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Review

The State of the Art in Post-Mortem Redistribution and Stability of New Psychoactive Substances in Fatal Cases: A Review of the Literature

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Abstract: In post-mortem (PM) investigations, forensic toxicologists attempt to identify legal or illegal substances present before death and determine how they contributed to the cause of death. A critical challenge is ensuring that PM sample concentrations accurately reflect those at the time of death, as postmortem redistribution (PMR) can alter these levels due to anatomical and physiological changes. The PMR phenomenon is called a 'toxicological nightmare'. PMR significantly affects post-mortem drug concentrations, particularly for lipophilic drugs and those with a high volume of distribution. The emergence of new psychoactive substances (NPSs) has led to a growing recognition of their role as a significant public health concern, frequently associated with fatalities related to polydrug use. These substances are renowned for their ability to induce intoxication at low doses, which has led to the continuous updating of toxicological and forensic methods to improve detection and adopt new analytical standards. The comprehensive detection of NPS metabolites, some of which are still undiscovered, presents an additional analytical challenge, as do their metabolic pathways. This complicates their identification in fatal cases using standard analytical methods, potentially leading to an underestimation of their actual prevalence in toxicological results. Furthermore, the interpretation of analytical results is hindered by the absence of data on PM blood levels and the specific contributions of NPS to causes of death, exacerbated by the lack of knowledge of whether the PMR phenomenon influences them. This paper presents a comprehensive review of the literature on post-mortem cases involving various NPS, categorized according to classifications by the United Nations Office on Drugs and Crime (UNODC) and the European Union Drugs Agency (EUDA). These categories include cathinones, phenylethylamines, arylalkylamines, phencyclidine-type substances, phenmetrazines, piperazines, phenidates, aminoindanes, LSD-like NPSs, tryptamines, fentanyl analogs, designer benzodiazepines, synthetic cannabinoids, and nitazenes. This review covers not only postmortem blood levels but also the stability of the substances studied, the methods of analysis, and attempts to shed some light on the PMR phenomenon. This review used various key terms, such as PMR, NPS, and the names of previously categorized substances and drug analyses across multiple peer-reviewed journals and databases, including Scopus, Google Schoolar, Springer, PubMed, and Wiley Online Library. In addition, references from retrieved articles were examined to identify additional relevant research. Interpreting post-mortem toxicological results is complex and lacks definitive guidelines, requiring a nuanced understanding of its challenges and potential pitfalls. As a result, post-mortem toxicology is often regarded as an art. The primary aim of this review is

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to provide forensic toxicologists with a comprehensive framework to assist in the evaluation and interpretation of NPS analysis. This guide is intended to complement the existing knowledge and practices applied in forensic laboratories within the toxicological analysis of post-mortem cases.

Keywords: NPS; PMR; Postmortem concentration; Cardiac-to-peripheral blood (C/P) ratios; Liver-to-peripheral blood (L/P) ratios; Stability; Cardiac blood concentrations; Peripherical blood concentrations

1. Introduction

During an autopsy, the forensic toxicologist attempts to identify any legal or illegal drug use prior to death and determine how it may have contributed to the cause of death. However, for many years, it has been understood that the results obtained from analyzing various samples of the body, such as blood, may not accurately reflect the nature or concentration of substances present at the time of death. In the deceased, the concentration and composition of drugs in the blood and organs of the body change depending on the location and timing of sampling. PRM describes these changes, which are influenced by events at the cellular, tissue, and organ levels as well as by the characteristics of the drugs themselves. Therefore, the concentration and type of drugs found during an autopsy depend on factors like the location of the sample, the time elapsed since death, movement between organs, metabolism, postmortem degradation, and the compound's chemical properties [1,2].

The phenomenon of PMR refers to the post-mortem study of how drugs (psychoactive substances) migrate from organs, particularly the lungs, liver, heart muscle, or gastrointestinal tract, into the bloodstream after death. The highest concentrations are found in the heart and central vessels blood. For this reason, a central-blood-to-peripheral-blood ratio (C/P) is typically used to determine postmortem susceptibility. Another proposed approach is a liver-to-peripheral-blood ratio (L/P); so, samples of central blood, peripheral blood, and liver are often collected to calculate both the C/P and L/P ratios [3]. A C/P ratio greater than 1 is often indicative of postmortem redistribution [1,4,5], whereas an L/P ratio greater than 20 suggests a propensity for significant PMR, and ratios below 5 indicate no propensity for PMR [6]. PMR can change the drug composition in the body of a deceased person, sometimes significantly, compared to the levels before death. Enzymes or bacterial activity during the postmortem period may continue to metabolize these drugs. The decomposition process can also produce new compounds such as ethyl alcohol, hydrogen sulfide, or gamma-aminobutyric acid (GHB).

Therefore, it is crucial to consider PMR during sampling at autopsy, the subsequent analytical procedures, and result interpretation.

This comprehensive postmortem review of NPSs, classified by structural families, aims to contribute to the scientific field by facilitating the analysis and understanding of these substances and their structural analogs.

1.1. Drug Properties That Determine Postmortem Redistribution

Not all drugs are equally affected by the PMR phenomenon because it largely depends on their chemical and pharmacokinetic properties. These properties determine the compound's distribution through the organs and tissues after consumption and, subsequently, its behavior after death. The key properties involved are lipophilicity, pKa, the volume of distribution, and plasma and tissue protein binding. The PMR phenomenon primarily affects lipophilic alkaline drugs with a high volume of distribution, a strong affinity for tissue proteins, and low plasma protein binding.

The volume of distribution (Vd) is a concept used in pharmacology to describe how a drug is distributed in the body in relation to plasma concentration. It is calculated by dividing the amount of drug present in the body by the plasma concentration and is

expressed in liters per kilogram (L/kg). Compounds with high volume-of-distribution (Vd) values above 3 L/kg are the most susceptible to being affected by PMR [1,2]. Vd directly correlates with the compound's lipophilicity and affinity towards plasma and tissue proteins. Drugs that are lipophilic and easily diffuse through cell membranes tend to accumulate in adipose and muscle tissue, as well as in specific intracellular components, resulting in high Vd values. The same is true for compounds with a high affinity for tissue proteins, especially in the lungs. Conversely, drugs with high plasma protein binding and low affinity for tissue proteins have low Vd values close to their plasma concentration. These substances are minimally affected by the PMR phenomenon.

Most drugs are weak acids or bases and are normally found in both ionized and non-ionized forms in equilibrium, which depends on the medium's pH. In life, the intracellular pH ranges between 6.8 and 7.2, slightly more acidic than the blood's pH, which is approximately 7.4. The pKa of basic lipophilic drugs enables them to be more soluble in lipids at a physiological pH. This facilitates their absorption by tissues and their distribution and accumulation in tissues through binding to proteins. For this reason, these compounds have a high Vd value and will be significantly affected by PMR due to the pH changes in the corpse.

1.2. Postmortem Changes: General Considerations

After death, the immediate consequence is the cessation of oxygen supply to the tissues, which leads to the halting of cellular respiration and the production of ATP [7,8]. This causes the beginning of anaerobic metabolism and the production of lactic acid, which leads to an immediate decrease in pH. Basic drugs with high pKa values become more ionized in acidic conditions and are trapped within the cells. Additionally, the lack of ATP stops the sodium–potassium pump associated with the ATPase enzyme, resulting in an increase in the intracellular concentration of sodium and subsequent cellular edema. The process continues with the destruction of organelles, and lysosomal enzymes are released into the cytoplasm, where they digest the membranes, including the plasma membrane. When the cell collapses, the basic drugs trapped within the cells are released into the extracellular space, producing deposits that move by passive diffusion along a concentration gradient.

After death, enzyme activity gradually decreases over time. However, succinic dehydrogenase and cytochrome oxidase in the myocardium, kidney, and liver continue to function in the first 24–48 h after death. For the cytochrome P450 system enzyme, activity gradually decreases to 90% within the first 48 h. Plasma cholinesterase can maintain its activity even during the storage of blood samples. This is a relevant factor if storage conditions are not adequate. The metabolism of compounds in the PM interval is another factor that contributes to altering the concentration of drugs and their metabolites and must be considered in the interpretation of results.

There are certain organs where drugs tend to accumulate due to their characteristics and functions, acting as reservoirs from which the compounds are released during PMR. These organs include the lungs, liver, myocardium, and gastrointestinal tract (GI). Lung tissue is a site where large amounts of lipophilic alkaline compounds accumulate. After death, they are released and reach the heart cavities through the pulmonary veins. The liver often exhibits higher drug concentrations due to its role in metabolism and elimination. The primary pathway for drug redistribution from the liver is through the hepatic vein into the inferior vena cava and then into the cardiac chambers. Direct diffusion from the liver to adjacent organs has minimal significance. Some compounds may accumulate in the myocardium and be released into the blood within the cardiac cavities, central vessels, and subclavian vein, leading to increased concentration compared to the moments just before death. After being taken orally or intranasally, drugs result in high concentrations in the stomach and GI. After death, drugs can move to the cardiac chambers, aorta, left lung, and left lobe of the liver. Aspirated stomach contents may also lead to drug transfer into the lungs. After death, blood can still move through the blood vessels, which helps to move

drugs around the body. This movement happens because of changes in pressure caused by rigor mortis in the early stages and by gasses in the later stages of decomposition. Drug movement within the thoracic cavity can result in elevated concentrations in central blood sources, which may not accurately represent the drug levels at the time of death. This could potentially lead to incorrect conclusions in toxicological analyses.

Drug concentrations can be significantly affected by bacteria involved in the putrefaction process. Normally, the human body is a sterile environment, except for areas such as the gastrointestinal tract, lungs, oral cavity, and vagina. In the hours leading up to death, the body's resistance to infection diminishes, increasing the likelihood of pathogenic bacterial invasion. After death, bacteria from the gastrointestinal tract decompose and are released, invading surrounding tissues and the bloodstream. Bacterial activity degrades proteins in the blood, releasing protein-bound drugs, increasing the concentration of free drugs, and causing blood to coagulate, thus further altering its composition and drug concentrations. The dehydration that comes with putrefaction also increases the concentration of drugs in an analytical matrix. The presence of bacterial activity resulting from putrefaction may also lead to the metabolism of certain drugs, such as nitrobenzodiazepines, or the production of compounds like ethyl alcohol.

2. Methodology

This review has been conducted using the following databases: PubMed (National Center for Biotechnology Information, U.S. National Library of Medicine, Maryland, USA), Scopus (Elsevier's abstract and citation database of peer-reviewed literature, Amsterdam, The Netherlands), Google Scholar (Google, Inc. California, USA), Wiley Online Library (John Wiley & Sons, New Jersey, USA), and Springer (Springer Nature, Berlin, Germany).

Initially, a search using the following query: ("new psychoactive substances" OR "new psychoactive substance" OR "synthetic drug" OR "synthetic drugs" OR "designer drug" OR "designer drugs") AND ("death" OR "deaths" OR "fatal poisoning" OR "fatal intoxication") AND ("postmortem" OR "distribution") was performed in PubMed, Wiley and Google Scholar [9] as can be seen in workflow diagram, see Figure 1. This search returned approximately 563 publications in PubMed, 603 in Wiley, and 2910 in Google Scholar. By refining these results using inclusion criteria—specifically, publication years 2000–2024, presence of toxicological data in blood samples (AND ("blood" OR "level")), and removal of duplicates—we narrowed the selection to about 300 studies. Further filtering for studies that reported postmortem levels in cardiac or peripheral blood as well as liver concentrations reduced the pool to 43 relevant publications.

To refine the search further, specific drug classes—such as "designer benzodiazepines", "tryptamines", "synthetic cathinones", "synthetic opiates", etc.—were incorporated into the search algorithm. This expanded search also included Scopus and Springer databases, ultimately yielding 94 works that met the specified criteria.

NPSs have been categorized into eleven groups according to their chemical structure, as detailed in the subsections of Section 3, Results and Discussion. This classification helps to clarify their chemical properties, such as pKa and logP, which are valuable for understanding their potential tendency for PMR. Based on our experience [10] and the current classifications by UNODC and EUDA [11,12], the chemical structures of these groups are presented in Supplementary Table S1, which includes the following:

- **Phenylethylamines (PEAs)**
  - **Alpha and phenyl-substituted phenylethylamines.**
    - "Classical phenylethylamines derivatives", "DOX series", "2C-X series", "NBOMes" and "benzofuranethylamines type".
    - Aminoindanes.
    - Diarylalkylamines—Diphenidines.
  - **Cathinones (β-oxo-substituted phenethyl-amines).**

- **Phenmetrazines.**
- **Piperazines.**
- **Phenidates.**
- **Arylcyclohexylamines (phencyclidines).**
- **Lysergamides.**
- **Tryptamines.**
- **Designer benzodiazepines.**
- **Synthetic opioids.**
- **Nitazenes.**
- **Synthetic cannabinoids.**

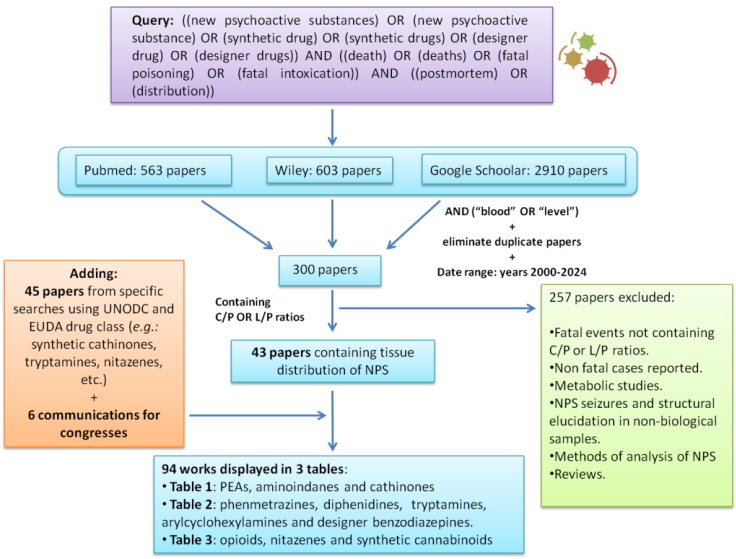


Figure 1. Schematic representation of the bibliographic workflow used. In purple the initial hypothesis of the text to be reviewed or query performed. In blue the flow of texts and manuscripts pre-selected and reflected in the text. In green texts discarded in the selection process, in red texts added ad-hoc in the initial selection process.

Each of the 94 selected papers has been thoroughly reviewed, and summaries are provided in a series of tables throught the text.These tables categorize NPSs by chemical structure based on the previously mentioned groups and outline the details of each case, including age, sex, cause of death, and postmortem interval (PMI). Additionally, they include samples collected during autopsy, pretreatment methods, analytical techniques, detected postmortem levels, calculated C/P and L/P ratios, and co-occurring substances and metabolites, as well as reference numbers and publication years, all organized in columns for easy reference.

The remaining articles identified in the initial search were also reviewed, as they provide valuable insights into the physicochemical properties, stability, analytical methods, metabolism, and postmortem levels in a single blood type (typically femoral) for various NPS. These findings will be discussed throughout the document.

3. Results and Discussion

For each family of NPS, a brief monograph is provided regarding physical and chemical properties, comparing them to PMR studies associated with their classical counterparts, and assess their stability across various studies. Additionally, postmortem levels in fatal intoxications will be reviewed from studies not included intables due to the absence of cardiac blood samples. Finally, we will discuss the C/P and L/P ratios provided in the relevant tables, which are derived from the 94 selected studies. The most reliable blood sample for accurately reflecting drug concentrations at the time of death is femoral blood. It

is recommended to collect both femoral and cardiac blood samples, as well as liver wedges, to calculate the C/P and L/P ratios, respectively [13]. However, some of the reviewed publications have used blood from subclavian, iliac, and carotid sources for comparison with cardiac blood to establish C/P ratios. The summary tables will indicate the origin of the blood whenever specified in the studies.

3.1. Phenylethylamines

3.1.1. Alpha and Phenyl-Substituted Phenylethylamines

3.1.1.1. "Classical Phenylethylamines Derivatives", "DOx Series", "2C-X Series", "NBOMes" and "Benzofuranethylamines Type"

Phenylethylamines (PEAs) share a common core structure consisting of a phenyl ring and an ethylamine chain. Phenethylamines refer to a class of substances with documented psychoactive and stimulant effects and include classical drugs of abuse like amphetamine, methamphetamine, and MDMA.

Some notable subcategories include the following: **amphetamine-type NPS** (known for their stimulant effects, e.g., 4-chloro-amphetamine), **cathinones** (known for their stimulating effects and discussed separately in Section 3.2, e.g., mephedrone), **2C series** (known for their psychedelic effects, e.g., 2C-B, 2C-P), NBOMes (*N*-methoxybenzyl-derivatives known for their potent hallucinogen activity, **e.g.,** 25I-NBOMe), and DOx series (the general chemical formula is 2,5-dimethoxy-4-X-amphetamine, where "X" represents a halogen atom, known for their psychedelic effects and their long-lasting effects, e.g., DOC, DOB). See Figure 2.

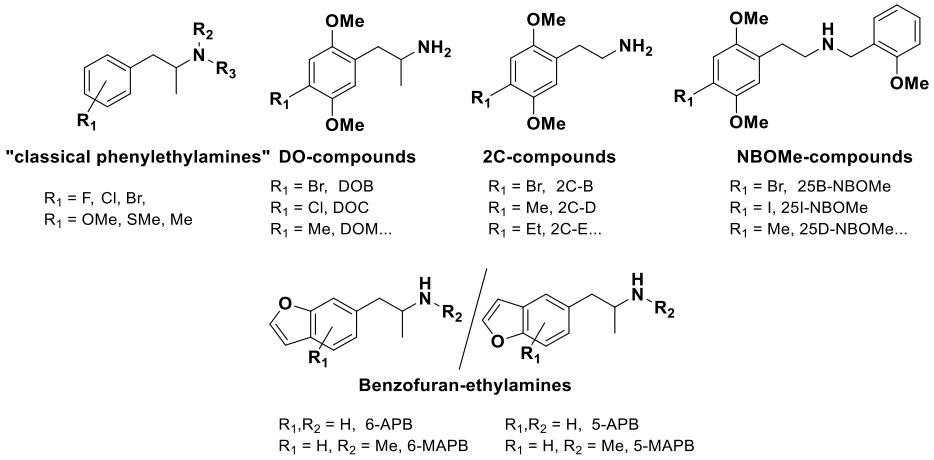


Figure 2. Chemical structures of phenylethylamine-type new psychoactive substances.

Amphetamine and methamphetamine, the classical representatives of this group, are basic drugs with a pKa of 9.9, log P values of 1.85 and 2.23, and a volume of distribution (Vd) ranging from 3.2 to 5.6 L/kg and 3.0 to 7.0 L/kg, respectively. Their fractions bound to plasma proteins (Fb) are 0.16 and 0.10–0.20, respectively [14]. MDMA is also a basic drug with a pKa of 8.7, a log P of 1.65, a Vd of 3–7 L/kg, and an Fb of 0.65 [14]. These chemical properties indicate that phenylethylamines are likely to undergo PMR. For example, amphetamine has exhibited PMR, with central-to-peripheral blood (C/P) ratios averaging 2.4 (range, 1.2–5.6) in 20 cases [15] and 2.1 (range, 0.67–6.6) in 75 cases [16]. Methamphetamine may also display PMR, with C/P ratios averaging 1.6 (range, 0.9–2.4) in 18 cases [17], 1.9 (range, 1.0–3.8) in 5 additional cases [18], and 2.1 (range, 1.2–5.0) in a series of 20 deaths [14]. MDMA has shown potential for PMR as well, with C/P ratios averaging 2.4 (range, 1.0–3.9) in 5 fatal cases [18] and 2.6 (range, 0.91–7.4) in 39 cases [16]. MDA also exhibited PMR, with a C/P ratio averaging 2.3 (range, 0.82–5.3) in 35 deaths [16].

Although peripheral blood is considered less prone to PMR, the peripheral blood concentrations of amphetamines do not necessarily reflect the blood concentrations of

these compounds at the time of death, according to previous studies. A postmortem concentration increase of approximately 1.5 times was observed for both methamphetamine and amphetamine. Similarly, in the case of MDMA and MDA, the concentrations in various bodily fluids collected during autopsy (including femoral blood) were higher in all postmortem samples compared to antemortem blood levels across five cases [18,19].

The stability of MDA, MDMA, and MDEA in serum, blood, water, and urine was studied [20]. No significant degradation in any of the analytes was detected in urine and water samples over the 21-week period at any temperature. Analytes could no longer be detected in serum and blood samples stored at room temperature after 17 and 5 weeks, respectively, and when stored at 4 °C after a period of 13 weeks, they were not detected. The stability of seven amphetamine-type stimulants in urine was studied over a period of 201 days at room temperature, refrigerated (4–8 °C), and frozen (−20 °C). All samples stored were stable during the studied period [21].

Regarding the stability of NBOMes series, 25B-, 25C-, 25D-, 25E-, 25G-, 25H-, and 25I-NBOMe were studied [22] in whole blood stored at room temperature, 4, and −20 °C for a period of up to 180 days. After 15 days, 25B-, 25C-, 25I-, and 25E-NBOMe concentrations decreased approximately 40%. Except for 25H-NBOMe, all were deemed unstable when stored at 4 °C. When stored at −20 °C, all NBOMes studied remained stable for 180 days. Regarding the 2-C compounds, most of them were stable at 4 °C overnight and −20 °C for a week. Reduced stability was seen however for 2C-N, 2C-B-fly, and 2C-E [23].

