zolpidem and its metabolite, zolpidem phenyl-4-carboxylic acid, in various body fluids and solid tissues revealed PM distribution and PMR [595]. In a comparative study of PM concentrations of antidepressants in different matrices [596] from 173 PM cases to evaluate the interpretation values of matrices other than peripheral blood (PB) which was considered as golden standard for measuring PM drug concentration. It was found that the antidepressant levels in the peripheral and cardiac blood (CB), pericardial fluid (PF), muscle and VH can provide important indications of the corresponding concentration in PB, with a ratio of 0.5–2, while PB is not available. The concentrations of drug in VH were found generally lower, while antidepressants of high degree of protein binding, the levels in VH were much lower than in other matrices, VH is therefore not recommended for determination of concentrations of these antidepressants.

In another study, the PM distribution of cannabinoids [597] in blood, urine, vitreous humor, liver, lung, kidney, spleen, muscle, brain, heart and bile was evaluated with an LC-MS/MS method capable of identification and quantification of cannabinoids at level as low as 1 ng/mL. It was found that there is no consistent distribution of cannabinoids between blood and any other fluids or tissues, therefore the values for non-blood specimens could be for qualitative cannabinoid detection only.

A study of distribution of heroin metabolites in different PM matrices [598] proposed that these will be useful information for interpretation of heroin intoxication, such as assessment of the approximate time span between intake of heroin and death. The ratios of morphine-3-glucuronide (M3G) level to morphine (MOR) level were evaluated for rapid and delayed heroin death in a range of specimens including peripheral and cardiac blood, pericardial fluid, VH. The authors suggested that M3G/MOR ratios of less than 2 indicated a rapid death, while ratios of more than 3 indicated a delayed death after heroin intake, while the muscle was less useful for this assessment. For the ratio of morphine to codeine level above unity in specimens such as peripheral blood, cardiac blood, pericardial fluid of skeletal muscle, could possibly be regarded as an indication of heroin intake, while such ratio in VH seemed less useful.

For the interpretation of gamma-hydroxybutyrate (GHB), a review by Busardò and Jones [599] amplified the current knowledge about the concentration of GHB in various biological specimens, both endogenous level and after administration of GHB. The review also indicated that urine extended the GHB detection window by 3–4 h compared to blood; while for longer delays after last intake, hair or nails might be the only options. In another study of GHB in different matrices, urine and blood in 37 GHB intoxication deaths were evaluated [600]. GHB levels in urine were higher than that in femoral blood with highly variable urine/blood ratios. This could be explained by a rapid metabolism occurring in blood but not in the urinary bladder. That was the reason for the extended detection window of GHB in urine than blood samples. It was also suggested that the urinary GHB concentration could give a hint on its concentration in blood at the time urine was produced in the kidney and stored in the bladder since the previous void. The higher the ratio of GHB level between urine and blood, the longer the delay in death after GHB intake.

Reference for PM drug level for assessment of intoxication is scarce. A study presented PM femoral blood concentration for 24 antipsychotic substances [601], with samples from 4949 autopsy cases, complied PM fatal and non-fatal reference concentrations of antipsychotics, such as amisulpride, chlorpromazine, haloperidol, olanzapine, quetiapine and *etc*. In addition, this study also provided information about the prevalence of different antipsychotics in accidental, suicidal, homicidal and uncertain deaths. With reference to the toxic and lethal femoral blood limits based on the aforesaid study, a study on the distribution of eight QT-prolonging drugs and their main metabolites between PM cardiac tissue and femoral blood revealed potential pitfalls in toxicology interpretation [602], especially for citalopram. It was found that 64% of citalopram cases with non-toxic femoral blood concentration, but the cardiac tissue concentrations were similar to toxic or lethal cases. In view of the cardiac tissue being an active site for cardiotoxicity, it is possible for intoxications to be missed or over-interpreted by solely relying on toxicological interpretation of peripheral blood concentration.

Factors affecting the level of drugs in PM sample including postmortem redistribution (PMR) and drug stability are discussed below.

4.4.1. Postmortem redistribution (PMR)

It is well-known that PMR poses difficulties in the interpretation of drug concentration in postmortem analysis. As it is impossible to predict the extent of postmortem changes for individual cases, Steuer suggested interpretation needs to be done with care, considering case circumstances and all available information [603]. To enrich the knowledge on PMR, a review on PMR of drugs [604] discussed the mechanisms and factors influencing redistribution phenomena, and gave recommendations concerning anatomic sampling sites, sampling methods and sample storage making it possible to limit these phenomena. And other study evaluated and verified the theoretical PMR factor based on the liver-to PB (L/P) ratio using antemortem (AM) and PM analytical results for 44 drugs [605]. The theoretical PMR factor suggested the drugs' propensity for PMR, assisted with a rational interpretation of PM drug concentrations for forensic experts.

The ratio of central (C) to peripheral (P) drug concentration (C/P ratio) is another option for assessing PMR. A comparison of drugs concentrations at different sampling sites [606] studied the correlation between central blood from right heart and PB from the external iliac vein for 48 PM cases with blood sampled from six different sites. The results confirmed previous studies that C/P ratios were generally large than unity, and the ratios increased with PM interval (PMI). This study also gave additional information about the concentration differences in atrial and venous blood, where there were virtually no concentration differences at short PMI, with the differences increased with PMI. Therefore, timely collection of PM sample is important.

In addition to the importance of sampling site, sampling technique for study of PMR is also important, a research team studied the PMR of diazepam, methadone and morphine with different sampling techniques including blind stick and dissection/clamping techniques [607,608]. In their earlier study the authors suggested the importance of isolating vessels from thorac-abdominal viscera by clamping a vessel before sampling [607]. In addition to sampling technique, authors also discussed the site- and time-related aspects, and concluded that the popliteal vein may represent a site more resistant to changes caused by PMR [608].

For studying the time-related factors of PMR, there are researches which make use of computed tomography (CT) to collect biopsies using a robotic arm (virtobot). Such sampling technique provides a valuable tool for systematic studies on time-dependent PMR and have been used for evaluation of time-dependent PMR of

opioids, including methadone, fentanyl, tramadol, codeine, oxycodone and hydrocodone [609], as well as, morphine and its metabolites [610]. In the study for opioids, it was found that fentanyl and methadone showed significant PMR over time while other opioids showed no consistent trend. Interestingly, methadone metabolite, EDDP, showed a less significant trend for PMR [609]. In the study for morphine, morphine also showed significant PMR over time, while metabolites did not undergo extensive PMR, especially the conjugates [610].

Intoxication cases with multi-drug, the PMR of MDMA in acute alcohol and MDMA combined use was studied using rats [611]. In comparison of combined use against the alcohol or MDMA alone, the levels of alcohol and MDMA in combined use were significantly higher than cases with mono alcohol or MDMA alone. These findings suggested that the effect of other drugs in PMR should also be considered in toxicology evaluation.

4.4.2. Stability

Understanding the stability of drugs in biological specimens is of crucial importance in the interpretation of the toxicological findings in postmortem forensic toxicology. The study of drug stability required a reliable analytical method, usually LC-MS/MS or LC-HRMS, as well as planning of experiment. With the study of stability for an unstable cancer drug, gemcitabine, as an example, Reed shared a protocol for evaluation of drug and drug metabolite stability in whole blood [612]. In the protocol, elements which could stop or retard degradation process would be introduced, and therefore understanding the degradation pathways of analytes deemed important.

The degradation of drugs in biological specimens may lead to decrease in drug levels or even false negative results. Cannabinoids are prone to degradation leading to difficulties in analysis and interpretation. The common degradative pathways of cannabinoids leading to poor recovery in urine, oral fluid and hair were critically discussed [613]. The stability of benzodiazepines in hair and nail, as well as zolpidem in nails, after prolonged exposure to chlorinated water was studied [112,614]. It was also found that the longer the exposure time, the higher the degree of degradation. The degradation pathways and factors should be considered as possible cause of false negative results.

Considering potential false negative due to degradation, stable metabolites or degradation products of a drug could be considered as useful markers for evaluating the exposure of unstable drugs. Degradation of bupropion was evaluated [615] with PM cases samples stored at frozen (−20 °C), refrigerated (4 °C) and room temperature (20 °C). Results showed that it degraded in PM blood, liver and liver homogenate in all storage conditions, with the most drastic decrease at room temperature (RT) but its metabolite, threobupropion, appeared to be relatively stable. Hence, threobupropion can be used as an indicator for the extent of exposure to bupropion. The stability of biomarkers for ethanol consumption was studied [616], and concluded that ethylglucurondie is a reliable marker, stable at 4 and -20 °C. In a stability study of 26 sedative hypnotics in 6 biological matrices at different storage conditions [617], it was found that except zopiclone, alprazolam and clonazepam, most hypnotics were stable (less than 20% of drug decrease) in all specimens, when refrigerated/frozen for a month or more. Zopiclone in blood was stable if refrigerated/frozen for about a week. It was stable for a month or longer in other specimens, such as urine, liver, brain and stomach contents. Alprazolam and clonazepam in blood were stable for about 2 weeks if refrigerated/frozen. They had longer storage period in other specimens. Furthermore, their metabolites, α-hydroxyalprazolam and 7-aminoclonazepam were found to be more stable in blood, which could be used as indicators for exposure of alprazolam and clonazepam, respectively. The stability of 21 drugs including cocaine, opioid and benzodiazepines in meconium at different temperatures was evaluated by spiking the drugs into meconium [618]. It was found that a marked decrease in the levels of 6-acetylmorphine (MAM), nordiazepam, temazepam and oxazepam at 37 °C (body temperature) over a 2-week period. Such finding proposed that if a pregnant woman used these drugs 2 weeks before delivery, the use of meconium for drug detection might not reflect the drug uses during pregnancy, and other biomarkers might be required for assessing the prenatal exposure of these unstable analytes.

In some stability studies [619–621], the use of preservatives was discussed. For the stability of PM methemoglobin, the use of EDTA as preservative plus refrigeration (4 °C) are recommended as storage condition prior to analysis, while frozen with cryoprotectant at −80 °C or lower for maintaining methemoglobin stable in extended storage [619]. In the study for stability of opiate compounds in PM sample after heroin exposure [620], it was shown that the use of 1% sodium fluoride in blood sample would be useful for slowing down the degradation, especially important for the most liable opiate, MAM. However, the study for methamidophos in PM blood and liver [621] suggested that addition of sodium fluoride in blood and fixation of liver in formaldehyde accelerated the degradation of methamidophos and should be avoided. This suggested the presence of additives did not necessarily prolong storage period.

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Declaration of competing interests

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References

[1] ISO/IEC 17025:2017, General Requirements for the Competence of Testing and Calibration Laboratories, Organization for Standardization (ISO)/International Electrotechnical Commission (IEC), 2017. Geneva.
[2] J.M. Collins, HR Management in the Forensic Science Laboratory: A 21st Century Approach to Effective Crime Lab Leadership, 1sted, Academic Press, 2018, pp. 457–475 (Chapter 26).
[3] American Academy of Forensic Sciences Standards Board, Standard Practices for Method Validation in Forensic Toxicology. ASB Standard, 2017, 036, 1sted.
[4] F.T. Peters, D.K. Wissenbach, F.P. Busardo, E. Marchei, S. Pichini, Method development in forensic toxicology, Curr. Pharmaceut. Des. 23 (36) (2017 Oct) 5455–5467.
[5] L.K. Nahar, R.E. Cordero, D. Nutt, A. Lingford-Hughes, S. Turton, C. Durant, Sue Wilson, S. Paterson, Validated method for the quantification of baclofen in human plasma using solid-phase extraction and liquid chromatography-tandem mass spectrometry, J. Anal. Toxicol. 41 (5) (2017 Jun) 441–450.
[6] J.M. Colby, K.L. Thoren, K.L. Lynch, Optimization and validation of high-resolution mass spectrometry data analysis parameters, J. Anal. Toxicol. 41 (1) (2017 Jan) 1–5.
[7] D. Cappelle, M.D. Doncker, C. Gys, K. Krysiak, S.D. Keukeleire, W. Maho,

C.L. Crunelle, G. Dom, A. Covaci, A.L. van Nuijs, H. Neels, A straightforward, validated liquid chromatography coupled to tandem mass spectrometry method for the simultaneous detection of nine drugs of abuse and their metabolites in hair and nails, Anal. Chim. Acta 960 (2017 Apr) 101–109.
[8] P. Prego-Meleiro, E. Lendoiro, M. Concheiro, A. Cruz, M. López-Rivadulla, A. de Castro, Development and validation of a liquid chromatography tandem mass spectrometry method for the determination of cannabinoids and phase I and II metabolites in meconium, J. Chromatogr. A 1497 (2017 May) 118–126.
[9] M. Williams, J. Martin, P. Galettis, A validated method for the detection of 32 bath salts in oral fluid, J. Anal. Toxicol. 41 (8) (2017 Oct) 659–669.
[10] C. Hess, K. Sydow, T. Kueting, M. Kraemer, A. Maas, Considerations regarding the validation of chromatographic mass spectrometric methods for the quantification of endogenous substances in forensics, Forensic Sci. Int. 283 (2018 Feb) 150–155.
[11] N.B. Tiscione, K. Wegner, Validation of the Neogen® Fentanyl ELISA kit for blood and urine, J. Anal. Toxicol. 41 (4) (2017 May) 313–317.
[12] H. Chung, S. Choe, Overview of forensic toxicology, yesterday, today and in the future, Curr. Pharmaceut. Des. 23 (36) (2017) 5429–5436.
[13] L. Wilson-Wilde, The international development of forensic science standards – a review, Forensic Sci. Int. 288 (2018 Jul) 1–9.
[14] O.H. Drummer, Good practices in forensic toxicology, Curr. Pharmaceut. Des. 23 (36) (2017) 5437–5441.
[15] S. Cosbey, S. Elliott, S. Paterson, The United Kingdom and Ireland Association of Forensic Toxicologists; establishing best practice for professional training & development in forensic toxicology, Sci. Justice 57 (1) (2017 Jan) 63–71.
[16] S.P. Elliott, D.W.S. Stephen, S. Paterson, The United Kingdom and Ireland association of forensic toxicologists forensic toxicology laboratory guidelines (2018), Sci. Justice 58 (5) (2018 Sep) 335–345.
[17] American Academy of Forensic Sciences Standards Board, Standard practices for measurement traceability in forensic toxicology, ASB Standard (2017) first Edition. 2017.
[18] N. Milinković, S. Ignjtović, Z. Šumarac, N. Majkić-Singh, Uncertainty of measurement in laboratory medicine, J. Med. Biochem. 37 (3) (2018 Jul) 279–288.
[19] F. Ceriotti, Deriving proper measurement uncertainty from internal quality control data: an impossible mission? Clin. Biochem. 57 (2018 Jul) 37–40.
[20] W.P. Oosterhuis, H. Bayat, D. Armbruster, A. Coskun, K.P. Freeman, A. Kallner, D. Koch, F. Mackenzie, G. Migliarino, M. Orth, S. Sandberg, M.S. Sylte, D. Westgard, E. Theodorsson, The use of error and uncertainty methods in the medical laboratory, J. clinica. Chem. Lab. Med. 56 (2) (2018 Jan) 209–219.
[21] E. Theodorsson, Uncertainty in measurement and total error tools for coping with diagnostic uncertainty, J. Clincl. Lab. Med. 37 (1) (2017 Mar) 15–34.
[22] J.O. Westgard, Error methods are more practical, but uncertainty methods may still be preferred, Clin. Chem. 64 (4) (2018 Apr) 636–638.
[23] R. Kadis, Evaluation of the measurement uncertainty: some common mistakes with a focus on the uncertainty from linear calibration, J. Chromatogr. A 1499 (2017 May) 226–229.
[24] P.D. Maskell, R.A. Speers, D.L. Maskell, Improving uncertainty in Widmark equation calculations: alcohol volume, strength and density, Sci. Justice 57 (5) (2017 Sep) 321–330.
[25] R.J. Hwang, J. Beltran, C. Rogers, J. Barlow, G. Razatos, Measurement of uncertainty for blood alcohol concentration by headspace chromatography, J. Can. Soc. Forensic. Sci. 50 (3) (2017 Apr) 114–124.
[26] R.J. Hwang, J. Beltran, C. Rogers, J. Barlow, G. Razatos, Measurement of uncertainty for aqueous ethanol wet-bath simulator solutions used with evidential breath testing instruments, J. Forensic Sci. 61 (5) (2016 Sep) 1359–1363.
[27] P.D. Maskell, C. Holmes, M. Huismann, S. Reid, M. Carr, B.J. Jones, D.L. Maskell, The influence of alcohol content variation in UK packaged beers on the uncertainty of calculations using the Widmark equation, Sci. Justice 58 (4) (2018 Jul) 271–275.
[28] Y. Ustundağ, K. Huysal, Measurement uncertainty of blood ethanol concentration in drink-driving cases in an emergency laboratory, Biochem. Med. 27 (3) (2017 Oct), 030708.
[29] L. Zamengo, G. Frison, G. Tedeschi, S. Frasson, Forensic-metrological considerations on assessment of compliance (or non-compliance) in forensic blood alcohol content determinations: a case study with software application, Forensic Sci. Int. 265 (2016 Aug) 144–152.
[30] S.N. Ayyildiz, The importance of measuring the uncertainty of second-generation total testosterone analysis, Int. J. Med. Biochem. 1 (1) (2018) 34–39.
[31] R. Rigo-Bonnin, A. Blanco-Font, F. Canalias, Different top-down approaches to estimate measurement uncertainty of whole blood tacrolimus mass concentration values, Clin. Biochem. 57 (2018 Jul) 56–61.
[32] D.P. Arfsten, E. Roman Perez, N.C. Goebel, Estimation of measurement uncertainty in quantitation of benzoylecgonine (BZE) and 11-nor-Δ^9-tetrahydrocannabinol-9-carboxylic acid (THCA), J. Anal. Toxicol. 42 (3) (2018 Apr) 141–148.
[33] S.C. Franco de Oliveira, M. Yonamine, Measurement uncertainty for the determination of amphetamines in urine by liquid-phase microextraction and gas chromatography-mass spectrometry, Forensic Sci. Int. 265 (2016 Aug) 81–88.
[34] H. Furuhaugen, R.E.G. Jamt, G. Nilsson, V. Vindenes, H. Gjerde, Roadside survey of alcohol and drug use among Norwegian drivers in 2016-17: a follow up of the 2008-9 survey, Traffic Inj. Prev. 21 (2018 Jun) 1–32.
[35] F. Herrera-Gómez, M. García-Mingo, M. Colás, J.C. González-Luque, F.J. Álvarez, Opioids in oral fluid of Spanish drivers, Drug Alcohol Depend. 187 (2018 Jun) 35–39.
[36] I. Fierro, M. Colás, J.C. González-Luque, F.J. Álvarez, Roadside opioid testing of drivers using oral fluid: the case of a country with a zero tolerance law, Spain, Subst. Abuse Treat. Prev. Pol. 12 (2017 May) 22.
[37] T.M. Watson, R.E. Mann, International approaches to driving under the influence of cannabis: a review of evidence on impact, Drug Alcohol Depend. 169 (2016 Dec) 148–155.
[38] E. Kim, S. Choe, J. Lee, M. Jang, H. Choi, H. Chung, Detection of drugs in 275 alcohol-positive blood samples of Korean drivers, Forensic Sci. Int. 265 (2016 Aug) 186–192.
[39] K.W. Simonsen, K. Linnet, B.S. Rasmussen, Driving under the influence of alcohol and drugs in the eastern part of Denmark in 2015 and 2016: abuse patterns and trends, Traffic Inj. Prev. 19 (5) (2018 Jul) 468–475.
[40] R.E.G. Jamt, H. Gjerde, P.T. Normann, S.T. Bogstrand, Roadside survey on alcohol and drug use among drivers in the Arctic county of Finnmark (Norway), Traffic Inj. Prev. 18 (7) (2017 Oct) 681–687.
[41] J. Damsere-Derry, G. Palk, M. King, Prevalence of alcohol-impaired driving and riding in northern Ghana, Traffic Inj. Prev. 17 (3) (2016) 226–232.
[42] J.L. Martin, B. Gadegbeku, D. Wu, V. Viallon, B. Laumon, Cannabis, alcohol and fatal road accidents, PloS One 12 (11) (2017 Nov) 1–16.
[43] A. Valen, S.T. Bogstrand, V. Vindenes, H. Gjerde, Toxicological findings in suspected drug-impaired drivers in Norway - trends during 1990-2015, Forensic Sci. Int. 280 (2017 Nov) 15–24.
[44] Y.S. Chan, C.S. Chen, L. Huang, Y.I. Peng, Sanction changes and drunk-driving injuries/deaths in Taiwan, Accid. Anal. Prev. 107 (2017 Oct) 102–109.
[45] B. Kirsch, C.G. Birngruber, R. Dettmeyer, Senior driving under the influence: a five-year retrospective study of alcoholized road-users aged 70 and over, Forensic Sci. Int. 277 (2017 Aug) 10–15.
[46] F. Cittadini, N. De Giovanni, L. Caradonna, G. Vetrugno, A. Oliva, N. Fucci, C. Zuppi, V.L. Pascali, M. Covino, Prevalence of alcohol and other drugs in injured drivers and their association with clinical outcomes, Eur. Rev. Med. Pharmacol. Sci. 21 (9) (2017 May) 2008–2014.
[47] A. Valen, S.T. Bogstrand, V. Vindenes, H. Gjerde, Increasing use of cannabis among arrested drivers in Norway, Traffic Inj. Prev. 18 (8) (2017 Nov) 801–806.
[48] P. Papa, L. Rocchi, L.M. Rolandi, M. Di Tuccio, M. Biffi, A. Valli, Illicit drugs in Emergency Department patients injured in road traffic accidents, Ann. Ist. Super Sanita 53 (1) (2017 Jan-Mar) 35–39.
[49] R.N. Lipari, A. Hughes, J. Bose, Driving under the Influence of Alcohol and Illicit Drugs. The CBHSQ Report. Rockville (MD): Substance Abuse and Mental Health Services Administration (US), Dec, 2016.
[50] K.E. MacLeod, K.J. Karriker-Jaffe, W.A. Satariano, T. Kelley-Baker, J.H. Lacey, D.R. Ragland, Drinking and driving and perceptions of arrest risk among California drivers: relationships with DUI arrests in their city of residence, Traffic Inj. Prev. 18 (6) (2017 Aug) 566–572.
[51] A. Paulke, C. Wunder, S.W. Toennes, Field study to detect illicit and medicinal drugs in car drivers in Southern and Western Hesse, Archiv für Kriminologie 238 (5–6) (2016 Nov) 173–187.
[52] J.L. Sobngwi-Tambekou, T.G. Brown, J.A. Bhatti, Driving under the influence of alcohol in professional drivers in Cameroon, Traffic Inj. Prev. 17 (Suppl 1) (2016 Sep) 73–78.
[53] T.M. Rudisill, M. Zhu, M. Abate, D. Davidov, V. Delagarza, D.L. Long, U. Sambamoorthi, J.D. Thornton, The characterization of drug and alcohol use among senior drivers fatally injured in U.S. motor vehicle collisions, 2008-2012, Traffic Inj. Prev. 17 (8) (2016 Nov) 788–795.
[54] T.S. Naimi, Z. Xuan, V. Sarda, S.E. Hadland, M.C. Lira, M.H. Swahn, R.B. Voas, T.C. Heeren, Association of state alcohol policies with alcohol-related motor vehicle crash fatalities among US adults, JAMA. Int. Med 178 (7) (2018 Jul) 894–901.
[55] A. Carfora, C.P. Campobasso, P. Cassandro, R. Petrella, R. Borriello, Alcohol and drugs use among drivers injured in road accidents in Campania (Italy): a 8-years retrospective analysis, Forensic Sci. Int. 288 (2018 Jul) 291–296.
[56] A.H. Eichelberger, A.T. McCartt, J.B. Cicchino, Fatally injured pedestrians and bicyclists in the United States with high blood alcohol concentrations, J. Saf. Res. 65 (2018 Jun) 1–9.
[57] M.P. Cameron, M.J. Roskruge, N. Droste, P.G. Miller, Judgement of breath alcohol concentration levels among pedestrians in the night-time economy-a street-intercept field study, Alcohol Alcohol 53 (3) (2018 May) 245–250.
[58] G. Del Balzo, R. Gottardo, S. Mengozzi, R.M. Dorizzi, F. Bortolotti, S. Appolonova, F. Tagliaro, Positive" urine testing for Cannabis is associated with increased risk of traffic crashes, J. Pharmaceut. Biomed. Anal. 151 (2018 Mar) 71–74.
[59] K.K. Harland, R. Bedford, H. Wu, M. Ramirez, Prevalence of alcohol impairment and odds of a driver injury or fatality in on-road farm equipment crashes, Traffic Inj. Prev. 19 (3) (2018 Apr) 230–234.
[60] L. Wundersitz, S. Raftery, Understanding the context of alcohol impaired driving for fatal crash-involved drivers: a descriptive case analysis, Traffic Inj. Prev. 18 (8) (2017 Nov) 781–787.
[61] W.C. Cheng, K.L. Dao, The occurrence of alcohol/drugs by toxicological examination of selected drivers in Hong Kong, Forensic Sci. Int. 275 (2017 Jun) 242–253.
[62] J. Ferris, J. Killian, B. Lloyd, Alcohol-related serious road traffic injuries