- **Postmortem Levels in Fatal Case Reports**

In a series of 6 fatalities resulting from the ingestion of a combination of 4-fluoroamphetamine (4-FA) and 25C-NBOMe, femoral blood samples collected during autopsy showed median concentrations of 345 ng/mL (range, 21–682) for 4-FA and 3.2 ng/mL (range, 1.4–12) for 25C-NBOMe [24]. 2-Fluoromethamphetamine (2-FMA) was detected in postmortem peripheral blood samples from 2 reported cases, with levels of 6.31 and 6.9 ng/mL. Other toxicological findings in these cases included the presence of the synthetic opioid AH-7921, synthetic cathinone 3-MMC, and codeine [25–27]. 4-Methylthioamphetamine (4-MTA) was identified in two fatal intoxication cases, with postmortem blood concentrations of 4700 ng/mL and 8380 ng/mL, respectively [28,29].

A 23-year-old woman died after inhaling an unknown substance, suspected to be "synthetic LSD" [30]. Toxicological analysis revealed a combined drug toxicity involving 25I-NBOMe, 25H-NBOMe, and 25C-NBOMe, with concentrations of 28 ng/mL, 1 ng/mL, and 0.7 ng/mL, respectively. Additionally, methylamphetamine, tetrahydrocannabinol, and promethazine were detected. In another study, 25B-NBOMe was detected in postmortem blood at levels of 66.5 and 661 ng/mL [31].

5-(2-Aminomethylpropyl)benzofuran (5-MAPB) was found in postmortem peripheral blood at a concentration of 2880 ng/mL. Additionally, 5-(2-Aminopropyl)benzofuran (5-APB) was detected at 129 ng/mL, alongside THC, 11-hydroxy-THC, and THC-COOH [32]. In another fatal case [33], 5-MAPB, along with alpha-methyltryptamine (AMT), was implicated as a contributing factor to the cause of death. The peripheral-blood concentration of 5-MAPB was measured at 101 ng/mL. In another fatality, (5-APB) was detected in peripheral blood at a concentration of 4970 ng/mL. Toxicological analysis also revealed the presence of other psychoactive substances, including methiopropamine (MPA) at 1041 ng/mL, methylphenidate (MPH) at 44 ng/mL, and 3,4-methylendioxypyrovalerone (MDPV) metabolite, as well as aripiprazole, mirtazapine, tropatepine, and oxazepam [32]. 5/6-APB was detected in postmortem blood samples from 10 cases, with a median concentration of 1460 ng/mL and a range of 110 to 4190 ng/mL [34]. 6-(2-Aminopropyl)-2,3-dihydrobenzofuran (6-APDB) was found in postmortem femoral blood at a level of 600 ng/mL [35]. 5-(2-Ethylaminopropyl)benzofuran (5-EAPB) was identified in a fatal intoxication case along with 5,6-methylenedioxy-2-aminoindane (MDAI) [36]. The blood concentrations were 6450 ng/mL for 5-EAPB and 2090 ng/mL for MDAI. *N*-Methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (MBDB) was identified in postmortem blood samples from 2 reported cases, with concentrations of 435 ng/mL and 1200 ng/mL. Both

cases also contained the *N*-demethylated metabolite (BDB) and amphetamine [37]. *para*-methoxymethamphetamine (PMMA) was identified in blood samples from 5 reported deaths, with a median concentration of 2180 ng/mL and a range of 1640 to 3300 ng/mL [34]. Additionally, *para*-methoxyamphetamine (PMA) was detected in 13 postmortem cases, with a median blood concentration of 1500 ng/mL and a range of <625 to 29,200 ng/mL [34]. Designer amphetamine *para*-methoxyethylamphetamine (PMEA) was found in a case report [38] where a 27-year-old male had drunk an unidentified liquid sold as a recreational drug on the internet; its postmortem blood concentration was 12,200 ng/mL. 4-Methylamphetamine (4-MA) was identified in 6 reported death cases [34], with a median postmortem blood concentration of 3050 ng/ mL, ranging from 580 to 5800 ng/mL.

DOB (2,5-Dimethoxy-4-bromoamphetamine) was implicated in two overdose cases involving men who consumed a new "hallucinogen LSD-like" designer drug [39]. One individual survived, while the other succumbed to the effects six days later. The serum concentrations of DOB were 13 ng/mL in the surviving patient and 19 ng/mL in the deceased patient. The differing body masses of the two men significantly influenced the outcomes of their intoxication.

- **Tissue Distribution and PMR**

The current literature provides limited insights into the PMR of phenylethylamine derivatives across different tissues. Table 1 summarizes the tissue distribution observed in reviewed cases involving PEA-type new NPSs. The substances in the Table exhibit pKa values similar to those of classic amphetamine derivatives (pKa between 9 and 10). In terms of lipophilicity, only the NBOMe derivatives show higher lipophilicity. The addition of the NBOMe group to the parent compounds significantly enhances their lipophilicity, brain permeability, and cytotoxic effects.

MDDM and MDDA [40] exhibit a C/P blood ratio of 4.6, suggesting PMR similar to that seen with the analog MDMA. Case series involving NBOMe compounds [41–43], which analyzed both central and peripheral blood, report C/P ratios of 1 or lower. Only one case of a 2C-X substance was found, specifically 2C-T-7, which showed a C/P ratio of 0.5 [44]. Aminoalkylbenzofuran derivatives, including 5-APB, 6-APB, and 2-MAPB, exhibited C/P ratios above 1, indicating a tendency toward PMR in some case reports, as detailed in Table 1 [45–47].

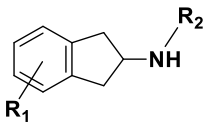
These findings indicate that, like traditional drugs such as amphetamine, methamphetamine, and MDMA, PEA-type NPSs may also experience PMR. However, the instability of NBOMe and 2C-X derivatives in blood likely accounts for the low levels detected in cardiac blood, resulting in C/P ratios of 1 or less. Studies of 25B-NBOMe in animals [48] show that concentrations in the cardiac blood increased by more than 10-fold at 6 h postmortem and present a tendency to accumulate primarily in the lung. It is important to note that fatal concentrations of these compounds in peripheral blood are inherently low, with prior studies also confirming their instability. Special care should be taken regarding the postmortem interval, the condition of the body at the time of recovery, and the storage of samples, which should consistently be at −20 °C to prevent losses.

To conclude, it could be said that aminoalkylbenzofurans, like their classical counterparts, amphetamine, methamphetamine, and MDMA, tend to follow PMR. Nevertheless, additional postmortem studies are needed to better understand the factors affecting the distribution of these substances in various tissues.

3.1.1.2. Aminoindanes

Aminoindanes are structurally rigid analogs of phenylethylamines, characterized by a closed ring system. This core structure can be modified in various ways, such as adding functional groups to the aromatic ring, incorporating a methylenedioxy bridge, or *N*-alkylation. 2-Aminoindane (2-AI) is a mild central nervous system (CNS) stimulant with slight bronchodilator activity and strong analgesic effects. Unlike the corresponding amphetamines, some animal studies have shown that these substances do not cause long-term neurotoxicity. Aminoindanes have been explored as bronchodilator and analgesic agents

and, more recently, as neuroprotective and antipsychotic medicines. Common derivatives of the aminoindane group include: 2-AI, 5,6-methylenedioxy-2-aminoindane (MDAI), 5,6-methylenedioxy-*N*-methyl-2-aminoindane (MDMAI), 5-iodo-2-aminoindane (5-IAI), 5-methoxy-2-aminoindane (MEAI), and 5-methoxy-6-methyl-2-aminoindane (MMAI), as shown in Figure 3.



Aminoindanes

R_1,R_2 = H, 2-AI
R_1 = I, R_2 = H, 5-IAI
R_1 = H, R_2 = Me, NM-2AI
R_1 = 5,6-methylendioxy, MDAI
R_1 = 5,6-methylendioxy, R_2 = Me, MDMAI

Figure 3. Chemical structures of 2-aminoindane derivatives.

Despite being marketed as safer alternatives to conventional stimulants and entactogens, aminoindanes carry risks of acute toxicity, particularly at high doses or when combined with other substances. They act primarily on serotonin, dopamine, and norepinephrine transporters, with specific effects that vary according to their structural changes.

Like amphetamine-type derivatives, 2-AI, MDAI, MDMAI, 5-IAI, MEAI, and MMAI, they are basic drugs and present the following predicted pKa (9.64, 9.58, 9.49, 9.58, 9.64, and 9.65) and log P (1.32, 1.1, 1.62, 2.67, 1.19, and 1.68), respectively [49]. There are no relevant pharmacokinetic parameters available, like volume of distribution. Only an experimental study about MEAI exhibited a moderate Vd (0.3–1.8 L/kg) in rat [50]. *N*-Methyl-2-aminoindane (NM-2-AI) undergoes extensive metabolism in rats, producing several metabolites. The primary metabolites identified are 2-aminoindane (2-AI), along with two hydroxylated derivatives of 2-AI and four hydroxylated derivatives of NM-2-AI. These hydroxylated derivatives are excreted as glucuronide conjugates [51,52]. Rasagiline (*N*-propargyl-1(*R*)-aminoindan) is a drug used primarily in the treatment of Parkinson's disease and is hepatically metabolized to form 1-aminoindan, which may cause false-positive results with 2-AI if the laboratory does not have a proper separation method to identify both.

MDAI, 2-AI, 5-IAI, and MDAT (6,7-methylenedioxy-2-aminotetralin) showed stability in blood and plasma after 21 days at room temperature [53].

- **Postmortem Levels in Fatal Case Reports and PMR**

Regarding postmortem levels, in one case of fatal ethylphenidate poisoning, 2-AI was detected at a concentration of 0.101 mg/L. Additionally, the presence of methadone, ethanol, aripiprazole, dehydroaripiprazole, zopiclone, and sertraline was noted in the toxicological analysis [54]. In two fatalities associated with MDAI, postmortem blood levels were 26.3 and 3.3 mg/L [55]. In another documented case [36], a 28-year-old male was discovered deceased at his home, seated on the floor with his head resting on a chair. Two unidentified powders were found near his body, later identified as MDAI and 5-(2-ethylaminopropyl) benzofuran (5-EAPB or 5-MAPB). The toxicological analysis revealed significant concentrations of these substances in the blood: MDAI: 2.09 mg/L and 5-EAPB: 6.45 mg/L. Additionally, other NPSs, such as 5-methylaminopropylbenzofuran (5-MAPB) and 5-aminopropylbenzofuran (5-APB), were also detected in the bloodstream. This case highlights the presence of multiple NPSs in the individual's bloodstream, indicating recent ingestion or exposure to these substances. Such findings are critical in forensic toxicology to understand the circumstances surrounding the death and to ascertain the role these substances may have played in the fatality.

Table 1. Summary of the results found in the papers included in this review that investigated the distribution of NPS from fatal cases in relation to phenylethylamines, aminoindanes, and cathinones.

Classification	NPS	pKa	logP	Age and Sex	Cause of Death	PMI	Samples Collected	Extraction Method	Analytical Technique	Results	C/P or L/P Ratios	Other Toxicological Findings	Reference
Phenyl-substituted PEAs	MDDM or MDDA	9.90 *	2.35 *	31-year-old man	fatal MDMA overdose	Advanced state of putrefaction	b, ur, gc, bile, pericardial fluid, pleural fluid, liver, lung, kidney, muscle	LLE	LC-MS/MS	FB: 2.5 ng/mL HB: 11.6 ng/mL	C/P = 4.6	MDMA: 13,500 ng/mL	De Letter E.A. et al. (2007) [40]
	25C-NBOMe	9.05 *	3.79 *	teenager, male	Drowning	Unknown	b, ur	SPE	GC-MS: screening LC-MS/MS	PB: 2.80 ng/mL CB: 1.43 ng/mL	C/P = 0.51	THC: 15.5 ng/mL; THCCOH: 56.0 ng/mL	Morini L. et al. (2017) [41]
	25H-NBOMe	9.11 *	3.23 *							PB: 0.29 ng/mL CB: 0.13 ng/mL	C/P = 0.44		
	25I-NBOMe	9.07 *	4.59 *	19-year-old man	Skull fractures with contusions of brainstem and lacerations after falling from balcony	Unknown + 7 h (autopsy)	b, vh, ur, bil, gc, liver, brain	SPE	LC-MS/MS	PB: 0.405 ng/mL HB: 0.410 ng/mL L: 5.640 ng/g	C/P = 1.01 L/P = 13.9	---	Poklis J.L. et al. (2013) [42]
	25C-NBOMe	9.05 *	3.79 *	22-year-old man	Fatal overdose of 25C-NBOMe	12 h at hospital postingestion + 48 h (autopsy)	b, vh,ur, gc, liver	alkaline LLE	LC-QTOF: screening; LC-MS/MS (Q)	FB: 0.60 ng/mL L: 0.82 ng/g	L/P = 1.4	Amphetamine: 470 ng/mL, THC: 1.5 ng/mL, THCCOOH: 8.9 ng/mL, amiodarone: 120 ng/mL, acetominophene: 5000 ng/mL, fentanyl: 0.47 ng/mL, ketamine: 120 ng/mL, midazolam: <6 ng/mL, diazepam: 99 ng/mL, nordiazepam: 12 ng/mL, quetiapine: 13 ng/ mL	Andreasen M.F. et al. (2015) [43]
	2C-T-7	9.9 *	2.37 *	20-year-old man	Toxicity associated with 2C-T-7	90 min after insufflating + unknow h (autopsy) 1 year for analysis	b, vh,ur, liver	LLE	GC-MS, GC-NPD	FB: 100 ng/mL HB: 57 ng/mL L: 854 ng/g	C/P = 0.5 L/P = 8.5	---	Curtis B. et al. (2003) [44]
	5-APB	10.1 *	1.21 *	---, male	5-APB and 6-APB intoxication	4 days after the discovery of the corpse	b, vh, ur, gc, bile,liver, kidney, lung, muscle	PP	LC-MS/MS	FB: 850 ng/mL HB: 2400 ng/mL L: 6900 ng/g	C/P = 2.8 L/P = 8.1	---	Hofmann V. et al. (2022) [45]
	6-APB	10.1 *	1.29 *							FB: 300 ng/mL HB: 660 ng/mL L: 1600 ng/g	C/P = 2.2 L/P = 5.3		
	5-APB	10.1 *	1.21 *	20-year-old man	Acute 5-APB intoxication	Unknown + 9 h (autopsy)	b, vh, ur, gc, liver	SPE	GC-MS	PB: 2500 ng/mL CB: 2900 ng/mL L: 16,000 ng/g	C/P = 1.2 L/P = 6.4	5-APDB (presumptively identified)	McIntyre I.M. et al. (2015) [46]

Table 1. *Cont.*

Classification	NPS	pKa	logP	Age and Sex	Cause of Death	PMI	Samples Collected	Extraction Method	Analytical Technique	Results	C/P or L/P Ratios	Other Toxicological Findings	Reference
Phenyl-substituted PEAs	2-MAPB	9.4 *	1.69 *	23-year-old man	Multidrug intoxication	Unknown	b, ur, bile, gc, liver	Unknown	LC-MS/MS	FB: 7300 ng/mL HB: 16,700 ng/mL L: 22,200 ng/ g	C/P = 2.3 L/P = 3.0	2C-B: (only in urine), flephedrone: 8 ng/mL, diazepam: 20 ng/mL, nordiazepam: 10 ng/mL, temazepam: 5 ng/mL, THC: 44 ng/mL, THCCOOH: 67 ng/mL	Theofel N. et al. (2021) [47]
	2-MAPB	9.4 *	1.69 *	27-year-old male	Drug intoxication	t1 = 11 h after death t2 = 29 h after death	b, ur, bile, adipose, kidney, liver, lung, heart muscle, spleen, cerebellum	LLE	LC-MS/MS	FB: ca. 13 ng/mL HB: ca. 19 ng/mL FB: ca. 15 ng/mL HB: ca. 17 ng/mL	C/P = 1.5 C/P = 1.1	MDAI	Staeheli S.N. et al. (2017) [56]
Aminoindanes	MDAI	9.58 *	1.1 *	27-year-old male	Drug intoxication	t1 = 11 h after death t2 = 29 h after death	b,ur, bile, adipose, kidney, liver, lung, heart muscle, spleen, cerebellum frontal lobe	LLE	LC-MS/MS	FB: ca. 18 ng/mL HB: ca. 22 ng/mL FB: ca. 22 ng/mL HB: ca. 19 ng/mL	C/P = 1.2 C/P = 0.9	2-MAPB	Staeheli S.N. et al. (2017) [56]
Diaryl alkylamines	DPH	9.33 *	4.7 *	30-year-old man	Poisoning by multiple drugs	3.5 days (1.5 days after death death + 2 days autopsy)	b, ur, bile, lung,adipose, kidney, liver, ,pancreas, brain, spleen, heart muscle	QuEChERS	LC-MS/MS	FB: 715 ng/mL HB: 923 ng/mL L: 2960 ng/g	C/P = 1.3 L/P = 4.1	AB-CHMINACA (detected in adipose, kidney, liver, lung, pancreas, brain)and 5F-AMB (detected only in adipose tissue)	Hasegawa K. et al. (2014) [57]
	DPH	9.33	4.7 *	aprox 30, female	Poisoning by 3 types of cathinone drugs and diphenidine under the influence of 3 benzodiazepines and alcohol.	4 days after the estimated time of death (autopsy)	b, ur, gc	QuEChERS	GC-MS: screening LC-MS/MS (Q)	FB: 1380 ng/mL HB: 1680 ng/mL	C/P = 1.2	4-MeO-PV8: 2690 ng/mL, PV9: 743 ng/mL, 4-MeO-PV9: 261 ng/mL, triazolam: 14 ng/mL, flunitrazepam: 2 ng/mL, nitrazepam: 8 ng/mL, α-hydroxytriazolam: 22 ng/mL, 7-aminoflunitrazepam: 137 ng/mL, and 7-aminonitrazepam: 826 ng/mL, alcohol: 1.52 mg/mL	Kudo K. et al. (2015) [58]

Table 1. *Cont.*

Classification	NPS	pKa	logP	Age and Sex	Cause of Death	PMI	Samples Collected	Extraction Method	Analytical Technique	Results	C/P or L/P Ratios	Other Toxicological Findings	Reference
Cathinones	3-MMC	7.97 *	1.76 *	32-year-old man	3-MMC intoxication	Unknown	b, vh, ur, bile	SPE	GC-MS, HPLC-DAD; GC-MS/MS	PB: 249 ng/mL CB: 609 ng/mL	C/P = 2.4	---	Bottinelli C. et al. (2017) [59]
	Mephedrone	7.97 *	1.76 *	50-year-old man	Mephedrone fatal intoxication in a subject with existing cardiovascular disease	48 h after death (autopsy)	b, ur, bile, liver, lung, kidney, hair	PP+SPE	LC-MS/MS	FB: 1088 ng/mL HB: 1632 ng/mL L: 1080 ng/g	C/P = 1.5 L/P = 1.0	Cocaine: 52 ng/mL and benzoylecgonine: 994 ng/mL	Palazzoli F. et al. (2021) [60]
	Normephedrone	8.07 *	1.24 *							FB: 47.1 ng/mL HB: 50.2 ng/mL L: 9.5 ng/g	C/P = 1.1 L/P = 0.2		
	Mephedrone-M (dihydro-)	9.36 *	1.87 *							FB: 15.5 ng/mL HB: 49.2 ng/mL L: 169.2 ng/g	C/P = 3.2 L/P = 10.9		
	Methedrone	8.00 *	1.15 *	NA	NA	NA	b, ur	SPE	LC–Q-TOF-MS	IB: 70 ng/mL AB: 79 ng/mL	C/P = 1.1	---	Glicksberg L. et al. (2018) [3]
	4-MEC	8.0 *	2.1 *	35-year-old man	4-MEC intoxication	Unknown	b, vh, bile, gc	LLE	GC-MS/MS	PB: 14,600 ng/mL CB: 43,400 ng/mL	C/P = 2.9	Hydroxyzine: 160 ng/ mL	Braham M.Y. et al. (2021) [61]
	MPHP	7.7 *	3.78 *	39-year-old man	Non-specific and moderate asphyxic syndrome with bilateral pulmonary and pericerebral edema	Death 24 and 72 h before the body-lift examination + 2 days (autopsy)	b, ur, nasal swabs, gastric liquid and bile	LLE	GC-MS: screening LC-MS/MS	FB: 47 ng/mL HB: 97 ng/mL	C/P = 2	Alcohol in CB: 0.5 g/L THC: 1.4 ng/mL, THCCOOH: 6.6 ng/mL, 4′-carboxi-PHP (metabolite)	Benedicte, L. et al. (2020) [62]
	N-ethyl-4′-methyl-norpentedrone	8.03 *	3.01 *							FB: 1.6 ng/mL HB: 3.5 ng/mL	C/P = 2.2		
	Pyrovalerone	7.69 *	3.36 *	33-year-old man	Autoerotic asphyxia	Unknown	b, vh, bile brain, liver	LLE	LC-MS/MS	FB: 42 ng/mL HB: 59 ng/mL L: 124 ng/g	C/P = 1.4 L/P = 2.9	Pentylone, amphetamine <50 ng/mL, MDPV (urine)	Marinetti L.J. et al. (2013) [63]
	3,4-DMMC	7.98 *	2.25 *	26-year-old man	Acute poisoning caused by NPS	Unknown	b, ur, gc, liver	PP	GC-MS: screening LC-MS/MS	FB: 500 ng/mL HB: 1500 ng/mL L: 20,000 ng/g	C/P = 3.0 L/P = 40.0	Heliomethylamine, MDMA, fluorofentanyl, THC	Strehmel N. et al. (2017) [64]
	4-methoxy-PV8 (4-MeO-PV8)	7.72 *	3.58 *	aprox 30, male	Acute poisoning by "bath salts"containing acetylfentany and 4-methoxy-PV8	Unknown	b, ur, gc	QuEChERS	GC-MS: screening LC-MS/MS (Q)	FB: 389 ng/mL HB: 960 ng/mL	C/P = 2.5	Acetylfentanyl: 153 ng/mL, 7-aminonitrazepam: 200 ng/mL, Phenobarbital: 7700 ng/mL, methylphenidate: 30 ng/mL, chlorpromazine (<LOQ) and risperidone (<LOQ)	Yonemitsu K. et al. (2016) [65]

Table 1. *Cont.*

Classification	NPS	pKa	logP	Age and Sex	Cause of Death	PMI	Samples Collected	Extraction Method	Analytical Technique	Results	C/P or L/P Ratios	Other Toxicological Findings	Reference
Cathinones	4-MeO-PV8	7.72 *	3.58 *	aprox 30, female	Poisoning by 3 types of cathinone drugs and diphenidine under the influence of 3 benzodiazepines and alcohol.	4 days after the estimated time of death (autopsy)	b, ur, gc	QuEChERS	GC-MS: screening LC-MS/MS (Q)	FB: 2690 ng/mL LHB: 5680 ng/mL RHB: 5360 ng/mL	C/P = 2.1	DPH: 1380 ng/ mL, triazolam: 14 ng/mL, flunitrazepam: 2 ng/mL, nitrazepam: 8 ng/mL, α-hydroxytriazolam: 22 ng/mL, 7-aminoflunitrazepam: 137 ng/mL, and 7-aminonitrazepam: 826 ng/mL, alcohol: 1.52 mg/mL	Kudo K. et al. (2015) [58]
	4-MeO-PV9	7.73 *	4.0 *							FB: 261 ng/mL LHB: 799 ng/mL RHB:641 ng/mL	C/P = 3.0		
	PV9	7.69 *	4.1 *							FB: 743 ng/mL LHB: 3130 ng/mL RHB: 2790 ng/mL	C/P = 4.2		
	Methylone	7.92 *	1.06 *	NA	NA	NA	b, ur	SPE	LC–Q-TOF-MS	FB: 2 ng/mL AB: 3 ng/mL	C/P = 1.5	---	Glicksberg L. et al. (2018) [3]
	Methylone	7.92 *	1.06 *	NA	NA	NA	b, ur, liver	SPE	LC–Q-TOF-MS	SB: 20 ng/mL AB: 48 ng/mL L: 61 ng/g	C/P = 2.4 L/P = 3.1	---	
	Methylone	7.92 *	1.06 *	NA	NA	NA	b	SPE	LC–Q-TOF-MS	FB: 4 ng/mL AB: 14 ng/mL	C/P = 3.4	---	
	Methylone	7.92 *	1.06 *	NA	NA	NA	b, ur	SPE	LC–Q-TOF-MS	FB: 3 ng/mL AB: 20 ng/mL	C/P = 6.1	---	
	Methylone	7.92 *	1.06 *	NA	NA	NA	b, liver	SPE	LC–Q-TOF-MS	IB: 28 ng/mL AB: 119 ng/mL L: 1110 ng/g	C/P = 4.2 L/P = 40	---	
	Methylone	7.92 *	1.06 *	23-year-old man	Methylone intoxication	Unknown	b, vh, uri, gc, liver	LLE	GC-MS	FB: 560 ng/mL HB: 580 ng/mL L: 880 ng/g	C/P = 1.0 L/P = 1.6	Alcohol: 0.03 g/dL, midazolam: 20 ng/mL, fentanyl: 2.1 ng/mL, lorazepam: 29 ng/mL (hospital)	Pearson J.M. et al. (2013) [66]
				23-year-old man	Cardiac arrest	24 h after admission + unknown h (autopsy)	b, vh, uri, gc,			Iliac blood: 840 ng/mL HB: 1000 ng/mL	C/P = 1.2	Dextromethorphan (<0.02 ng/mL), cotinine, caffeine and lidocaine	
	Methylone	7.92 *	1.06 *	21-year-old man	Mixed drug intoxication	19 h approximately	b, vh, ur, bile, liver, heart, kidney	LLE	GC-MS	FB: 500 ng/mL L: 1470 ng/g	L/P = 2.9	Oxymorphone: 106 ng/ mL, ethanol: 130 mg/dL, cocaine (traces in urine)	Shimomura E.T. et al. (2016) [67]
	Methylone	7.92 *	1.06 *	19-year-old man	Cardiac arrest associated with methylone	Unknown	b, ur, bile, liver, spleen, kidney	LLE	GC-MS	PB: 670 ng/mL CB: 740 ng/mL L: 1800 ng/g	C/P = 1.1 L/P = 2.7	---	Cawrse B.M. et al. (2012) [68]

Table 1. *Cont.*

Classification	NPS	pKa	logP	Age and Sex	Cause of Death	PMI	Samples Collected	Extraction Method	Analytical Technique	Results	C/P or L/P Ratios	Other Toxicological Findings	Reference
Cathinones	Methylone	7.92 *	1.06 *	58-year-old man	Acute methylone intoxication	Unknown	b, hv, ur, gc, bile, lier	SPE	GC-MS	PB: 11,900 ng/mL CB: 15,300 ng/mL L: positive	C/P = 1.4	---	Lightfoot C. et al. (2014) [69] (abstract only)
	Butylone	7.93 *	1.54 *	Unknown	Unknown	Unknown	b, ur, liver	SPE	LC–Q-TOF-MS	IB: 8 ng/mL AB: 6 ng/mL L: 116 ng/g	C/P = 0.7 L/P = 14	---	Glicksberg L. et al. (2018) [3]
	Butylone	7.93 *	1.54 *	21-year-old man	Multi organ failure resulting from malignant serotonin syndrome	4 h hospital before deah + 24 h autops	b, liver	SPE	LC-MS/MS	FB: 20,000 ng/mL L: 33,000 ng/g	L/P = 1.6	---	Rojek S. et al. (2012) [70]
	MDPV	7.63 *	2.65 *	NA	NA	NA	b, ur	SPE	LC–Q-TOF-MS	FB: 80 ng/mL AB: 80 ng/mL	C/P = 1	---	Glicksberg L. et al. (2018) [3]
	MDPV	7.63 *	2.65 *	47-year-old man	Multiple drug intoxication; accident	Unknown	b, vh, ur, bile, liver, CSF, brain	LLE	GC-MS: screening LC-MS/MS	PB: 162 ng/mL HB: 280 ng/mL L: 3720 ng/g	C/P = 1.7 L/P = 22.9	Oxymorphone: 43 ng/mL, diazepam: 313 ng/L, nordiazepam: 494 ng/mL, temazepam: 33 ng/mL, diphenhydramine: 80 ng/g	Marinetti L.J. et al. (2013) [64]
				43-year-old female	Multiple drug intoxication; accident	Unknown	blood, brain, liver, bile, vh, CSF	LLE	GC-MS: screening LC-MS/MS	PB: 18 ng/mL HB: 28 ng/mL L: 52 ng/g	C/P = 1.6 L/P = 2.9	Fentanyl: 8 ng/mL, norfentanyl: <1 ng/mL, trazodone: 540 ng/mL, gabapentin: 6800 ng/mL, norvenlafaxine: 220 ng/mL, tramadol: <50 ng/mL, diazepam: 301 ng/mL, nordiazepam: 281 ng/mL	
				32-year-old man	Natural	Unknown	blood, brain, liver, bile, vh, CSF	LLE	GC-MS: screening LC-MS/MS	PB: 36 ng/mL HB: 56 ng/mL L: 668 ng/g	C/P = 1.6 L/P = 18.6	Citalopram: 200 ng/mL, trazodone: 50 ng/mL, JWH-122: positive, JWH-210: positive	
				32-year-old man	Hanging, suicide	Unknown	b, vh, ur, bile, liver, CSF, brain	LLE	GC-MS: screening LC-MS/MS	PB: 102 ng/mL HB: 133 ng/mL L: 256 ng/g	C/P = 1.3 L/P = 2.5	Chlorpheniramine: <50 ng/mL, dextromethorphan: 60 ng/mL	
				51-year-old man	Multiple drug intoxication	Unknown	b, vh, liver	LLE	GC-MS: screening LC-MS/MS	FB: 129 ng/mL L: 388 ng/g	L/P = 3.0	Bupropion/Metab: 24/216 ng/mL, morphine: 40 ng/mL, oxycodone, 20 ng/mL, diazepam: 303 ng/mL, nordiazepam: 229 ng/mL	

Table 1. *Cont.*

Classification	NPS	pKa	logP	Age and Sex	Cause of Death	PMI	Samples Collected	Extraction Method	Analytical Technique	Results	C/P or L/P Ratios	Other Toxicological Findings	Reference
Cathinones	MDPV	7.63 *	2.65 *	24-year-old man	Hanging, suicide	Unknown	b, vh, bile, liver, brain	LLE	GC-MS: screening LC-MS/MS	FB: 640 ng/mL L: 6080 ng/g	L/P = 9.5	---	Marinetti L.J. et al. (2013) [64]
	Ethylone	7.94 *	1.4 *	NA	NA	NA	b, ur, liver	SPE	LC–Q-TOF-MS	IB: 780 ng/mL AB: 872 ng/mL L: 170	C/P = 1.1 L/P = 0.2	---	Glicksberg L. et al. (2018) [3]
	Ethylone	7.94 *	1.4 *	NA	NA	NA	b, ur	SPE	LC–Q-TOF-MS	IB: 10 ng/mL HB: 5 ng/mL	C/P = 0.5	---	
	Ethylone	7.94 *	1.4 *	NA	NA	NA	b, ur	SPE	LC–Q-TOF-MS	FB: 19 ng/mL CB: 19 ng/mL	C/P = 1.0	---	
	Ethylone	7.94 *	1.4 *	NA	NA	NA	b	SPE	LC–Q-TOF-MS	FB: 298 ng/mL AB: 2740 ng/mL	C/P = 9.2	---	
	Ethylone	7.94 *	1.4 *	NA	NA	NA	b, ur, liver	SPE	LC–Q-TOF-MS	FB: 69 ng/mL AB: 193 ng/mL L: 116 ng/g	C/P = 2.8 L/P = 1.7	---	
	Ethylone	7.94 *	1.4 *	NA	NA	NA	b, ur	SPE	LC–Q-TOF-MS	IB: 59 ng/mL AB: 146 ng/mL	C/P = 2.5	---	
	Ethylone	7.94 *	1.4 *	30-year-old man	Mixed ethylone, heroin, and alprazolam intoxication	24-after discovery of the corpse (autopsy)	b, vh, ur, gc, liver	PP+SPE	GC-MS	PB: 390 ng/mL CB: 380 ng/mL L: 1400 ng/g	C/P = 0.9 L/P = 3.6	Morphine: 50 ng/mL, alprazolam: <50 ng/mL, THC: <1 ng/mL, THCCOOH: 3.6 ng/mL, naproxen	McIntyre I.M. et al. (2015) [71]
	Pentylone	7.94 *	1.96 *	NA	NA	NA	b, ur	SPE	LC–Q-TOF-MS	IB: 160 ng/mL AB: 323 ng/mL	C/P = 2.0	---	Glicksberg L. et al. (2018) [3]
	N-Ethyl pentylone	7.96 *	2.30 *	NA	Natural	Unknown	b, vh, ur, bile, liver, kidney	LLE	GC-NPD GC-MS	SB: 130 ng/mL HB: 130 ng/mL L: >500 ng/g	C/P = 1.0 L/P = 3.8	---	Poston A. et al. (2017) [72] (abstract only)
		7.96 *	2.30 *	NA	Mixed-drug intoxication	Unknown	b, vh, liver, kidney	LLE	GC-NPD GC-MS	FB: 300 ng/mL HB: 390 ng/mL L: 430 ng/g	C/P = 1.3 L/P = 1.4	Fentanyl and Meth adone	
		7.96 *	2.30 *	NA	Mixed-drug intoxication	Unknown	b, liver	LLE	GC-NPD GC-MS	SB: 40 ng/mL HB: 50 ng/mL L: 180 ng/g	C/P = 1.2 L/P = 4.5	Morphine, Furanyl fentanyl, 4-FIBF, DPF	
		7.96 *	2.30 *	NA	*N*-ethylpentylone intoxication	Unknown	b, vh, ur	LLE	GC-NPD GC-MS	FB: 13 ng/mL HB: 16 ng/mL	C/P = 1.2	Morphine, Furanyl fentanyl, 4-FIBF, DPF	

Table 1. *Cont.*

Classification	NPS	pKa	logP	Age and Sex	Cause of Death	PMI	Samples Collected	Extraction Method	Analytical Technique	Results	C/P or L/P Ratios	Other Toxicological Findings	Reference
	Pentedrone α-PVP	7.98 * 7.67 *	2.18 * 2.87 *	28-year-old man	Multiple drug toxicity associated with α-PVP and pentedrone use	Unknown	b, gc, liver, kidney, brain	LLE	LC-MS/MS	FB: 8.794 ng/mL L: 100.044 ng/g FB: 901 ng/mL L: 2610 ng/g	L/P = 11.2 L/P = 2.9	OH-α-PVP	Sykutera M. et al. (2015) [73]
	4-MPD	8.00 *	2.67 *	57-year-old man	Combination of drugs of abuse (4-MPD and cocaine), plus benzodiazepine	24-after discovery of the corpse (autopsy)	b, vh, ur, bile, and nasal swabs	PP+ SPE	GC-MS	FB: 1285 ng/mL CB: 1128 ng/ mL	C/P = 0.9	Cocaine: 66 ng/mL, benzoylecgonine: 2084 ng/mL, sildenafil: <1 ng/mL, bromazepam: 140 ng/mL, nevirapine (positive)	Cartiser N. et al. (2021) [74]
	N-Propyl-pentedrone	8.02 *	3.01 *	29-year-old woman	Acute respiratory distress	Unknown	b, vh, liver, kidney, brain	LLE	LC-MS/MS	PB: 3200 ng/mL L: 5900 ng/g	L/P = 1.8	---	Majchrzak M. et al. (2018) [75]
	α-PBP	7.66 *	2.46 *	21-year-old man	Subarachnoid hemorrhage	2 days after death (autopsy)	b, ur, gc, CSF, liver, lung, kidney, spleen, pancreas	QuEChERS	LC-MS/MS	FB: 55.2 ng/mL HB: 68.3 ng/mL L: 82.6 ng/g	C/P = 1.2 L/P = 1.5	Caffeine: 349 ng/mL, acetominophen: 752 ng/mL	Wurita A. et al. (2014) [76]
Cathinones	α-PVP	7.67 *	2.87 *	NA	NA	NA	b, ur	SPE	LC–Q-TOF-MS	FB: 30 ng/mL AB: 15 ng/mL	C/P = 0.5	---	Glicksberg L. et al. (2018) [3]
	α-PVP	7.67 *	2.87 *	NA	NA	NA	b	SPE	LC–Q-TOF-MS	IB: 8 ng/mL AB: 8 ng/mL	C/P = 1	---	
	α-PVP	7.67 *	2.87 *	NA	NA	NA	b, ur	SPE	LC–Q-TOF-MS	IB: 234 ng/mL AB: 218 ng/mL	C/P = 0.9	--	
	α-PVP	7.67 *	2.87 *	NA	NA	NA	b, ur	SPE	LC–Q-TOF-MS	IB: 2 ng/mL AB: 3 ng/mL	C/P = 1.5	---	
	α-PVP	7.67 *	2.87 *	NA	NA	NA	b, ur	SPE	LC–Q-TOF-MS	IB: 21 ng/mL AB: 41 ng/mL	C/P = 1.9	---	
	α-PVP	7.67 *	2.87 *	NA	NA	NA	b, liver	SPE	LC–Q-TOF-MS	FB: 208 ng/mL AB: 224 ng/mL Liver: <60 ng/g	C/P = 1.1 L/P = <0.3	---	
	α-PVP	7.67 *	2.87 *	NA	NA	NA	b, liver	SPE	LC–Q-TOF-MS	IB: 1020 ng/mL AB: 1090 ng/mL Liver: <60 ng/g	C/P = 1.1 L/P = <0.1	---	
	α-PVP	7.67 *	2.87 *	NA	NA	NA	b, ur, liver	SPE	LC–Q-TOF-MS	FB: 44 ng/mL AB: 58 ng/mL Liver: <60	C/P = 1.3 L/P = <1.4	---	
	α-PVP	7.67 *	2.87 *	NA	NA	NA	b, ur	SPE	LC–Q-TOF-MS	FB: 84 ng/mL HB: 79 ng/mL	C/P = 0.9	---	

Table 1. *Cont.*

Classification	NPS	pKa	logP	Age and Sex	Cause of Death	PMI	Samples Collected	Extraction Method	Analytical Technique	Results	C/P or L/P Ratios	Other Toxicological Findings	Reference
Cathinones	α-PVP	7.67 *	2.87 *	28-year-old man	Intoxication with α-PVP with subsequent cardiac arrest	<5 h after death (autopsy)	b, ur, gc, liver, kidney	LLE	LC-MS/MS	PB (carotid): 174 ng/mL L: 190 ng/g	L/P = 1.1	---	Potocka-Banaś B. et al. (2017) [77]
	α-PVP	7.67 *	2.87 *	41-year-old man	α-PVP poisoning	40 h after death (autopsy)	b, ur, gc, liver, kidney	SPE	LC-MS/MS	FB: 654 ng/mL LHB: 442 ng/mL RHB: 458 ng/mL L: 681 ng/g	C/P = 0.7 L/P = 1.0	---	Hasegawa K. et al. (2014) [78]
	OH-α-PVP (dihydrometab)	9.07 *	2.98 *							FB: 364 ng/mL LHB: 311 ng/mL RHB: 298 ng/mL L: 1080 ng/g	C/P = 0.8 L/P = 2.9		
	α-PiHP	7.68 *	3.20 *	37-year-old man	Fatal intoxication with α-PiHP	~48 h after death (autopsy)	b, vh, gc, bile, CSF, liver, brain, spleen, lung, adipose, heart,kidney, thyroid, pancreas	LLE	LC-MS/MS	FB: 2377 ng/mL HB: 1133 ng/mL L: 504 ng/g	C/P = 0.5 L/P = 0.2	---	Wachholz P. et al. (2023) [79]
	OH-α-PiHP (dihydrometab)	9.08 *	3.31 *							FB: 223 ng/mL HB: 28 ng/mL L: 310 ng/g	C/P = 0.1 L/P = 1.4		
	Flephedrone (4-FMC)	7.90 *	1.44 *	23-year-old man	Multidrug intoxication	Unknow	b, ur, bile, gc, liver	Unknown	LC-MS/MS	FB: 8 ng/mL HB: 3 ng/mL L: 3 ng/g	C/P = 0.4 L/P = 0.4	2-MAPB: 7300 ng/mL, 2C-B (urine), diazepam: 20 ng/mL, nordiazepam: 10 ng/mL, temazepam: 5 ng/mL, THC: 44 ng/mL, THCCOOH: 67 ng/mL	Theofel N. et al. (2021) [47]
	3-Methyl-4-fluoro-PVP	7.62 *	3.52 *	30-year-old man	Fluoro-methyl-PVP toxicity	Unknown	b, vh	SPE	GC-MS	FB: 26 ng/mL HB: 30 ng/mL	C/P = 1.1	---	Hobbs J.M. et al. (2022) [80]
	4-FMC	7.90 *	1.44 *	male, in his 20 s	Acute poisoning with a combination of 4-FMC, 4-MeO-α-PVP, 4-F-α- PVP, and PV8	48–60 h after death (autopsy)	b	SPE	LC-LIT-MS; GC-MS	FB/HB: 397/365 ng/mL	C/P = 0.9	---	Mochizuki A. et al. (2021) [81]
	4-MeO-α-PVP	7.72 *	2.75 *							FB/HB: 383/449 ng/mL	C/P = 1.2		
	4-F-α-PVP	7.62 *	3.03 *							FB/HB: 127/145 ng/mL	C/P = 1.1		
	PV8	7.68 *	3.71 *							FB/HB: 167/218 ng/mL	C/P = 1.3		

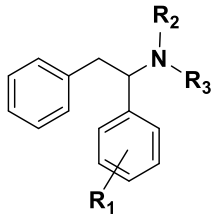
Samples: PB: peripheral blood, FB: femoral blood, IB: iliac blood, SB: subclavian blood, CB: central blood, HB: heart blood, RHB: right heart blood, LHB: left heart blood, AB: aorta blood, L: liver, ur: urine, vh: vitreous humor, SA: serum antemortem, SC: serum cardiac, SF: subcutaneous fat, IS: injection site.**Analytical techniques**: GC-NPD: gas chromatography coupled to nitrogen–phosphorus detector, GC-MS: gas chromatography coupled to mass spectrometry; GC-MS/MS: gas chromatography coupled to tandem mass spectrometry, LC-Q-TOF-MS: liquid chromatography quadrupole–time of flight mass spectrometry, LC-MS/MS: liquid chromatography–tandem mass spectrometry, LC-LIT-MS: liquid chromatography–linear ion trap mass spectrometry.**Extraction methods:** LLE: liquid–liquid extraction, SPE: solid-phase extraction, QuEChERS: quick, easy, cheap, effective, rugged, and safe, PP: protein precipitation. **Substances:** 2-MAPB: 1-(1-Benzofuran-2-yl)-*N*-methylpropan-2-amine, 25B-NBOMe: 2-(4-Bromo-2,5-dimethoxyphenyl)-*N*-(2-methoxyphenyl)methyl-ethanamine,

2C-T-7: 2-(2,5-Dimethoxy-4-(n)-propylthio)phenylethylamine, 25C-NBOMe: 2-(4-Chloro-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine, 25H-NBOMe: 2-(2,5-Dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine, 25I-NBOMe: 2-(4-Iodo-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine, 3-MMC: 3-methylmethcathinone, 3,4-DMMC: 3,4-dimethylmethcathinone, 4-F-α-PVP: 4-fluoro-alpha: 4-Fluoro-alpha-pyrrolidinovalerophenone, 4-FMC (flephedrone): 4-Fluoromethcathinone, 4-MEC: 4-methylethcathinone, 4-Methoxy-PV8: 1-(4-Methoxyphenyl)-2-(pyrrolidin-1-yl)heptan-1-one, 4-MeO-PV9: 1-(4-Methoxyphenyl)-2-(1-pyrrolidinyl)-1-octanone, 4-MPD: 4-Methylpentedrone, 5-APB: 5-(2-Aminopropyl)benzofuran, 6-APB: 6-(2-Aminopropyl)benzofuran, DPH (diphenidine): 1-(1,2-Diphenylethyl)piperidine, MDAI: 5,6-Methylenedioxy-2-aminoindane, MDDM/MDDA: Methylenedioxy-*N*,*N*-dimethylamphetamine, MDMA: methylendioxymethamphetamine, MDPV: 3,4-Methylenedioxypyrovalerone, PV8: 1-phenyl-2-(1-pyrrolidinyl)-1-heptanone, PV9: 1-phenyl-2-(1-pyrrolidinyl)-1-octanone, α-PBP: Alpha-pyrrolidinobutiophenone, α-PiHP: Alpha-pyrrolidinoisohexanophenone, α-PVP: Alpha-pyrrolidinovalerophenone. * Values of pKa and logP predicted using ChemDraw Professional 15.0 © Copyright 1998-2015 Perkin-Elmer Informatics Inc.