between 2000 and 2010: a new perspective to deal with administrative data in Australia, Int. J. Drug Pol. 43 (2017 May) 104–112.
[63] G.A. Wagner, Z.M. Sanchez, Patterns of drinking and driving offenses among nightclub patrons in Brazil, Int. J. Drug Pol. 43 (2017 May) 96–103.
[64] A.E. Steuer, L. Eisenbeiss, T. Kraemer, Blood alcohol analysis alone versus comprehensive toxicological analysis - systematic investigation of missed co-ingested other drugs in suspected alcohol-impaired drivers, Forensic Sci. Int. 267 (2016 Oct) 52–59.
[65] S. Maximus, C. Figueroa, J. Pham, E. Kuncir, C. Barrios, DUI histories in intoxicated injured bicyclists 81 (4) (2016 Oct) 638–643.
[66] A. Domingo-Salvany, M.J. Herrero, B. Fernandez, J. Perez, P. Del Real, J.C. González-Luque, R. de la Torre, Prevalence of psychoactive substances, alcohol and illicit drugs, in Spanish drivers: a roadside study in 2015, Forensic Sci. Int. 278 (2017 Sep) 253–259.
[67] C. Richeval, S.M.R. Wille, M. Nachon-Phanithavong, N. Samyn, D. Allorge, J.M. Gaulier, New psychoactive substances in oral fluid of French and Belgian drivers in 2016, Int. J. Drug Pol. 57 (2018 Jul) 1–3.
[68] L. Institóris, E. Hidvégi, A. Dobos, Sija É, É.M. Kereszty, L.B. Tajti, G.P. Somogyi, T. Varga, The role of illicit, licit, and designer drugs in the traffic in Hungary, Forensic Sci. Int. 275 (2017 Jun) 234–241.
[69] S.M.R. Wille, C. Richeval, M. Nachon-Phanithavong, J.M. Gaulier, V. Di Fazio, L. Humbert, N. Samyn, D. Allorge, Prevalence of new psychoactive substances and prescription drugs in the Belgian driving under the influence of drugs population, Drug Test. Anal. 10 (3) (2018 Mar) 539–547.
[70] G. Høiseth, S.S. Tuv, R. Karinen, Blood concentrations of new designer benzodiazepines in forensic cases, Forensic Sci. Int. 268 (2016 Nov) 35–38.
[71] C. Monteiro, P. Proença, C. Tavares, A. Castañera, F. Corte Real, Interference of anesthetics in blood alcohol analysis by HS-GC-FID: a case report, Forensic Sci. Int. 265 (2016 Aug) 65–69.
[72] M.E. Rossheim, D.L. Thombs, Estimated blood alcohol concentrations achieved by consuming supersized alcopops, Am. J. Drug Alcohol Abuse 44 (3) (2018) 317–320.
[73] J. Ljungblad, B. Hök, A. Allalou, H. Pettersson, Passive in-vehicle driver breath alcohol detection using advanced sensor signal acquisition and fusion, Traffic Inj. Prev. 18 (sup1) (2017 May) S31–S36.
[74] T.P. Rohrig, C.M. Moore, K. Stephens, K. Cooper, C. Coulter, T. Baird, M. Garnier, S. Miller, J. Tuyay, K. Osawa, J. Chou, C. Nuss, J. Collier, K.C. Wittman, Roadside drug testing: an evaluation of the Alere DDS® 2 mobile test system, Drug Test. Anal. 10 (4) (2018 Apr) 663–670.
[75] L.D. Edwards, K.L. Smith, T. Savage, Drugged driving in Wisconsin: oral fluid versus blood, J. Anal. Toxicol. 41 (6) (2017 Jul) 523–529.
[76] H. Gjerde, G.B. Clausen, E. Andreassen, H. Furuhaugen, Evaluation of dräger DrugTest 5000 in a naturalistic setting, J. Anal. Toxicol. 42 (4) (2018 May) 248–254.
[77] C. Cohier, B. Mégarbane, O. Roussel, Illicit drugs in oral fluid: evaluation of two collection devices, J. Anal. Toxicol. 41 (1) (2017 Jan) 71–76.
[78] A.J. Krotulski, A.L. Mohr, M. Friscia, B.K. Logan, Field detection of drugs of abuse in oral fluid using the Alere™ DDS® 2 mobile test system with confirmation by liquid chromatography tandem mass spectrometry (LC–MS/MS), J. Anal. Toxicol. 42 (3) (2018 Apr) 170–176.
[79] M.H. Tang, C.K. Ching, S. Poon, S.S. Chan, W.Y. Ng, M. Lam, C.K. Wong, R. Pao, A. Lau, T.W. Mak, Evaluation of three rapid oral fluid test devices on the screening of multiple drugs of abuse including ketamine, Forensic Sci. Int. 286 (2018 May) 113–120.
[80] A.M. Veitenheimer, J.R. Wagner, Evaluation of oral fluid as a specimen for DUID, J. Anal. Toxicol. 41 (6) (2017 Jul) 517–522.
[81] V. Di Fazio, S.M.R. Wille, S.W. Toennes, J.H.P. van Wel, J.G. Ramaekers, N. Samyn, Driving under the influence of cocaine: quantitative determination of basic drugs in oral fluid obtained during roadside controls and a controlled study with cocaine users, Drug Test. Anal. 10 (8) (2018 Mar) 1285–1296.
[82] H. Jin, S.Z. Williams, S.T. Chihuri, G. Li, Q. Chen, Validity of oral fluid test for delta-9-tetrahydrocannabinol in drivers using the 2013 national roadside survey data, Injury. Epidemol. 5 (1) (2018 Feb) 3.
[83] B.D. Plouffe, S.K. Murthy, Fluorescence-based lateral flow assays for rapid oral fluid roadside detection of cannabis use, Electrophoresis 38 (3–4) (2017 Feb) 501–506.
[84] M. Di Rago, M. Chu, L.N. Rodda, E. Jenkins, A. Kotsos, D. Gerostamoulos, Ultra-rapid targeted analysis of 40 drugs of abuse in oral fluid by LC-MS/MS using carbon-13 isotopes of methamphetamine and MDMA to reduce detector saturation, Anal. Bioanal. Chem. 408 (14) (2016 May) 3737–3749.
[85] A. Lu, K.S. Scott, A. Chan-Hosokawa, B.K. Logan, Impact of expanding ELISA screening in DUID investigations to include carisoprodol/meprobamate and zolpidem, J. Anal. Toxicol. 41 (2) (2017 Mar) 134–139.
[86] C.B. Mollerup, P.W. Dalsgaard, M. Mardal, K. Linnet, Targeted and non-targeted drug screening in whole blood by UHPLC-TOF-MS with data-independent acquisition, Drug Test. Anal. 9 (7) (2017 Jul) 1052–1061.
[87] R. Telving, J.B. Hasselstrøm, M.F. Andreasen, Targeted toxicological screening for acidic, neutral and basic substances in postmortem and antemortem whole blood using simple protein precipitation and UPLC-HR-TOF-MS, Forensic Sci. Int. 266 (2016 Sep) 453–461.
[88] T. Rosado, A. Gonçalves, C. Margalho, M. Barroso, E. Gallardo, Rapid analysis of cocaine and metabolites in urine using microextraction in packed sorbent and GC/MS, Anal. Bioanal. Chem. 409 (8) (2017 Mar) 2051–2063.
[89] P. Trefz, S. Kamysek, P. Fuchs, P. Sukul, J.K. Schubert, W. Miekisch, Drug detection in breath: non-invasive assessment of illicit or pharmaceutical drugs, J. Breath Res. 11 (2) (2017 Mar), 024001.
[90] S. Ullah, S. Sandqvist, O. Beck, A liquid chromatography and tandem mass spectrometry method to determine 28 non-volatile drugs of abuse in exhaled breath, J. Pharmaceut. Biomed. Anal. 148 (2018 Jan) 251–258.
[91] G. Høiseth, E. Wiik, L. Kristoffersen, J. Mørland, Ethanol elimination rates at low concentrations based on two consecutive blood samples, Forensic Sci. Int. 266 (2016 Sep) 191–196.
[92] A. Himemiya-Hakucho, T. Fujimiya, Pharmacokinetic analyses using absorption kinetics in low-alcohol dose cases of drunken driving, Leg. Med. 26 (2017 May) 98–101.
[93] P.J. Perry, S. Doroudgar, P. Van Dyke, Ethanol forensic toxicology, J. Am. Acad. Psychar. Law 45 (4) (2017 Dec) 429–438.
[94] M.C. Strand, J. Mørland, L. Slørdal, B. Riedel, C. Innerdal, T. Aamo, G. Mathisrud, V. Vindenes, Conversion factors for assessment of driving impairment after exposure to multiple benzodiazepines/z-hypnotics or opioids, Forensic Sci. Int. 281 (2017 Dec) 29–36.
[95] Road Safety Annual Report, OECD International Transport Forum, International Traffic Safety Data and Analysis Group, 2017.
[96] F.P. Busardò, S. Pichini, R. Pacifici, Driving under the influence of drugs: looking for reasonable blood cutoffs and realistic analytical values, Clin. Chem. 63 (3) (2017 Mar) 781–783.
[97] B. Nistal-Nuño, Impact of a new law to reduce the legal blood alcohol concentration limit - a Poisson regression analysis and descriptive approach, J. Res. Health Sci. 17 (1) (2017 Mar), e00374.
[98] B. Nistal-Nuño, Segmented regression analysis of interrupted time series data to assess outcomes of a South American road traffic alcohol policy change, Publ. Health 150 (2017 Sep) 51–59.
[99] H.J. Hamnett, H. Poulsen, The effect of lowering the legal drink-drive limit on the toxicological findings in driver fatalities: a comparison of two jurisdictions, J. Forensic Sci. 63 (5) (2018 Sep) 1457–1465.
[100] J.C. Fell, M. Scherer, Estimation of the potential effectiveness of lowering the blood alcohol concentration (BAC) limit for driving from 0.08 to 0.05 grams per deciliter in the United States, Alcohol Clin. Exp. Res. 41 (12) (2017 Dec) 2128–2139.
[101] N.A. Van Dyke, M.T. Fillmore, Laboratory analysis of risky driving at 0.05% and 0.08% blood alcohol concentration, Drug Alcohol Depend. 175 (2017 Jun) 127–132.
[102] S. Otero, T. Rau, The effects of drinking and driving laws on car crashes, injuries, and deaths: evidence from Chile, Accid. Anal. Prev. 106 (2017 Sep) 262–274.
[103] D. Favretto, S. Visentin, G. Stocchero, S. Vogliardi, R. Snenghi, M. Montisci, Driving under the influence of drugs: prevalence in road traffic accidents in Italy and considerations on "per se" limits legislation, Traffic Inj. Prev. (2018 Jul) 1–29.
[104] B. Rooney, G.J. Gouveia, N. Isles, L. Lawrence, T. Brodie, Z. Grahovac, M. Chamberlain, G. Trotter, Drugged drivers blood concentrations in England and Wales prior to the introduction of per Se limits, J. Anal. Toxicol. 41 (2) (2017 Mar) 140–145.
[105] S. Petković, K. Palić, I. Samojlik, Blood alcohol concentration in fatally injured drivers and the efficacy of alcohol policies of the new law on road traffic safety: a retrospective 10-year study in autonomous province of Vojvodina, Republic of Serbia, Traffic Inj. Prev. 17 (6) (2016 Aug) 553–557.
[106] D. Ferrari, M. Manca, G. Banfi, M. Locatelli, Alcohol and illicit drugs in drivers involved in road traffic crashes in the Milan area. A comparison with normal traffic reveals the possible inadequacy of current cut-off limits, Forensic Sci. Int. 282 (2018 Jan) 127–132.
[107] S.Y. Lin, H.H. Lee, J.F. Lee, B.H. Chen, Urine specimen validity test for drug abuse testing in workplace and court settings, J. Food Drug Anal. 26 (1) (2018 Jan) 380–384.
[108] V.J. Kim, C.K. Okano, C.R. Osborne, D.M. Frank, C.T. Meana, M.S. Castaneto, Can synthetic urine replace authentic urine to “beat” workplace drug testing? Drug Test. Anal. (2018) 1–5.
[109] M.M. Goggin, C. Tann, A. Miller, A. Nguyen, G.C. Janis, Catching fakes: new markers of urine sample validity and invalidity, J. Anal. Toxicol. 41 (2) (2017 Mar) 121–126.
[110] J. Kluge, L. Rentzsch, D. Remane, F.T. Peters, D.K. Wissenbach, Systematic investigations of novel validity parameters in urine drug testing and prevalence of urine adulteration in a two-year cohort, Drug Test. Anal. (2018 Jun) 1–7.
[111] A.E. Steuer, K. Arnold, T.D. Schneider, M. Poetzsch, T. Kraemer, A new metabolomics-based strategy for identification of endogenous markers of urine adulteration attempts exemplified for potassium nitrite, Anal. Bioanal. Chem. 409 (26) (2017 Oct) 6235–6244.
[112] L. Morini, F. Pozzi, A. Groppi, Stability of benzodiazepines in hair after prolonged exposure to chlorinated water, Forensic Sci. Int. 278 (2017 Jul) 217–220.
[113] J. Ettlinger, M. Yegles, Influence of thermal hair straightening on cannabis and cocaine content in hair, Forensic Sci. Int. 265 (2016 Aug) 13–16.
[114] K.B. Scheidweiler, M. Andersson, M.J. Swortwood, C. Sempio, M.A. Huestis, Long-term stability of cannabinoids in oral fluid after controlled cannabis administration, Drug Test. Anal. 9 (1) (2017 Jan) 143–147.
[115] M.M. Madry, T. Kraemer, M.R. Baumgartner, Systematic assessment of different solvents for the extraction of drugs of abuse and pharmaceuticals from an authentic hair pool, Forensic Sci. Int. 282 (2018 Jan) 137–143.