In terms of PMR, as shown in Table 1, only a single case of tissue distribution has been documented [56]. Samples were collected during hospitalization (6 h before death), upon admission to the mortuary (11 h after death), and during autopsy (29 h after death). No significant postmortem concentration changes were observed for MDAI, as C/P ratios at 11 and 29 h remained close to 1 in both periods of time. This suggests that, in this case, MDAI did not undergo significant postmortem redistribution. However, the results from a single observation cannot be generalized, and more observations are needed, especially considering that its closest structural analog, MDMA, does exhibit postmortem redistribution PMR.

3.1.1.3. Diarylalkylamines—Diphenidines

Diphenidines refer to a class of chemical compounds that are derivatives or analogs of diphenidine. Diphenidine itself is a dissociative anesthetic belonging to the diarylethylamine class. It acts primarily as an NMDA receptor antagonist, similar to other dissociative drugs, such as ketamine and PCP (phencyclidine). The main representants of the series are 1-(1,2-diphenylethyl)piperidine (diphenidine, DPH), *N*-Ethyl-(1,2-diphenyl)ethanamine (ephenidine, EPE), 2-methoxphenidine (2-MXP), 3-methoxphenidine (3-MXP) and 2-Cl-diphenidine (2-Cl-DPH), see Figure 4.



Diarylalkylamines

R_1 = H, R_2,R_3 = -$(CH_2)_2$-, Diphenidine (DPH)
R_1 = H, R_2 = H, R_3 = Et, Ephenidine (EPE)
R_1 = OMe, R_2,R_3 = -$(CH_2)_2$-, MXP
R_1 = 2-Cl, R_2,R_3 = -$(CH_2)_2$-, 2-Cl-DPH

Figure 4. Chemical structures of diphenidine derivatives.

Similar to other phenylethylamines, diarylalkylamines are basic drugs. The predicted pKa values for DPH, EPE, 2-MXP, 3-MXP, and 2-Cl-DPH are 9.33, 9.55, 9.13, 9.24, and 8.97, respectively, while the log P values are 4.7, 5.11, 4.58, 4.58, and 5.26, respectively [49]. These log P values indicate that they are highly lipophilic substances due to the presence of aromatic rings. No pharmacokinetic data are currently available.

DPH is extensively metabolized through mono- or di-hydroxylation, *N*-dealkylation, keto oxidation, and conjugation, with hydroxylation potentially occurring on any of the three rings of the compound [82]. This complexity makes analysis challenging, and these metabolites should be included as biomarkers of substance use in analytical procedures.

- **Postmortem Levels in Fatal Case Reports and PMR**

Regarding DPH toxicity, 17 overdose victims had serum DPH concentrations averaging 88 ng/mL (range, 2–262) [83]. In a reported case, a 53-year-old male was found dead in his apartment. An open package of a branded herbal blend labeled "Heart Shot BLACK" was found next to the body; DPH heart blood level was 12 ng/mL, and a synthetic cannabinoid, 5F-ADB, was found as well [84]. Two cases were reported with cardiac and peripheral blood analysis, as reported in Table 1. The first one [57] exhibited C/P and L/P ratios of 1.3 and 4.1, with synthetic cannabinoids AB-CHMINACA and 5F-AMB present in several tissues as well. The second one [58] showed a C/P ratio of 1.2, consistent with the previous case reported; 4-Methoxy PV8, PV9, and 4-Methoxy PV9 were also found in biological samples. These findings suggest that diphenidine and probably related compounds may suffer low–moderate PMR, but more data are needed to validate this claim.

On the other hand, 2-MXP overdosage serum or plasma levels ranged between 187 and 409 ng/mL [83,85]. Three adult men were found dead after an acute overdosage with 2-MXP; they exhibited postmortem femoral blood MXP levels of 1360, 2000, and 24,000 ng/mL [86].

3.1.2. Cathinones (β-oxo-Substituted Phenethyl-Amines)

Cathinones (β-oxo-substituted phenethyl-amines) and its derivatives are closely related to the phenethylamine family. Often referred to as "bath salts", they are a class of drugs chemically similar to the monoamine alkaloid cathinone found in the khat plant (*Catha edulis*), which is native to East Africa and the Arabian Peninsula. Synthetic cathinones are usually sold as a white or brown crystalline powder and are often labeled 'not for human consumption' to avoid regulation. Cathinone itself is a β-keto-amphetamine or 2-amino-1-phenyl-1-propanone. Cathinone itself is a β-keto-amphetamine or 2-amino-1-phenyl-1-propanone. This backbone can undergo various modifications, leading to a wide range of synthetic cathinone derivatives, like primary (*N*,*N*-dihydrocathinones), secondary (*N*-alkylcathinones), and tertiary (*N*,*N*-dialkylcathinones and pyrrolidine derivatives), and different types of aromatic ring substituents (methylenedioxy, chlorine, fluorine, methyl, etc.), see Figure 5.

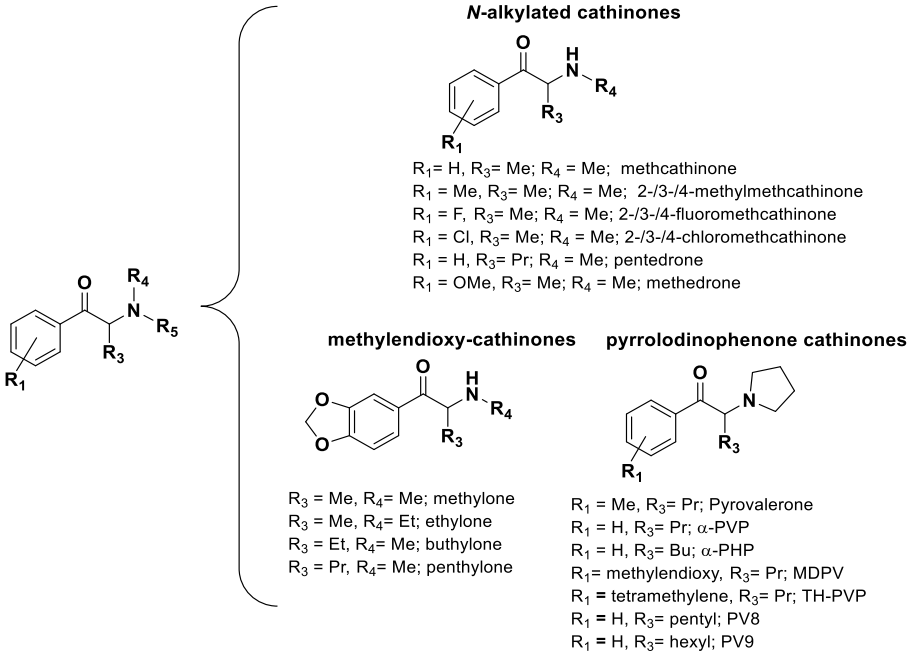


Figure 5. Chemical structures of synthetic cathinones.

Synthetic cathinones share common pharmacological effects with amphetamine, leading to an increased release of monoamines such as dopamine (DA), noradrenaline (NE), and serotonin (5-HT). These neurotransmitters are believed to play a role in the euphoric and rewarding effects of various drugs of abuse.

Regarding its chemical properties, they are basic drugs, like amphetamines. Some of the pKa and log P have been consulted in bibliography, and others have been simulated [14,49].

Physicochemical properties, including Vd, pKa, and protein binding, are unknown for many synthetic cathinones. Only some of them are known as 3-methylmethcathinone (3-MMC), which has a Vd = 8 L/kg [87]. Given the structural similarity and chemical properties between methamphetamine, MDMA, and cathinones, and the fact that PMR has been observed in amphetamine tissue distribution studies [8,15,18,88–93], it is expected that methyl- and methylenedioxy-cathinones will exhibit some form of PMR. In general chemical and pharmacokinetic properties seem to indicate that they are susceptible to PMR.

The stability of cathinones, influenced by the type and position of substituents on the aromatic ring, can be explained by the Hammet equation [94]. Substituents that are electron-withdrawing (e.g., nitro, cyano) generally increase the rate or equilibrium constant for reactions where the transition state or the final state is stabilized by negative charge, and vice versa for electron-donating substituents (e.g., methoxy, amino). Methylendioxy derivatives are more stable than other types of aromatic substituents. Regarding the position of aromatic substituents, meta-substituted cathinones exhibited higher decomposition rate constants compared to para-substituted ones. For fluoromethcathinone (FMC), it was shown that depending on the substitution on the aromatic ring, the order of stability is 4 (*para*) > 3 (*meta*) > 2 (*ortho*). It is presumed that oxidants such as dissolved oxygen contribute to this decomposition, as the addition of antioxidants like *L*-ascorbic acid or sodium sulfite had suppressive effects. Tertiary amines appeared to be more stable due to resistance to oxidative deamination, unlike secondary aliphatic amines, which typically undergo oxidative deamination. Combining all the observations made, a schematic figure of general cathinone stability is displayed in Figure 6.

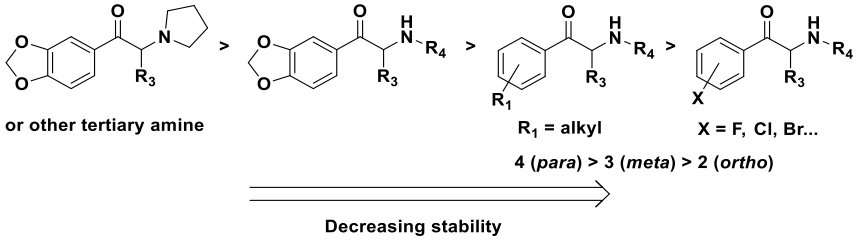


Figure 6. Stability of synthetic cathinones.

Studies have found that synthetic cathinones with a secondary amine group and no methylenedioxy substitution on the aromatic ring are highly unstable [95]. At 20 °C, their degradation half-lives ranged from 22 h to 7 days but decreased to 8–29 h at 32 °C. Refrigeration at 4 °C extended their half-lives, though 3-FMC was notably unstable. Stability is also affected by pH and additives [96], with samples being more stable in acidic environments and with fluoride citrate additives. Storing alkaline or urine samples at room temperature decreases stability, though preservatives can help prevent degradation [97–99].

Recently, metabolite profile of several synthetic cathinones has been proposed [100], reduction in the β-keto group constituted one of the main metabolic transformation of cathinones. Parent analytes containing halogen, such as 4-chloro-ethcathinone (4-CEC), 4-chloro-alpha-pyrrolidinopropiophenone (4-Cl-α-PPP), 4-chloro-alpha-pyrrolidinovalerophenone (4-Cl-α-PVP), and 4-fluoro-pyrrolidinohexanophenone (4-F-PHP), are characterized by extreme instability, but marked stability differences are observed for their respective dihydrometabolites in all storage conditions, making them potentially better biomarkers for synthetic cathinones use [101,102]. Post-mortem interval and decomposition phenomena, alkalinizing the pH of body fluids, may lead to cathinone degradation and decrease the detected post-mortem concentration of the parent drug. Samples suspected of containing synthetic cathinones should be analyzed as soon as possible after collection to ensure accurate interpretation of toxicological results.

- **Postmortem Levels in Fatal Case Reports**

The concentrations of synthetic cathinones vary significantly in both fatal and nonfatal cases, often overlapping. Non-fatal incidents typically show concentrations up to several hundred ng/ mL, especially in hospitalized patients shortly after drug administration. Higher concentrations in deceased individuals can indicate recent drug use before death, while lower concentrations may occur if death followed extended hospital treatment. Factors like the postmortem interval and drug instability also affect concentration levels. Postmortem blood concentrations over 1000 ng/mL in individuals without tolerance may be considered lethal if synthetic cathinones are suspected as the cause of death [103].

The following cathinones exhibit the lowest concentrations in postmortem cases. In two fatal instances, the blood concentrations of 4-Cl-α-PVP were 9 and 11 ng/mL [104]. The postmortem blood concentrations of ethylcathinone ranged from 5 to 83 ng/mL in three reported cases [105]. In two fatal cases, the blood concentration of α-PBP ranged from 52 to 200 ng/mL [76,106–108]. For PV8, blood concentrations in two fatalities were at 70 and 270 ng/mL [109]. *N*-Ethylhexedrone postmortem blood concentration in five fatal cases range from 4 to 285 ng/mL [104,110]. In six reported cases where pentylone was detected, the concentrations in blood range from 5 to 340 ng/mL [3,34,111,112]. 3,4-MDPHP ranged in five fatal cases from 7 to 399 ng/mL [104,113,114]. On the opposite side are ephylone, 3,4-methylendioxypyrovalerone (MDPV), 3,4-dimethylcathinone (3,4-DMMC), methylone, α-pyrrolodinovalerophenone (α-PVP), mephedrone (4-MMC), and 3-methylmethcathinone (3-MMC), which have the highest postmortem blood concentrations of 1–50,000, <1–29,000, 53–22,000, 1 ≥ 20,000, <1–11,000, and <1–4400 ng/mL, respectively, in several reported deaths [103].

- **Tissue Distribution and PMR**

According to the case report referenced in Table 1, several cathinones—including mephedrone (4-MMC), 3-methylmethcathinone (3-MMC), 4-methylethcathinone (4-MEC), 3,4-dimethylmethcathinone (3,4-DMMC), methylone, 4-methoxy-PV8, 4′-methyl-α-pyrrolidinohexanophenone (MPHP), *N*-ethyl-4′-methylnorpentedrone (4-MEAP), *N*-propylpentedrone, and methylendioxypyrovalerone (MDPV)—show the highest C/P ratios, suggesting that these substances may be particularly prone to postmortem redistribution [3,59–72,114].

In one case, a 32-year-old man was found deceased in his home in the context of chemsex. Toxicological analysis of postmortem peripheral and cardiac blood yielded a C/P ratio of 2.4 [59]. In another instance, a 50-year-old man was discovered dead in a friend's apartment after a night of using psychoactive substances for sexual activity [60]. An autopsy performed 48 h later revealed the presence of mephedrone, normephedrone, and dihydromephedrone in both femoral and cardiac blood, with C/P ratios of 1.5, 1, and 3.2, respectively, which are consistent with the findings for 3-MMC.

In another reported case, a 35-year-old man was discovered dead and naked at home by a friend. Although the autopsy did not reveal any anatomical cause of death, toxicological analysis detected 4-MEC and hydroxyzine at therapeutic levels. The concentration of 4-MEC was measured in peripheral blood, and the C/P ratio in cardiac blood was found to be 2.9, suggesting potential postmortem redistribution (PMR) [61]. Another case report [62] identified the presence of ethanol, tetrahydrocannabinol, and two cathinones: MPHP and 4-MEAP. The C/P ratios for MPHP and 4-MEAP were 2.0 and 2.2, respectively, indicating possible PMR. A review of 43 cases [63], which included incidents such as driving under the influence, domestic violence, suicides, overdoses, accidents, drug-facilitated assaults, and homicides, found cathinones in six of these cases. In one instance, pyrovalerone was detected in both femoral and cardiac blood, resulting in a C/P ratio of 1.4. In three other cases, toxicological analysis of femoral and cardiac blood revealed MDPV, with C/P ratios ranging from 1.6 to 1.7.

In a postmortem toxicological report [64], 3,4-DMMC was identified in femoral blood and cardiac blood, indicating a C/P ratio of 3. In another case [65], 4-methoxy-PV8 was identified and quantified in both femoral and cardiac blood, yielding a C/P ratio of 2.5.

Not all observed C/P ratios of methylenedioxycathinones follow a PMR behavior similar to that of their MDMA analog (C/P = 2.7) [3]. For instance, methylone has a median C/P ratio of 1.5 (range 1–6.1) [3,66–69], and pentylone has a C/P ratio of 2 [3]. In contrast, ethylone displays a median C/P of 1.1 (range 0.5–9.2) [3,71], while butylone has a C/P ratio of 0.7 [3] and an L/P ratio of 1.6 [70]. *N*-ethylpentylone shows a median C/P of 1.2 (range 1–2) [72], and MDPV has a median C/P of 1.3 (range 0.6–1.7) [3,63], suggesting a mild tendency toward PMR.

Pentedrone had an L/P ratio of 11.2 in a reported case [73], while 4-methylpentedrone (4-MPD) has a C/P of 0.9 [74], and *N*-propyl-pentedrone recorded L/P ratios of 1.8 in an-

other case [75]. Conversely, "α"-cathinone derivatives, such as α-PBP [76], α-PVP [3,77,78], and α-PiHP [79], exhibited the lowest C/P ratios, as shown in Table 1.

Halogenated cathinones, such as methyl-Fluoro-PVP [80] and 4-FMC [81], exhibited C/P ratios of 1.1 and 0.9, respectively. However, as noted earlier, these C/P ratios may be affected by the instability of the parent drug in postmortem blood.

According to the data reported, the more stable a cathinone is and the less tendency it has to degrade, the more likely it is to undergo PMR. Their instability can result in concentration fluctuations during the storage and handling of biological samples, meaning that measured concentrations may not accurately represent the levels present at the time of blood collection. This inconsistency could lead to misleading conclusions regarding the C/P ratios of the parent cathinone. Therefore, it is highly recommended to store samples at −20 °C to prevent losses and to analyze metabolites, such as dihydrometabolites, which are much more stable, in order to establish C/P ratios and better assess potential PMR. However, we recognize the challenge posed by the lack of certified reference materials for these dihydrometabolites, which complicates this analysis.

3.2. Phenmetrazines

Phenmetrazine, a sympathomimetic drug primarily used as an appetite suppressant with effects similar to dextroamphetamine, was removed from the market due to widespread abuse. In 2013, a patent was published detailing the synthesis and potential therapeutic uses of phenmetrazine analogs, likely prompting the development of morpholine derivatives as legal alternatives. Several analogs were subsequently launched, including 2-(4-fluorophenyl)-3-methylmorpholine (4-FPM), 2-phenyl-3,6-dimethylmorpholine (3,6-DMPM), phenetrazine, 3-fluorophenetrazine, 4-methylphendimetrazine, phenmetetrazine, and viloxazine, see Figure 7.

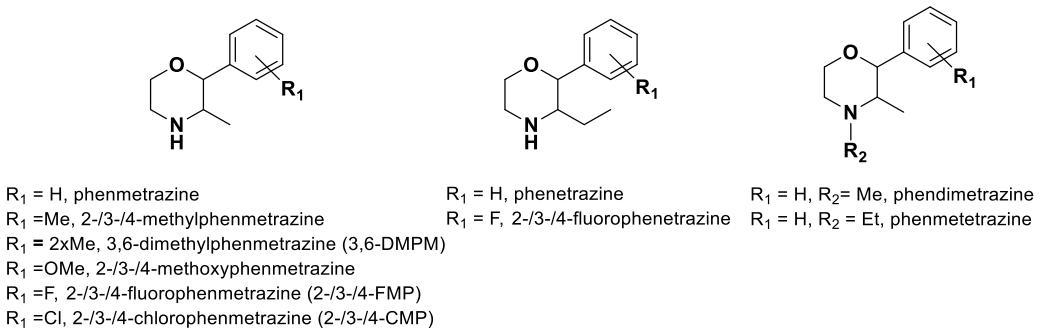


Figure 7. Chemical structures of phenmetrazines.

Phenmetrazine is a basic drug with a pKa of 8.5, a log P of 1.5, and a Fb of 0.20 [14]. Similarly, 3-fluorophenmetrazine (3-FPM) is also a basic drug, with a pKa of 7.8, a log P of 1.66, and a volume of distribution (Vd) of 5.3 L/kg [115]. Other derivatives, including 3-methylphenmetrazine (3-MPM), 3-methoxyphenmetrazine, 4-FPM, phenetrazine, 3-fluorophenetrazine, and 4-methylphendimetrazine, have predicted pKa values of 7.9, 7.94, 7.9, 7.98, 7.85, and 7.93, and log P values of 1.99, 1.37, 1.66, 1.98, 2.14, and 2.36, respectively [49]. These parameters indicate, from a theoretical point of view, that they may be predisposed to PMR.

Phenmetrazine is metabolized by *p*-hydroxylation and conjugation and also by oxidation at the 3-position in the morpholine ring to a lactam. *N*-hydroxylation may occur to a certain extent. 3-FPM is subject to a minor degree of biotransformation via *N*-oxide formation, phenolic hydroxylation, and keto oxidation and/or fission of the morpholine ring [14,115].