[116] K. Kuwayama, H. Miyaguchi, T. Yamamuro, K. Tsujikawa, T. Kanamori, Y.T. Iwata, H. Inoue, Highly sensitive quantification of unconjugated 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol in a cannabis user's hair using micro-pulverized extraction, Forensic Sci. Int. 262 (2016 May) e34–e36.
[117] G. Tassoni, M. Cippitelli, G. Ottaviani, R. Froldi, M. Cingolani, Detection of cannabinoids by ELISA and GC-MS methods in a hair sample previously used to detect other drugs of abuse, J. Anal. Toxicol. 40 (6) (2016 Jul) 408–413.
[118] S. Heinl, O. Lerch, F. Erdmann, Automated GC-MS determination of d^9-tetrahydrocannabinol, cannabinol and cannabidiol in hair, J. Anal. Toxicol. 40 (7) (2016 Aug) 498–503.
[119] A. Salomone, J.J. Palamar, E. Gerace, D. Di Corcia, M. Vincenti, Hair testing for drugs of abuse and new psychoactive substances in a high-risk population, J. Anal. Toxicol. 41 (5) (2017 Jun) 376–381.
[120] A. Salomone, J.J. Palamar, R. Bigiarini, E. Gerace, D. Di Corcia, M. Vincenti, Detection of fentanyl analogs and synthetic opioids in real hair samples, J. Anal. Toxicol. (2018 Nov), https://doi.org/10.1093/jat/bky093.
[121] Nicolas Van Elsué, Cleo L. Crunelle, Cor A. Verbrugge, Kim van Baarle, Anaïs Rodrigues, Hugo Neels, Michel Yegles, Gammahydroxybutyrate in hair of non-GHB and repeated GHB users: a new and optimized method, Forensic Sci. Int. 291 (2018 Oct) 193–198.
[122] S.M. Wille, J. Eliaerts, V. Di Fazio, N. Samyn, Challenges concerning new psychoactive substance detection in oral fluid, Toxic. Anal. Cliniq 29 (1) (2017 Feb) 11–17.
[123] K.L. Miller, B.L. Puet, A. Roberts, C. Hild, J. Carter, D.L. Black, Urine drug testing results and paired oral fluid comparison from patients enrolled in long-term medication-assisted treatment in Tennessee, J. Subst. Abuse Treat. 76 (2017 May) 36–42.
[124] P. Kintz, P. Mura, C. Jamey, J.S. Raul, Detection of Δ^9-tetrahydrocannabinol in exhaled breath after cannabis smoking and comparison with oral fluid, Forensic Toxicol. 35 (1) (2017 Jan) 173–178.
[125] D. Favretto, S. Vogliardi, M. Tucci, I. Simoncello, R. El Mazloum, R. Snenghi, Occupational exposure to ketamine detected by hair analysis: a retrospective and prospective toxicological study, Forensic Sci. Int. 265 (2016 Aug) 193–199.
[126] G.S. Doran, R. Deans, C. De Filippis, C. Kostakis, J.A. Howitt, The presence of licit and illicit drugs in police stations and their implications for workplace drug testing, Forensic Sci. Int. 278 (2017 Sep) 125–136.
[127] G.S. Doran, R. Deans, C. De Filippis, C. Kostakis, J.A. Howitt, Work place drug testing of police officers after THC exposure during large volume cannabis seizures, Forensic Sci. Int. 275 (2017 Jun) 224–233.
[128] A. Berthet, M. De Cesare, B. Favrat, F. Sporkert, M. Augsburger, A. Thomas, C. Giroud, A systematic review of passive exposure to cannabis, Forensic Sci. Int. 269 (2016 Dec) 97–112.
[129] A. Salomone, A. Bozzo, D. Di Corcia, E. Gerace, M. Vincenti, Occupational exposure to alcohol-based hand sanitizers: the diagnostic role of alcohol biomarkers in hair, J. Anal. Toxicol. 42 (3) (2017 Nov) 157–162.
[130] V.A. Hill, G.N. Stowe, R.B. Paulsen, M. Schaffer, Nail analysis for drugs: a role in workplace testing? J. Anal. Toxicol. 42 (6) (2018 Jul) 425–436.
[131] K. Kulig, Interpretation of workplace tests for cannabinoids, J. Med. Toxicol. 13 (1) (2017 Mar) 106–110.
[132] G.L. Rosso, C. Montomoli, L. Morini, S.M. Candura, Seven years of workplace drug testing in Italy: a systematic review and meta-analysis, Drug Test. Anal. 9 (6) (2017 Mar) 844–852.
[133] E.J.D. Ogden, J.C. Verster, A.C. Hayley, L.A. Downey, B. Hocking, C.K. Stough, When should the driver with a history of substance misuse be allowed to return to the wheel? A review of the substance misuse section of the Australian national guidelines, Intern. Med. J. 48 (8) (2018 Aug) 908–915.
[134] M. Montgomery, M. LeBeau, C. Morris-Kukoski, New hair testing conclusions, J. Anal. Toxicol. 41 (2) (2017 Mar) 161–162.
[135] X. Wang, S.S. Johansen, Y. Zhang, J. Jia, Y. Rao, F. Jiang, K. Linnet, Deposition of diazepam and its metabolites in hair following a single dose of diazepam, Int. J. Leg. Med. 131 (1) (2017 Jan) 131–141.
[136] P. Kintz, A. Farrugia, A. Ameline, A. Eibel, J.S. Raul, High risk of misinterpreting hair analysis results for children tested for methadone, Forensic Sci. Int. 28 (2017 Nov) 176–180.
[137] J.C. Alvarez, L. Lasne, I. Etting, G. Chéron, V. Abadie, N. Fabresse, I.A. Larabi, Hair analysis does not allow to discriminate between acute and chronic administrations of a drug in young children, Int. J. Leg. Med. 132 (1) (2018 Jan) 165–172.
[138] A. Salomone, M. Vincenti, E. Gerace, Interpretation of NPS results in real hair samples, Toxic. Anal. Cliniq 29 (1) (2017 Feb) 4–10.
[139] R. Solimini, A. Minutillo, C. Kyriakou, S. Pichini, R. Pacifici, F.P. Busardo, Nails in forensic toxicology: an update, Curr. Pharmaceut. Des. 23 (36) (2017) 468–5479.
[140] F. Franz, K. Mueller, H. Jechle, V. Angerer, B. Moosmann, B. Schwarze, Prevalence of synthetic cannabinoid use among persons undergoing drug testing for cannabis, Zeitschrift fuer Verkehrssicherheit 63 (2) (2017 May) 111–112.
[141] M. Brcak, O. Beck, T. Bosch, D. Carmichael, N. Fucci, C. George, European guidelines for workplace drug testing in oral fluid, Drug Test. Anal. 10 (3) (2018 Mar) 402–415.
[142] S. Crumpton, J. Mitchell, Changes to the mandatory guidelines for US federal workplace drug testing programs using urine, Forensic Sci. Rev. 30 (1) (2018 Jan) 5–7.
[143] M. Mohammadzadeh Shabestari, L. Alizadeh, M. Moshiri, E. Darchini-Maragheh, M. Balali-Mood, Late cardiac complications of sulfur mustard poisoning in 38 Iranian veterans, Cardiovasc. Toxicol. 19 (3) (2019 Jun) 220–228, https://doi.org/10.1007/s12012-018-9481-z.
[144] S. Sezigen, K. Ivelik, M. Ortatatli, M. Almacioglu, M. Demirkasimoglu, R.K. Eyison, Z.I. Kunak, L. Kenar, Victims of chemical terrorism, a family of four who were exposed to sulfur mustard, Toxicol. Lett. 303 (2019 Mar) 9–15.
[145] A. Schmidt, D. Steinritz, K.D. Rudolf, H. Thiermann, E. Striepling, Accidental sulfur mustard exposure: a case report, Toxicol. Lett. 293 (2018 Sep) 62–66.
[146] O. Isono, A. Kituda, M. Fujii, T. Yoshinaka, G. Nakagawa, Y. Suzuki, Long-term neurological and neuropsychological complications of sulfur mustard and Lewisite mixture poisoning in Chinese victims exposed to chemical warfare agents abandoned at the end of WWII, Toxicol. Lett. 293 (2018 Sep) 9–15.
[147] E. Manandhar, A. Pay, L.A. Veress, B.A. Logue, Rapid analysis of sulfur mustard oxide in plasma using gas chromatography-chemical ionization-mass spectrometry fordiagnosis of sulfur mustard exposure, J. Chromatogr. A 1572 (2018 Oct) 106–111.
[148] T. Zubel, A. Bürkle, A. Mangerich, Mass spectrometric analysis of sulfur mustard-induced biomolecular adducts: are DNA adducts suitable biomarkers of exposure? Toxicol. Lett. 293 (2018 Sep) 21–30.
[149] D. Rose, A. Schmidt, M. Brandenburger, T. Sturmheit, M. Zille, J. Boltze, Sulfur mustard skin lesions: a systematic review on pathomechanisms, treatment options and future research directions, Toxicol. Lett. 293 (2018 Sep) 82–90.
[150] G. Menacher, D. Steinritz, A. Schmidt, T. Popp, F. Worek, T. Gudermann, H. Thiermann, F. Balszuweit, Effects of anti-inflammatory compounds on sulfur mustard injured cells: recommendations and caveats suggested by in vitro cell culture models, Toxicol. Letts 293 (2018) 91–97. Sep.
[151] M. Siegert, A. Kranawetvogl, H. Thiermann, H. John, Glutathione as an antidote for sulfur mustard poisoning: mass spectrometric investigations of its potency as a chemical scavenger, Toxicol. Lett. 293 (2018 Sep) 31–37.
[152] T. Rozsypal, E. Halamek, Extraction-spectrophotometric determination of tris(2-chloroethyl)amine using phthaleins, Drug Test. Anal. 9 (6) (2017 Jun) 916–923.
[153] D.G. Goswami, R. Kant, N. Tewari-Singh, R. Agarwal, Efficacy of anti-inflammatory, antibiotic and pleiotropic agents in reversing nitrogen mustard-induced injury in ex vivo cultured rabbit cornea, Toxicol. Lett. 293 (2018 Sep) 127–132.
[154] J.M. Li, J. Gan, T.F. Zeng, J.W. Sander, D. Zhou, Tetramethylenedisulfotetramine intoxication presenting with de novo Status Epilepticus: a case series, Neurotoxicology 33 (2) (2012 Mar) 207–211.
[155] J. Patocka, T.C.C. Franca, Q. Wu, K. Kuca, Tetramethylenedisulfotetramine: a health risk compound and a potential chemical warfare agent, Toxics 6 (3) (2018 Aug) 51–57.
[156] N. Vasylieva, B. Barnych, A. Rand, B. Inceoglu, S.J. Gee, B.D. Hammock, Sensitive immunoassay for detection and quantification of the neurotoxin, tetramethylenedi-sulfotetramine (TETS), Anal. Chem. 89 (10) (2017 May) 5612–5619.
[157] T. Nakagawa, A.T. Tu, Murders with VX: aum shinrikyo in Japan and the assassination of Kim jong-nam in Malaysia, Forensic Toxicol. 36 (2018 July) 542–544.
[158] A. Kranawetvogl, J. Küppers, M. Gütschow, F. Worek, H. Thiermann, P.W. Elsinghorst, H. John, Identification of novel disulfide adducts between the thiol containing leaving group of the nerve agent VX and cysteine containing tripeptides derived from human serum albumin, Drug Test. Anal. 9 (8) (2017 Aug) 1192–1203.
[159] J.Y. Lee, C. Kim, Y.H. Lee, Simultaneous time-concentration analysis of soman and VX adducts to butyrylcholinesterase and albumin by LC-MS-MS, J. Anal. Toxicol. 42 (5) (2018 Jun) 293–299.
[160] C. Whitmore, A.R. Cook, T. Mann, M.E. Price, E. Emery, N. Roughley, D. Flint, S. Stubbs, S.J. Armstrong, H. Rice, J.E.H. Tattersall, The efficacy of HI-6 DMS in a sustained infusion against percutaneous VX poisoning in the Guinea-pig, Toxicol. Lett. 293 (2018 Sep) 207–215.
[161] T.M. Mann, M.E. Price, C.L. Whitmore, R.L. Perrott, T.R. Laws, R.R. McColm, E.R. Emery, J.E.H. Tattersall, A.C. Green, H. Rice, Bioscavenger is effective as a delayed therapeutic intervention following percutaneous VX poisoning in the Guinea-pig, Toxicol. Lett. 293 (2018 Sep) 198–206.
[162] I. Trenque, G.C. Magnano, M.A. Bolzinger, L. Roiban, F. Chaput, I. Pitault, S. Briançon, T. Devers, K. Masenelli-Varlot, M. Bugnet, D. Amans, Shape-selective synthesis of nanoceria for degradation of paraoxon as a chemical warfare simulant, Phys. Chem. Chem. Phys. 21 (10) (2019 Mar) 5455–5465.
[163] H. John, M.J. van der Schans, M. Koller, H.E.T. Spruit, F. Worek, H. Thiermann, D. Noort, Fatal sarin poisoning in Syria 2013: forensic verification within an international laboratory network, Forensic Toxicol. 36 (1) (2018) 61–71.
[164] S.A. Young, B.R. Capacio, The Application of a single-column GC-MS-MS method for the rapid analysis of chemical warfare agents and breakdown products, J. Anal. Toxicol. 43 (3) (2019 Apr) 179–187, https://doi.org/10.1093/jat/bky085.
[165] D.H. Read, K.E. Achyuthan, C.S. Fix, R.P. Manginell, M.W. Moorman, D.R. Wheeler, J.J. Whiting, Thermodynamic studies on a hydrogen bonded acidic (HBA) 3,5-bis(trifluoromethyl)phenol-functionalized polymer as a gas chromatography stationary phase for selectively speciating chemical warfare agents, Anal. Sci. 35 (6) (2019 Jun) 671–677, https://doi.org/10.2116/analsci.18P537.
[166] J. McKenna, E.S. Dhummakupt, T. Connell, P.S. Demond, D.B. Miller, J. Michael Nilles, N.E. Manicke, T. Glaros, Detection of chemical warfare agent simulants and hydrolysis products in biological samples by paper spray mass

spectrometry, Analyst 142 (9) (2017 May) 1442–1451.
[167] E. Nepovimova, K. Kuca, Chemical warfare agent NOVICHOK - mini-review of available data, Food Chem. Toxicol. 121 (2018 Nov) 343–350.
[168] M. Kloske, Z. Witkiewicz, Novichoks - the A group of organophosphorus chemical warfare agents, Chemosphere 221 (2019 Apr) 672–682.
[169] L.J. Anderson, A. Flynn, J.L. Pilgrim, A global epidemiological perspective on the toxicology of drug facilitated sexual assault: a systematic review, Journal of Forensic and Legal Medicine 47 (2017 Apr) 46–54.
[170] A. Grela, L. Gautam, M.D. Cole, A multifactorial critical appraisal of substances found in drug facilitated sexual assault cases, Forensic Sci. Int. 292 (2018 Nov) 50–60.
[171] M. Tiemensma, B. Davies, Investigating drug-facilitated sexual assault at a dedicated forensic centre in Cape Town, South Africa, Forensic Sci. Int. 288 (2018 Jul) 115–122.
[172] E. Bertol, M.G. Di Milia, A. Fioravanti, F. Mari, D. Palumbo, J.P. Pascali, F. Vaiano, Proactive drugs in DFSA cases: toxicological findings in an eight-years study, Forensic Sci. Int. 291 (2018 Oct) 207–215.
[173] A. Basher, M. Abul Faiz, S.M. Arif, M. Abul Kashem Khandaker, U. Kuch, S.W. Tonnes, Toxicological screening of drug facilitated crime among travelers in Dhaka, Bangladesh, Asia. Pacific. J. Med. Toxicol. 6 (2017) 47–49.
[174] M. Kapitány-Fövény, G. Zacher, J. Posta, Z. Demetrovics, GHB-involved crimes among intoxicated patients, Forensic Sci. Int. 275 (2017 Jun) 23–29.
[175] H.H. Lee, S.C. Chen, J.F. Lee, H.Y. Lin, B.H. Chen, Simultaneous drug identification in urine of sexual assault victims by using liquid chromatography tandem mass spectrometry, Forensic Sci. Int. 282 (2018 Jan) 35–40.
[176] C. de Paula, M. Jurisch, E. Piccin, R. Augusti, Recognizing drug-facilitated crimes: detection and quantification of benzodiazepines in beverages using fast liquid-liquid extraction with low temperature partitioning and paper spray mass spectrometry, Drug Test. Anal. 10 (9) (2018 Sep) 1348–1357.
[177] N. Van Elsué, C.L. Crunelle, C.A. Verbrugge, K. van Baarle, A. Rodrigues, H. Neels, M. Yegles, Gammahydroxybutyrate in hair of non-GHB and repeated GHB users: a new and optimized method, Forensic Sci. Int. 291 (2018 Oct) 193–198.
[178] K. Kuwayama, M. Nariai, H. Miyaguchi, Y.T. Iwata, T. Kanamori, K. Tsujikawa, T. Yamamuro, H. Segawa, H. Abe, H. Iwase, H. Inoue, Micro-segmental hair analysis for proving drug-facilitated crimes: evidence that a victim ingested a sleeping aid, diphenhydramine, on a specific day, Forensic Sci. Int. 288 (2018 July) 23–28.
[179] X. Wang, S.S. Johansen, M.K.K. Nielsen, K. Linnet, Hair analysis in toxicological investigation of drug-facilitated crimes in Denmark over a 8-year period, Forensic Sci. Int. 285 (2018 Apr) e1–e12.
[180] F.P. Busardò, F. Vaiano, G. Mannocchi, E. Bertol, S. Zaami, E. Marinelli, Twelve months monitoring of hair GHB decay following a single dose administration in a case of facilitated sexual assault, Drug Test. Anal. 9 (6) (2017 Jun) 953–959.
[181] P. Kintz, A. Ameline, J.S. Raul, Interpretation of tramadol findings in hair. Concentrations after a single exposure and application to a Munchausen's syndrome by proxy case, J. Anal. Toxicol. 42 (3) (2018 Apr) e35–e37.
[182] C. Richeval, D. Allorge, V. Lopez, B. Boyer, J.M. Gaulier, Unusual case of drug-facilitated sexual assault using chloroform, J. Anal. Toxicol. 41 (3) (2017 Apr) 256–257.
[183] I.A. Larabi, M. Martin, I. Etting, P. Penot, N. Fabresse, J.C. Alvarez, Drug-facilitated sexual assault (DFSA) involving 4-methylethcathinone (4-MEC), 3,4-methylenedioxypyrovalerone (MDPV), and doxylamine highlighted by hair analysis, Drug Test. Anal. 10 (8) (2018 Mar) 1280–1284.
[184] S.S. Johansen, Detection of the antipsychotic drug quetiapine in the blood, urine and hair samples of the victim of a drug-facilitated sexual assault, Forensic Sci. Int. 270 (2017 Jan) e12–e15.
[185] K.J. Lusthof, I.J. Bosman, B. Kubat, M.J. Vincenten-van Maanen, Toxicological results in a fatal and two non-fatal cases of scopolamine-facilitated robberies, Forensic Sci. Int. 274 (2017 May) 79–82.
[186] H. Andresen-Streichert, S. Iwersen-Bergmann, A. Mueller, S. Anders, Attempted drug-facilitated sexual assault-xylazine intoxication in a child, J. Forensic Sci. 62 (1) (2017 Jan) 270–273.
[187] J. Krongvorakul, S. Auparakkitanon, S. Trakulsrichai, P. Sanguanwit, J. Sueajai, N. Noumjad, W. Wananukul, Use of xylazine in drug-facilitated crimes, J. Forensic Sci. 63 (4) (2018 Jul) 1325–1330.
[188] United Nations Office on Drugs and Crime, World drug report 2018, book 1 executive summary. https://www.unodc.org/wdr2018/.
[189] EMCDDA, Fentanils and synthetic cannabinoids: driving greater complexity into the drug situation — an update from the EU Early Warning System. http://www.emcdda.europa.eu/publications/rapid-communications/fentanils-and-synthetic-cannabinoids-ews-update, 2018 June.
[190] United Nations Office ON Drugs and Crime (UNODC), Understanding the synthetic drug market: the NPS factor, Global SMART Update 19 (2018). March 2018, http://www.unodc.org/unodc/en/scientists/global-smart-update-2018-vol-19.html.
[191] D. Gerostamoulos, S. Elliott, H.C. Walls, F.T. Peters, M. Lynch, O.H. Drummer, To measure or not to measure? That is the NPS question, J. Anal. Toxicol. 40 (4) (2016 May) 318–320.
[192] M.J. Bogusz, Letter to the editor concerning the letter: Gerostamoulos D, elliott S, walls HC, Peters FT, lynch M, drummer OH. (2016) To measure or not to measure? That is the NPS question, J. Anal. Toxicol. 40 (9) (2016 Nov) 767–768.
[193] S. Elliott, R. Sedefov, M. Evans-Brown, Assessing the toxicological significance of new psychoactive substances in fatalities, Drug Test. Anal. 10 (1) (2018 Jan) 120–126.
[194] J. Suzuki, S. El-Haddad, A review: fentanyl and non-pharmaceutical fentanyls, Drug Alcohol Depend. 171 (2017 Feb) 107–116.
[195] S. Mayer, J. Boyd, A. Collins, M.C. Kennedy, N. Fairbairn, R. McNeil, Characterizing fentanyl-related overdoses and implications for overdose response: findings from a rapid ethnographic study in Vancouver, Canada, Drug Alcohol Depend. 193 (2018 Dec) 69–74.
[196] J.J. Carroll, B.D.L. Marshall, J.D. Rich, T.C. Green, Exposure to fentanyl-contaminated heroin and overdose risk among illicit opioid users in Rhode Island: a mixed methods study, Int. J. Drug Pol. 46 (2017 Aug) 136–145.
[197] R.T. DeRienz, D.D. Baker, N.E. Kelly, A.M. Mullins, R.Y. Barnett, J.M. Hobbs, J.A. Daniels, K.E. Harshbarger, A.M. Ortiz, Child fatalities due to heroin/fentanyl exposure: what the case history missed, J. Anal. Toxicol. 42 (8) (2018 Oct) 581–585.
[198] A. Macmadu, J.J. Carroll, S.E. Hadland, T.C. Green, B.D. Marshall, Prevalence and correlates of fentanyl-contaminated heroin exposure among young adults who use prescription opioids non-medically, Addict. Behav. 68 (2017 May) 35–38.
[199] L.N. Rodda, J.L. Pilgrim, M. Di Rago, K. Crump, D. Gerostamoulos, O.H. Drummer, A cluster of fentanyl-laced heroin deaths in 2015 in melbourne, Australia, J. Anal. Toxicol. 41 (4) (2017 May) 318–324.
[200] R.A. Rudd, N. Aleshire, J.E. Zibbell, R.M. Gladden, Increases in drug and opioid overdose deaths–United States, 2000-2014, MMWR (Morb. Mortal. Wkly. Rep.) 64 (50–51) (2016 Jan) 1378–1382.
[201] United Nations Office on Drugs and Crime (Unodc), Fentanyl and its analogues-50 years on, Global SMART Update (2017 Mar). https://www.unodc.org/unodc/en/scientists/global-smart-update-2017-vol-17.html.
[202] A.B. Peterson, R.M. Gladden, C. Delcher, E. Spies, A. Garcia-Williams, Y. Wang, J. Halpin, J. Zibbell, C.L. McCarty, J. DeFiore-Hyrmer, M. DiOrio, B.A. Goldberger, Increases in fentanyl-related overdose deaths - Florida and Ohio, MMWR (Morb. Mortal. Wkly. Rep.) 65 (33) (2013-2015) 844–849, 2016 Aug 26.
[203] R. Daniulaityte, M.P. Juhascik, K.E. Strayer, I.E. Sizemore, K.E. Harshbarger, H.M. Antonides, R.R. Carlson, Overdose deaths related to fentanyl and its analogs - Ohio, january-february 2017, MMWR (Morb. Mortal. Wkly. Rep.) 66 (34) (2017 Sep 1) 904–908.
[204] I. Sinicina, H. Sachs, W. Keil, Post-mortem review of fentanyl-related overdose deaths among identified drug users in Southern Bavaria, Germany, 2005-2014, Drug Alcohol Depend. 180 (2017 Nov 1) 286–291.
[205] L. Brinkley-Rubinstein, A. Macmadu, B.D.L. Marshall, A. Heise, S.I. Ranapurwala, J.D. Rich, T.C. Green, Risk of fentanyl-involved overdose among those with past year incarceration: findings from a recent outbreak in 2014 and 2015, Drug Alcohol Depend. 185 (2018 Apr 1) 189–191.
[206] N.J. Somerville, J. O'Donnell, R.M. Gladden, J.E. Zibbell, T.C. Green, M. Younkin, S. Ruiz, H. Babakhanlou-Chase, M. Chan, B.P. Callis, J. Kuramoto-Crawford, H.M. Nields, A.Y. Walley, Characteristics of fentanyl overdose - Massachusetts, 2014-2016, MMWR (Morb. Mortal. Wkly. Rep.) 66 (14) (2017 Apr 14) 382–386.
[207] D. Guerrieri, E. Rapp, M. Roman, G. Thelander, R. Kronstrand, Acrylfentanyl: another new psychoactive drug with fatal consequences, Forensic Sci. Int. 277 (2017 Aug) e21–e29.
[208] P. Nikolaou, M. Katselou, I. Papoutsis, C. Spiliopoulou, S. Athanaselis, U-47700. An old opioid becomes a recent danger, Forensic Toxicol. 35 (2017) 11–19.
[209] Emcdda, Report on the risk assessment of N-(1-phenethylpiperidin-4-yl)-N-phenylacrylamide (acryloylfentanyl) in the framework of the Council Decision on new psychoactive substances, 2017 Dec. http://www.emcdda.europa.eu/publications/risk-assessments/acryloylfentanyl_en.
[210] O.H. Drummer, Fatalities caused by novel opioids: a review, Foren. Sci. Res. (2018 May), https://doi.org/10.1080/20961790.2018.1460063.
[211] N. Misailidi, I. Papoutsis, P. Nikolaou, C. Katselou, C. Spiliopoulou, S. Athanaselis, Furanylfentanyl: another fentanyl analogue, another hazard for public health, Forensic Toxicol. 36 (1) (2018 Jan) 1–11.
[212] Emcdda, Report on the risk assessment of N-phenyl-N-[1-(2-phenylethyl) piperidin-4-yl]furan-2-carboxamide (furanylfentanyl) in the framework of the Council Decision on new psychoactive substances. http://www.emcdda.europa.eu/publications/risk-assessments/furanylfentanyl_en.
[213] J.K. O'Donnell, J. Halpin, C.L. Mattson, B.A. Goldberger, R.M. Gladden, Deaths involving fentanyl, fentanyl analogs, and U-47700 - 10 states, Morb. Mortal 66 (43) (July-December 2016) 1197–1202. Weekly Report., 2017 Nov.
[214] D. Guerrieri, E. Rapp, M. Roman, H. Druid, R. Kronstrand, Postmortem and toxicological findings in a series of furanylfentanyl-related deaths, J. Anal. Toxicol. 41 (3) (2017 Apr) 242–249.
[215] S. Sofalvi, H.E. Schueler, E.S. Lavins, C.K. Kaspar, I.T. Brooker, C.D. Mazzola, D. Dolinak, T.P. Gilson, S. Perch, An LC-MS-MS method for the analysis of carfentanil, 3-methylfentanyl, 2-furanyl fentanyl, acetyl fentanyl, fentanyl and norfentanyl in postmortem and impaired-driving cases, J. Anal. Toxicol. 41 (6) (2017 Jul) 473–483.
[216] H.F.H. Martucci, E.A. Ingle, M.D. Hunter, L.N. Rodda, Distribution of furanyl fentanyl and 4-ANPP in an accidental acute death: a case report, Forensic Sci. Int. 283 (2018 Feb) e13–e17.
[217] R. Carlson, L. Li, R. Daniulaityte, Montgomery County Poisoning Death Review, 2010-2016, Public Health, Dayton & Montgomery County, Dayton, OH, 2017. http://www.phdmc.org/epidemiology/poisoning-death-review.

[218] J. O'Donnell, R.M. Gladden, C.L. Mattson, M. Kariisa, Notes from the Field: overdose deaths with carfentanil and other fentanyl analogs detected - 10 states, Morb. Mortal. vol. 67 (27) (July 2016-June 2017) 767–768. Weekly Report 2018 Jul 13.

[219] N.B. Tiscione, I. Alford, Carfentanil in impaired driving cases and the importance of drug seizure data, J. Anal. Toxicol. 42 (7) (2018 Sep) 476–484.

[220] K.G. Shanks, G.S. Behonick, Detection of carfentanil by LC-MS-MS and reports of associated fatalities in the USA, J. Anal. Toxicol. 41 (6) (2017 Jul) 466–472.

[221] S.P. Elliott, E. Hernandez Lopez, A series of deaths involving carfentanil in the UK and associated post-mortem blood concentrations, J. Anal. Toxicol. 42 (4) (2018 May) e41–e45.

[222] L. Hikin, P.R. Smith, E. Ringland, S. Hudson, S.R. Morley, Multiple fatalities in the North of England associated with synthetic fentanyl analogue exposure: detection and quantitation a case series from early 2017, Forensic Sci. Int. 282 (2018 Jan) 179–183.

[223] E.N. Shoff, M.E. Zaney, J.H. Kahl, G.W. Hime, D.M. Boland, Qualitative identification of fentanyl analogs and other opioids in postmortem cases by UHPLC-ion trap-MS^n, J. Anal. Toxicol. 41 (6) (2017 Jul) 484–492.

[224] Emcdda, Europol Joint Report on a new psychoactive substance: methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl)amino]piperidine-4-carboxylate (carfentanil), November 2017. http://www.emcdda.europa.eu/publications/joint-reports/carfentanil_en.