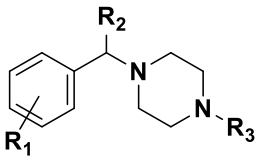
Phenmetrazine kept stable in plasma for 2 weeks at 4 °C, and it was stable in urine for 1 month at 4 °C and 3 months at −20 °C [116,117].

- **Postmortem Levels in Fatal Case Reports and PMR**

Phenmetrazine intoxication was the cause of death of a 17-year-old boy after intravenous use of the drug, with a blood concentration of 4 mg/L, a liver concentration of 5 mg/kg, and a urine concentration of 24 mg/L [118]. For 3-FPM, doses of 20–60 mg taken orally or injected are reported to produce effects that last 2–8 h. The mean serum 3-FPM levels were 303 ng/mL (range, 2.7–1416 ng/mL) in 15 adults treated for poisoning as described in the literature [119]. Acute intoxication and lethal concentrations of 3-FPM were reported, with levels in blood ranging from 0.5 to 4.0 mg/L for acute intoxication and 0.1–4.9 mg/L for lethal cases, indicating a significant overlap between acute and lethal concentrations [120–123]. Regarding PMR of phenmetrazine, a pair of cases has been reported (see Table 2). The first one resulted in a C/P ratio of 1.08 [124]. In the second one, a 27-year-old man was found dead in his room, with the estimated time of death ranging between 4 and 10 days prior [125]. Toxicological analysis revealed a 3-FPM in femoral blood and heart blood, resulting in a C/P ratio of 0.9, similar to the previously reported case. This consistency in C/P ratios suggests minimal potential for postmortem redistribution of 3-FPM and possibly its derivatives, although this conclusion is only extracted from only two cases.

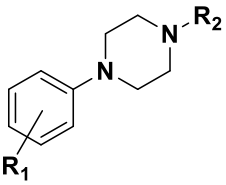
3.3. Piperazines

Piperazine designer drugs are a category of synthetic substances that have emerged on the illicit market since the late 1990s. The most common derivatives include [126] 1-benzylpiperazines (1-benzyl-4-methylpiperazine (MBZP), 1-benzylpiperazine (BZP), 1-(4-fluorobenzyl)-piperazine (FBZP) and 1,4-dibenzylpiperazine (DBZP)) and 1-phenylpiperazines subtype (1-(3-chlorophenyl)-4-(3-chloropropyl)piperazine (mCPCPP), 1-(3/4-chlorophenyl) piperazine (m/p-CPP), 1-(4-fluorophenyl)piperazine (pFPP), 1-(2/4-methoxyphenyl) piperazine (o/p-MeOPP), 1-(3/4-methylphenyl)piperazine (m/p-MPP), and 1-(3-trifluoromethylphenyl) piperazine (TFMPP)), see Figure 8. Initially, piperazines were present on the market, but they were very quickly replaced by cathinones.



1-benzylpiperazines

R_1, R_2, R_3 = H, Benzylpiperazine (BZP)
R_2, R_3= H, R_1 = Me, 1-Benzyl-4-methylpiperazine (MBZP)
R_2, R_3 = H, R_1 = F, 1-(4-Fluorobenzyl)-piperazine (FBZP)
R_1, R_2 = H, R_3 = CH_2Ph, 1,4-dibenzylpiperazine (DBZP)



1-phenylpiperazine

R_1 = Me, R_2 =H,1-(3/4-Methylphenyl)piperazine (m/p-MPP)
R_1 = Cl, R_2 =H, 1-(3-Chlorophenyl)piperazine (mCPP)
R_1 = F, R_2 =H, 1-(4-Fluorophenyl)piperazine (pFPP)
R_1 = OMe, R_2 =H, 1-(2/4-Methoxyphenyl)piperazine (o/p-MeOPP)
R_1 = CF_3, R_2 =H, 1-(3-Trifluoromethylphenyl)piperazine (TFMPP)

Figure 8. Chemical structures of piperazines.

Table 2. Summary of the results found in the papers included in this review that investigated the distribution of NPS from fatal cases in relation to phenmetrazines, phenidates, arylcyclohexylamines, tryptamines, and designer benzodiazepines.

Classification	NPS	pKa	logP	Age and Sex	Cause of Death	PMI	Samples Collected	Extraction Method	Analytical Technique	Results	C/P or L/P Ratios	Other Toxicological Findings	Classification
Phenmetrazines	3-FPM	7.8	1.66 *	34-year-old man	Multiple drug-toxicity	Unknown	b, vh, ur	LLE	GC/MS LC–MS/MS	FB: 2400 ng/mL CB: 2600 ng/mL	C/P = 1.1	Amitriptyline: 440 ng/mL, nortriptyline: 290 ng/mL, methamphetamine: <40 ng/mL, amphetamine:70 ng/mL, diazepam: 200 ng/mL, nordiazepam: 180 ng/mL, temazepam: 11 ng/mL, flubromazolam: positive, delorazepam: positive, U-47700: 360 ng/mL	Ellefsen K.N. et al. (2017) [124]
	3-FPM	7.8	1.66 *	27-year-old man	Positional asphyxia promoted by poly-drug intoxication arising from designer benzodiazepines and the presence of synthetic stimulants	≥ 4 and ≤10 days before autopsy	b, pericardial fluid, ur, bile, gc, CSF, liver, kidney, lung, muscle, brain	ITSP-SPE®	HPLC-DAD LC–MS/MS	FB: 10 ng/mL HB: 9 ng/mL L: 160 ng/g	C/P = 0.9 L/P = 16	Pyrazolam: 28 ng/mL, diclazepam: 1 ng/L, delorazepam: 100 ng/mL, lormetazepam: 6 ng/mL, lorazepam: 22 ng/mL, 2-FMA (urine), 2-FA (aprox 28 ng/mL), methiopropamine (aprox 2.2 ng/mL), amphetamine (aprox 21), diphenhydramine (urine).	Lehmann S. et al. (2019) [125]
Phenidates	MPH	8.9	1.5 *	62-year-old woman	acute MPD intoxication	Unknown (known to be alive 3 days prior to death)	b, vh, liver	SPE	GC-NPD, GC-MS	PB: 1100 ng/mL CB: 980 ng/mL L: 3690 ng/g	C/P = 0.9 L/P = 3.3	---	Cantrell F.L. et al. (2014) [127]
Arylcyclohexyl amines	2-oxo-PCE	7.4 *	2.24 *	52-year-old man	Multidrug intoxication	Unknown	b, ur, gc, bile, liquor	SPE	LC-MS/MS	FB: 375 ng/mL HB: 2159 ng/mL L: 6137 ng/g	C/P = 5.8 L/P = 16.4	Venlafaxine: 200 ng/mL, *O*-desmethylvenlafaxine: 50 ng/mL, *N*-desmethylvenlafaxine: 40 ng/mL	Theofel N. et al. (2019) [128]
	4-MeO-PCP	9.4 *	4.01 *	54-year-old man	Acute mixed drug intoxication	Unknown + 25 h after he was found (autopsy)	b, liver	LLE	LC-MS/MS	FB: 8200 ng/mL CB: 14,000 ng/mL L: 120,000 ng/g	C/P = 1.7 L/P = 15	4-Hydroxy-*N*-methyl-*N*-ethyltryptamine, venlafaxine (510 ng/mL), olanzapine (420 ng/mL), lorazepam (50 ng/mL) and hydroxyzine (detected) in the PB	McIntyre I.M. et al. (2015) [129]

Table 2. *Cont.*

Classification	NPS	pKa	logP	Age and Sex	Cause of Death	PMI	Samples Collected	Extraction Method	Analytical Technique	Results	C/P or L/P Ratios	Other Toxicological Findings	Classification
	5-API or 5-IT	10.3 *	1.22 *	25-year-old man	Toxic effects of 5-IT.	Unknown	b, vh, ur, gc	LLE	HPLC-DAD	FB: 800 ng/mL HB: 1200 ng/mL	C/P = 1.5	MDMA: <80 ng/mL	Seetohul L.N. et al. (2013) [130]
				25-year-old woman	Toxic 'cocktail effects' of the drugs		b, vh, ur			FB: 900 ng/mL HB: 2600 ng/mL	C/P = 2.9	Methylone, not quantitated, 6-APB in FB: <80 ng/mL	
				22-year-old man	Toxic effects of the drugs, with the role of epilepsy being indeterminate		b, vh, ur			FB: 400 ng/mL HB: 800 ng/mL	C/P = 2.0	6-APB: 200 ng/mL in FB	
				25-year-old woman	'Cocktail effect' of the drugs		b, vh, ur			FB:300 ng/ mL HB: 400 ng/ mL	C/P = 1.3	Amphetamine: 400 ng/mL (FB), MDMA: 1500 ng/mL (FB), 4-methyl-*N*-ethylcathione,MDA, benzylpiperazine and 6-APB	
Tryptamines	*N*,*N*-Dipropyl tryptamine	10.06 *	3.45 *	18-year-old male	Mixed-drug intoxication	Unknown	b, vh, ur, gc, bile, liver, kidney	LLE	GC-NPD GC-MS	FB:1200 ng/mL HB: 1300 ng/mL L: 4500 ng/g	C/P = 1.1 L/P = 3.7	Bupropion: 0.08 mg/L Citalopram: 0.5 mg/L	Timko C. et al. (2019) [131] (abstract only)
	Mitragynine	7.3	1.73	24-year-old man	Mixed-drug intoxication—primarily mitragynine	An autopsy was performed 29.5 h after death	b, vh, ur, gc	PP + SPE	GC/MS	PB: 230 ng/mL CB: 190 ng/mL L: 430 ng/g	C/P = 0.8 L/P = 1.9	Venlafaxine: 1100 ng/mL,*O*-desmethylvenlafaxine: 1600 ng/mL, diphenhydramine: 450 ng/mL, mirtazapine: 240 ng/mL, ethanol 0.02%	McIntyre I.M. et al. (2015) [132]
				32-year-old	Acute mitragynine intoxication combined with cardiomegaly with left ventricular hypertrophy, with severe hepatomegaly and obesity	The autopsy was performed 50 h after death	b, vh, ur, liver, brain, gc	PP	LC-QTOF: screening LC-MS/MS	FB: 3300 ng/mL CB: 7500 ng/mL L: 42,200 ng/g	C/P = 2.3 L/P = 12.8	7-Hydroxymitragynine detected in cardiac blood	Mata D.C. et al. (2023) [133]
				NA	Acute and chronic drug and alcohol abuse	Unknown	b, vh, ur	LLE	LC-MS/MS	FB: 57 ng/mL HB: 100 ng/mL	C/P = 1.7	Mirtazapine, desmethylmirtazapine, EDDP, methadone, aloxone, atropine, acetone	Crichton M.L. et al. (2015) [134]

Table 2. *Cont.*

Classification	NPS	pKa	logP	Age and Sex	Cause of Death	PMI	Samples Collected	Extraction Method	Analytical Technique	Results	C/P or L/P Ratios	Other Toxicological Findings	Classification
Designer Benzodi-azepines	Phenazepam	2.2 – 11.2	3.57 *	NA	Adverse effects of heroin and amphetamine.	Unknown	b, vh, ur	LLE	LC-MS/MS	FB: 148 ng/mL HB: 310 ng/mL	C/P = 2.1	Paracetamol, nicotine, diazepam, nordiazepam, oxazepam, temazepam, codeine, morphine, morphine-3-glucuronide (M3G), morphine-6-glucuronide (M6G), noscapine, papaverine	Crichton M.L. et al. (2015) [134]
				NA	Chronic alcoholism	Unknown	b, vh, ur, liver, muscle, brain	LLE	LC-MS/MS	FB: 38 ng/mL HB: 41 ng/mL L: 382 ng/g	C/P = 1.1 L/P = 10.0	Dihydrocodeine, M3G, M6G, Ethanol	
				NA	Hanging	Unknown	b, vh, ur	LLE	LC-MS/MS	FB: 90 ng/mL HB: 138 ng/mL	C/P = 1.5	Citalopram, desmethylcitalopram, ethanol	
				NA	Adverse effects of heroin, methadone and buprenorphine	Unknown	b, vh, ur, liver, muscle, brain	LLE	LC-MS/MS	FB: 9 ng/mL HB: 14 ng/mL L: 125 ng/g	C/P = 1.6 L/P = 13.9	Nicotine, cotinine, levamisole, cocaine, benzoylecgonine, codeine, paracetamol, mirtazapine, caffeine, noscapine, papaverine, methadone, EDDP, fluoxetine, nordiazepam, diazepam, morphine, buprenorphine, M3G, M6G	
				NA	No anatomical cause (posible drug related)	Unknown	b, vh, ur	LLE	LC-MS/MS	FB: 310 ng/mL HB: 390 ng/mL	C/P = 1.2	Naloxone, methadone, EDDP, diazepam, nordiazepam, temazepam, ibuprofen metabolite	
				NA	No anatomical cause(possible choking on food bolus	Unknown	b, vh, ur	LLE	LC-MS/MS	FB: 164 ng/mL HB: 132 ng/mL	C/P = 0.8	Mirtazapine, desmethylmirtazapine, diazepam, nordiazepam, temazepam, ethanol	
				NA	Adverse effects of methadone and aspiration pneumonia	Unknown	b, vh, ur	LLE	LC-MS/MS	FB: 176 ng/mL HB: 194 ng/mL	C/P = 1.1	Diazepam, nordiazepam, temazepam, oxazepam, methadone, EDDP, mirtazapine, desmethylmirtazapine, gabapentin	
				NA	Adverse effects of methadone	Unknown	b, vh, ur	LLE	LC-MS/MS	FB: 71 ng/mL HB: 95 ng/mL	C/P = 1.3	Citalopram, desmethylcitalopram, methadone, EDDP, diazepam, nordiazepam	
				NA	Acuteadverse effects of methadone	Unknown	b, vh, ur	LLE	LC-MS/MS	FB: 232 ng/mL HB: 191 ng/mL	C/P = 0.8	Paracetamol, methadone, EDDP, diazepam, nordiazepam, temazepam, citalopram, desmethylcitalopram	

Table 2. *Cont.*

Classification	NPS	pKa	logP	Age and Sex	Cause of Death	PMI	Samples Collected	Extraction Method	Analytical Technique	Results	C/P or L/P Ratios	Other Toxicological Findings	Classification
Designer Benzodiazepines	Phenazepam	2.2 – 11.2	3.57 *	NA	Cor Pulmonale and adverse effects of methadone	Unknown	b, vh, ur	LLE	LC-MS/MS	FB: 80 ng/mL HB: 37 ng/mL	C/P = 0.5	Trazadone, methadone, EDDP, diazepam, nordiazepam, oxazepam, temazepam	Crichton M.L. et al. (2015) [134]
				NA	Acute and chronic adverse effects of heroin	Unknown	b, vh, ur, liver, muscle, brain	LLE	LC-MS/MS	FB: 370 ng/mL HB: 287 ng/mL L: 807 ng/g	C/P = 0.8 L = 2.2	Paracetamol, noscapine, papaverine, methadone, EDDP, nordiazepam, diazepam, temazepam, 4-MEC, codeine, morphine, M3G, M6G	
				NA	Pulmonary thromboembolism	Unknown	b, vh, ur	LLE	LC-MS/MS	FB: 97 ng/mL HB: 74 ng/mL	C/P = 0.8	Naloxone, DHC, mirtazapine, desmethylmirtazapine, EDDP, methadone, diazepam, nordiazepam, oxazepam temazepam, morphine, M3G, M6G	
				NA	Adverse effects of morphine and diazepam	Unknown	b, vh, ur, liver, muscle, brain	LLE	LC-MS/MS	FB: 18 ng/mL CB: 30 ng/mL L: 99 ng/g	C/P = 1.7 L = 5.5	Mirtazapine, desmethylmirtazapine, diazepam, nordiazepam oxazepam, temazepam, morphine, M3G, M6G, codeine	
				NA	Adverse effects of methadone	Unknown	b, vh, ur, liver, muscle, brain	LLE	LC-MS/MS	FB: 126 ng/mL HB: 181 ng/mL L: 2125 ng/g	C/P = 1.4 L = 16.8	Acetone, EDDP, methadone, diazepam, nordiazepam	
				NA	Methadone and morphine intoxication associated with aspiration bronchopneumonia	Unknown	b, vh, ur	LLE	LC-MS/MS	FB: 19 ng/mL HB: 15 ng/mL	C/P = 0.8	Morphine, M3G, M6G, methadone, EDDP, diazepam, nordiazepam	
				NA	Adverse effects of heroin, diazepam and amitriptyline	Unknown	b, vh, ur	LLE	LC-MS/MS	FB: 28 ng/mL HB: 77 ng/mL	C/P = 2.7	Paracetamol, amitriptyline, nortriptyline, 6-acetylcodeine, mirtazapine, noscapine, papaverine, diazepam, nordiazepam, oxazepam, temazepam, naloxone, codeine, morphine, M3G, M6G	
				NA	Tramadol toxicity	Unknown	b, vh, ur	LLE	LC-MS/MS	FB: 54 ng/mL HB: 67 ng/mL	C/P = 1.2	Paracetamol, tramadol, *O*-desmethyltramadol, quetiapine and metabolites, mirtazapine	

Table 2. *Cont.*

Classification	NPS	pKa	logP	Age and Sex	Cause of Death	PMI	Samples Collected	Extraction Method	Analytical Technique	Results	C/P or L/P Ratios	Other Toxicological Findings	Classification
Designer Benzodiazepines	Phenazepam	2.19–11.21	3.57 *	NA	Phenazepam and opiate toxicity	Unknown	b, ur	LLE	LC-MS/MS	FB: 960 ng/mL HB: 1430 ng/mL	C/P = 1.5	3-hydroxyphenazepam, nicotine, naloxone, promazine and metabolites, morphine, M3G, M6G, diazepam, nordiazepam, temazepam	Crichton M.L. et al. (2015) [134]
	3-hydroxyphenazepam	11.6 *	3.91 *							FB: 230 ng/mL HB: 280 ng/mL	C/P = 1.2		
	Phenazepam	2.19–11.21	3.57 *	NA	Phenazepam toxicity	Unknown	b, ur	LLE	LC-MS/MS	FB: 960 ng/mL HB: 1240 ng/mL	C/P = 1.3	3-hydroxyphenazepam, diazepam, nordiazepam, DHC, M6G, nicotine	
	3-hydroxyphenazepam	11.6 *	3.91 *							FB: 270 ng/mL HB: 321 ng/mL	C/P = 1.2		
	Flualprazolam	2.27	4.39 *	21-year-old man	CNS and respiratory depression with agonal aspiration of stomach contents	Unknown	Serum antemortem serum cardiac, b, ur, gc, liver, kidney, brain	LLE	LC-MS/MS	SA: 37 ng/mL FB: 21.9 ng/mL SC: 25.4 ng/mL	B/S = 0.86	Bromazepam: 9.4 ng/mL, amphetamine: 28 ng/mL tilidine: 86 ng/mL, nortilidine: 250 ng/mL, naloxone: 4.9 ng/mL, GHB: <2.5 mg/L, THCCOOH: <5 ng/mL	Giorgetti A. et al. (2022) [135]
	Etizolam	4.55–18.16	4.06	49-year-old man	Acute toxic effects of etizolam and caffeine	Unknown	b, ur, hair	SPE	GC/MS, HPLC-DAD	FB: 770 ng/mL HB: 2820 ng/mL	C/P = 3.7	Caffeine: 190 mg/L, THCCOOH: 192 ng/mL (urine), ethanol 0.19%	Kolbe V. et al. (2020) [136]
				27-year-old woman	Acute polydrug toxicity of fentanyl, cocaine, and ethanol with a contributing factor of methamphetamine presence	1 week	b, vh	PP	LC-MS/MS	PB: 237 ng/mL HB: 813 ng/mL	C/P = 3.4	Ethanol: 0.12 ng/mL, fentanyl: 21 ng/mL, norfentanyl: postive, alprazolam: 282 ng/mL, nordiazepam: positive, cocaine: 302 ng/mL, benzoylecgonine and cocaethylene: positive, methamphetamine: positive, diphenhydramine: positive	Gevorkyan J. et al. (2021) [137]
				34-year-old man	Mixed-drug intoxication	1 h	b	PP	LC-MS/MS	PB: 9 ng/mL HB: <5 ng/mL	C/P = <0.5	Ethanol: 0.23 ng/mL, 6-MAM: 11 ng/mL, morphine: 185 ng/mL, codeine: positive, hydrocodone: positive, diphenhydramine: positive, citalopram: positive, nordiazepa: positive, desalkylfurazepam: positive	
				34-year-old man	Mixed-drug intoxication	1 day	b, ur	PP	LC-MS/MS	PB: 15 ng/mL HB: 15 ng/mL	C/P = 1	Alprazolam: 179 ng/mL, α-OH-alprazolam: positive, diazepam and nordiazepam: positive, 7-amino-clonazepam: positive, fentanyl: positive, methamphetamine: posive, chlorpheniramine: positive	

Table 2. *Cont.*

Classification	NPS	pKa	logP	Age and Sex	Cause of Death	PMI	Samples Collected	Extraction Method	Analytical Technique	Results	C/P or L/P Ratios	Other Toxicological Findings	Classification
Designer Benzodiazepines	Flubromazolam	---	4.66 *	30-year-old man	Acute mixed-drug intoxication of fentanyl, benzodiazepine, and ethanol	1 day	b, vh, ur	PP	LC-MS/MS	PB: 619 ng/mL HB: 878 ng/mL	C/P = 1.4	Ethanol: 0.02 ng/mL, fentanyl: 17 ng/mL, norfentanyl: positive, methamphetamine and amphetamine: positive, lorazepam: positive, delorazepam: positive flualprazolam: positive, alprazolam: positive	Gevorkyan J. et al. (2021) [137]
	Etizolam	4.55–18.16	4.06							PB: 187 ng/mL HB: 214 ng/mL	C/P = 1.1		
	Etizolam	4.55–18.16	4.06	Unknown	Accidental multiple-drug intoxication	Unknown	b, hv	LLE+SPE	LC-MS/MS	FB: 351 ng/mL HB: 549 ng/mL	C/P = 1.6	NA	Miller C. et al. (2014) [138] (abstract only)
				Unknown	Accidental multiple-drug intoxication	Unknown	b			FB: 16 ng/mL HB: 30 ng/mL	C/P = 1.9	NA	
	Diclazepam	2.3	3.53 *	27-year-old man	Poly-drug intoxication	≥4 and ≤10 days before autopsy	b, ur, gc, bile, CSF, liver, kidney, lung brain, muscle	SPE (blood) QuEChERS (liver)	LC-MS/MS	FB: 1 ng/mL HB: 1 ng/mL L: 34 ng/g	C/P = 1 L/P = 34	Lormetazepam: 6 ng/mL, lorazepam: 22 ng/mL 3-Fluorofenmetrazine: 10 ng/mL, 2-Fluoroanfetamine: aprox 89 ng/mL, amphetamine: aprox 21 ng/mL methiopropamine: aprox 2.2 ng/mL, diphenhydramine (urine)	Lehmann S. et al. (2019) [125]
	Delorazepam	2.05–12.3	3.30 *							FB: 100 ng/mL HB: 250 ng/mL L: 640 ng/g	C/P = 2.5 L/P = 6.4		
	Pyrazolam	3.3	3.59 *							FB: 28 ng/mL HB: 28 ng/mL L: 92 ng/g	C/P = 1 L/P = 3.3		

Samples:PB: peripheral blood, FB: femoral blood, IB: iliac blood, SB: subclavian blood, CB: central blood, HB: heart blood, RHB: right heart blood, LHB: left heart blood, AB: aorta blood, L: liver, ur: urine, vh: vitreous humor, gc: gastric content, SA: serum antemortem, SC: serum cardiac, SF: subcutaneous fat, IS: injection site. **Analytical techniques:** GC-NPD: gas chromatography coupled to nitrogen–phosphorus detector, GC-MS: gas chromatography coupled to mass spectrometry; GC-MS/MS: gas chromatography coupled to tandem mass spectrometry, HPLC-DAD: High performance liquid chromatography–diode-array detector, LC-Q-TOF-MS: liquid chromatography quadrupole–time of flight mass spectrometry, LC-MS/MS: liquid chromatography–tandem mass spectrometry, LC-LIT-MS: liquid chromatography–linear ion trap mass spectrometry. **Extraction methods:** LLE: liquid–liquid extraction, SPE: solid-phase extraction, QuEChERS: quick, easy, cheap, effective, rugged, and safe, PP: protein precipitation. **Substances:** 2-oxo-PCE: 2-(Ethylamino)-2-phenylcyclohexanone, 3-FPM: 3-Fluorophenmetrazine, 4-MeO-PCP: 4-Methoxyphencyclidine, 5-API (5-IT): 5-(2-Aminopropyl)indole, MPH: methylphenidate. * Values of pKa and logP predicted using ChemDraw Professional 15.0 © Copyright 1998-2015 Perkin-Elmer Informatics Inc.