[225] Emcdda, Report on the risk assessment of methyl 1-(2-phenylethyl)-4-[phenyl(propanoyl)amino]piperidine-4-carboxylate (carfentanil) in the framework of the Council Decision on new psychoactive substances, July 2018. http://www.emcdda.europa.eu/publications/risk-assessments/carfentanil_en.

[226] A. Cannaert, L. Ambach, P. Blanckaert, C.P. Stove, Activity-based detection and bioanalytical confirmation of a fatal carfentanil intoxication, Front. Pharmacol. 9 (2018 May) 486.

[227] D. Fomin, V. Baranauskaite, E. Usaviciene, A. Sumkovskaja, S. Laima, A. Jasulaitis, Z.N. Minkuviene, S. Chmieliauskas, J. Stasiuniene, Human deaths from drug overdoses with carfentanyl involvement-new rising problem in forensic medicine: a STROBE-compliant retrospective study, Medicine 97 (48) (2018 Nov), e13449.

[228] D.M. Swanson, L.S. Hair, S.R. Strauch Rivers, B.C. Smyth, S.C. Brogan, A.D. Ventoso, S.L. Vaccaro, J.M.1 Pearson, Fatalities involving carfentanil and furanyl fentanyl: two case reports, J. Anal. Toxicol. 41 (6) (2017 Jul) 498–502.

[229] V. Coopman, J. Cordonnier, M. De Leeuw, V. Cirimele, Ocfentanil overdose fatality in the recreational drug scene, Forensic Sci. Int. 266 (2016 Sep) 469–473.

[230] P. Quintana, M. Ventura, M. Grifell, A. Palma, L. Galindo, I. Fornís, C. Gil, X. Carbón, F. Caudevilla, M. Farré, M. Torrens, The hidden web and the fentanyl problem: detection of ocfentanil as an adulterant in heroin, Int. J. Drug Pol. 40 (2017 Feb) 78–83.

[231] S. Casati, M. Minoli, I. Angeli, A. Ravelli, G.D.L. Crudele, M. Orioli, An ocfentanil-related death case: UHPLC-MS/MS analysis of the drug, Drug Test. Anal. 11 (1) (2019 Jan) 173–177.

[232] F.E. Dussy, S. Hangartner, C. Hamberg, C. Berchtold, U. Scherer, G. Schlotterbeck, D. Wyler, T.A. Briellmann, An acute ocfentanil fatality: a case report with postmortem concentrations, J. Anal. Toxicol. (9) (2016 Nov) 761–766.

[233] N. Allibe, C. Richeval, M. Phanithavong, A. Faure, D. Allorge, F. Paysant, F. Stanke-Labesque, H. Eysseric-Guerin, J.M. Gaulier, Fatality involving ocfentanil documented by identification of metabolites, Drug Test. Anal. (6) (2018 Jun) 995–1000.

[234] N. Allibe, F. Billault, C. Moreau, A. Marchard, Y. Gaillard, G. Hoizey, H. Eysseric-Guerin, N. Milan, Ocfentanil in France: seven case reports (2016-2018). Toxicologie Analytique et Clinique. https://doi.org/10.1016/j.toxac.2018.12.003, 2019 Jan.

[235] N. Misailidi, I. Papoutsis, P. Nikolaou, A. Dona, C. Spiliopoulou, S. Athanaselis, Fentanyls continue to replace heroin in the drug arena: the cases of ocfentanil and carfentanil, Forensic Toxicol. 36 (1) (2018) 12–32.

[236] Unodc, Recommended methods for the identification and analysis of fentanyl and its analogues in biological specimens, 2017 November. https://www.unodc.org/unodc/en/scientists/recommended-methods-for-the-identification-and-analysis-of-fentanyl-and-its-analogues-in-biological-specimens.html.

[237] Emcdda, Report on the risk assessment of 2-methoxy-N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl]acetamide (methoxyacetylfentanyl) in the framework of the Council Decision on new psychoactive substances, 2018 September. http://www.emcdda.europa.eu/publications/risk-assessments/methoxyacetylfentanyl_en.

[238] Emcdda, EMCDDA–Europol Joint Report on a new psychoactive substance: 2-methoxy-N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl]acetamide (methoxyacetyl-fentanyl), 2018 Feb. http://www.emcdda.europa.eu/publications/joint-reports/methoxyacetylfentanyl_en.

[239] M. Mardal, S.S. Johansen, A.B. Davidsen, R. Telving, J.R. Jornil, P.W. Dalsgaard, J.B. Hasselstrøm, Å.M. Øiestad, K. Linnet, M.F. Andreasen, Postmortem analysis of three methoxyacetylfentanyl-related deaths in Denmark and in vitro metabolite profiling in pooled human hepatocytes, Forensic Sci. Int. 290 (2018 Sep) 310–317.

[240] M.F. Fogarty, D.M. Papsun, B.K. Logan, Analysis of fentanyl and 18 novel fentanyl analogs and metabolites by LC-MS-MS, and report of fatalities associated with methoxyacetylfentanyl and cyclopropylfentanyl, J. Anal. Toxicol. 42 (9) (2018 Nov) 592–604.

[241] Emcdda, Europol Joint Report on a new psychoactive substance: N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl]cyclopropanecarboxamide (cyclopropylfentanyl). http://www.emcdda.europa.eu/publications/joint-reports/cyclopropylfentanyl_en.

[242] S. Maher, S.P. Elliott, S. George, The analytical challenges of cyclopropylfentanyl and crotonylfentanyl: an approach for toxicological analysis, Drug Test. Anal. 10 (9) (2018 Sep) 1483–1487.

[243] Emcdda, Report on the risk assessment of N-phenyl-N-[1-(2-phenylethyl) piperidin-4-yl]cyclopropanecarboxamide in the framework of the Council Decision on new psychoactive substances. http://www.emcdda.europa.eu/publications/risk-assessments/cyclopropylfentanyl_en.

[244] M. Fagiola, T. Hahn, J. Avella, Five postmortem case reports with qualitative analysis of cyclopropylfentanyl by LC-MS-MS, J. Anal. Toxicol. (2018 Nov), https://doi.org/10.1093/jat/bky094.

[245] W.R. Brede, H.M. Krabseth, L.S. Michelsen, H. Aarset, J.P. Jamt, L. Slørdal, A wolf in sheep's clothing, J. Anal. Toxicol. 43 (2) (2019 Mar) e7–e8.

[246] L. Brockbals, S.N. Staeheli, S. Gentile, M. Schlaepfer, C. Bissig, S.A. Bolliger, T. Kraemer, A.E. Steuer, Fatal poisoning involving cyclopropylfentanyl - investigation of time-dependent postmortem redistribution, Forensic Sci. Int. 294 (2019 Jan) 80–85.

[247] S. Avedschmidt, C. Schmidt, D. Isenschmid, K. Kesha, D. Moons, A. Gupta, Acetyl fentanyl: trends and concentrations in metro detroit, J. Forensic Sci. 64 (1) (2019 Jan) 149–153.

[248] P. Armenian, K.T. Vo, J. Barr-Walker, K.L. Lynch, Fentanyl, fentanyl analogs and novel synthetic opioids: a comprehensive review, Neuropharmacology 134 (Pt A) (2018 May 15) 121–132.

[249] Emcdda, EMCDDA–Europol Joint Report on a new psychoactive substance: N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl]acetamide (acetylfentanyl), 2016 June. http://www.emcdda.europa.eu/publications/joint-reports/acetylfentanyl_en.

[250] J.B. Dwyer, J. Janssen, T.M. Luckasevic, K.E. Williams, Report of increasing overdose deaths that include acetyl fentanyl in multiple counties of the southwestern region of the commonwealth of Pennsylvania in 2015-2016, J. Forensic Sci. 63 (1) (2018 Jan) 195–200.

[251] J.B. Zawilska, An expanding world of novel psychoactive substances: opioids, Front. Psychiatr. 8 (2017 Jun 30) 110.

[252] M. Concheiro, R. Chesser, J. Pardi, G. Cooper, Postmortem toxicology of new synthetic opioids, Front. Pharmacol. 9 (2018 Oct 26) 1210.

[253] Emcdda, Europol Joint Report on a new psychoactive substance: N-(1-phenethylpiperidin-4-yl)-N-phenylacrylamide (acryloylfentanyl), 2017 Feb. http://www.emcdda.europa.eu/publications/joint-reports/acryloylfentanyl_en.

[254] I. Ujváry, R. Jorge, R. Christie, T. Le Ruez, H.V. Danielsson, R. Kronstrand, S. Elliott, A. Gallegos, R. Sedefov, M. Evans-Brown, Acryloylfentanyl, a recently emerged new psychoactive substance: a comprehensive review, Forensic Toxicol. 35 (2) (2017 July) 232–243.

[255] A. Helander, M. Bäckberg, P. Signell, O. Beck, Intoxications involving acrylfentanyl and other novel designer fentanyls- results from the Swedish STRIDA project, Clin. Toxicol. 55 (6) (2017 Jul) 589–599.

[256] D.C. Butler, K. Shanks, G.S. Behonick, D. Smith, S.E. Presnell, L.M. Tormos, Three cases of fatal acrylfentanyl toxicity in the United States and a review of literature, J. Anal. Toxicol. 42 (1) (2018 Jan) e6–e11.

[257] P. Duccio, S. Fabrizio, O. Laura, Synthetic Cannabinoids and Synthetic Cannabinoid-Induced Psychotic Disorders. The Complex Connection between Cannabis and Schizophrenia, Academic Press, 2018, pp. 199–220. Chapter 9.

[258] United Nations Office on Drugs and Crime, World drug report 2018, book 3 analysis of drug markets opiates, cocaine, cannabis, synthetic drugs. https://www.unodc.org/wdr2018/.

[259] S.L. Hill, J. Najafi, M. Dunn, P. Acheampong, A. Kamour, J. Grundlingh, P.G. Blain, S.H. Thomas, Clinical toxicity following analytically confirmed use of the synthetic cannabinoid receptor agonist MDMB-CHMICA. A report from the Identification of Novel psychoActive substances (IONA) study, Clin. Toxicol. 54 (8) (2016 Sep) 638–643.

[260] Drug Enforcement Administration, Department of Justice, Schedules of controlled substances: temporary placement of six synthetic cannabinoids (5F-ADB, 5F-AMB, 5F-APINACA, ADB-FUBINACA, MDMB- CHMICA and MDMB-FUBINACA) into schedule I. Notice of intent, Fed. Regist. 81 (245) (2016 Dec 21) 93595–93599.

[261] M. Haden, D.M. Wood, P.I. Dargan, The impact of the Psychoactive Substances Act 2016 on the online availability of MDMB-CHMICA, QJM: Int. J. Med. 110 (10) (2017 Oct) 619–622.

[262] Emcdda, Europol joint report on MDMB-CHMICA. http://www.emcdda.europa.eu/publications/joint-reports/mdmb-chmica_en, 2016 July.

[263] Emcdda, Report on the risk assessment of methyl 2-[[1-(cyclohexylmethyl)-1H-indole-3-carbonyl]amino]-3,3-dimethylbutanoate (MDMB-CHMICA) in the framework of the Council Decision on new psychoactive substances, 2017 March. http://www.emcdda.europa.eu/publications/risk-assessments/mdmb-chmica_en.

[264] M. Bäckberg, L. Tworek, O. Beck, A. Helander, Analytically confirmed intoxications involving MDMB-CHMICA from the STRIDA project, J. Med. Toxicol. 13 (1) (2017 Mar) 52–60.

[265] F. Gaunitz, S. Lehmann, A. Thomas, M. Thevis, M.A. Rothschild, K. Mercer-Chalmers-Bender, Post-mortem distribution of the synthetic cannabinoid

MDMB-CHMICA and its metabolites in a case of combined drug intoxication, Int. J. Leg. Med. 132 (6) (2018 Nov) 1645–1657.
[266] F. Franz, V. Angerer, B. Moosmann, V. Auwärter, Phase I metabolism of the highly potent synthetic cannabinoid MDMB-CHMICA and detection in human urine samples, Drug Test. Anal. 9 (5) (2017 May) 744–753.
[267] Emcdda, Europol Joint Report on a new psychoactive substance: methyl 2-{[1-(5-fluoropentyl)-1H-indazole-3-carbonyl]amino}-3,3-dimethylbutanoate (5F-MDMB-PINACA; 5F-ADB). http://www.emcdda.europa.eu/publications/joint-reports/5F-MDMB-PINACA_en.
[268] Emcdda, Report on the risk assessment of methyl 2-{[1-(5-fluoropentyl)-1H-indazole-3-carbonyl]amino}-3,3-dimethylbutanoate (5F-MDMB-PINACA) in the framework of the Council Decision on new psychoactive substances, 2018 July. http://www.emcdda.europa.eu/publications/risk-assessments/5f-mdmb-pinaca_en.
[269] L. Mogler, F. Franz, D. Rentsch, V. Angerer, G. Weinfurtner, M. Longworth, S.D. Banister, M. Kassiou, B. Moosmann, V. Auwärter, Detection of the recently emerged synthetic cannabinoid 5F-MDMB-PICA in 'legal high' products and human urine samples, Drug Test. Anal. 10 (1) (2018 Jan) 196–205.
[270] P. Adamowicz, J. Gieron, D. Gil, W. Lechowicz, A. Skulska, B. Tokarczyk, The effects of synthetic cannabinoid UR-144 on the human body-A review of 39 cases, Forensic Sci. Int. 273 (2017) e18–e21.
[271] S. Halter, V. Angerer, J. Röhrich, O.4 Groth, G. Roider, M. Hermanns-Clausen, V. Auwärter, Cumyl-PEGACLONE: a comparatively safe new synthetic cannabinoid receptor agonist entering the NPS market? Drug Test. Anal. 11 (2) (2019 Feb) 347–349.
[272] Emcdda, Europol Joint Report on a new psychoactive substance: N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1H-indazole-3-carboxamide (AB-CHMINACA), 2017 Sept. http://www.emcdda.europa.eu/publications/joint-reports/ab-chminaca_en.
[273] Emcdda, Europol Joint Report on a new psychoactive substance: N-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1H-indazole-3-carboxamide (ADB-CHMINACA), 2017 Sept. http://www.emcdda.europa.eu/publications/joint-reports/adb-chminaca_en.
[274] Emcdda, Europol Joint Report on a new psychoactive substance: 1-(4-cyanobutyl)-N-(2-phenylpropan-2-yl)indazole-3-carboxamide (CUMYL-4CN-BINACA), 2017 Sept. http://www.emcdda.europa.eu/publications/joint-reports/cumyl-4cn-binaca_en.
[275] Emcdda, Report on the risk assessment of N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1H-indazole-3-carboxamide (AB-CHMINACA) in the framework of the Council Decision on new psychoactive substances, 2018 July. http://www.emcdda.europa.eu/publications/risk-assessments/ab-chminaca_en.
[276] Emcdda, Report on the risk assessment of N-(1-Amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1H-indazole-3-carboxamide (ADB-CHMINACA) in the framework of the Council Decision on new psychoactive substances, 2018 May. http://www.emcdda.europa.eu/publications/risk-assessments/adb-chminaca_en.
[277] Emcdda, Report on the risk assessment of 1-(4-Cyanobutyl)-N-(2-phenylpropan-2-yl)-1H-indazole-3-carboxamide (CUMYL-4CN-BINACA) in the framework of the Council Decision on new psychoactive substances, 2018 May. http://www.emcdda.europa.eu/publications/risk-assessments/cumyl-4cn-binaca_en.
[278] M. Krpo, H.C. Luytkis, A.M. Haneborg, G. Høiseth, A fatal blood concentration of 5-APB, Forensic Sci. Int. 291 (2018) e1–e3.
[279] M. Kusano, K. Zaitsu, K. Taki, K. Hisatsune, J. Nakajima, T. Moriyasu, T. Asano, Y. Hayashi, H. Tsuchihashi, A. Ishii, Fatal intoxication by 5F–ADB and diphenidine: detection, quantification, and investigation of their main metabolic pathways in humans by LC/MS/MS and LC/Q-TOFMS, Drug Test. Anal. 10 (2) (2018 Feb) 284–293.
[280] V. Angerer, S. Jacobi, F. Franz, V. Auwärter, J. Pietsch, Three fatalities associated with the synthetic cannabinoids 5F-ADB, 5F-PB-22, and AB-CHMINACA, Forensic Sci. Int. 281 (2017 Dec) e9–e15.
[281] A.B.M. Paul, L. Simms, S. Amini, A.E. Paul, Teens and spice: a review of adolescent fatalities associated with synthetic cannabinoid use, J. Forensic Sci. 63 (4) (2018) 1321–1324.
[282] B. Ferreira, D. Dias da Silva, F. Carvalho, M. de Lourdes Bastos, H. Carmo, The novel psychoactive substance 3-methylmethcathinone (3-MMC or metaphedrone): a review, Forensic Sci. Int. 295 (2019 Feb) 54–63.
[283] M. Majchrzak, R. Celiński, P. Kuś, T. Kowalska, M. Sajewicz, The newest cathinone derivatives as designer drugs: an analytical and toxicological review, Forensic Toxicol. 36 (1) (2018) 33–50.
[284] B. Silva, C. Fernandes, P. Guedes de Pinho, F. Remião, Chiral resolution and enantioselectivity of synthetic cathinones: a brief review, J. Anal. Toxicol. 42 (1) (2018 Jan) 17–24.
[285] L. Glicksberg, S. Kerrigan, Stability of synthetic cathinones in blood, J. Anal. Toxicol. 41 (9) (2017 Nov) 711–719.
[286] L. Glicksberg, S. Kerrigan, Stability of synthetic cathinones in urine, J. Anal. Toxicol. 42 (2) (2018 Mar) 77–87.
[287] L. Glicksberg, S. Rana, S. Kerrigan, Cathinone stability in authentic urine specimens, Forensic Sci. Int. 286 (2018 May) 54–60.
[288] B. Miller, J. Kim, M. Concheiro, Stability of synthetic cathinones in oral fluid samples, Forensic Sci. Int. 274 (2017 May) 13–21.
[289] L. Karila, G. Lafaye, A. Scocard, O. Cottencin, A. Benyamina, MDPV and α-PVP use in humans: the twisted sisters, Neuropharmacology 134 (Pt A) (2018 May) 65–72.
[290] T. Matsunaga, Y. Morikawa, M. Tanigawa, K. Kamata, A. Shibata, Y. Sasajima, et al., Structure-activity relationship for toxicity of α-pyrrolidinophenones in human aortic endothelial cells, Forensic Toxicol. 35 (2017) 309–316.
[291] B. Potocka-Banaś, T. Janus, S. Majdanik, T. Banaś, T. Dembińska, K. Borowiak, Fatal intoxication with α-PVP, a synthetic cathinone derivative, J. Forensic Sci. 62 (2) (2017 Mar) 553–556.
[292] B. Desharnais, Y. Dazé, L.M. Huppertz, P. Mireault, C.D. Skinner, A case of fatal idiosyncratic reaction to the designer drug 3,4-methylenedioxypyrovalerone (MDPV) and review of the literature, Forensic Sci. Med. Pathol. 13 (3) (2017 Sep) 350–354.
[293] M. Grapp, C. Kaufmann, M. Ebbecke, Toxicological investigation of forensic cases related to the designer drug 3,4-methylenedioxypyrovalerone (MDPV): detection, quantification and studies on human metabolism by GC-MS, Forensic Sci. Int. 273 (2017 Apr) 1–9.
[294] K. Liveri, M.A. Constantinou, M. Afxentiou, P. Kanari, A fatal intoxication related to MDPV and pentedrone combined with antipsychotic and antidepressant substances in Cyprus, Forensic Sci. Int. 265 (2016 Aug) 160–165.
[295] L. Franzén, M. Bäckberg, O. Beck, A. Helander, Acute intoxications involving α-pyrrolidinobutiophenone (α-PBP): results from the Swedish STRIDA project, J. Med. Toxicol. 14 (4) (2018 Dec) 265–271.
[296] N. Patel, L. Ford, R. Jones, S.M. Bradberry, J.A. Vale, Poisoning to α-pyrrolidinovalerophenone (α-PVP), a synthetic cathinone, Clin. Toxicol. 55 (2) (2017 Feb) 159–160.
[297] E.E. Richman, N.J. Skoller, B. Fokum, B.A. Burke, C.A. Hickerson, R.O. Cotes, α-Pyrrolidinopentiophenone ("Flakka") catalyzing catatonia: a case report and literature review, J. Addiction Med. 12 (4) (2018 Jul/Aug) 336–338.
[298] J.B. Zawilska, J. Wojcieszak, α-Pyrrolidinophenones: a new wave of designer cathinones, Forensic Toxicol. 35 (2017) 201–216.
[299] Y. Fujita, T. Mita, K. Usui, Y. Kamijo, S. Kikuchi, M. Onodera, Y. Fujino, Y. Inoue, Toxicokinetics of the synthetic cathinone α-pyrrolidinohexanophenone, J. Anal. Toxicol. 42 (1) (2018 Jan) e1–e5.
[300] M. Majchrzak, R. Celiński, T. Kowalska, M. Sajewicz, Fatal case of poisoning with a new cathinone derivative: α-propylaminopentiophenone (N-PP), Forensic Toxicol. 36 (2) (2018) 525–533.
[301] J. Wojcieszak, D. Andrzejczak, M. Kedzierska, K. Milowska, J.B. Zawilska, Cytotoxicity of α-pyrrolidinophenones: an impact of α-aliphatic side-chain length and changes in the plasma membrane fluidity, Neurotox. Res. 34 (3) (2018 Oct) 613–626.
[302] S. Matsuta, N. Shima, H. Kakehashi, H. Kamata, S. Nakano, K. Sasaki, T. Kamata, H. Nishioka, A. Miki, K. Zaitsu, H. Tsuchihashi, M. Katagi, Metabolism of α-PHP and α-PHPP in humans and the effects of alkyl chain lengths on the metabolism of α-pyrrolidinophenone-type designer drugs, Forensic Toxicol. 36 (2) (2018) 486–497.
[303] E. Tomczak, M.K. Woźniak, M. Kata, M. Wiergowski, B. Szpiech, M. Biziuk, Blood concentrations of a new psychoactive substance 4-chloromethcathinone (4-CMC) determined in 15 forensic cases, Forensic Toxicol. 36 (2) (2018) 476–485.
[304] A.J. Krotulski, A.L.A. Mohr, D.M. Papsun, B.K. Logan, Dibutylone (bk-DMBDB): intoxications, quantitative confirmations and metabolism in authentic biological specimens, J. Anal. Toxicol. 42 (7) (2018 Sep) 437–445.
[305] J.L. Costa, K.F. Cunha, R. Lanaro, R.L. Cunha, D. Walther, M.H. Baumann, Analytical quantification, intoxication case series, and pharmacological mechanism of action for N-ethylnorpentylone (N-ethylpentylone or ephylone), Drug Test. Anal. 11 (3) (2018 Sep) 461–471.
[306] A.J. Krotulski, D.M. Papsun, B.S. De Martinis, A.L.A. Mohr, B.K. Logan, N-ethyl pentylone (ephylone) intoxications: quantitative confirmation and metabolite identification in authentic human biological specimens, J. Anal. Toxicol. 42 (7) (2018 Sep) 467–475.
[307] C. Ikeji, C.D. Sittambalam, L.M. Camire, D.S. Weisman, Fatal intoxication with N-ethylpentylone: a case report, J. Community Hosp. Intern. Med. Perspect. 8 (5) (2018 Oct) 307–310.
[308] P. Thirakul, S. Hair L, L. Bergen K, M. Pearson J, Clinical presentation, autopsy results and toxicology findings in an acute N-ethylpentylone fatality, J. Anal. Toxicol. 41 (4) (2017 May) 342–346.
[309] Drug Enforcement Administration, Department of Justice, Schedules of controlled substances: temporary placement of N-ethylpentylone in schedule I. Temporary amendment; temporary scheduling order, Fed. Regist. 83 (170) (2018 Aug) 44474–44478.
[310] J.A. Michely, S.K. Manier, A.T. Caspar, S.D. Brandt, J. Wallach, H.H. Maurer, New psychoactive substances 3-methoxyphencyclidine (3-MeO-PCP) and 3-methoxyrolicyclidine (3-MeO-PCPy): metabolic fate elucidated with rat urine and human liver preparations and their detectability in urine by GC-MS, "LC-(high resolution)-MSn" and "LC-(high resolution)-MS/MS, Curr. Neuropharmacol. 15 (5) (2017) 692–712.
[311] E. Bakota, C. Arndt, A.A. Romoser, S.K. Wilson, Fatal intoxication involving 3-MeO-PCP: a case report and validated method, J. Anal. Toxicol. 40 (7) (2016 Sep) 504–510.
[312] C. Mitchell-Mata, B. Thomas, B. Peterson, F. Couper, Two fatal intoxications involving 3-methoxyphencyclidine, J. Anal. Toxicol. 41 (6) (2017 Jul) 503–507.
[313] P. Kintz, A. Ameline, A. Walch, A. Farrugia, J.S. Raul, Murdered while under the influence of 3-MeO-PCP, Int. J. Leg. Med. 133 (2) (2019 Mar) 475–478.
[314] A. Johansson, D. Lindstedt, M. Roman, G. Thelander, E.I. Nielsen, U. Lennborn, H. Sandler, S. Rubertsson, J. Ahlner, R. Kronstrand, F.C. Kugelberg, A non-fatal