Although piperazines are generally less potent compared to amphetamines, they exhibit dopaminergic and serotonergic activities. This means they affect neurotransmitters in the brain, influencing dopamine and serotonin levels. These actions contribute to their psychoactive effects and potential for abuse.

BZP is a basic drug, pKa value is 9.3, and log P is 1.35 [14]. Other derivatives such as mCPP, pFPP, p-MPP, p-MeOPP, and TFMPP have the following predicted pKa (8.9, 8.6, 8.65, 8.62, and 8.49) and log P (2.26, 1.86, 2.18, 1.57, and 2.62) values, respectively [49]. mCPP has a Vd of 2.5–2.9 L/kg [14]. The moderate pKa values indicate that these drugs tend to ionize in physiological pH conditions, which can influence their distribution in the body. Additionally, their moderate-to-high log P values suggest that they have a propensity to partition into lipids, affecting their solubility and potential for accumulation in fatty tissues. The combination of these properties, moderate pKa, log P, and Vd suggests that these piperazine derivatives may exhibit low-to-moderate tendencies for PMR.

BZP is metabolized primarily by cytochrome P450 enzymes and catechol-*O*-methyltransferase (COMT). These enzymes can exhibit genetic polymorphisms, leading to potential inter-individual differences in metabolism. In both animal and human studies, the main metabolites of BZP include 4-hydroxy-BZP, 3-hydroxy-BZP, 4-hydroxy-3-methoxy-BZP, piperazine, benzylamine, and *N*-benzylethylenediamine. The hydroxy-metabolites are excreted as glucuronic acid and/or sulfate conjugates in urine [139]. mCPP, on the other hand, is well characterized as a metabolite of the antidepressant trazodone and other therapeutics like nefazodone, etoperidone, and mepiprazole. All of them, by *N*-dealkylation, give rise to mCPP (see Figure S1 in Supplementary Materials). In rats, mCPP undergoes metabolism primarily through hydroxylation of the aromatic ring and to a lesser extent by degradation of the piperazine ring, resulting in metabolites such as hydroxy-mCPP (two isomers), *N*-(3-chlorophenyl)ethylenediamine, 3-chloroaniline, and hydroxy-3-chloroaniline (two isomers) [139]. Similar pathways of metabolism are observed for other piperazine derivatives [139]. It is important to note that special care is needed regarding 2,3-dichlorophenylpiperazine (DCPP), a secondary metabolite of the anti-psychotic drug aripiprazole, due to its potential implications and interactions in toxicological and pharmacological contexts (see Figure S2 in Supplementary Materials).

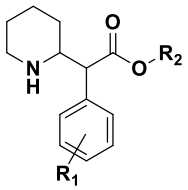
BZP was stable in plasma for 24 h at room temperature, 2 weeks at 4 °C, and 3 months at −20 °C, but it lost 96% of its original concentrations after 2 weeks at room temperature [140]. mCPP was stable in plasma for 3 h at room temperature and 21 h at −20 °C and in urine for 6 months at −20 °C. It was stable in urine for 24 h at room temperature but lost 29% of its original value after 1 week at that temperature [141,142]. The stability of eight piperazines in whole blood at −20 °C, 4 °C, and room temperature was studied. 1-Phenylpiperazines were less stable than 1-BZP, MBZP, and FBZP. MBZP was the most stable piperazine assessed, but it ultimately lost 30% of its analytes over the 12-month study period [143]. These findings indicate that storage conditions significantly impact the stability of piperazine derivatives in biological fluids. BZP and MBZP demonstrate better stability compared to other derivatives like mCPP and 1-phenylpiperazines, especially at higher temperatures. Proper storage at lower temperatures (−20 °C) generally extends stability, but prolonged exposure at room temperature can lead to notable degradation, affecting the accuracy of toxicological analysis in forensic investigations.

- **Postmortem Levels in Fatal Case Reports**

Regarding postmortem levels, BZP was implicated in the death of a young man, who exhibited a postmortem blood level of 1.7 mg/L together with unreported amounts of MDMA and MDA [144]. In two other fatal cases, postmortem blood levels of 0.5 to 1.0 were found together with unreported amounts of TFMPP [14]. BZP and 3-TFMPP have been detected and measured in three fatalities, with two cases involving both drugs [145]. BZP was found at concentrations of 0.71, <0.50, and 1.39 mg/L and 3-TFMPP was found at concentrations of 0.05 and 0.15 mg/L in postmortem blood. To the best of our knowledge and based on the bibliographic search conducted, there are no data available on C/P ratios; therefore, interpretation of post-mortem levels of piperazines requires careful consideration.

3.4. Phenidates

Phenidates are psychostimulant drugs and closely related to methylphenidate (MPH), a prescribed drug for the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy. Ethylphenidate (EPH) is the main representant of the phenidate-like NPS family. Other compounds of this family are 4-fluoroethylphenidate (4F-EPH), 4-fluoromethylphenidate (4F-MPH), 4-methylmethylphenidate (4M-MPH), 3,4-dichloromethylphenidate, and isopropylphenidate (IIPH), see Figure 9. EPH, often sold under the street name "nopaine" or "gogaine", is also produced in vivo as a metabolite following the co-ingestion of methylphenidate and ethanol [146].



R_1 = H, R_2 = Me, methylphenidate (MPH)
R_1 = H, R_2 = Et, ethylphenidate (EPH)
R_1 = F, R_2 = Me, 2-/3-/4-fluoromethylphenidate (2-/3-/4F-MPH)
R_1 = F, R_2 = Et, 2-/3-/4-fluoroethylphenidate (2-/3-/4F-EPH)
R_1 = Me, R_2 = Me, 2-/3-/4-methylmethylphenidate (2-/3-/4M-MPH)
R_1 = 2xCl, R_2 = Me, 3,4-dichloromethylphenidate
R_1 = H, R_2 = isopropyl, isopropylphenidate

Figure 9. Chemical structures of phenidate-type NPS.

Phenidates, such as MPH and EPH, are basic drugs with pKa values of 8.8 and 8.9, respectively, and log P values of 2.16 and 2.49. MPH has a volume of distribution (Vd) ranging from 11 to 33 L/kg and a fraction bound (Fb) of 0.15 [14]. Based on their log P values, these compounds exhibit high lipophilicity, attributed to the presence of cyclic rings, making them potential candidates for PMR.

MPH and probably related compounds are bio-transformed by hydrolysis of the ester moiety to ritanilic acid and derivatives, depending on the type of substituent in the aromatic ring. The hydrolysis of the ester group is expected to generate ritalinic acid as a primary metabolite in all pathways from R_2, as occurs in MPH and EPH. In addition, minor pathways involving aromatic hydroxylation, microsomal oxidation, and conjugation have been reported to form the p-hydroxy, oxo, and conjugated metabolites, such as 6-oxo-ritalic acid. MPH can undergo transesterification with ethanol to form EPH [146].

MPH and ritanilic acid were stable in fluorinated blood or plasma after 3 months at −20 °C, but the parent drug lost 64–70% of its original value in fluorinated blood after 1 week at room temperature [147,148]. EPH was stable in plasma for 4 h at room temperature [149].

- **Postmortem Levels in Fatal Case Reports and PMR**

MPH-related deaths in the literature show postmortem blood MPH levels of 1.1 and 2.8 mg/L [127,150]. Despite its pharmacokinetic parameters and chemical properties, MPH did not appear to exhibit PMR in one case, with C/P and L/P ratios recorded at 0.9 and 3.3, respectively [127]. Femoral blood concentrations of d-methylphenidate ranged from 5 to 58 ng/mL and of l-methylphenidate from undetectable to 48 ng/mL in 12 postmortem samples in which methylphenidate was not implicated in the cause of death. In comparison, blood from 10 living subjects who had no suspected methylphenidate intoxication had concentration ranges and patterns similar to those of the postmortem cases. Therefore, it does not appear to be affected by PMR [151].

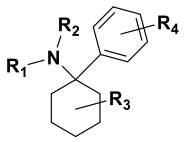
One case of death due to overdose with EPH has been reported in the literature, with a postmortem blood concentration of 2180 ng/mL [152]. Median postmortem femoral blood EPH levels were 280 ng/mL (range, 8–1200) in 10 adults whose deaths were attributed to polydrug use [153]. With regard to other phenidate-like NPSs, a 25-year-old man

was found unconscious in bed, with blood toxicology showing 4F-MPH at a level of 17 ng/mL [154]; other findings were heroin metabolites, methamphetamine, and 3-MeO-PCP. Another publication reports the case of a man who died in police custody. The antemortem toxicological results show 4F-EPH at a level of 0.36 mg/L together with alcohol, MDMA, and MDA; the postmortem femoral blood sample shows 4F-EPH at 0.078 mg/L together with MDMA and MDA [155].

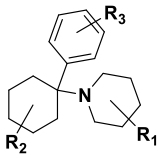
Unfortunately, although there are some specific data on the post-mortem levels of certain types of phenidates, there is practically no published information on the distribution of phenidate NPSs across different tissues. This makes interpretation of post-mortem concentrations in cardiac blood difficult.

3.5. Arylcyclohexylamines (Phencyclidines)

Arylcyclohexylamines, like ketamine and phencyclidine (PCP), are well-known drugs of abuse. The arylcyclohexylamine core has been used in the synthesis of a range of NPSs. The arylcyclohexylamines most frequently involved in cases of intoxication are ketamine, deschloroketamine (DCK), 2-fluoro-deschloroketamine (2F-DCK), PCP, 3-methoxy-phencyclidine (3-MeO-PCP), 3-hydroxy-phencyclidine (3-OH-PCP), eticyclidine (PCE), 2-oxo-eticyclidine (2-oxo-PCE), methoxetamine (MXE), and methoxpropamine (MXPr) [156], see Figure 10.



R_1 = H, R_2 = Me, R_3 = O, R_4 = 2-Cl, Ketamine
R_1,R_4 = H, R_2 = Me, R_3 = O, Deschloroketamine (DCK)
R_1 = H, R_2 = Me, R_3 = O, R_4 = 2-/3-/4-F, 2-/3-/4-fluoro-deschloroketamine (2-/3-/4-F-DCK)
R_1 = H, R_2 = Et, R_3 = O, R_4 = OMe, Methoxetamine (MXE)
R_1 = H, R_2 = Pr, R_3 = O, R_4 = OMe, Methoxpropamine (MXPr)
R_1, R_3, R_4= H, R_2 = Et, Eticyclidine
R_1,R_4 = H, R_2 = Et, R_3 = O, 2-Oxo-eticyclidine (2-oxo-PCE)



R_1, R_2, R_3 = H, Phencyclidine (PCP)
R_1, R_2= H, R_3 = OMe, 2-/3-/4-Methoxy-phencyclidine (2-/3-/4-MeO-PCP)
R_1, R_2= H, R_3 = OH, 2-/3-/4-Hydroxy-phencyclidine (2-/3-/4-OH-PCP)
R_1, R_3 = H, R_2 = OMe, 2'-/3'-/4'-Methoxy-phencyclidine (2'-/3'-/4'-MeO-PCP)

Figure 10. Chemical structures of arylcyclohexylamines NPS.

Ketamine is a basic drug with the following chemical properties: pKa = 7.5, log P = 2.69, Vd = 3–5 L/kg, and Fb ranging between 0.30 and 0.35 [14]. PCP is also a basic drug with the following chemical properties: pKa = 8.5, log P = 5.31, Vd = 5.3–7.5 L/ Kg, and Fb = 0.65 [14]. According to their chemical properties, both drugs and derivatives are prone to PMR.

At the beginning, ketamine was used as racemic mixture, but currently in human medicine, *S*-ketamine is preferable due to its higher potency together with faster post-anesthetic recovery times. Illicit trafficking keeps synthesizing racemic mixtures. Ketamine and norketamine were stable in blood for 2 h at room temperature or 4 °C, and they were stable in serum for 2 days at 4 °C and 2.5 months at −20 °C; other studies show stability in urine for 2 weeks at 4 °C [157].

Regarding PCP stability, in fluorinated whole blood, it lost 17% of its original concentration after 1 year and 69% after 5 years when stored at room temperature, but it was stable for 2 years at −20 °C and for 6 months in urine at 4 °C [158].

- **Postmortem Levels in Fatal Case Reports and PMR**

In a study of 114 ketamine-related deaths, the average postmortem blood concentration was found to be 2400 ng/mL [14]. For PCP, an average postmortem blood concentration of 4800 ng/mL (ranging from 0.3 to 25) was observed in 17 related deaths [14].

There are 16 recorded fatalities [159,160] where 3-MeO-PCP was found and measured in postmortem blood, with a median concentration of 145.5 ng/mL (ranging from 1 to 3525 ng/mL). In only one instance (380 ng/mL), 3-MeO-PCP was determined to be the cause of death. In the other cases, the deaths were attributed to polydrug intoxication. In another case, a 42-year-old man was discovered dead on his bed at home [161]. Nearby, several drug tablets (alprazolam, tramadol, loxapine, lorazepam, and quetiapine) were found, along with three plastic bags of powdered "research chemicals" labeled "2F-DCK," "3-MeO-PCE," and "5-MeO-DMT." Peripheral blood analysis revealed concentrations of 1780 ng/mL for 2F-DCK, 90 ng/mL for 3-MeO-PCE, and 52 ng/mL for 5-MeO-DMT. MXE was documented in two fatalities, with a postmortem blood concentration of 8600 and 320 ng/mL [162,163]. In both cases, MXE was found alongside other drugs. Only in the first case was MXE the cause of death attributed to an accidental acute overdose [162].

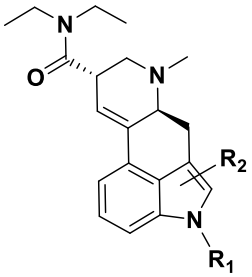
Few studies, based on the consulted bibliography, report both heart and femoral blood concentrations of ketamine. One study found C/P ratios of 3.8 and 2.7 [164]. In another study that compiled C/P ratios for various drugs, ketamine ratios of 0.8 and 2.3 were reported [4]. Since ketamine can be administered through multiple routes, including intravenous and intramuscular injections, the differences between heart and femoral blood concentrations observed in postmortem samples may be due to incomplete distribution. If the drug is injected into the upper body and death occurs rapidly, the concentration in the heart blood may be higher than in peripheral samples. PCP also may show PMR, with average C/P ratios of 1.1 (ranging from 0.5 to 3.3) across 11 cases [17].

With respect to PMR of ketamine and PCP derivatives, there is a scarce amount of data. 2-Oxo-PCE was detected in a case report [128] where C/P and L/P were 5.7 and 16.3 pointing to a possible PMR. In another case report [129] involving 4-MeO-PCP, the C/P and L/P ratios were 1.4 and 15, respectively, pointing, as well, to a moderate PMR. This deduction, which results from single observations, must be taken with caution.

3.6. Lysergamides

After being declared a Schedule I substance, the use of LSD has gradually declined since the sixties. However, in recent years, there has been a resurgence, with the rise of LSD-like NPSs, which has created a new horizon to be explored. Designing molecules closely related to LSD, the most potent hallucinogen known to date, has been increasing in recent years [165–175]. Reports describe molecules substituted at the indole nitrogen (position N_1) of LSD, e.g., with acyl groups (ALD-52, 1P-LSD, 1B-LSD, 1cP-LSD, and 1V-LSD), that produce LSD-like effects. Furthermore, in vivo biotransformation to LSD by *N_1*-deacetylation of these N_1-acyl-substituted ergoline derivatives has been reported to act as prodrugs [176] (Figure 11).

LSD is a basic drug with the following chemical properties: pKa = 7.8, log P = 2.70, Vd = 0.28 L/kg, and Fb = 0.90 [14]; the low Vd makes it a poor candidate for PMR. The instability of lysergic acid diethylamide (LSD) has been documented since the 1970s. The degradation of LSD was accelerated when exposed to ultraviolet light. However, when LSD was not exposed to light, it remained stable even at high temperatures. LSD and *N*-desmethyl-LSD were stable in blood and serum protected from light for 2 weeks at 4 and −20 °C [177], while in another study, LSD and 2-oxo-3-hydroxy-LSD were stable in serum for 6 months at −20 °C [178]. LSD undergoes extensive biotransformation via *N*-demethylation and hydroxylation. In addition to *N*-desmethyl-LSD and hydroxy-LSD, other metabolites are 2-oxo-LSD and 2-oxo-3-hydroxy-LSD, all of them being inactive. The LSD-like NPS metabolism of 9 LSD derivatives was studied in vitro using pooled human liver microsomes for reliable analytical detection in biological samples and for differentiation of the LSD-like compounds [179].



R_1, R_2 = H, Lysergic acid diethylamide (LSD)
R_1 = $COCH_3$, R_2 = H, ALD-52
R_1 = $COCH_2CH_3$, R_2 = H, 1-propanoyl-LSD (1p-LSD)
R_1 = $CO(CH_2)_2CH_3$, R_2 = H,1-butyryl-LSD (1B-LSD)
R_1 = $CO(CH_2)_3CH_3$, R_2 = H, 1-valeryl-LSD (1V-LSD)
R_1 = COcP, R_2 = H,1-(cyclopropylmethanoyl)-LSD (1cP-LSD)
R_1 = H, R_2 = Br, 2-Bromo-LSD

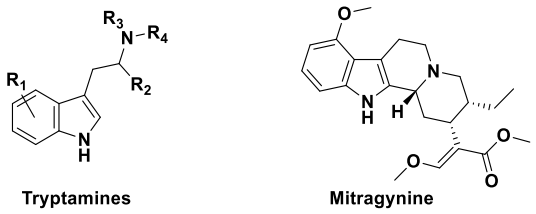
Figure 11. Chemical structures of LSD-like NPS.

- **Postmortem Levels in Fatal Case Reports**

Given the low concentrations of LSD administered (usual oral doses as the tartrate salt are 25–250 μg) and its short plasma half-life of 3.6 h [14], LSD blood levels are commonly very low. A case in which death was directly attributed to LSD presented antemortem serum and postmortem blood concentrations of 14.4 and 4.8 ng/mL, respectively [180]. Blood LSD levels were 8 and 1250 ng/mL in two other deaths in which LSD and metabolites were found in routine postmortem toxicology [181]. To the best of our knowledge, there are no reports of post-mortem blood levels of either LSD-like NPS, and no studies have been able to establish a C/P ratio for LSD.