intoxication and seven deaths involving the dissociative drug 3-MeO-PCP, Forensic Sci. Int. 275 (2017 Jun) 76–82.
[315] E. Bertol, J. Pascali, D. Palumbo, V. Catalani, M.G. Di Milia, A. Fioravanti, F. Mari, F. Vaiano, 3-MeO-PCP intoxication in two young men: first in vivo detection in Italy, Forensic Sci. Int. 274 (2017 May) 7–12.
[316] M. Zidkova, T. Hlozek, M. Balik, O. Kopecky, P. Tesinsky, J. Svanda, M.A. Balikova, Two cases of non-fatal intoxication with a novel street hallucinogen: 3-methoxy-phencyclidine, J. Anal. Toxicol. 41 (4) (2017 May) 350–354.
[317] S. Thornton, D. Lisbon, T. Lin, R. Gerona, Beyond ketamine and phencyclidine: analytically confirmed use of multiple novel arylcyclohexylamines, J. Psychoact. Drugs 49 (4) (2017 Sep-Oct) 289–293.
[318] Y.K. Chong, M.H. Tang, C.L. Chan, Y.K. Li, C.K. Ching, T.W. Mak, 2-oxo-PCE: ketamine analogue on the streets, Hong Kong Med. J. 23 (6) (2017 Dec) 665–666.
[319] M.H.Y. Tang, Y.K. Chong, C.Y. Chan, C.K. Ching, C.K. Lai, Y.K. Li, T.W.L. Mak, Cluster of acute poisonings associated with an emerging ketamine analogue, 2-oxo-PCE, Forensic Sci. Int. 290 (2018 Sep) 238–243.
[320] N. Theofel, P. Möller, E. Vejmelka, K. Kastner, S. Roscher, S. Scholtis, M. Tsokos, A fatal case involving N-ethyldeschloroketamine (2-oxo-PCE) and venlafaxine, J. Anal. Toxicol. 43 (2) (2019 Mar) e2–e6.
[321] J.H. Kahl, J. Gonyea, S.M. Humphrey, G.W. Hime, D.M. Boland, Quantitative analysis of fentanyl and six fentanyl analogs in postmortem specimens by UHPLC-MS-MS, J. Anal. Toxicol. 42 (8) (2018 Oct) 570–580.
[322] K. Nowak, P. Szpot, M. Zawadzki, Unstability of 4-CMC in human serum specimen, Forensic Toxicol. 37 (1) (2019) 261–264.
[323] K. Francisco da Cunha, M.N. Eberlin, M.A. Huestis, J.L. Costa, NBOMe instability in whole blood, Forensic Toxicol. 37 (2019) 82–89.
[324] M.T. Moody, S. Diaz, P. Shah, D. Papsun, B.K. Logan, Analysis of fentanyl analogs and novel synthetic opioids in blood, serum/plasma, and urine in forensic casework, Drug Test. Anal. 10 (9) (2018 Sep) 1358–1367.
[325] N. Misailidi, S. Athanaselis, P. Nikolaou, M. Katselou, Y. Dotsikas, C. Spiliopoulou, I. Papoutsis, A GC-MS method for the determination of furanylfentanyl and ocfentanil in whole blood with full validation, Forensic Toxicol. 37 (2019) 238–244.
[326] C. Fort, T. Jourdan, J. Kemp, B. Curtis, Stability of synthetic cannabinoids in biological specimens: analysis through liquid chromatography tandem mass spectrometry, J. Anal. Toxicol. 41 (2017) 360–366.
[327] C. Hess, L. Krueger, M. Unger, B. Madea, Freeze-thaw stability and long-term stability of 84 synthetic cannabinoids in serum, Drug Test. Anal. 9 (10) (2017 Oct) 1506–1511.
[328] K. Francisco da Cunha, M.N. Eberlin, J.L. Costa, Development and validation of a sensitive LC–MS/MS method to analyze NBOMes in dried blood spots: evaluation of long-term stability, Forensic Toxicol. 36 (2018) 113–121.
[329] K. Francisco da Cunha, M.N. Eberlin, J.L. Costa, Long-term stability of synthetic cathinones in dried blood spots and whole blood samples: a comparative study, Forensic Toxicol. 36 (2018) 424–434.
[330] P. Adamowicz, A. Malczyk, Stability of synthetic cathinones in blood and urine, Forensic Sci. Int. 295 (2019 Feb) 36–45.
[331] T. Lau, R. LeBlanc, S. Botch-Jones, Stability of synthetic Piperazines in human whole blood, J. Anal. Toxicol. 42 (2) (2018 Mar) 88–98.
[332] S.N. Staeheli, M.R. Baumgartner, S. Gauthier, D. Gascho, J. Jarmer, T. Kraemer, A.E. Steuer, Time-dependent postmortem redistribution of butyrfentanyl and its metabolites in blood and alternative matrices in a case of butyrfentanyl intoxication, Forensic Sci. Int. 266 (2016 Sep) 170–177.
[333] S.N. Staeheli, M.I. Boxler, A. Oestreich, M. Marti, D. Gascho, S.A. Bolliger, T. Kraemer, A.E. Steuer, Postmortem distribution and redistribution of MDAI and 2-MAPB in blood and alternative matrices, Forensic Sci. Int. 279 (2017 Oct) 83–87.
[334] L. Glicksberg, R. Winecker, C. Miller, S. Kerrigan, Postmortem distribution and redistribution of synthetic cathinones, Forensic Toxicol. 36 (2018) 291–303.
[335] C. Vignali, M. Moretti, A. Groppi, A.M.M. Osculati, L. Tajana, L. Morini, Distribution of the synthetic cathinone α-pyrrolidinohexiophenone in biological specimens, J. Anal. Toxicol. 43 (1) (2019 Jan) e1–e6.
[336] S. Lehmann, B. Schulze, A. Thomas, T. Kamphausen, M. Thevis, M.A. Rothschild, et al., Organ distribution of 4-MEC, MDPV, methoxetamine and α-PVP: comparison of QuEChERS and SPE, Forensic Toxicol. 36 (2018) 320–333.
[337] E. Pieprzyca, R. Skowronek, M. Korczyńska, J. Kulikowska, M. Chowaniec, A two fatal cases of poisoning involving new cathinone derivative PV8, Leg. Med. 33 (2018 May) 42–47.
[338] I. Yamagishi, K. Minakata, H. Nozawa, K. Hasegawa, M. Suzuki, T. Kitamoto, O. Suzuki, K. Watanabe, A case of intoxication with a mixture of synthetic cannabinoids EAM-2201, AB-PINACA and AB-FUBINACA, and a synthetic cathinone α-PVP, Leg. Med. 35 (2018 Nov) 44–49.
[339] A. Mochizuki, H. Nakazawa, N. Adachi, K. Takekawa, H. Shojo, Identification and quantification of mepirapim and acetyl fentanyl in authentic human whole blood and urine samples by GC-MS/MS and LC-MS/MS, Forensic Toxicol. 36 (1) (2018) 81–87.
[340] A. Mochizuki, H. Nakazawa, N. Adachi, K. Takekawa, H. Shojo, Postmortem distribution of mepirapim and acetyl fentanyl in biological fluid and solid tissue specimens measured by the standard addition method, Forensic Toxicol. 37 (2019) 27–33.
[341] J. Poklis, A. Poklis, C. Wolf, C. Hathaway, E. Arbefeville, L. Chrostowski, K. Devers, L. Hair, M. Mainland, M. Merves, J. Pearson, Two fatal intoxications involving butyryl fentanyl, J. Anal. Toxicol. 40 (8) (2016 Oct) 703–708.
[342] C. Fort, B. Curtis, C. Nichols, C. Niblo, Acetyl fentanyl toxicity: two case reports, J. Anal. Toxicol. 40 (9) (2016 Nov) 754–757.
[343] K. Yonemitsu, A. Sasao, S. Mishima, Y. Ohtsu, Y. Nishitani, A fatal poisoning case by intravenous injection of "bath salts" containing acetyl fentanyl and 4-methoxy PV8, Forensic Sci. Int. 267 (2016 Oct) e6–e9.
[344] I.M. McIntyre, R.D. Gary, S. Joseph, R. Stabley, A fatality related to the synthetic opioid U-47700: postmortem concentration distribution, J. Anal. Toxicol. 41 (2) (2017 Mar) 158–160.
[345] M. Dziadosz, M. Klintschar, J. Teske, Postmortem concentration distribution in fatal cases involving the synthetic opioid U-47700, Int. J. Leg. Med. 131 (6) (2017 Nov) 1555–1556.
[346] T.P. Rohrig, S.A. Miller, T.R. Baird, U-47700: a not so new opioid, J. Anal. Toxicol. 42 (2018) e12–e14.
[347] C. Noble, M. Mardal, N. Bjerre Holm, S. Stybe Johansen, K. Linnet, In vitro studies on flubromazolam metabolism and detection of its metabolites in authentic forensic samples, Drug Test. Anal. 9 (8) (2017 Aug) 1182–1191.
[348] K.N.1 Ellefsen, E.A.1 Taylor, P.1 Simmons, V.1 Willoughby, B.J.1 Hall, Multiple drug-toxicity involving novel psychoactive substances, 3-fluorophenmetrazine and U-47700, J. Anal. Toxicol. 41 (9) (2017 Nov) 765–770.
[349] L. Mogler, S. Halter, M. Wilde, F. Franz, V. Auwärter, Human phase I metabolism of the novel synthetic cannabinoid 5F-CUMYL-PEGACLONE, Forensic Toxicol. 37 (2019) 154–163.
[350] X. Diao, M.A. Huestis, Approaches, challenges, and advances in metabolism of new synthetic cannabinoids and identification of optimal urinary marker metabolites, Clin. Pharmacol. Ther. 101 (2) (2017) 239–253.
[351] F. Franz, V. Angerer, S.D. Brandt, G. McLaughlin, P.V. Kavanagh, B. Moosmanna, V. Auwärtera, In vitro metabolism of the synthetic cannabinoid 3,5-AB-CHMFUPPYCA and its 5,3-regioisomer and investigation of their thermal stability, Drug Test. Anal. 9 (2017) 311–316.
[352] P. Kavanagh, A. Grigoryev, N. Krupina, Detection of metabolites of two synthetic cannabimimetics, MDMB-FUBINACA and ADB-FUBINACA, in authentic human urine specimens by accurate mass LC-MS: a comparison of intersecting metabolic patterns, Forensic Toxicol. 35 (2017) 284–300.
[353] J. Carlier, X. Diao, A. Wohlfarth, K. Scheidweiler, M.A. Huestis, In Vitro metabolite profiling of ADB-FUBINACA, A new synthetic cannabinoid, Curr. Neuropharmacol. 15 (5) (2017 Jul) 682–691.
[354] L.H.J. Richter, H.H. Maurer, M.R. Meyer, Metabolic fate of the new synthetic cannabinoid 4'N-5F-ADB in rat, human, and pooled human S9 studied by means of hyphenated high-resolution mass spectrometry, Drug Test. Anal. 11 (2) (2019 Feb) 305–317.
[355] M. Hutter, S. Broecker, S. Kneisel, F. Franz, S.D. Brandt, V. Auwarter, Metabolism of nine synthetic cannabinoid receptor agonists encountered in clinical casework: major in vivo phase I metabolites of AM-694, AM-2201, JWH-007, JWH-019, JWH-203, JWH-307, MAM-2201, UR-144 and XLR-11 in human urine using LC-MS/MS, Curr. Pharmaceut. Biotechnol. 19 (2) (2018) 144–162.
[356] M. Mardal, P.W. Dalsgaard, B. Qi, C.B. Mollerup, P. Annaert, K. Linnet, Metabolism of the synthetic cannabinoids AMB-CHMICA and 5C-AKB48 in pooled human hepatocytes and rat hepatocytes analyzed by UHPLC-(IMS)-HR-MS^{E}, J. Chromatogr. B 1083 (2018) 189–197.
[357] S. Savchuk, S. Appolonova, A. Pechnikov, L. Rizvanova, K. Shestakova, F. Tagliaro, In vivo metabolism of the new synthetic cannabinoid APINAC in rats by GC-MS and LC-QTOF-MS, Forensic Toxicol. 35 (2017) 359–368.
[358] J. Hwang, J. Hwang, B. Ganganna, I. Song, M.Y. Heo, S.H. Ahn, et al., Metabolic and pharmacokinetic characterization of a new synthetic cannabinoid APINAC in rats, Forensic Toxicol. 36 (2018) 88–101.
[359] K. Minakata, K. Hasegawa, H. Nozawa, I. Yamagishi, T. Saitoh, A. Yoshino, et al., Sensitive quantification of BB-22 and its metabolite BB-22 3-carboxyindole, and characterization of new metabolites in authentic urine and/or serum specimens obtained from three individuals by LC-QTRAP-MS/MS and high-resolution LC-Orbitrap-MS/MS, Forensic Toxicol. 37 (2019) 164–173.
[360] J. Carlier, X. Diao, M.A. Huestis, Synthetic cannabinoid BB-22 (QUCHIC): human hepatocytes metabolism with liquid chromatography-high resolution mass spectrometry detection, J. Pharmaceut. Biomed. Anal. 157 (2018 Aug) 27–35.
[361] O. Yeter, Y. Erol Öztürk, Metabolic profiling of synthetic cannabinoid 5F-ADB by human liver microsome incubations and urine samples using high-resolution mass spectrometry, Drug Test. Anal. 11 (6) (2019 Jun) 847–858, https://doi.org/10.1002/dta.2566.
[362] R.C. Kevin, T.W. Lefever, R.W. Snyder, P.R. Patel, T.R. Fennell, J.L. Wiley, et al., In vitro and in vivo pharmacokinetics and metabolism of synthetic cannabinoids CUMYL-PICA and 5F-CUMYL-PICA, Forensic Toxicol. 35 (2017) 333–347.
[363] S.N. Staeheli, M. Poetzsch, V.P. Veloso, M. Bovens, C. Bissig, A.E. Steuer, T. Kraemer, In vitro metabolism of the synthetic cannabinoids CUMYL-PINACA, 5F-CUMYL-PINACA, CUMYL-4CN-BINACA, 5F-CUMYL-P7AICA and CUMYL-4CN-B7AICA, Drug Test. Anal. 10 (2018) 148–157.
[364] V. Angerer, F. Franz, B. Moosmann, P. Bisel, V. Auwärter, 5F-Cumyl-PINACA in 'e-liquids' for electronic cigarettes: comprehensive characterization of a new type of synthetic cannabinoid in a trendy product including investigations on the in vitro and in vivo phase I metabolism of 5F-Cumyl-PINACA and its

non-fluorinated analog Cumyl-PINACA, Forensic Toxicol. 37 (1) (2019) 186–196.
[365] S.N. Staeheli, A.E. Steuer, T. Kraemer, Identification of urinary metabolites of the synthetic cannabinoid 5F-CUMYL-P7AICA in human casework, Forensic Sci. Int. 294 (2019) 76–79.
[366] L. Mogler, M. Wilde, L.M. Huppertz, G. Weinfurtner, F. Franz, V. Auwärter, Phase I metabolism of the recently emerged synthetic cannabinoid CUMYL-PEGACLONE and detection in human urine samples, Drug Test. Anal. 10 (5) (2018 May) 886–891.
[367] Y.E. Öztürk, O. Yeter, S. Öztürk, G. Karakus, I. Ates, Y. Buyuk, T. Yurdun, Detection of metabolites of the new synthetic cannabinoid CUMYL-4CN-BINACA in authentic urine samples andHLM using high-resolution mass spectrometry, Drug Test. Anal. 10 (2018) 449–459.
[368] X. Diao, J. Carlier, M. Zhu, Metabolism of the new synthetic cannabinoid EG-018 in human hepatocytes by high-resolution mass spectrometry, Forensic Toxicol. 36 (2018) 304–312.
[369] L. Mogler, F. Franz, M. Wilde, L.M. Huppertz, S. Halter, V. Angerer, B. Moosmann, V. Auwärter, Phase I metabolism of the carbazole-derived synthetic cannabinoids EG-018, EG-2201, and MDMB-CHMCZCA and detection in human urine samples, Drug Test. Anal. 10 (9) (2018 Sep) 1417–1429.
[370] J.H. Kim, T.Y. Kong, J.Y. Moon, K.H. Choi, Y.Y. Cho, H.C. Kang, J.Y. Lee, H.S. Lee, Targeted and non-targeted metabolite identification of MAM-2201 in human, mouse, and rat hepatocytes, Drug Test. Anal. 10 (8) (2018 Aug) 1328–1335.
[371] R.C. Kevin, T.W. Lefever, R.W. Snyder, O.R. Patel, T.F. Gamage, T.R. Fennell, et al., Kinetic and metabolic profiles of synthetic cannabinoids NNEI and MN-18, Drug Test. Anal. 10 (2018) 137–147.
[372] X. Diao, J. Carlier, M. Zhu, S. Pang, R. Kronstrand, K.B. Scheidweiler, M.A. Huestis, In vitro and in vivo human metabolism of a new synthetic cannabinoid NM-2201 (CBL-2201), Forensic Toxicol. 35 (2017) 20–32.
[373] M. Mardala, P. Annaert, C. Noble, M. Oorts, K. Linnet, Metabolism of the synthetic cannabinoid 5F-PY-PICA by human andrat hepatocytes and identification of biliary analytical targets bydirectional efflux in sandwich-cultured rat hepatocytes usingUHPLC-HR-MS/MS, J. Pharmaceut. Biomed. Anal. 149 (2018) 296–307.
[374] X. Diao, J. Carlier, K.B. Scheidweiler, M.A. Huestis, In vitro metabolism of new synthetic cannabinoid SDB-006 in human hepatocytes by high-resolution mass spectrometry, Forensic Toxicol. 35 (2017) 252–262.
[375] P. Vervliet, O. Mortelé, C. Gys, M. Degreef, K. Lanckmans, K. Maudens, et al., Suspect and non-target screening workflows to investigate the in vitro and in vivo metabolism of the synthetic cannabinoid 5Cl-THJ-018, Drug Test. Anal. 11 (3) (2019 Mar) 479–491.
[376] S.K. Manier, L.H.J. Richter, J. Schäper, H.H. Maurer, M.R. Meyer, Different in vitro and in vivo tools for elucidating the human metabolism of alpha-cathinone-derived drugs of abuse, Drug Test. Anal. 10 (7) (2018 Jul) 1119–1130.
[377] S. Mesihää, I. Rasanen, I. Ojanperä, Quantitative estimation of α-PVP metabolites in urine by GC-APCI-QTOFMS with nitrogen chemiluminescence detection based on parent drug calibration, Forensic Sci. Int. 286 (2018 May) 12–17.
[378] T. Kanamori, Y. Togawa Iwata, H. Segawa, T. Yamamuro, K. Kuwayama, K. Tsujikawa, H. Inoue, Metabolism of fentanyl and acetylfentanyl in human-induced pluripotent stem cell-derived hepatocytes, Biol. Pharm. Bull. 41 (1) (2018) 106–114.
[379] T. Kanamori, Y. Togawa-Iwata, H. Segawa, T. Yamamuro, K. Kuwayama, K. Tsujikawa, H. Inoue, Use of hepatocytes isolated from a liver-humanized mouse for studies on the metabolism of drugs: application to the metabolism of fentanyl and acetylfentanyl, Forensic Toxicol. 36 (2) (2018) 467–475.
[380] S. Watanabe, S. Vikingsson, M. Roman, H. Green, R. Kronstrand, A. Wohlfarth, In Vitro and in vivo metabolite identification studies for the new synthetic opioids acetylfentanyl, acrylfentanyl, furanylfentanyl, and 4-fluoro-isobutyrylfentanyl, AAPS J. 19 (4) (2017 Jul) 1102–1122.
[381] A.E. Steuer, E. Williner, S.N. Staeheli, T. Kraemer, Studies on the metabolism of the fentanyl-derived designer drug butyrfentanyl in human in vitro liver preparations and authentic human samples using liquid chromatography-high resolution mass spectrometry (LC-HRMS), Drug Test. Anal. 9 (7) (2017 Jul) 1085–1092.
[382] M. Pettersson Bergstrand, L.H.J. Richter, H.H. Maurer, L. Wagmann, M.R. Meyer, In vitro glucuronidation of designer benzodiazepines by human UDP-glucuronyltransferases, Drug Test. Anal. 11 (1) (2019 Jan) 45–50.
[383] L.M. Huppertz, B. Moosmann, V. Auwärter, Flubromazolam-Basic pharmacokinetic evaluation of a highly potent designer benzodiazepine, Drug Test. Anal. 10 (1) (2018 Jan) 206–211.
[384] A.T. Caspar, F. Westphal, M.R. Meyer, H.H. Maurer, LC-high resolution-MS/MS for identification of 69 metabolites of the new psychoactive substance 1-(4-ethylphenyl-)-N-[(2-methoxyphenyl)methyl] propane-2-amine (4-EA-NBOMe) in rat urine and human liver S9 incubates and comparison of its screening power with further MS techniques, Anal. Bioanal. Chem. 410 (3) (2018 Jan) 897–912.
[385] A. Wohlfarth, M. Roman, M. Andersson, F.C. Kugelberg, X. Diao, J. Carlier, C. Eriksson, X. Wu, P. Konradsson, M. Josefsson, M.A. Huestis, R. Kronstrand, 25C-NBOMe and 25I-NBOMe metabolite studies in human hepatocytes, in vivo mouse and human urine with high-resolution mass spectrometry, Drug Test. Anal. 9 (5) (2017 May) 680–698.
[386] J.A. Michely, S.D. Brandt, M.R. Meyer, H.H. Maurer, Biotransformation and detectability of the new psychoactive substances N,N-diallyltryptamine (DALT) derivatives 5-fluoro-DALT, 7-methyl-DALT, and 5,6-methylenedioxy-DALT in urine using GC-MS, LC-MSn, and LC-HR-MS/MS, Anal. Bioanal. Chem. 409 (6) (2017 Feb) 1681–1695.
[387] A.T. Caspar, J.B. Gaab, J.A. Michely, S.D. Brandt, M.R. Meyer, H.H. Maurer, Metabolism of the tryptamine-derived new psychoactive substances 5-MeO-2-Me-DALT, 5-MeO-2-Me-ALCHT, and 5-MeO-2-Me-DIPT and their detectability in urine studied by GC-MS, LC-MSn, and LC-HR-MS/MS, Drug Test. Anal. 10 (1) (2018 Jan) 184–195.
[388] A.J. Krotulski, A.L.A. Mohr, D.M. Papsun, B.K. Logan, Metabolism of novel opioid agonists U-47700 and U-49900 using HLM with confirmation in authentic urine specimens from drug users, Drug Test. Anal. 10 (1) (2018 Jan) 127–136.
[389] A. Helander, K. Stojanovic, T. Villén, O. Beck, Detectability of fentanyl and designer fentanyls in urine by 3 commercial fentanyl immunoassays, Drug Test. Anal. 10 (8) (2018 Aug) 1297–1304.
[390] D. Guerrieri, F. Kjellqvist, R. Kronstrand, H. Gréen, Validation and cross-reactivity data for fentanyl analogs with the immunalysis fentanyl ELISA, J. Anal. Toxicol. 43 (1) (2019 Jan) 18–24.
[391] M. Schackmuth, S. Kerrigan, Immunoassay-based detection of fentanyl analogs in forensic toxicology, Forensic Toxicol. 37 (2019) 231–237.
[392] M. Pettersson Bergstrand, A. Helander, T. Hansson, O. Beck, Detectability of designer benzodiazepines in CEDIA, EMIT II Plus, HEIA, and KIMS II immunochemical screening assays, Drug Test. Anal. 9 (4) (2017 Apr) 640–645.
[393] M. Nieddu, L. Burrai, E. Baralla, V. Pasciu, M.V. Varoni, I. Briguglio, M.P. Demontis, G. Boatto, ELISA detection of 30 new amphetamine designer drugs in whole blood, urine and oral fluid using Neogen® "amphetamine" and "methamphetamine/MDMA" kits, J. Anal. Toxicol. 40 (7) (2016 Sep) 492–497.
[394] V. Háda, A. Bagdi, Z. Bihari, S.B. Timári, Fizil Á, C. Szántay Jr., Recent advancements, challenges, and practical considerations in the mass spectrometry-based analytics of protein biotherapeutics: a viewpoint from the biosimilar industry, J. Pharmaceut. Biomed. Anal. 161 (2018 Nov) 214–238.
[395] B. Bobály, J.L. Veuthey, D. Guillarme, S. Fekete, New developments and possibilities of wide-pore superficially porous particle technology applied for the liquid chromatographic analysis of therapeutic proteins, J. Pharmaceut. Biomed. Anal. 158 (2018 Sep) 225–235.
[396] M. Qu, B. An, S. Shen, M. Zhang, X. Shen, X. Duan, J.P. Balthasar, J. Qu, Qualitative and quantitative characterization of protein biotherapeutics with liquid chromatography mass spectrometry, Mass Spectrom. Rev. 36 (6) (2017 Nov) 734–754.
[397] J.T. Chen, X.M. Guo, P. Yang, Q. Mu, Quantitative analysis of the cyclic peptide GG-8-6 in rat plasma using LC-MS/MS and its application to a pharmacokinetic study, J. Pharmaceut. Biomed. Anal. 159 (2018 Sep) 217–223.
[398] Y. Zhu, S. Yang, J. Wang, Y. Mao, Y. Xu, An J. LC-MS/MS assay for the determination of a novel D-peptide anatagonist of CXCR4 in rat plasma and its application to a preclinical pharmacokinetic study, J. Pharmaceut. Biomed. Anal. 161 (2018 Nov 30) 159–167.
[399] P. Judák, J. Grainger, C. Goebel, P. Van Eenoo, K. Deventer, DMSO assisted electrospray ionization for the detection of small peptide hormones in urine by dilute-and-shoot-liquid-chromatography-high resolution mass spectrometry, J. Am. Soc. Mass Spectrom. 28 (8) (2017 Aug) 1657–1665.
[400] E. Semenistaya, I. Zvereva, G. Krotov, G. Rodchenkov, Solid-phase extraction of small biologically active peptides on cartridges and microelution 96-well plates from human urine, Drug Test. Anal. 8 (9) (2016 Sep) 940–949.
[401] D. Cuervo, C. Loli, M. Fernández-Álvarez, G. Muñoz, D. Carreras, Determination of doping peptides via solid-phase microelution and accurate-mass quadrupole time-of-flight LC-MS, J. Chromato B, Anal. Tecnol. Biomed. Life. Sci. 1065–1066 (2017 Oct) 134–144.
[402] K.J. Bronsema, F. Klont, F.B. Schalk, R. Bischoff, I.P. Kema, N.C. van de Merbel, A quantitative LC-MS/MS method for insulin-like growth factor 1 in human plasma, Clin. Chem. Lab. Med. 56 (11) (2018 Oct) 1905–1912.
[403] A. Thomas, K. Walpurgis, P. Delahaut, E. Fichant, W. Schänzer, M. Thevis, Determination of LongR(3)-IGF-I, R(3)-IGF-I, Des1-3 IGF-I and their metabolites in human plasma samples by means of LC-MS, Growth Hormone IGF Res. 35 (2017 Aug) 33–39.
[404] D. Moncrieffe, M.C. Parkin, D.A. Cowan, Peptide selection for the quantification of P-III-NP in human serum by mass spectrometry, Rapid Commun. Mass Spectrom. 32 (7) (2018 Apr 15) 535–542.
[405] C. Arsene, D. Schulze, A. Röthke, M. Thevis, A. Henrion, Growth hormone isoform-differential mass spectrometry for doping control purposes, Drug Test. Anal. 10 (6) (2018 Jun) 938–946.
[406] A. Knoop, A. Thomas, E. Fichant, P. Delahaut, W. Schänzer, M. Thevis, Qualitative identification of growth hormone-releasing hormones in human plasma by means of immunoaffinity purification and LC-HRMS/MS, Anal. Bioanal. Chem. 408 (12) (2016 May) 3145–3153.
[407] S.H. Tan, A. Lee, D. Pascovici, N. Care, V. Birzniece, K. Ho, M.P. Molloy, A. Khan, Plasma biomarker proteins for detection of human growth hormone administration in athletes, Sci. Rep. 7 (1) (2017 Aug) 10039.
[408] K.S. Wong, G.H.M. Chan, E.N.M. Ho, T.S.M. Wan, Simultaneous detection of recombinant growth hormones in equine plasma by liquid chromatography/high-resolution tandem mass spectrometry for doping control,

J. Chromatogr. A 1478 (2016 Dec) 35–42.
[409] A.W. Butch, B.D. Ahrens, N.K. Avliyakulov, Urine reference intervals for human chorionic gonadotropin (hCG) isoforms by immunoextraction-tandem mass spectrometry to detect hCG use, Drug Test. Anal. 10 (6) (2018 Jun) 956–960.
[410] A.W. Butch, G.A. Woldemariam, Urinary human chorionic gonadotropin isoform concentrations in doping control samples, Drug Test. Anal. 8 (11–12) (2016 Nov) 1147–1151.
[411] I. Zvereva, G. Dudko, M. Dikunets, Determination of GnRH and its synthetic analogues' abuse in doping control: small bioactive peptide UPLC-MS/MS method extension by addition of in vitro and in vivo metabolism data; evaluation of LH and steroid profile parameter fluctuations as suitable biomarkers, Drug Test. Anal. 10 (4) (2018 Apr) 711–722.
[412] A. Knoop, A. Thomas, M. Thevis, Development of a mass spectrometry based detection method for the mitochondrion-derived peptide MOTS-c in plasma samples for doping control purposes, Rapid Commun. Mass Spectrom. 33 (4) (2019 Feb) 371–380.
[413] K. Walpurgis, A. Thomas, T. Lange, C. Reichel, H. Geyer, M. Thevis, Combined detection of the ActRII-Fc fusion proteins Sotatercept (ActRIIA-Fc) and Luspatercept (modified ActRIIB-Fc) in serum by means of immunoaffinity purification, tryptic digestion, and LC-MS/MS, Drug Test. Anal. 10 (11–12) (2018 Nov) 1714–1721.
[414] N.V. Mesonzhnik, P.V. Postnikov, S.A. Appolonova, G.I. Krotov, Characterization and detection of erythropoietin Fc fusion proteins using liquid chromatography-mass spectrometry, J. Proteome Res. 17 (1) (2018 Jan) 689–697.
[415] F. Guan, M.A. Robinson, L.R. Soma, Confirmatory analysis of etanercept in equine plasma by LC-MS for doping control, Drug Test. Anal. 9 (9) (2017 Sep) 1421–1431.
[416] F. Guan, Y. You, X. Li, M.A. Robinson, Detection and confirmation of α-cobratoxin in equine plasma by solid-phase extraction and liquid chromatography coupled to mass spectrometry, J. Chromatogr. A 1533 (2018 Jan) 38–48.
[417] L. Bailly-Chouriberry, P. Garcia, F. Cormant, B. Loup, M.A. Popot, Y. Bonnaire, Use of split-free nano-liquid chromatography-mass spectrometry/high resolution mass spectrometry interface to improve the detection of α-cobratoxin in equine plasma for doping control, Drug Test. Anal. 10 (5) (2018 May) 880–885.
[418] F. Tong, R. Wu, W. Huang, Y. Yang, L. Zhang, B. Zhang, X. Chen, X. Tang, Y. Zhou, Forensic aspects of homicides by insulin overdose, Forensic Sci. Int. 278 (2017 Sep) 9–15.
[419] R. Lv, Y. Chen, N. Xia, Y. Liang, Q. He, M. Li, Z. Qi, Y. Lu, S. Zhao, Development of a double-antibody sandwich ELISA for rapid detection to C-peptide in human urine, J. Pharmaceut. Biomed. Anal. 162 (2019 Jan) 179–184.
[420] A. Thomas, P.T. Brinkkötter, W. Schänzer, M. Thevis, Simultaneous determination of insulin, DesB30 insulin, proinsulin, and C-peptide in human plasma samples by liquid chromatography coupled to high resolution mass spectrometry, Forensic Toxicol. 35 (2017) 106–113.
[421] S. Wendt, I. Eder, R. Wölfel, P. Braun, N. Lippmann, A. Rodloff, Botulism: diagnosis and therapy, Deutsche Mediziniche Wochenschrift 142 (17) (2017 Sep) 1304–1312.
[422] F. Anniballi, B. Auricchio, A. Fiore, D. Lonati, C.A. Locatelli, F. Lista, S. Fillo, G. Mandarino, D. De Medici, Botulism in Italy, 1986 to 2015, Euro Surveill. 22 (24) (2017 Jun) 30550.
[423] D. Hellmich, K.E. Wartenbery, S. Zierz, T.J. Mueller, Foodborne botulism due to ingestion of home-canned green beans: two case reports, J. Med. Case Rep. 12 (1) (2018 Jan) 1.
[424] L. Bai, X. Peng, Y. Liu, Y. Sun, X. Wang, X. Wang, G. Lin, P. Zhang, K. Wan, Z. Qiu, Clinical analysis of 86 botulism cases caused by cosmetic injection of botulinum toxin (BoNT), Medicine (Baltim.) 97 (34) (2018 Aug), e10659.
[425] T.L. Dinh, K.C. Ngan, C.B. Shoemaker, D.R. Walt, Rapid and ultrasensitive detection of botulinum neurotoxin serotype A1 in human serum and urine using single-molecule array method, Forensic Toxicol. 35 (2017) 179–184.
[426] J. Liu, S. Gao, L. Kang, B. Ji, W. Xin, J. Kang, P. Li, J. Gao, H. Wang, J. Wang, H. Yang, An ultrasensitive gold nanoparticle-based lateral flow test for the detection of active botulinum neurotoxin type A, Nonoscale. Res. Letts. 12 (1) (2017 Dec) 227.
[427] D. Wang, J. Baudys, K.M. Hoyt, J.R. Barr, S.R. Kalb, Further optimization of peptide substrate enhanced assay performance for BoNT/A detection by MALDI-TOF mass spectrometry, Anal. Bioanal. Chem. 409 (20) (2017 Aug) 4779–4786.
[428] M.J. Perry, D.A. Centurioni, S.W. Davis, G.E. Hannett, K.A. Musser, C.T. Egan, Implementing the bruker MALDI biotyper in the public health laboratory for C. Botulinum neurotoxin detection, Toxins 9 (3) (2017 Mar 9) e94.
[429] A. Khalilpour, T. Kilic, S. Khalilpour, M.M. Álvarez, I.K. Yazdi, Proteomic-based biomarker discovery for development of next generation diagnostics, Appl. Microbiol. Biotechnol. 101 (2) (2017 Jan) 475–491.
[430] D. Soetkamp, K. Raedschelders, M. Mastali, K. Sobhani, C.N. Bairey Merz, J. Van Eyk, The continuing evolution of cardiac troponin I biomarker analysis: from protein to proteoform, Expet Rev. Proteonomics 14 (11) (2017 Nov) 973–986.
[431] C. Tettamanti, T. Hervet, S. Grabherr, C. Palmiere, Elevation of NT-proBNP and cardiac troponins in sepsis-related deaths: a forensic perspective, Int. Legal. Med. 130 (4) (2016 Jul) 1035–1043.
[432] C. Palmiere, C. Tettamanti, A. Bonsignore, F. De Stefano, J. Vanhaebost, G. Rousseau, M.P. Scarpelli, D. Bardy, Cardiac troponins and NT-proBNP in the forensic setting: overview of sampling site, postmortem interval, cardiopulmonary resuscitation, and review of the literature, Forensic Sci. Int. 282 (2018 Jan) 211–218.
[433] T. Beausire, M. Faouzi, C. Palmiere, T. Fracasso, K. Michaud, High-sensitive cardiac troponin hs-TnT levels in sudden deaths related to atherosclerotic coronary artery disease, Forensic Sci. Int. 289 (2018 Aug) 238–243.
[434] N.A. Schneck, K.W. Phinney, S.B. Lee, M.S. Lowenthal, Quantification of cardiac troponin I in human plasma by immunoaffinity enrichment and targeted mass spectrometry, Anal. Bioanal. Chem. 410 (11) (2018 Apr) 2805–2813.
[435] R. García-Repetto, Sample preparation for pesticide analysis in a forensic toxicology laboratroy: a review, J. Forsenic. Sci. Dig. Invest 1 (1) (2018 May) 27–45.
[436] S. Velghe, R. De Troyer, C. Stove, Dried blood spots in therapeutic drug monitoring and toxicology, Expet Opin. Drug Metabol. Toxicol. 14 (1) (2018 Jan) 1–3.
[437] L. Ambach, C. Stove, Determination of cocaine and metabolites in dried blood spots by LC-MS/MS, Methods Mol. Biol. 1872 (2019) 261–272.
[438] L. Ambach, E. Menzies, M.C. Parkin, A. Kicman, J.R.H. Archer, D.M. Wood, P.I. Dargan, C. Stove, Quantification of cocaine and cocaine metabolites in dried blood spots from a controlled administration study using liquid chromatography–tandem mass spectrometry, Drug Test. Anal. 11 (5) (2019 May) 709–720, https://doi.org/10.1002/dta.2537.
[439] M. Moretti, S.D. Visonà, F. Freni, I. Tomaciello, C. Vignali, A. Groppi, L. Tajana, A.M.M. Osculati, L. Morini, A liquid chromatography-tandem mass spectrometry method for the determination of cocaine and metabolites in blood and in dried blood spots collected from postmortem samples and evaluation of the stability over a 3-month period, Drug Test. Anal. 10 (9) (2018 Sep) 1430–1437.
[440] S. Sadler Simões, A. Castañera Ajenjo, M.J. Dias, Dried blood spots combined to an UPLCMS/MS method for the simultaneous determination of drugs of abuse in forensic toxicology, J. Pharmaceut. Biomed. Anal. 147 (2018 Jan) 634–644.
[441] S. Soares, T. Castro, T. Rosado, N. Fernández, M. Barroso, E. Gallardo, New analytical approach to determine organophosphorus insecticides in blood by dried matrix spots sampling and GCMS/MS, Anal. Bioanal. Chem. 410 (30) (2018 Dec) 7955–7964.
[442] D. Wen, Y. Yang, P. Xiang, F. Yu, F. Zheng, T. Liu, Y. Shi, X. Zhang, M. Dong, B. Cong, C. Ma, A novel approach for determination of paraquat based on dried blood spot (DBS) extraction and UHPLC-HRMS analysis, J. Pharmaceut. Biomed. Anal. 159 (2018 Sep) 11–17.
[443] A. Valen, Å.M. Leere Øiestad, D.H. Strand, R. Skari, T. Berg, Determination of 21 drugs in oral fluid using fully automated supported liquid extraction and UHPLC-MS/MS, Drug Test. Anal. 9 (5) (2017 May) 808–823.
[444] L. Kristoffersen, M. Langødegård, K.I. Gaare, I. Amundsen, M.N. Terland, D.H. Strand, Determination of 12 commonly found compounds in DUID cases in whole blood using fully automated supported liquid extraction and UHPLC-MS/MS, J. Chromato B, Anal. Tecnol. Biomed. Life. Sci. 1093–1094 (2018 Sep) 8–23.
[445] A. Chisvert, S. Cárdenas, R. Lucena, Dispersive micro-solid phase extraction, Trends Anal. Chem. 112 (2019 Mar) 226–233.
[446] M. Andersson, K.B. Scheidweiler, C. Sempio, A.J. Barnes, M.A. Huestis, Simultaneous quantification of 11 cannabinoids and metabolites in human urine by liquid chromatography tandem mass spectrometry using WAX-S tips, Anal. Bioanal. Chem. 408 (23) (2016 Sep) 6461–6471.
[447] A.L. Oenning, J. Merib, E. Carasek, An effective and high-throughput analytical methodology for pesticide screening in human urine by disposable pipette extraction and gas chromatography-mass spectrometry, J. Chromato B, Anal. Tecnol. Biomed. Life. Sci. 1092 (2018 Aug) 459–465.
[448] Y. Zhang, Y.G. Zhao, W.S. Chen, H.L. Cheng, X.Q. Zeng, Y. Zhu, Three-dimensional ionic liquid-ferrite functionalized graphene oxide nanocomposite for pipette-tip solid phase extraction of 16 polycyclic aromatic hydrocarbons in human blood sample, J. Chromatogr. A 1552 (2018 Jun) 1–9.
[449] J. Carmical, S. Brown, The Impact of phospholipids and phospholipid removal on bioanalytical method performance, Biomed. Chromatogr. 30 (5) (2016 May) 710–720.
[450] M. Lei, W. Gan, Y. Sun, HPLC-MS/MS analysis of peramivir in rat plasma: elimination of matrix effect using the phospholipid-removal solid-phase extraction method, Biomed. Chromatogr. 32 (3) (2018 Mar), e4103.
[451] L.K. Sørensen, J.B. Hasselstrøm, Sensitive determination of cannabinoids in whole blood by LC-MS-MS after rapid removal of phospholipids by filtration, J. Anal. Toxicol. 41 (5) (2017 Jun) 382–391.
[452] H. Guo, J. Wang, Y. Wu, W. Liu, J. Bu, Q. Zhao, Sensitive and simultaneous determination of nine anticoagulant rodenticides in human blood by UPLC-MS-MS with phospholipid removal pretreatment, J. Anal. Toxicol. 42 (7) (2018 Sep) 459–466.
[453] X. Gao, Y. Sun, H. You, Y. Dai, H. Guo, Q. Zhao, Simultaneous determination of amitraz, chlordimeform, formetanate and metabolites in human blood by liquid chromatography tandem mass spectrometry with phospholipid-removal pretreatment, Biomed. Chromatogr. 33 (4) (2019 Apr) e4477, https://doi.org/10.1002/bmc.4477.
[454] S. Casati, A. Ravelli, I. Angeli, R. Durello, M. Minoli, M. Orioli, An automated sample preparation approach for routine liquid chromatography tandem-