3.7. Tryptamines

Tryptamines are psychedelic drugs derived from decarboxylation of the amino acid tryptophan, which produces the typical indole ring. Because of their structural similarity to serotonin, they act primarily as agonists at the 5-HT_{2A} receptor, producing profound changes in sensory perception, mood, and thought in humans. Dimethyltryptamine (DMT) is a short-acting hallucinogenic that occurs with β-carbonile alkaloids, like harmine, harmaline, and tetrahydroharmine (THH), in certain South American plants (*Banisteriopsis caapi* and *Psychotria viridis*) with a long traditional use by Amazonian tribes in an herbal preparation known as ayahuasca. Other natural tryptamines are psilocybin and psilocin present in the '*Magic mushrooms*' belonging to *Psilocybe cubensis* species. Psilocybin is rapidly dephosphorylated after oral ingestion. Due to the acidic environment of the stomach and enzymatic action from alkaline phosphatase and other esterases in the intestine, kidney, and possibly blood, psilocybin is dephosphorylated into psilocin. Psilocin, which can easily cross the blood–brain barrier, is the primary agent responsible for psychoactive effects and can be seen as a pro-drug. Psilocin is then metabolized by monoamine oxidase (MAO) and probably aldehyde dehydrogenase (ALDH) to 4-hydroxyindoles-3-acetic acid and 4-hydroxytryptohole. Notably, psilocybin itself has not been detected in biological fluids in reported cases of poisoning following the ingestion of hallucinogenic mushrooms. [182,183]. The psychoactive substances bufotenine and 5-MeO-DMT are found in the skin secretions of the desert toad *Bufo alvarius* and in certain South American plants of genus *Anadenanthera* or *Bromisum*. Mitragynine is an indole alkaloid with a *tryptamine*-like structure found in the *Kratom* plant (*Mitragyna speciosa*), a tree commonly found in Southeast Asia. Mitragynine and 7-hydroxymitragynine are considered the primary psychoactive alkaloids. Synthetic modifications to the indolealkylamine core produce a huge list of novel tryptamine structures [184–186], see Figure 12.



R_1, R_2, R_3, R_4 = H, Tryptamine
R_1, R_2 = H, R_3, R_4 = Me, Dimethyltryptamine (DMT)
R_1, R_3, R_4= H, R_2 = Me, alpha-Methyltryptamine (AMT)
R_1, R_2 = H, R_3, R_4 = Et, Diethyltryptamine (DET)
R_1, R_2 = H, R_3, R_4 = ^{i}Pr, Diisopropyltryptamine (DiPT)
R_1 = OH, R_2 = H, R_3, R_4 = Me, 5-OH-*N*,*N*-DMT (Bufotenin)
R_1 = OH, R_2 = H, R_3, R_4 = Me, 4-OH-*N*,*N*-DMT (Psilocin)
R_1 = OH, R_2 = H, R_3, R_4 = ^{i}Pr, 5-Hydroxy-*N*,*N*-diisopropyltryptamine (5-OH-DiPT)
R_1 = OMe, R_2 = HR_3, R_4 = ^{i}Pr, 5-Methoxy-*N*,*N*-diisopropyltryptamine (5-MeO-DiPT)

Figure 12. Chemical structures of tryptamine derivatives.

After death, a significant number of putrefactive indol derivatives are formed [187], which are partly derived from the autolysis of tissues to their major constituents. Skatole (3-methylindole) and tryptamine are formed in the intestine by the bacterial decarboxylation of the amino acid tryptophan. In decayed samples, they can mask or alter the way a drug is detected, leading even to false-positive results. This depends on the analytical method used.

DMT, bufotenine, 5-MeO-DMT, harmine, psilocybin, and mitragynine [188] are basic drugs that have pKa values of 8.7, 9.7, 7.6, 9.3, 8.8, and 7.3, respectively [14]. Log P values are 1.90, 2.04, 2.38, 8.68, 1.25, and 1.73, showing lipophilicity [189,190]. Vds are available only for DMT, psilocybin, and mitragynine: 38–53, 2.5–5, and 40–90 L/kg [14]. Only mitragynine has a Fb value > 0.90 [14]. These compounds are good candidates for post-mortem redistribution because they are basic compounds with large distribution volumes.

In fluorinated blood, psilocin lost nearly 40% after 1 day at room temperature, 10% after 3 days at 4 °C, and 80% after 7 days at −20 °C [191]. Re-examination of a DUID case stored at 4 °C after 26 days saw a 44% reduction in psilocin concentration [192]. Several publications have found that the degradation of psilocin in urine and serum can however be minimized by the addition of ascorbic acid at the time of collection [193,194]. Indoles are electron-rich compounds and therefore easily oxidized.

Stability studies of mitragynine [195] revealed that its stability is significantly affected by pH and temperature. These compounds are particularly sensitive to acidic conditions, especially in alkaline environments, where mitragynine hydrolyzes the methyl ester, leading to the formation of 16-carboxymitragynine. Of the alkaloids studied, 7-OH-mitragynine was identified as the most unstable. In another study [196], mitragynine remained stable in plasma for 2 days at room temperature and for 1 month at −20 °C. In urine, it was stable for 5 days at room temperature, as well as at 4 °C or −20 °C [197]. No data have been reported for other tryptamine derivatives, at least in the literature revised.

- **Postmortem Levels in Fatal Case Reports and PMR**

Hallucinogens, in general, are powerful drugs capable of producing altered states of consciousness in doses considered organically harmless. Few studies have been reported on PMR (See Table 2). Nevertheless, synthetic tryptamines have been associated with fatal cases in recent years. A 25-year-old white male was found dead after consuming herbal extracts containing β-carbolines and hallucinogenic tryptamines [198]; the C/P ratios for DMT, 5-MeO-DMT, tetrahydroharmine (THH), harmine, and harmaline were 2, 1.6, 1.6, 2.1, and 1.7, respectively. To differentiate fatal intoxications associated with ayahuasca from those involving synthetic DMT, various alkaloids in these herbal preparations—such as harmine, harmaline, and tetrahydroharmine (THH)—can be monitored. Additionally, metabolic biomarkers from phase I metabolism, including harmol, harmalol, and tetrahy-

droharmalol, as well as their elimination in glucuronide form during phase II metabolism, can also be assessed [188].

Dipropyltryptamine (DPT) was recently found in a case report of a 20-year-old man who sniffed an unknown amount of DPT; toxicological findings revealed DPT levels of 210, 110, and 180 ng/mL in antemortem serum, postmortem heart blood, and urine, respectively [199]. *N,N*-diisopropyltryptamine (5-MeO-DIPT, "*foxy*") has been found in a fatal overdose during a chemsex session [200]. The level of 5-MeO-DIPT and its two metabolites, 5-hydroxy-*N,N*-diisopropyltryptamine (5-OH-DIPT) and 5-methoxy-*N*-isopropyltryptamine (5-MeO-NIPT), in blood were 412, 327, and 20 ng/mL, respectively. Those concentrations are higher than those published in other cases of 5-MeO-DIPT intoxications [201,202]. The literature reports a case involving a female who died after jumping from a second-floor height following the consumption of hallucinogenic mushrooms. Postmortem analysis detected and quantified psilocin in femoral and cardiac blood, resulting in a C/P ratio of 1.1 [203].

Alpha-methyltryptamine (AMT) has also been linked to a fatal case involving a young student, where toxicological analysis found concentrations of 2.0 mg/L in iliac blood and 24.7 mg/kg in liver tissue [204]. A related compound, alpha-ethyltryptamine (AET), was detected in another fatal case [205]. Toxicological findings revealed AET levels of 1100 ng/mL in blood (without indicating the source) and 3300 ng/g in the liver.

5-(2-Aminopropyl)indole (5-API or 5-IT) has been associated with four deaths, with an average C/P ratio of 1.9, ranging from 1.3 to 2.9, raising the possibility of postmortem redistribution [130]. Although 5-IT is a positional isomer of AMT, it is not a tryptamine because its indole ring is substituted at the 5 position instead of the 3 position. It is included here due to its structural similarities. In another case [131], *N,N*-Dipropyltryptamine (DPT) was identified in a fatal case involving a young man who died after snorting a white powder purchased from the dark web. Postmortem analysis of femoral and cardiac blood revealed a C/P ratio of 1.1.

Finally, regarding mitragynine, post-mortem blood concentrations ranged from 20 to 180 ng/mL in 9 deaths where mitragynine was detected [206]. In another case, a 17-year-old man was found unresponsive in bed with a bag labeled "Bali Kraton". Post-mortem blood analysis revealed a mitragynine level of 0.60 mg/L [207]. In another case report, a middle-aged man was found dead at home. At autopsy, mitragynine (1.06 mg/L) and 7-hydroxymitragynine (0.15 mg/L) were found in his blood, and both substances were also found in his urine [208]. As previously described, mitragynine may exhibit PMR according to its chemical properties, but in a case report [132], the central C/P ratio was 0.83, and the L/P ratio was 1.9. These ratios suggest no potential PMR for mitragynine. In another study [209], mitragynine's C/P ratios ranged from 0.04 to 1.26, with a mean and median of 0.75 and 0.79, respectively. In contrast, in another death [133], the C/P ratio was 2.3, with a post-mortem interval of 50 h, suggesting PMR.

The data suggest that DMT, 5-MeO-DMT, 5-API, and 5-IT show signs of PMR, while DPT has a C/P ratio close to 1, and results for mitragynine remain inconclusive. It is likely that tryptamines may exhibit some form of PMR, but further studies are needed to confirm that, and special care must be taken when interpreting postmortem levels.

3.8. Designer Benzodiazepines

In this study, 'designer benzodiazepines (BZDs)' refer to NPSs that feature a benzodiazepine core and are not regulated by the international drug control system. We also include three benzodiazepines—phenazepam, **etizolam**, and **flutazolam**—which were previously classified as NPSs but have recently come under international regulation. Etizolam was initially developed and clinically used in Japan and is now licensed in India and Italy; phenazepam originated in the Soviet Union and remains authorized in Russia and neighboring countries; flutazolam was developed primarily for use in Japan. While these drugs are not technically classified as designer BZs, they are monitored by the EUDA and are often categorized with them.

BZDs are widely prescribed for neurological and psychiatric disorders. They are also frequently abused. Discovered in the mid-1950s, BZDs have been developed as pharmacotherapies for anxiety, panic attacks, sleep disorders, and epilepsy. They have also been used as myorelaxants during surgical and orthopedic procedures. A large number of new synthetic compounds, mainly 1,4-benzodiazepines, triazolobenzodiazepines, and thienotriazolodiazepines, known as designer BZDs, have been produced by making small changes to the BZD nucleus at different positions, see Figure 13.

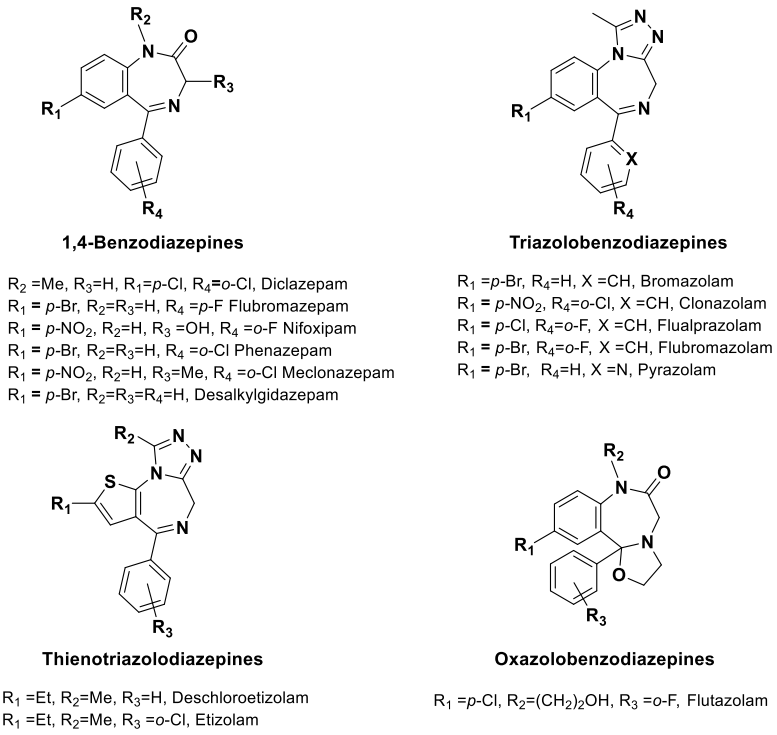


Figure 13. Chemical structures of the primary groups of designer benzodiazepines.

BZDs derivatives are amphoteric compounds. Thus, they show a weak basic property, due to the nitrogen heteroatom in the 4th position in the molecule, and a weak acidic property, due to the lactam bond in 1,4-benzodiazepinas and oxazolobenzodiazepines. On the other hand, most of the 'classic' and designer BZDs have comparatively high values for log P and are extensively bound to plasma proteins (80–98%) [210]. Most benzodiazepines have a moderate volume of distribution between 0.2 and 3 L/kg, but some, such as flunitrazepam, loprazolam, lormetazepam, quazepam, and tetrazepam, have much larger volumes, between 3 and 9 L/kg. Prazepam has the largest Vd, ranging between 12 and 14 L/kg [14]. Their amphoteric nature makes them poor candidates for PMR, although some of them have a large volume of distribution, as has been described.

Previously published C/P blood ratios support this asseveration [1,4,16,17,211]. In another study, the average autopsy/mortuary admission ratios (PM/AM) for the BZDs group were 0.76 to 1.26 and suggest minor changes in this PM period [1,212]. Although benzodiazepines are generally considered to exhibit limited PMR, there are some exceptions, such as alprazolam with C/P ratios averaging 1.5 (range: 1.0–2.8) in 4 fatal cases [4]; bromazepam, whose C/P ratios averaged 1.5 (range 0.8–4.2) in a series of 6 fatalities and 1.91 (1.49–2.33) in two fatalities [1]; and midazolam, whose C/P ratios averaged 3.3 (range, 0.2–10.5) in another series of 9 deaths [213]. A recent study of 179 benzodiazepine-positive cases examined differences in the C/P ratios of BZDs (diazepam, nordazepam, temazepam, oxazepam, midazolam, and α-hydroxymidazolam) between subgroups of 13 potentially significant variables and showed that the C/P ratios of midazolam and α-hydroxymidazolam were close to 2 in all subgroups studied, suggesting possible PMR [16].

Most BZDs are stable under refrigeration conditions, and some are even stable at room temperature. Stability over 8 months at 4 and −20 °C was evaluated in a comprehensive study of 23 benzodiazepines and metabolites in antemortem (blood and urine) and postmortem (blood, brain, liver, and stomach contents) matrices [214]. Concentrations decreased over time and storage conditions had little effect on the decrease for most of the drugs studied, regardless of the initial enriched concentration. Urine was found to be the most stable matrix. Only phenazepam, 7-aminoclonazepam, 7-aminoflunitrazepam, and 2-hydroxyethylflurazepam decreased by more than 20% over the 8-month period in both storage conditions. The nitrobenzodiazepines, like clonazepam, flunitrazepam, and nitrazepam, are well known for being converted to their corresponding 7-aminometabolites in postmortem specimens, a process accelerated by enteric bacteria like *Streptococcus faecalis* and *Clostridium perfringens* [215,216]. With flunitrazepam being the most unstable, complete or almost complete conversion of the parent drugs has been reported. As a result, these three nitrobenzodiazepines are primarily identified in post-mortem cases as the inactive 7-aminometabolites of their parent drugs. The median PM/AM ratios of the nitrobenzodiazepines, clonazepam and nitrazepam (0.35 and 0.14), are consistent with their instability [211]. In the five cases where both nitrazepam and 7-aminonitrazepam were detected, the median PM/AM ratio of the total concentration was 1.0 (range: 0.60–2.1), confirming previous studies and concluding that nitrobenzodiazepines do not show a significant PMR in femoral blood. Clonazolam, like other classic nitrobenzodiazepines, undergoes microbial degradation, so it is always recommended to look for its metbolite, 8-aminoclonazolam, in postmortem blood [217]. Two studies [218,219] have been carried out investigating the stability of designer benzodiazepines (pyrazolam, diclazepam, flubromazepam, meclonazepam, phenazepam, etizolam, nifoxipam, deschloroetizolam, clonazolam, flubromazolam, and flutazolam) but only in urine for 1 month and 7 months. These studies showed that flubromazepam, clonazolam, nifoxipam, and meclonazepam (the latter three are nitrobenzodiazepines) were unstable in urine (at ambient temperature and at 4 °C). Meclonazepam was only detected at 8% of its original concentration after 4 weeks at 4 °C and −20 °C after 4 weeks.

- **Postmortem Levels of Designer Benzodiazepines in Fatal Case Reports and PMR**

Regarding PMR studies on designer benzodiazepines, the existing literature is scarce (see Table 2). There are several papers reporting on the post-mortem levels of designer benzodiazepines, but there are few studies on the PMR phenomenon. The quantitative results of 29 post-mortem cases in which phenazepam was detected are reported in one study [134]. C/P ratios averaged 1.3 (range, 0.5–2.7) and L/P ratios averaged 8.8 (range 2.2–16.8). Flualprazolam was detected in a series of postmortem cases, the median concentration was 8.2 ng/mL, and the range of blood concentrations was 2.0–620 ng/mL [220]. In another study, flualprazolam was detected in 8 postmortem cases, and the range of blood concentrations was 2.83–35.1 ng/mL [221]. A case report on the tissue distribution of flualprazolam has been documented in the literature [135]. Flualprazolam was detected in antemortem serum (37 ng/mL), postmortem cardiac serum (25.4 ng/mL), and postmortem femoral blood (21.9 ng/mL). The lower concentration in peripheral blood compared to cardiac serum suggests a blood-to-serum ratio of approximately 0.86, which is comparable to that of diazepam (0.71). The similar levels in the clinical serum sample and postmortem cardiac serum indicate no significant postmortem redistribution. Flubromazolam was present in 5 autopsy cases in unpreserved post-mortem femoral blood, and the concentrations ranged from 1 to 70 ng/mL. None of the cases were directly attributed to flubromazolam toxicity alone [222]. Diclazepam, delorazepam, lormetazepam, lorazepam, and pyrazolam C/P ratios were 1.0, 2.5, 0.7, 1.0, and 1.0, respectively, in a case report [125]. Etizolam detected in postmortem femoral blood was 8.5 ng/mL (range 1.0–172.0 ng/mL) in 24 cases [223]. In another reported case, where a male died after consuming adulterated XANAX® tablets, postmortem concentrations of etizolam in femoral and cardiac blood resulted in a C/P ratio of 3.7 [136]. In another set of postmortem cases, etizolam was detected and quantified in four instances, with C/P ratios varying from <0.5 to 3.4. The highest C/P ratio occurred in a

case with a one-week postmortem interval [137]. Flubromazolam was also identified in one of these cases, showing a C/P ratio of 1.4. Additionally, etizolam was detected in two other postmortem cases, with C/P ratios of 1.6 and 1.9 [138]. Bromazolam was detected in 41 postmortem cases, the median bromazolam concentration observed was 1.6, ranging from 0.5 to 319.3 ng/mL, and the majority of cases co-occurred with fentanyl [224]. Desalkylgidazepam (bromonordiazepam) is the latest designer benzodiazepine to appear in postmortem blood samples. In a study report performed on 63 cases [225], the average desalkylgidazepam concentration was 42.2 ng/mL, ranging from 3.7 to 220.6 ng/mL. Desalkylgidazepam (bromonordiazepam) is the latest designer benzodiazepine to appear in postmortem blood samples [226]. The Vd of desalkygidazepam is, on average, 4.27 L/kg [225], which is relatively high compared to other benzodiazepines, indicating that desalkygidazepam is likely to show PMR.

While the results are still preliminary, it appears that designer benzodiazepines, like their traditional counterparts, have a low tendency for PMR.

3.9. Synthethic Opioids

Synthetic opioids such as fentanyl, methadone, and tramadol have different chemical structures from classical opioids such as morphine, oxycodone, hydrocodone, oxymorphone, hydromorphone, dihydrocodeine, and buprenorphine. Some of these compounds, including methadone and buprenorphine, were originally developed as treatments for heroin addiction but have since been increasingly used and trafficked in the illicit drug market. Fentanyl, for example, is a piperidine derivative with a phenylethyl group, featuring different moieties at the 4-piperidinyl position, along with a propionyl group and a benzene ring, see Figure 14. Various fentanyl derivatives exhibit substitutions in the propionyl moiety (such as butyrfentanyl and acetylfentanyl), phenethyl moiety (like alpha-methylfentanyl), *N*-phenyl ring (including 4-fluorofentanyl and 4-methoxy-butyryl fentanyl), and the piperidine ring (such as carfentanil and 3-methylfentanyl).

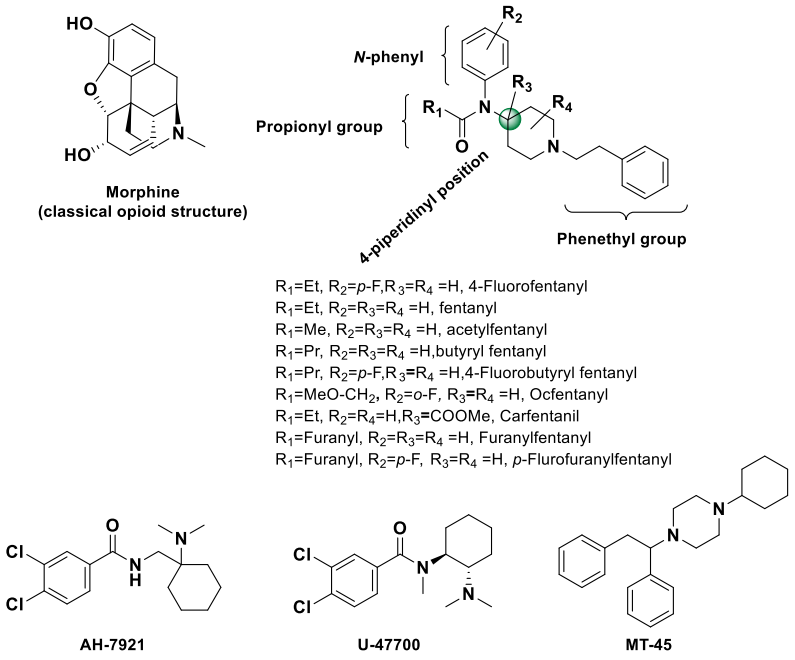


Figure 14. The chemical structure of classical opioid and fentanyl compared to unrelated new synthetic opioids.