mass spectrometry measurement of the alcohol biomarkers phosphatidylethanol 16:0/18:1, 16:0/16:0 and 18:1/18:1, J. Chromatogr. A 1589 (2019 Mar) 1–9, https://doi.org/10.1016/j.chroma.2018.12.048.
[455] A. Srivastava, S. Rai, A. Kumar Sonker, K. Karsauliya, C.P. Pandey, S.P. Singh, Simultaneous determination of multiclass pesticide residues in human plasma using a mini QuEChERS method, Anal. Bioanal. Chem. 409 (15) (2017 Jun) 3757–3765.
[456] E. Lehmann, C. Oltramare, L.F. de Alencastro, Development of a modified QuEChERS method for multi-class pesticide analysis in human hair by GC-MS and UPLC-MS/MS, Anal. Chim. Acta 999 (2018 Jan) 87–98.
[457] V. Alves, C. Conceição, J. Gonçalves, H.M. Teixeira, J.S. Câmara, Improved analytical approach based on QuEChERS UHPLC PDA for quantification of fluoxetine clomipramine & their active metabolites in human urine samples, J. Anal. Toxicol. 41 (1) (2017 Jan) 45–53.
[458] M.P. Dybowski, A.L. Dawidowicz, Application of the QuEChERS procedure for analysis of Δ9-tetrahydrocannabinol and its metabolites in authentic whole blood samples by GC-MS/MS, Forensic Toxicol. 36 (2) (2018) 415–423.
[459] A. Pouliopoulos, E. Tsakelidou, A. Krokos, H.G. Gika, G. Theodoridis, N. Raikos, Quantification of 15 psychotropic drugs in serum and postmortem blood samples after a modified mini-QuEChERS by UHPLC-MS-MS, J. Anal. Toxicol. 42 (5) (2018 Jun) 337–345.
[460] E. Ferrari Júnior, E.D. Caldas, Simultaneous determination of drugs and pesticides in postmortem blood using dispersive solid-phase extraction and large volume injection-programmed temperature vaporization-gas chromatography-mass spectrometry, Forensic Sci. Int. 290 (2018 Sep) 318–326.
[461] B. Waters, K. Hara, N. Ikematsu, M. Takayama, M. Kashiwagi, A. Matsusue, S.I. Kubo, Volatile hydrocarbon analysis in blood by head-space solid-phase microextraction: the interpretation of VHC patterns in fire-related incidents, J. Anal. Toxicol. 41 (4) (2017 May) 300–306.
[462] K.A. Perrault, P.H. Stefanuto, L.M. Dubois, V. Varlet, S. Grabherr, J.F. Focant, A minimally-invasive method for profiling volatile organic compounds within postmortem internal gas reservoirs, Int. J. Leg. Med. 131 (5) (2017 Sep) 1271–1281.
[463] S. Gentili, C. Mortali, L. Mastrobattista, P. Berretta, S. Zaami, Determination of different recreational drugs in sweat by headspace solid-phase microextraction gas chromatography mass spectrometry (HS-SPME GC/MS): application to drugged drivers, J. Pharmaceut. Biomed. Anal. 129 (2016 Sep) 282–287.
[464] M. Abbasian, M. Balali-Mood, H.S. Amoli, A. Masoumi, A new solid-phase microextraction fiber for separation and determination of methamphetamines in human urine using sol-gel technique, J. Sol. Gel Sci. Technol. 81 (1) (2017 Jan) 247–260.
[465] T. Inukai, S. Kaji, H. Kataoka, Analysis of nicotine and cotinine in hair by on-line in-tube solid-phase microextraction coupled with liquid chromatography-tandem mass spectrometry as biomarkers of exposure to tobacco smoke, J. Pharmaceut. Biomed. Anal. 156 (2018 Jul) 272–277.
[466] A.M. Ares, P. Fernández, M. Regenjo, A.M. Fernández, A.M. Carro, R.A. Lorenzo, A fast bioanalytical method based on microextraction by packed sorbent and UPLC-MS/MS for determining new psychoactive substances in oral fluid, Talanta 174 (2017 Nov 1) 454–461.
[467] R. Rocchi, M.C. Simeoni, C. Montesano, G. Vannutelli, R. Curini, M. Sergi, D. Compagnone, Analysis of new psychoactive substances in oral fluids by means of microextraction by packed sorbent followed by ultra-high-performance liquid chromatography-tandem mass spectrometry, Drug Test. Anal. 10 (5) (2018 May) 865–873.
[468] P. Fernández, M. González, M. Regenjo, A.M. Ares, A.M. Fernández, R.A. Lorenzo, A.M. Carro, Analysis of drugs of abuse in human plasma using microextraction by packed sorbents and ultra-high-performance liquid chromatography, J. Chromatogr. A 1485 (2017 Feb) 8–19.
[469] T. Rosado, L. Fernandes, M. Barroso, E. Gallardo, Sensitive determination of THC and main metabolites in human plasma by means of microextraction in packed sorbent and gas chromatography-tandem mass spectrometry, J. Chromato B, Anal. Tecnol. Biomed. Life. Sci. 1043 (2017 Feb) 63–73.
[470] C. Santos, D. Oppolzer, A. Gonçalves, M. Barroso, E. Gallardo, Determination of organophosphorous pesticides in blood using microextraction in packed sorbent and gas chromatography-tandem mass spectrometry, J. Anal. Toxicol. 42 (5) (2018 Jun) 321–329.
[471] E. Manandhar, N. Maslamani, I. Petrikovics, G.A. Rockwood, B.A. Logue, Determination of dimethyl trisulfide in rabbit blood using stir bar sorptive extraction gas chromatography-mass spectrometry, J. Chromatogr. A 1461 (2016 Aug) 10–17.
[472] Z. Eslami, M. Torabizadeh, Z. Talebpour, M. Talebpour, A. Ghassempour, H.Y. Aboul-Enein, Simple and sensitive quantification of Ghrelin hormone in human plasma using SBSE-HPLC/DAD-MS, J. Chromato. Sci 54 (9) (2016 Aug) 1652–1660.
[473] V. Babarahimi, Z. Talebpour, F. Haghighi, N. Adib, H. Vahidi, Validated determination of losartan and valsartan in human plasma by stir bar sorptive extraction based on acrylate monolithic polymer, liquid chromatographic analysis and experimental design methodology, J. Pharmaceut. Biomed. Anal. 153 (2018 May) 204–213.
[474] C. Wang, W. Zhou, X. Liao, X. Wang, Z. Chen, Covalent immobilization of metal organic frameworks onto chemical resistant poly(ether ether ketone) jacket for stir bar extraction, Anal. Chim. Acta 1025 (2018 Sep) 124–133.
[475] J. Grau, J.L. Benedé, J. Serrano, A. Segura, A. Chisvert, Stir bar sorptive-dispersive microextraction for trace determination of triphenyl and diphenyl phosphate in urine of nail polish users, J. Chromatogr. A 1593 (2019 May) 9–16, https://doi.org/10.1016/j.chroma.2019.02.014.
[476] A. Nazaripour, Y. Yamini, B. Ebrahimpour, J. Fasihi, Automated hollow-fiber liquid-phase microextraction followed by liquid chromatography with mass spectrometry for the determination of benzodiazepine drugs in biological samples, J. Separ. Sci. 39 (13) (2016 Jul) 2595–2603.
[477] M.A.M. Fernandez, L.C. André, Z.L. Cardeal, Hollow fiber liquid-phase microextraction-gas chromatography mass spectrometry method to analyze bisphenol A and other plasticizer metabolites, J. Chromatogr. A 1481 (2017 Jan) 31–36.
[478] S. Ranjbar Banforuzi, M.R. Hadjmohammadi, Two-phase hollow fiber-liquid microextraction based on reverse micelle for the determination of quercetin in human plasma and vegetables samples, Talanta 173 (2017 Oct) 14–21.
[479] R.P. Horta, B. do Amaral, P.G. Peralta-Zamora, B.J.G. Silva, Evaluation of a hollow-fiber liquid-phase microextraction technique for the simultaneous determination of PPI drugs in human plasma by LC-DAD, J. Chromato. Sci 56 (6) (2018 Jul) 564–573.
[480] A. Nazaripour, Y. Yamini, H. Bagheri, Extraction and determination of trace amounts of three anticancer pharmaceuticals in urine by three-phase hollow fiber liquid-phase microextraction based on two immiscible organic solvents followed by high-performance liquid chromatography, J. Chromato. Sci 41 (15) (2018 Aug) 3113–3120.
[481] N.N. Al-Hashimi, R.O. Shahin, A.N. Al-Hashimi, A.M. Al Ajeal, L.H. Tahtamouni, C. Basheer, Cetyl-alcohol-reinforced hollow fiber solid/liquid-phase microextraction and HPLC-DAD analysis of ezetimibe and simvastatin in human plasma and urine, Biomed. Chromatogr. 33 (2) (2019 Feb), e4410.
[482] M. De Boeck, S. Missotten, W. Dehaen, J. Tytgat, E. Cuypers, Development and validation of a fast ionic liquid-based dispersive liquid-liquid microextraction procedure combined with LC-MS/MS analysis for the quantification of benzodiazepine-like hypnotics in whole blood, Forensic Sci. Int. 274 (2017 May) 44–54.
[483] Z. Lin, J. Li, X. Zhang, M. Qiu, Z. Huang, Y. Rao, Ultrasound-assisted dispersive liquid-liquid microextraction for the determination of seven recreational drugs in human whole blood using gas-chromatography-mass spectrometry, J. Chromato B, Anal. Tecnol. Biomed. Life. Sci. 1046 (2017 Mar) 177–184.
[484] L.C. Sena, H.R. Matos, H.S. Dórea, M.F. Pimentel, D.C. de Santana, F.J. de Santana, Dispersive liquid-liquid microextraction based on solidification of floating organic drop and high-performance liquid chromatography to the analysis of cocaine's major adulterants in human urine, Toxicology 376 (2017 Feb) 102–112.
[485] G. Mercieca, S. Odoardi, M. Cassar, S. Strano Rossi, Rapid and simple procedure for the determination of cathinones, amphetamine-like stimulants and other new psychoactive substances in blood and urine by GC-MS, J. Pharmaceut. Biomed. Anal. 149 (2018 Feb) 494–501.
[486] S.C. Machado, B.M. Souza, L.P. de Aguiar Marciano, A.F. Souza Pereira, D.T. de Carvalho, I. Martins, A sensitive and accurate vortex-assisted liquid-liquid microextraction-gas chromatography-mass spectrometry method for urinary triazoles, J. Chromatogr. A 1586 (2019 Feb) 9–17.
[487] P. Fernández, M. Regenjo, A. Ares, A.M. Fernández, R.A. Lorenzo, A.M. Carro, Simultaneous determination of 20 drugs of abuse in oral fluid using ultrasound-assisted dispersive liquid-liquid microextraction, Anal. Bioanal. Chem. 411 (1) (2019 Jan) 193–203.
[488] C. Huang, A. Gjelstad, S. Pedersen-Bjergaard, Organic solvents in electromembrane extraction: recent insights, Rev. Anal. Chem. 35 (4) (2016 Sept) 169–183.
[489] N. Drouin, S. Rudaz, J. Schappler, New supported liquid membrane for electromembrane extraction of polar basic endogenous metabolites, J. Pharmaceut. Biomed. Anal. 159 (2018 Sep) 53–59.
[490] L. Vårdal, E.L. Øiestad, A. Gjelstad, S. Pedersen-Bjergaard, Electromembrane extraction of substances with weakly basic properties: a fundamental study with benzodiazepines, Bioanalysis 10 (10) (2018 May) 769–781.
[491] Z. Tahmasebi, S.S.H. Davarani, A.A. Asgharinezhad, Highly efficient electrochemical determination of propylthiouracil in urine samples after selective electromembrane extraction by copper nanoparticles-decorated hollow fibers, Biosens. Bioelectron. 114 (2018 Aug) 66–71.
[492] S. Yaripour, A. Mohammadi, I. Esfanjani, R.B. Walker, S. Nojavan, Quantitation of zolpidem in biological fluids by electro-driven microextraction combined with HPLC-UV analysis, EXCLI J 17 (2018 Apr) 349–361.
[493] L. Vårdal, A. Gjelstad, C. Huang, E.L. Øiestad, S. Pedersen-Bjergaard, Efficient discrimination and removal of phospholipids during electromembrane extraction from human plasma samples, Bioanalysis 9 (8) (2017 Apr) 631–641.
[494] C.L.H. Snozek, L.J. Langman, S.W. Cotten, An introduction to drug testing: the expanding role of mass spectrometry, Methods Mol. Biol. 1872 (2019) 1–10.
[495] N.G.S. Mogollón, C.D. Quiroz-Moreno, P.S. Prata, J.R. de Almeida, A.S. Cevallos, R. Torres-Guiérrez, F. Augusto, New advances in toxicological forensic analysis using mass spectrometry techniques, J. Anal. Method. Chem. 2018 (2018 Aug) 4142527.
[496] H.H. Maurer, Mass spectrometry for research and application in therapeutic drug monitoring or clinical and forensic toxicology, Ther. Drug Monit. 40 (4) (2018 Aug) 389–393.
[497] M.R. Meyer, H.H. Maurer, Review: LC coupled to low- and high-resolution mass spectrometry for new psychoactive substance screening in biological

matrices-Where do we stand today? Anal. Chim. Acta 927 (2016 Jul) 13–20.
[498] H.H. Maurer, M.R. Meyer, High-resolution mass spectrometry in toxicology-current status and future perspectives, Arch. Toxicol. 90 (9) (2016 Sept) 2161–2172.
[499] D. Pasin, A. Cawley, S. Bidny, S. Fu, Current applications of high-resolution mass spectrometry for the analysis of new psychoactive substances: a critical review, Anal. Bioanal. Chem. 409 (25) (2017 Oct) 5821–5836.
[500] D. Pasin, A. Cawley, S. Bidny, S. Fu, Characterization of hallucinogenic phenethylamines using high-resolution mass spectrometry for non-targeted screening purposes, Drug Test. Anal. 9 (10) (2017 Oct) 1620–1629.
[501] A.D. McEachran, K. Mansouri, C. Grulke, E.L. Schymanski, C. Ruttkies, A.J. Williams, "MS-Ready" structures for non targeted high-resolution mass spectrometry screening studies, J. Cheminf. 10 (1) (2018 Aug) 45.
[502] J. McKenna, R. Jett, K. Shanks, N.E. Manicke, Toxicological drug screening using paper spray high-resolution tandem mass spectrometry (HR-MS/MS), J. Anal. Toxicol. 42 (5) (2018 Jun) 300–310.
[503] C.B. Mollerup, B.S. Rasmussen, S.S. Johansen, M. Mardal, K. Linnet, P.W. Dalsgaard, Retrospective analysis for valproate screening targets with liquid chromatography-high resolution mass spectrometry with positive electrospray ionization: an omics-based approach, Drug Test. Anal. 11 (5) (2019 May) 730–738, https://doi.org/10.1002/dta.2543.
[504] A. López, P. Dualde, V. Yusà, C. Coscollà, Retrospective analysis of pesticide metabolites in urine using liquid chromatography coupled to high-resolution mass spectrometry, Talanta 160 (2016 Nov) 547–555.
[505] E. Partridge, S. Trobbiani, P. Stockham, C. Charlwood, C. Kostakis, A case study involving U47700, diclazepam and flubromazepam-applicatoin of retrospective analysis of HRMS data, Anal. Toxicol. 42 (9) (2018 Nov) 655–660.
[506] M. Grapp, C. Kaufmann, F. Streit, L. Binder, Systematic forensic toxicological analysis by liquid-chromatography-quadrupole-time-of-flight mass spectrometry in serum and comparison to gas chromatography-mass spectrometry, Forensic Sci. Int. 287 (2018 Jun) 63–73.
[507] S. Bidny, K. Gago, P. Chung, D. Albertyn, D. Pasin, Simultaneous screening and quantification of basic, neutral and acidic drugs in blood using UPLC-QTOF-MS, J. Anal. Toxicol. 41 (3) (2017 Apr) 181–195. Erratum: Journal of Analytical Toxicology 2017 Apr); 41(3):259.
[508] E. Partridge, S. Trobbiani, P. Stockham, T. Scott, C. Kostakis, A validated method for the screening of 320 forensically significant compounds in blood by LC/QTOF, with simultaneous quantification of selected compounds, J. Anal. Toxicol. 42 (4) (2018 May) 220–231.
[509] H.C. Liu, C.A. Yang, R.H. Liu, D.L. Lin, Developing a UHPLC-QTOF-MS and automated library search method for screening drugs and toxic compounds in postmortem specimens, J. Anal. Toxicol. 41 (5) (2017 Jun) 421–430.
[510] J.M. Colby, K.L. Thoren, K.L. Lynch, Suspect screening using LC-QqTOF is a useful tool for detecting drugs in biological samples, J. Anal. Toxicol. 42 (4) (2018 May) 207–213.
[511] H. Fels, T. Dame, H. Sachs, F. Musshoff, Liquid chromatography-quadrupole-time-of-flight mass spectrometry screening procedure for urine samples in forensic casework compared to gas chromatography-mass spectrometry, Drug Test. Anal. 9 (5) (2017 May) 824–830.
[512] K.B. Palmquist, M.J. Swortwood, Data-independent screening method for 14 fentanyl analogs in whole blood and oral fluid using LC-QTOF-MS, Forensic Sci. Int. 297 (2019 Apr) 189–197, https://doi.org/10.1016/j.forsciint.2019.02006.
[513] M. Sundström, A. Pelander, I. Ojanperä, Comparison of post-targeted and pre-targeted urine drug screening by UHPLC-HR-QTOFMS, J. Anal. Toxicol. 41 (7) (2017 Sep) 623–630.
[514] A.G. Helfer, J.A. Michely, A.A. Weber, M.R. Meyer, H.H. Maurer, Liquid chromatography-high resolution-tandem mass spectrometry using Orbitrap technology for comprehensive screening to detect drugs and their metabolites in blood plasma, Anal. Chim. Acta 965 (2017 May) 83–95.
[515] S. Allard, P.M. Allard, I. Morel, T. Gicquel, Application of a molecular networking approach for clinical and forensic toxicology exemplified in three cases involving 3-MeO-PCP, doxylamine, and chlormequat, Drug Test. Anal. (2019) 1–9.
[516] M. Pan, P. Xiang, Z. Yu, Y. Zhao, H. Yan, Development of a high-throughput screening analysis for 288 drugs and poisons in human blood using Orbitrap technology with gas chromatography-high resolution accurate mass spectrometry, J. Chromatogr. A 1587 (2019 Feb) 209–226.
[517] E. Jagerdeo, J.E. Schaff, Rapid screening for drugs of abuse in biological fluids by ultra high performance liquid chromatography/Orbitrap mass spectrometry, J. Chromato B, Anal. Tecnol. Biomed. Life. Sci. 1027 (2016 Aug) 11–18.
[518] X. Gao, H. Li, H. Li, S. Dong, J. Chu, H. Guo, Q. Zhao, Sensitive determination of nine anticoagulant rodenticides in blood by high resolution mass spectrometry with supported liquid extraction pretreatment, Forensic Sci. Int. 292 (2018 Nov) 39–44.
[519] A.T. Caspar, S.D. Brandt, A.E. Stoever, M.R. Meyer, H.H. Maurer, Metabolic fate and detectability of the new psychoactive substances 2-(4-bromo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine (25B-NBOMe) and 2-(4-chloro-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine (25C-NBOMe) in human and rat urine by GC-MS, LC-MS^n, and LC-HR-MS/MS approaches, J. Pharmaceut. Biomed. Anal. 134 (2017 Feb 5) 158–169.
[520] P.O.M. Gundersen, O. Spigset, M. Josefsson, Screening, quantification, and confirmation of synthetic cannabinoid metabolites in urine by UHPLC-QTOF-MS, Drug Test. Anal. 11 (1) (2019 Jan) 51–67.
[521] M. Pettersson Bergstrand, M.R. Meyer, O. Beck, A. Helander, Human urinary metabolic patterns of the designer benzodiazepines flubromazolam and pyrazolam studied by liquid chromatography-high resolution mass spectrometry, Drug Test. Anal. 10 (3) (2018 Mar) 496–506.
[522] A. Michely JA, S.K. Manier, A.T. Caspar, S.D. Brandt, J. Wallach, H.H. Maurer, New psychoactive substances 3-methoxyphencyclidine (3-MeO-PCP) and 3-methoxyrolicyclidine (3-MeO-PCPy): metabolic fate elucidated with rat urine and human liver preparations and their detectability in urine by GC-MS, "LC-(high resolution)-MSn" and "LC-(high resolution)-MS/MS, Curr. Neuropharmacol. 15 (5) (2017) 692–712.
[523] A.T. Caspar, M.R. Meyer, F. Westphal, A.A. Weber, H.H. Maurer, Nano liquid chromatography-high-resolution mass spectrometry for the identification of metabolites of the two new psychoactive substances N-(ortho-methoxybenzyl)-3,4-dimethoxyamphetamine and N-(ortho-methoxybenzyl)-4-methylmethamphetamine, Talanta 188 (2018 Oct) 111–123.
[524] B. Rochat, R. Mohamed, P.E. Sottas, LCHRMS metabolomics for untargeted diagnostic screening in clinical laboratory: a feasibility study, Metabolites 8 (2) (2018 Jun) E39.
[525] M.I. Boxler, T.D. Schneider, T. Kraemer, A.E. Steuer, Analytical considerations for (un)-targeted metabolomic studies with special focus on forensic applications, Drug Test. Anal. 11 (5) (2019 May) 678–696, https://doi.org/10.1002/dta.2540.
[526] D. Dudzik, C. Barbas-Bernardos, A. García, C. Barbas, Quality assurance procedures for mass spectrometry untargeted metabolomics. a review, J. Pharmaceut. Biomed. Anal. 147 (2018 Jan) 149–173.
[527] G. de Albuquerque Cavalcanti, L.M. Rodrigues, L. Dos Santos, X. Zheng, A. Gujar, J. Cole, M.C. Padilha, F.R. de Aquino Neto, Non-targeted acquisition strategy for screening doping compounds based on GC-EI-hybrid quadrupole-Orbitrap mass spectrometry: a focus on exogenous anabolic steroids, Drug Test. Anal. 10 (3) (2018 Mar) 507–517.
[528] T.L.S. Choi, K.Y. Kwok, W.H. Kwok, Y.Y.K. Tsoi, J.K.Y. Wong, T.S.M. Wan, Detection of seventy-two anabolic and androgenic steroids and/or their esters in horse hair using ultra-high performance liquid chromatography-high resolution mass spectrometry in multiplexed targeted MS^2 mode and gas chromatography-tandem mass spectrometry, J. Chromatogr. A 1566 (2018 Sep) 51–63.
[529] K.Y. Kwok, T.L.S. Choi, W.H. Kwok, J.K.Y. Wong, T.S.M. Wan, Detection of anabolic and androgenic steroids and/or their esters in horse hair using ultra-high performance liquid chromatography-high resolution mass spectrometry, J. Chromatogr. A 1493 (2017 Apr) 76–86.
[530] N. Fabresse, S. Grassin-Delyle, I. Etting, J.C. Alvarez, Detection and quantification of 12 anabolic steroids and analogs in human whole blood and 20 in hair using LC-HRMS/MS: application to real cases, Int. Legal. Med. 131 (4) (2017 Jul) 989–999.
[531] F. Ponzetto, J. Boccard, R. Nicoli, T. Kuuranne, M. Saugy, S. Rudaz, UHPLC-HRMS analysis for steroid profiling in serum, Methods. Molcul. Biol. 1738 (2018) 261–278.
[532] O. Karlsson, J. Hanrieder, Imaging mass spectrometry in drug development and toxicology, Arch. Toxicol. 91 (6) (2017 Jun) 2283–2294.
[533] A.E. Steuer, M. Poetzsch, T. Kraemer, MALDI-MS drug analysis in biological samples: opportunities and challenges, Bioanalysis 8 (17) (2016 Sep) 1859–1878.
[534] B. Flinders, E. Cuypers, T. Porta, E. Varesio, G. Hopfgartner, R.M.A. Heeren, Mass spectrometry imaging of drugs of abuse in hair, Methods Mol. Biol. 1618 (2017) 137–147.
[535] B. Flinders, E. Beasley, R.M. Verlaan, E. Cuypers, S. Francese, T. Bassindale, M.R. Clench, R.M.A. Heeren, Optimization of sample preparation and instrumental parameters for the rapid analysis of drugs of abuse in hair samples by MALDI-MS/MS imaging, J. Am. Soc. Mass Spectrom. 28 (11) (2017 Nov) 2462–2468.
[536] E. Beasley, S. Francese, T. Bassindale, Detection and mapping of cannabinoids in single hair samples through rapid derivatization and matrix-assisted laser desorption ionization mass spectrometry, Anal. Chem. 88 (20) (2016 Oct) 10328–10334.
[537] A. Kernalléguen, C. Enjalbal, J.C. Alvarez, O. Belgacem, G. Léonetti, D. Lafitte, A.L. Pélissier-Alicot, Synthetic cannabinoid isomers characterization by MALDI-MS3 imaging: application to single scalp hair, Anal. Chim. Acta 1041 (2018 Dec 24) 87–93.
[538] H. Wang, Y. Wang, G. Wang, L. Hong, Matrix-assisted laser-desorption/ionization mass spectrometric imaging of olanzapine in a single hair using esculetin as a matrix, J. Pharmaceut. Biomed. Anal. 141 (2017 Jul) 123–131.
[539] H. Wang, Y. Wang, Matrix-assisted laser desorption/ionization mass spectrometric imaging for the rapid segmental analysis of methamphetamine in a single hair using umbelliferone as a matrix, Anal. Chim. Acta 975 (2017 Jul) 42–51.
[540] N. Shima, K. Sasaki, T. Kamata, S. Matsuta, M. Wada, H. Kakehashi, S. Nakano, H. Kamata, H. Nishioka, T. Sato, H. Tsuchihashi, A. Miki, M. Katagi, Incorporation of zolpidem into hair and its distribution after a single administration, Drug Metabol. Dispos. 45 (3) (2017 Mar) 286–293.
[541] W.F. Duvivier, T.A. van Beek, M.W. Nielen, Critical comparison of mass analyzers for forensic hair analysis by ambient ionization mass spectrometry, Rapid Commun. Mass Spectrom. 30 (21) (2016 Nov) 2331–2340.
[542] K.L. Palmer, M.D. Krasowski, Alternate matrices: meconium, cord tissue, hair,

and oral fluid, Methods Mol. Biol. 1872 (2019) 191–197.
[543] C. Palmiere, C. Tettamanti, M.P. Scarpelli, R. Tse, The forensic spleen; morphological, radiological, and toxicological investigation, Forensic Sci. Int. 291 (2018 Oct) 94–99.
[544] R.E. Ferner, J.K. Aronson, The toxicological significance of postmortem drug concentrations in bile, Clin. Toxicol. 56 (1) (2018 Jan) 7–14.
[545] K.M. Rubin, The current state and future directions of skeletal toxicology: forensic and humanitarian implications of a proposed model for the in vivo incorporation of drugs into the human skeleton, Forensic Sci. Int. 289 (2018 Aug) 419–428.
[546] M. Vandenbosch, T. Somers, E. Cuypers, Distribution of clomipramine, citalopram, midazolam and metabolites in skeletal tissue after chronic dosing in rats, Drug Test. Anal. 11 (7) (2019 Jul) 1083–1093, https://doi.org/10.1002/dta.2578.
[547] A. Orfanidis, H. Gika, O. Mastrogianni, A. Krokos, G. Theodoridis, E. Zaggelidou, N. Raikos, Determination of drugs of abuse and pharmaceuticals in skeletal tissue by UHPLC-MS/MS, Forensic Sci. Int. 290 (2018 Sep) 137–145.
[548] L.M. Morrison, K.A. Unger, J.H. Watterson, Analysis of dextromethorphan and dextrorphan in skeletal remains following differential microclimate exposure: comparison of acute vs. repeated drug exposure, J. Anal. Toxicol. 41 (6) (2017 Jul) 566–572.
[549] H.M. Cornthwaite, L. Labine, J.H. Watterson, Semi-quantitative analysis of tramadol, dextromethorphan, and metabolites in decomposed skeletal tissues by ultra performance liquid chromatography quadrupole time of flight mass spectrometry, Drug Test. Anal. 10 (6) (2018 Jun) 961–967.
[550] M. Vandenbosch, T. Somers, E. Cuypers, Distribution of methadone and metabolites in skeletal tissue, J. Anal. Toxicol. 42 (6) (2018 Jul) 400–408.
[551] M. Chikhani, R. Wuhrer, H. Green, Optimization of sample Preparation processes of bone material for Raman Spectroscopy, J. Forensic Sci. 63 (6) (2018 Nov) 1809–1812.
[552] G. Ottaviani, R. Cameriere, M. Cippitelli, R. Froldi, G. Tassoni, M. Zampi, M. Cingolani, Determination of drugs of abuse in a single sample of human teeth by a gas chromatography-mass spectrometry method, J. Anal. Toxicol. 41 (1) (2017 Jan) 32–36.
[553] A. Orfanidis, H. Gika, E. Zaggelidou, O. Mastrogianni, N. Raikos, Alprazolam and zolpidem in skeletal tissue of decomposed body confirms exposure, J. Forensic Sci. 64 (2) (2019 Mar) 643–646.
[554] J. Markowska, M. Szopa, M. Zawadzki, W. Piekoszewski, Vitreous humor – routine or alternative material for analysis in forensic medicine, Archiwum Medycyny Sadownji Kryminologii 67 (3) (2017) 201–213.
[555] A.A. Ishikawa, D.M. Bordin, E.G. de Campos, L. Blanes, P. Doble, B.S. De Martinis, A Gas chromatography-Mass spectrometry method for toxicological analysis of MDA, MDEA and MDMA in Vitreous Humor Samples from victims of car accidents, J. Anal. Toxicol. 42 (9) (2018 Nov) 661–666.
[556] C.H. Thaulow, A.M.L. Oiestad, S. Rogde, R. Karinen, G.W. Brochmann, J.M. Anderson, G. Hoiseth, M. Handal, J. Morland, M. Arnestad, E.L. Oiestad, D.H. Strand, V. Vindenes, Metabolites of heroin in several different postmortem matrices, J. Anal. Toxicol. 42 (2018) 311–320.
[557] F.P. Busardò, G. Mannocchi, R. Giorgetti, M. Pellegrini, G. Baglio, S. Zaami, E. Marinelli, S. Pichini, Stability of endogenous GHB in vitreous humor vs peripheral blood in dead bodies, Forensic Sci. Int. 274 (2017) 64–69.
[558] L.N. Rodda, J.A. Volk, E. Moffat, C.M. Williams, K.L. Lynch, A.H.B. Wu, Evaluation of Intraosseous Fluid as an alternative biological specimen in Postmortem toxicology, J. Anal. Toxicol. 42 (5) (2018 Jun) 311–320.
[559] M. Knuth, O. Temme, T. Daldrup, E. Pawlik, Analysis of cocaine adulterants in human brain in cases of drug-related death, Forensic Sci. Int. 285 (2018 Apr) 86–92.
[560] M. Nedahl, S.S. Johansen, K. Linnet, Reference brain and blood concentrations of olanzapine in postmortem cases, J. Anal. Toxicol. 42 (9) (2018 Nov) 650–654.
[561] M. Nedahl, S.S. Johansen, K. Linnet, Reference Brain/blood concentrations of citalopram, duloxetine, mirtazapine and sertraline, J. Anal. Toxicol. 42 (3) (2018 Apr) 149–156.
[562] M. Nedahl, S.S. Johansen, K. Linnet, Postmortem brain-blood ratios of amphetamine, cocaine, ephedrine, MDMA and methylphenidate, J. Anal. Toxicol. 43 (5) (2019 Jun) 378–384, https://doi.org/10.1093/jat/bky110.
[563] L. Skov, K.M.D. Holm, S.S. Johansen, K. Linnet, Postmortem brain and blood reference concentrations of alprazolam, bromazepam, chlordiazepoxide, diazepam and their metabolites and a review of the literature, J. Anal. Toxicol. 40 (7) (2016 Sep) 529–536.
[564] R. Thomsen, B.S. Ramussen, S.S. Johansen, K. Linnet, Postmortem concentrations of gamma-hydroxybutyrate (GHB) in peripheral blood and brain tissue- differentiating between postmortem formation and antemortem intake, Forensic Sci. Int. 272 (2017 Mar) 154–158.
[565] L.J. Marinetti, Review of: hair analysis in clinical and forensic toxicology, J. Forensic Sci. 62 (5) (2017 Sept) 1426.
[566] R.M. White, Drugs in hair. Part I. Metabolisms of major drug classes, Forensic Sci. Rev. 29 (1) (2017 Jan) 23–55.
[567] P. Kintz, Hair analysis in forensic toxicology: an updated review with a special focus on pitfalls, Curr. Pharmaceut. Des. 23 (36) (2017) 5480–5486.
[568] L. Tsanaclis, M. Andraus, J. Wicks, Hair analysis when external contamination is in question: a review of practical approach for the interpretation of results, Forensic Sci. Int. 285 (2018 Apr) 105–110.
[569] J. Restolho, M. Barroso, B. Saramago, M. Dias, C.A. Afonso, Contactless decontamination of hair samples: cannabinoids, Drug Test. Anal. 9 (2) (2017 Feb) 282–288.
[570] R. Kronstrand, M. Forsman, M. Roman, Quantitative analysis of drugs in hair by UPLC high resolution mass spectrometry, Forensic Sci. Int. 283 (2018 Feb) 9–15.
[571] F. Musshoff, D. Thieme, G. Schwarz, Hans Sachs, G. Skopp, T. Franz, Determination of hydroxyl metabolites of cocaine in hair samples for proof of consumption, Drug Test. Anal. 10 (4) (2018 Apr) 681–688.
[572] K.W. Leung, Z.C.F. Wong, J.Y.M. Ho, A.W.S. Yip, J.K.H. Cheung, K.K.L. Ho, R. Duan, K.T.K. Tsim, Surveillance of drug abuse in Hong Kong by hair analysis using LC-MS/MS, Drug Test. Anal. 10 (6) (2018 Jun) 977–983.
[573] U. Meier, T. Briellmann, E. Scheurer, F. Dussy, Sample preparation method for the combined extraction of ethyl glucuronide and drugs of abuse in hair, Drug Test. Anal. 10 (4) (2018 Apr) 701–710.
[574] C. Gambelunghe, R. Rossi, K. Aroni, A. Gili, M. Bacci, V. Pascali, N. Fucci, Norcocaine and cocaethylene distribution patterns in hair samples from light, moderate, and heavy cocaine users, Drug Test. Anal. 9 (2) (2017 Feb) 161–167.
[575] G. Hoiseth, M. Arnestad, R. Karinen, L. Morini, S. Rodge, C. Sempio, V. Vindenes, A.M.L. Oiestad, Is hair analysis useful in postmortem cases? J. Anal. Toxicol. 42 (1) (2018 Jan) 49–54.
[576] K.N. Gunther, S.S. Johansen, M.K.K. Nielsen, P. Wicktor, J. Banner, K. Linnet, Postmortem quetiapine concentrations in hair segments of psychiatric patients- correlation between hair concentration, dose and concentration in blood, Forensic Sci. Int. 285 (2018 Apr) 58–64.
[577] L.A. Nisbet, R. Venson, F.M. Wylie, K.S. Scott, Application of a urine and hair validated LC-MS-MS method to determine the effect of hair color on the incorporation of 25B-NBOMe, 25C-NBOMe and 25I-NBOMe into hair in the rat, J. Anal. Toxicol. 41 (6) (2017 Jul) 559–565.
[578] F.P. Busardo, S. Pichini, S. Zaami, R. Pacifici, P. Kintz, Hair testing of GHB: an everlasting issue in forensic toxicology, Clin. Chem. Lab. Med. 56 (2) (2018 Jan) 198–208.
[579] N.V. Elsue, C.L. Crunelle, C.A. Verbrugge, K. van Baarle, A. Rodrigues, H. Neels, M. Yegles, Gammahydroxybutyrate in hair of non-GHB and repeated GHB users: a new and optimized method, Forensic Sci. Int. 291 (2018 Oct) 193–198.
[580] F.P. Busardo, F. Vaiano, G. Mannocchi, E. Bertol, S. Zaami, E. Marinelli, Twelve months monitoring of hair GHB decay following a single dose administration in a case of facilitated sexual assault, Drug Test. Anal. 9 (6) (2017 Jun) 953–956.
[581] T. Piper, L.M. Mehling, A. Spottke, A. Heidbreder, P. Young, B. Madea, C. Hess, W. Schanzer, M. Thevis, Potential of GHB phase-II-metabolites to complement current approaches in GHB post administration detection, Forensic Sci. Int. 279 (2017 Oct) 157–164.
[582] I.A. Larabi, N. Fabresse, A. Knapp, M. Forcet, F.J. Baud, G. Lorin de la Grandmaison, J.C. Alvarez, LC-MS/MS method for quanitification of baclofen in hair: a useful tool to assess compliance in alcohol dependent patients? Drug Test. Anal. 10 (4) (2018 Apr) 694–700.
[583] M. Luginbuhl, S. Nussbaumer, W. Weinmann, Decrease of ethyl glucuronide concentrations in hair after exposure to chlorinated swimming pool water, Drug Test. Anal. 10 (4) (2018 Apr) 689–693.
[584] E. Cuypers, R.J. Flanagan, The interpretation of hair analysis for drugs and drug metabolites, Clin. Toxicol. 56 (2) (2018 Feb) 90–100.
[585] A. Salomone, E. Gerace, D. Di Coricia, E. Alladio, M. Vincenti, P. Kintz, Hair analysis can provide additional information in doping and forensic cases involving clostebol, Drug Test. Anal. 11 (1) (2019 Jan) 95–101.
[586] K. Kuwayama, H. Miyaguchi, Y.T. Iwata, T. Kanamori, K. Tsujikawa, T. Yamamuro, H. Segawa, H. Inoue, Time-course measurements of drug concentrations in hair and toenails after single administrations of pharmaceutical products, Drug Test. Anal. 9 (4) (2017 Apr) 571–577.
[587] T.P. Magalhães, S. Cravo, D.D.D. Silva, R.J. Dinis-Oliveira, C. Afonso, M. Lourdes Bastos, H. Carmo, Quantification of methadone and main metabolites in nails, J. Anal. Toxicol. 42 (3) (2018 Apr) 192–206.
[588] E. Shokry, J.G. Marques, P.C. Ragazzo, N.Z. Pereira, N.R.A. Filho, Earwax as an alternative specimen for forensic analysis, Forensic Toxicol. 35 (2) (2017) 348–358.
[589] S.I. Meier, S.C. Koelzer, M. Schubert-Zsilavecz, S.W. Toennes, Analysis of drugs of abuse in cerumen-correlation of postmortem analysis results with those for blood, urine and hair, Drug Test. Anal. 9 (10) (2017 Oct) 1572–1585.
[590] R.A. deRegnier, Umbilical cord tissue vs meconium for neonatal toxicology testing, J. Pediatr. 205 (2019 Feb) 3.
[591] J.M. Colby, Comparison of umbilical cord tissue and meconium for the confirmation of in utero drug exposure, Clin. Biochem. 50 (13–14) (2017 Sep) 784–790.
[592] F. Wu, T.L. Scroggin, T.D. Metz, G.A. McMillin, Development of a liquid chromatography-tandem mass spectrometry method for the simultaneous determination of four cannabinoids in umbilical cord tissue, J. Anal. Toxicol. 42 (1) (2018 Jan) 42–48.
[593] J. Kim, A. de Castro, E. Lendoiro, A. Cruz-Landeira, M. López-Rivadulla, M. Concheiro, Detection of in utero cannabis exposure by umbilical cord analysis, Drug Test. Anal. 10 (4) (2018 Apr) 636–643.
[594] L. Paniagua-González, C. Jiménez-Morigosa, E. Lendoiro, M. Concheiro, A. Cruz, M. López-Rivadulla, A. de Castro, Development and validation of a liquid chromatography-tandem mass spectrometry method for the

determination of nicotine and its metabolites in placenta and umbilical cord, Drug Test. Anal. 10 (8) (2018 Aug) 1305–1314.
[595] K. Hasegawa, A. Wurita, H. Nozawa, I. Yamagishi, K. Minakata, K. Watanabe, O. Suzuki, Fatal zolpidem poisoning due to its intravenous self-injection: postmortem distribution/redistribution of zolpidem and its predominant metabolite zolpidem phenyl-4-carboxylic acid in body fluids and solid tissues in an autopsy case, Forensic Sci. Int. 290 (2018 Sep) 111–120.
[596] Å.M.L. Øiestad, R. Karinen, S. Rogde, S. Nilsen, K.B. Boye Eldor, G.W. Brochmann, M. Arnestad, E.L. Øiestad, M.D. Peres, L. Kristoffersen, V. Vindenes, Comparative study of postmortem concentrations of antidepressants in several different matrices, J. Anal. Toxicol. 42 (7) (2018 Sep) 446–458.
[597] S.R. Saenz, R.J. Lewis, M.K. Angier, J.R. Wagner, Postmortem fluid and tissue concentrations of THC, 11-OH-THC and THC-COOH, J. Anal. Toxicol. 41 (6) (2017 Jul) 508–516.
[598] C.H. Thaulow, Å.M.L. Øiestad, S. Rogde, J.M. Andersen, G. Høiseth, M. Handal, J. Mørland, V. Vindenes, Can measurement of heroin metabolites in postmortem matrices other than peripheral blood indicate if death was rapid or delayed? Forensic Sci. Int. 290 (2018 Sep) 121–128.
[599] F.P. Busardò, A.W. Jones, Interpreting γ-hydroxybutyrate concentrations for clinical and forensic purposes, Clin. Toxicol. 11 (2018 Oct) 1–15.
[600] A.W. Jones, A. Holmgren, F.C. Kugelberg, F.P. Busardò, Relationship between postmortem urine and blood concentrations of GHB furnishes useful information to help interpret drug intoxication deaths, J. Anal. Toxicol. 42 (9) (2018 Nov) 587–591.
[601] C. Söderberg, E. Wernvik, A. Tillmar, O. Spigset, R. Kronstrand, M. Reis, A.K. Jönsson, H. Druid, Antipsychotics-Postmortem fatal and non-fatal reference concentrations, Forensic Sci. Int. 266 (2016 Sep) 91–101.
[602] C.R. Mikkelsen, J.R. Jornil, L.V. Andersen, J. Banner, J.B. Hasselstrøm, Distribution of eight QT-prolonging drugs and their main metabolites between postmortem cardiac tissue and blood reveals potential pitfalls in toxicological interpretation, J. Anal. Toxicol. 42 (6) (2018 Jul) 375–383.
[603] A.E. Steuer, Cause of death: 'intoxication'-a matter of the concentration? Praxis 107 (22) (2018) 1211–1217.
[604] C. Sastre, C. Bartoli, V. Baillif-Couniou, G. Leonetti, A.L. Pelissier-Alicot, Post mortem redistribution of drugs: current state of knowledge, Curr. Pharmaceut. Des. 23 (36) (2017) 5530–5541.
[605] I.M. McIntyre, Analytical data supporting the "theoretical" postmortem redistribution factor (F_t): a new model to evaluate postmortem redistribution, Forensic. Sci. Res. 1 (1) (2016 Dec) 33–37.
[606] B. Zilg, G. Thelander, B. Giebe, H. Druid, Postmortem blood sampling-Comparison of drug concentrations at different sample sites, Forensic Sci. Int. 278 (2017 Sept) 296–303.
[607] E. Lemaire, C. Schmidt, R. Denooz, C. Charlier, P. Boxho, Postmortem concentration and redistribution of diazepam, methadone, and morphine with subclavian and femoral vein dissection/clamping, J. Forensic Sci. 61 (6) (2016 Nov) 1596–1603.
[608] E. Lemaire, C. Schmidt, N. Dubois, R. Denooz, C. Charlier, P. Boxho, Site-, technique-, and time-related aspects of the postmortem redistribution of diazepam, methadone, morphine, and their metabolites: interest of popliteal vein blood sampling, J. Forensic Sci. 62 (6) (2017 Nov) 1559–1574.
[609] L. Brockbals, S.N. Staeheli, D. Gascho, L.C. Ebert, T. Kraemer, A.E. Steuer, Time-dependent postmortem redistribution of opioids in blood and alternative matrices, J. Anal. Toxicol. 42 (6) (2018 Jul) 365–374.
[610] S.N. Staeheli, D. Gascho, L.C. Ebert, T. Kraemer, A.E. Steuer, Time-dependent postmortem redistribution of morphine and its metabolites in blood and alternative matrices-application of CT-guided biopsy sampling, Int. J. Leg. Med. 131 (2) (2017 Mar) 379–389.
[611] M. Liang, J. Zhang, N. Zheng, L. Liu, How postmortem redistribution of MDMA in acute alcohol-MDMA combined-use rats change under effects of alcohol, Sci. Rep. 7 (1) (2017 Jun) 4038.
[612] G.A. Reed, Stability of drugs, drug candidates, and metabolites in blood and plasma, Current. Protocols. Pharmacol. 75 (2016 Dec) 7.6.1–7.6.12.
[613] R.M. White, Instability and poor recovery of cannabinoids in urine, oral fluid, and hair, Forensic Sci. Rev. 30 (1) (2018 Jan) 33–49.
[614] M. Moretti, L. Andrello, S. Visonà, C. Vignali, A. Groppi, F. Freni, A. Osculati, L. Tajana, L. Morini, Evaluation of benzodiazepines and zolpidem in nails and their stability after prolonged exposure to chlorinated water, J. Pharmaceut. Biomed. Anal. 152 (2018 Apr) 137–142.
[615] S.C. Bishop-Freeman, E.M. Hensel, M.S. Feaster, R.E. Winecker, Degradation of bupropion: implications for interpretation of postmortem case data, J. Anal. Toxicol. 42 (8) (2018 Oct) 525–536.
[616] Y. Liu, X. Zhang, J. Li, Z. Huang, Z. Lin, J. Wang, C. Zhang, Y. Rao, Stability of ethyl glucuronide, ethyl sulfate, phosphatidylethanols and fatty acid ethyl esters in postmortem human blood, J. Anal. Toxicol. 42 (5) (2018 Jun) 346–352.
[617] D.C. Mata, Stability of 26 sedative hypnotics in six toxicological matrices at different storage conditions, J. Anal. Toxicol. 40 (2016) 663–668.
[618] F. Wu, S.J. Marin, G.A. McMillin, Stability of 21 Cocaine, Opioid and Benzodiazepine drug analytes in spiked meconium at three temperatures, J. Anal. Toxicol. 41 (2017) 196–204.
[619] V. Varlet, E. Ryser, M. Augsburger, C. Palmiere, Stability of postmortem methemoglobin: artifactual changes caused by storage conditions, Forensic Sci. Int. 283 (2018 Feb) 21–28.
[620] T. Huertas, C. Jurado, M. Salguero, T. Soriano, J. Gamero, Stability studies in biological fluids during post-analysis custody. Opiate compounds derived from heroin consumption, Forensic Sci. Int. 297 (2019 Feb) 326–334.
[621] Z. Wei, Q. Niu, F. Zhang, K. Xiao, L. Liu, Y. Wang, J. Jia, J. Cao, S. Fu, K. Yun, The effect of sodium fluoride, formaldehyde, and storage temperature on the stability of methamidophos in postmortem blood and liver, Int. Legal. Med. 131 (3) (2017 May) 667–675.