3,4-Dichloro-*N*-((1-(dimethylamino)cyclohexyl)-methylbenzamide (AH-7921), an opioid developed by Allen & Hanburys Ltd. in 1975, later appeared on online markets as a research chemical labeled "not for human consumption". Shortly thereafter, a related compound, U-47700, a structural isomer of AH-7921, emerged. Developed by Upjohn in

1978, trans-3,4-dichloro-*N*-(2-(dimethylamino) cyclohexyl)-*N*-methylbenzamide (U-47700) shares a 3,4-dichlorobenzamide core in common with AH-7921. In contrast, 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine (MT-45), a diarylethylamine derivative with synthetic opioid properties, was also developed in the 1970s.

Opioids are basic drugs with a pKa range between 7.5 and 10.9. Their log P values vary widely, from 0.8 to 5. Traditional opioids like morphine and its derivatives have the lowest log P values, while fentanyl and its analogs range from 1.5 (remifentanil) to 5.3 (MT-45) [49,189,227]. This suggests rapid diffusion throughout the body, allowing them to quickly cross the blood–brain barrier. Their lipophilicity and basic nature indicate a potential tendency for PMR.

The Vd and protein binding (Fb) are only known for some fentanyl derivatives with clinical applications, like fentanyl, remifentanyl, sufentanyl, and alfentanyl. Fentanyl and sufentanil have the highest Vd (1.5–8 L/kg), while the Fb values range from 0.6 to 0.9 for the four compounds [14].

The stability of fentanyl analogs has been studied in various matrices [228]. In one study, 13 fentanyl analogs were examined [229]. All of them (except acrylfentanyl) were stable in blood for 9 months under room and refrigerated temperatures. Acrylfentanyl was unstable after 24 h under elevated (70% loss) and room temperatures (53–60% loss), 48–72 h when refrigerated (28–40% loss), and 4 weeks when frozen (22% loss). Analyte degradation was observed in frozen samples after four freeze/thaw cycles; so, it is recommended to limit freeze/thaw cycles to maintain drug integrity [230]. This study shows that remifentanyl, although stable at −20 °C, was unstable when stored at 4 °C, losing 50% of analytes after 1 day. Regarding urine, 13 fentanyl analogs [231] were stable in urine stored at −20 °C or below for at least 2 months. However, remifentanyl decreased in urine by approximately 90% within 1 week at room temperature and by more than 50% in samples stored for 1 week at 4 °C; so, it is recommended to analyze the primary metabolite, remifentanyl acid. In a recent study [232], the influence of pH and temperature was studied in the stability of 17 fentanyl analogs, and the degradation products were studied as possible biomarkers. While all the fentanyl analogs studied were stable under acidic conditions, pH = 6, or lower, remifentanyl was the most unstable even in acidic conditions. *N*-dealkylated fentanyl analogs were the most stable. *N*-dealkylation followed closely by oxidation of the piperidine nitrogen and β-elimination were the main degradation pathways observed. More specifically, ester and amide hydrolysis (acetylfentanyl and 3-methylfentanyl), demethylation of the propenamide moiety (fentanyl), and *O*-demethylation (sulfentanil and alfentanil) were observed for the mentioned compounds.

- **Postmortem Levels in Fatal Case Reports**

The concentrations determined in postmortem specimens varied depending on the type of synthetic opioid detected. Additionally, many of these compounds, including morphine, can create a significant tolerance, meaning that higher doses are needed to achieve the same effect. If use is temporarily stopped, resuming it can lead to an overdose. Derivatives with potencies relative to morphine of more than 170 showed concentrations in femoral blood in the low ng/mL or pg/mL range, while those derivatives with potencies similar to morphine showed concentrations of hundreds and even thousands of ng/mL [233]. In 207 fentanyl-related deaths, the median postmortem blood concentration of fentanyl was 11 ng/mL, with a range of 1 to 60 ng/mL [233]. In several cases, 3-methylfentanyl was identified as the cause of death, with postmortem blood concentrations ranging from 0.4 to 2.6 ng/mL [234,235]. Acetyl fentanyl had a median postmortem blood concentration of 12 ng/mL in 52 reported cases, with levels ranging from 0.31 to 600 ng/mL in peripheral blood [159]. Acrylfentanyl showed a median postmortem femoral blood concentration of 0.24 ng/mL, with values ranging from 0.01 to 21 ng/mL in 45 reported cases [159].

In 15 fatalities involving AH-7921, the median postmortem femoral blood concentration was 430 ng/mL, with values ranging from 50 to 9100 ng/mL [159]. Butyrfentanyl had a median postmortem femoral concentration of 15.9 ng/mL, with a range of 0.33 to 99 ng/mL across 6 deaths [159,233]. Carfentanyl showed a median postmortem femoral concentration

of 0.24 ng/mL, ranging from 0.01 to 3.3 ng/mL in 75 deaths [159]. In 24 deaths related to cyclopropylfentanyl [159], the median postmortem femoral concentration was 8.4 ng/mL, with a range of 0.1 to 43.3 ng/mL [159]. *p*-Fluoroisobutyrylfentanyl (FIBF) had a median postmortem peripheral blood concentration of 22 ng/mL, ranging from 7.5 to 18 ng/mL across 4 cases [159].

The median postmortem femoral blood concentration of furanylfentanyl in 13 fatalities was 2.7 ng/mL, with concentrations ranging from 0.4 to 42.9 ng/mL [233]. For methoxyacetylfentanyl, the median postmortem femoral concentration in 15 fatalities was 15.6 ng/mL, with a range of 0.21 to 56 ng/mL [159]. In 31 cases involving the synthetic opioid MT-45, the median postmortem peripheral blood level was 380 ng/mL, ranging from 6 to 2900 ng/mL [159,236]. Ocfentanil had a median postmortem peripheral blood concentration of 9.1 ng/mL, with a range of 3.7 to 15.3 ng/mL across 5 cases [159]. U-47700 had a median postmortem femoral blood concentration of 252 ng/ mL, ranging from 7.8 to 1520 ng/mL in 20 cases [159].

In recent studies [159,237–241] examining fentanyl-related substances in postmortem samples, fentanyl was detected in 1264 cases, with a median peripheral blood concentration of 11 ng/mL, ranging from 1 to 1646 ng/mL. Acetyl fentanyl was identified in 70 cases, showing a median concentration of 5.5 ng/mL (range 1–83 ng/mL). *β*-Hydroxy thiofentanyl was reported in 6 cases, with a median concentration of 17 ng/mL (range 1.6–97 ng/mL). Carfentanyl appeared in 121 cases, with a median concentration of 0.43 ng/mL (range 0.16–8.5 ng/mL). Cyclopropyl fentanyl was present in 104 cases, with a median concentration of 19 ng/ mL (range 2–919 ng/mL). Furanylfentanyl was detected in 23 cases, with a median concentration of 3.2 ng/mL (range 1.2–59 ng/mL). Methoxyacetylfentanyl was found in 37 cases, with a median concentration of 0.32 ng/mL (range 0.12–232 ng/mL). Finally, *p*-fluoro isobutyryl fentanyl was identified in 17 cases, with a median concentration of 35 ng/mL (range 1–203 ng/mL). These results are similar to the studies reported in previous years.

Opioid tolerance plays a significant role in assessing possible causes of death, which is why "post-mortem levels" are discussed rather than "lethal concentrations"; levels may overlap depending on whether or not the individual was habituated to opioids. In most of the reported cases, including those displayed in Table 3, synthetic opioids were found in combination with other substances, particularly central nervous system (CNS) depressants like benzodiazepines, antidepressants, antipsychotics, antihistaminic drugs, ethanol, and other opioids. Such combinations can lead to pharmacodynamic interactions, raising the risk of respiratory depression. Mono-intoxication by a specific synthetic opioid is discussed only in certain cases where no other compounds are found in the toxicological results or pathological findings to account for the cause of death.

Published data indicate that acrylfentanyl, carfentanyl, and furanylfentanyl have the lowest median postmortem peripheral blood concentrations. Acrylfentanyl's low levels may result from its instability in blood. Carfentanyl, which is 10,000 times more potent than morphine [242], likely requires much smaller doses to produce similar effects as other fentanyl analogs, explaining the lower concentrations detected. In the case of furanylfentanyl, its low levels are likely due to its frequent co-occurrence with other opioids and substances of abuse in fatal cases, rather than being present alone.

- **Tissue Distribution and PMR**

As can be seen in displayed data in Table 3, studies on fentanyl have reported C/P ratios ranging from 0.7 to 4.6 (mean: 1.6) in 13 deaths and from 0.5 to 11.0 (mean: 2.7) in 80 deaths. The L/P ratio varied from 1.4 to 539.4 (mean: 6.6) in 75 deaths [14,159,231]. For 3-methylfentanyl, a C/P ratio of 1.5 was observed in only one case report involving a 31-year-old woman [235]. Acetylfentanyl exhibited C/P ratios ranging from 0.3 to 4.5 (mean: 1.6) in 14 deaths and L/P ratios ranging from 2.1 to 20 (mean: 6.2) in 12 deaths [65,235,243–249]. Butyrfentanyl showed C/P ratios ranging from 0.4 to 2.5 (mean: 1.7) in four reported cases [244,248,249]. In one study [249], blood samples were collected at two time points: the first 9 h after death, upon admission to the morgue, and the second during the autopsy,

28 h after death. Comparing the two time points (t1 and t2) revealed an increase in butyrfentanyl concentration of 120% in femoral blood and 55% in heart blood, while lung concentrations decreased by 30% over the 19 h period. 4-Fluorobutyryl-fentanyl had L/P ratios of 1.2 and 9.9 in two case reports [250]. Carfentanyl had C/P ratios of 5.3 and 2.1 in two reported cases [235,251]. In one case where cyclopropylfentanyl was involved together with methoxyacetylfentanyl and *p*-fluoroisobutyrylfentanyl, the C/P ratio was 1.5 [252]. Fluorofentanyl exhibited C/P ratios of 1.0 and 1.3 in two reported cases [64]. Lastly, *p*-fluoroisobutyryl fentanyl had C/P ratios of 1.1 and 4.0 in two reported cases, while the L/P ratios ranged from 7.9 to 21.3 (mean: 13.9) in five cases [253,254].

Furanylfentanyl C/P ratios ranged from 1.8 to 4.4 (mean: 2.5) across four cases [235,252,255,256]. Methoxyacetylfentanyl C/P ratios were 5.0 and 1.7 in two reported cases, with the latter involving a postmortem interval of 2–5 days [252,257]. Octfentanil C/P ratios ranged from 1.0 to 1.5 (mean: 1.2) in three reported deaths [258–260]. For *p*-fluorofuranylfentanyl, C/P ratios varied from 0.5 to 30 (mean: 4.5) in 19 deaths [261]. U-47700 showed C/P ratios ranging from 0.65 to 2.6 (mean: 1.6) in five reported deaths [251,257,262–264]. In another set of 26 U-47700-related fatalities, C/P ratios ranged from 0.6 to 7.3 (mean: 1.9), while L/P ratios varied between 1.1 and 15.8 (mean: 4.9) [265]. The PMR results for these substances are consistent with previous findings for fentanyl. AH-7921 had C/P ratios of 0.4 and 1.1 in two cases [266,267], while MT-45 showed a C/P ratio of 0.5 in only one reported case [267].

Only a few derivatives, such as acetylfentanyl, *p*-fluorofuranylfentanyl, and U-47700, have enough cases to suggest a potential PMR. For the remaining compounds, the limited data (1–4 cases per analyte) prevent definitive conclusions on PMR. However, for the remaining revised compounds, individual findings indicate that they may also be affected by PMR, as most showed a C/P ratio greater than 1 and tended to accumulate in the liver. The exceptions are methoxyacetylfentanyl [257] and possibly AH-7921 [266], which exhibited L/P ratios less than 1. Further studies are necessary to confirm these preliminary observations.

3.10. Nitazenes

Nitazenes are a type of benzimidazole opioids that emerged on the illicit drug market to meet the demand for cheaper alternatives to heroin, following the schedule of fentalogues. Nitazenes are synthetic analogs of etonitazene, a μ-opioid receptor agonist discovered in 1956 by the pharmaceutical company CIBA Aktiengesellschaft in Basel, Switzerland. The chemical structure of nitazenes includes a benzimidazole core with an *N*-ethylamine side chain at position 1 and a phenylalkyl chain at position 2, see Figure 15. Despite their structural differences from traditional opioids and fentanyl analogs, nitazenes have demonstrated strong affinity for the μ-opioid receptor, with many being more potent than fentanyl. The most relevant are metonitazene, isotonitazene, protonitazene, *N*-pyrrolidino etonitazene, etodesnitazene, *N*-pyrrolidino protonitazene, *N*-pyrrolidino metonitazene, and butonitazene.

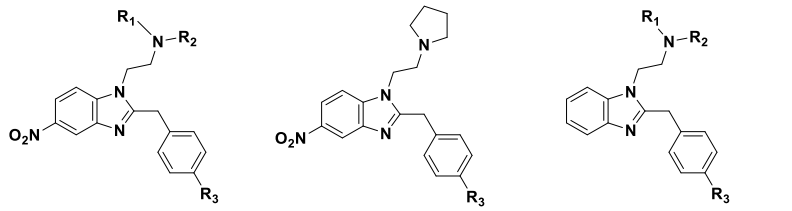


Figure 15. The chemical structure of the main nitazenes.

Table 3. Summary of the results found in the papers included in this review that investigated the distribution of NPS from fatal cases in relation to synthetic opioids, nitazenes, and synthetic cannabinoids.

Classification	NPS	pKa	logP	Age and Sex	Cause of Death	PMI	Samples Collected	Extraction Method	Analytical Technique	Results	C/P or L/P Ratios	Other Toxicological Findings	Classification
Synthethic Opioids	3-methyl-fentanyl	9.08	4.3	31-year-old woman	Acute intoxication by 3-methylfentanyl, accident	Unknown	b, vh	SPE	LC-MS/MS	FB: 1.7 ng/mL HB: 2.6 ng/mL	C/P = 1.5	Naloxone,cotinine, pseudoephedrine: 620 ng/mL, norpseudoephedrine: 22 ng/mL diazepam: <20 ng/mL, nordiazepam: <20 ng/mL	Sofalvi S. et al. (2017) [235]
	Acetyl-fentanyl	9.0	3.5	approx. 30, male	Acute poisoning by "bath salts"containing acetylfentany and 4-methoxy-PV8	Unknown	b, ur, gc	QuEChERS	GC-MS: LC-MS/MS (Q)	FB: 153 ng/mL HB: 239 ng/mL	C/P = 1.5	4-Mehoxy-PV8, 7-aminonitrazepam, phenobarbital, methylphenidate, chlorpromazine and risperidone	Yonemitsu K. et al. (2016) [65]
	Acetyl-fentanyl	9.0	3.5	54-year-old man	Unknown	Unknown	b, vh	SPE	LC-MS/MS	FB: 2.2 ng/mL HB: 7.2 ng/g	C/P = 3.3	Fentanyl: 35 ng/mL Norfentanyl: 0.53 ng/mL THC: 5.9 ng/mL 11-OH-THC: 1.1 ng/mL THC-COOH: 42 ng/mL	Sofalvi S. et al. (2017) [235]
	Acetyl-fentanyl	9.0	3.5	24-year-old man	Acetylfentanyl intoxication, accident	~12 h + 25 h after he was found (autopsy)	b, vh, ur liver,	LLE	GC–MS	PB: 260 ng/mL HB: 250 ng/mL L: 1 ng/g	C/P = 0.96 L/P = 0.004	---	McIntyre I.M. et al. (2015) [243]
	Acetyl-fentanyl	9.0	3.5	44-year-old man	Acute butyr-fentanyl, acetyl fentanyl, and cocaine intoxication	~3 h + ~18 h after he was found (autopsy)	b, ur, liver,	LLE	GC–MS	PB: 38 ng/mL HB: 32 ng/mL L: 110 ng/g	C/P = 0.84 L/P = 2.9	Butyrfentanyl: 58 ng/mL, benzoylecgonine: 0.08 mg/L, levamisole:positive	McIntyre I.M. et al. (2016) [244]
	Acetyl-fentanyl	9.0	3.5	46-year-old man	Intoxication by heroin, fentanyl, acetyl fentanyl, and cocaine	Unknown	b, vh, ur, bile liver, brain	LLE	GC–MS	PB: 9 ng/mL HB: 26 ng/mL L: 180 ng/g	C/P = 2.9 L/P = 20	Acetylnorfentanyl: 2 ng/mL, morphine (free): 30 ng/mL, morphine (total): 60 ng/mL, 6-acetylmorphine: positive, fentanyl: 21 ng/mL, norfentanyl: 3 ng/mL, cocaine: 70 ng/mL, benzoylecgonine: 970 ng/mL	Poklis J. et al. (2015) [245] Pearson J. et al. (2016) [246]
		9.0	3.5	39-year-old man	Intoxication by heroin, fentanyl, and acetyl fentanyl	Unknown	b, vh, ur, bile liver, brain	LLE	GC–MS	PB: 12 ng/mL HB: 6 ng/mL L: 29 ng/g	C/P = 0.5 L/P = 2.4	Fentanyl, norfentanyl, 6-MAM	
		9.0	3.5	41-year-old man	Intoxication by heroin, fentanyl, acetyl fentanyl, and alprazolam	Unknown	b, vh, ur, bile liver, brain	LLE	GC–MS	PB: 6 ng/mL HB: 2 ng/mL L: 36 ng/g	C/P = 0.3 L/P = 6	acetylnorfentanyl: 1 ng/mL, morphine (free): <20 ng/mL, morphine (total): <20 ng/mL, 6-acetylmorphine:positive, alprazolam: 30 ng/mL, fentanyl: 19 ng/mL, norfentanyl: 8 ng/mL	
		9.0	3.5	55-year-old man	Intoxication by acetyl fentanyl and oxycodone	Unknown	b, vh, ur, bile liver, brain	LLE	GC–MS	PB: 310 ng/mL HB: 700 ng/mL L: 690 ng/g	C/P = 2.2 L/P = 2.2	Acetylnorfentanyl: 63 ng/mL, oxycodone: 80 ng/mL, oxymorphone (total): 20 ng/mL, alprazolam: <20 ng/mL	

Table 3. *Cont.*

Classification	NPS	pKa	logP	Age and Sex	Cause of Death	PMI	Samples Collected	Extraction Method	Analytical Technique	Results	C/P or L/P Ratios	Other Toxicological Findings	Classification
Synthethic Opioids	Acetyl-fentanyl	9.0	3.5	26-year-old woman	Intoxication by acetyl fentanyl and morphine	Unknown	b, vh, bile liver, brain	LLE	GC–MS	PB: 400 ng/mL HB: 400 ng/mL L: 1800 ng/g	C/P = 1.0 L/P = 4.5	Acetylnorfentanyl: 3 ng/mL, morphine (free): 30 ng/mL, morphine (total): 70 ng/mL	Poklis J. et al. (2015) [245] Pearson J. et al. (2016) [246]
		9.0	3.5	30-year-old man	Intoxication by acetyl fentanyl and alprazolam	Unknown	b, vh, ur, bile liver, brain	LLE	GC–MS	PB: 560 ng/mL HB: 980 ng/mL L: 1200 ng/g.	C/P = 1.7 L/P = 2.1	Acetylnorfentanyl: 2 ng/mL, alprazolam: 20 ng/mL	
		9.0	3.5	28-year-old man	Intoxication by acetyl fentanyl and alprazolam	Unknown	b, vh, ur, bile liver, brain	LLE	GC–MS	PB: 600 ng/mL HB: 670 ng/mL L: 1900 ng/g	C/P = 1.1 L/P = 3.2	Acetylnorfentanyl: 36 ng/mL, alprazolam: 230 ng/mL	
	Acetyl-fentanyl	9.0	3.5	20-year-old man	Acute acetyl fentanyl toxicity	Unknown	b, vh, ur, gc, bile, liver, brain	LLE	GC-MS	FB: 192 ng/mL HB: 285 ng/mL L: 1100 ng/g	C/P = 1.5 L/P = 5.7	Fentayl, fluoxetine, methoxetamine	Fort C. et al. (2016) [247]
	Acetyl-fentanyl	9.0	3.5	50-year-old woman	Acute acetyl fentanyl toxicity	Unknown	b, vh, ur, gc, bile, liver, brain	LLE	GC-MS	FB: 255 ng/mL HB: 210 ng/mL	C/P = 1.5	Venlafaxine: 2000 ng/mL, chlordiazepoxide and nordiazepam	
	Acetyl-fentanyl	9.0	3.5	45-year-old female	Intoxication by the combined effects of butyrylfentanyl, acetylfentanyl, alprazolam, and ethanol	Unknown	B, vh, ur, gc, bile, liver, brain	LLE	GC/MS LC–MS/MS	PB: 21 ng/mL HB: 95 ng/mL L: 160 ng/g	C/P = 4.5 L/P = 7.6	Acetylfentanyl: 21 ng/mL Acetylnorfentanyl: <1 ng/mL Alprazolam:40 ng/mL	Poklis J. et al. (2016) [248]
	Butyrfentanyl	8.8	4.3	44-year-old man	Acute butyr-fentanyl, acetyl fentanyl and cocaine intoxication	~3 h + ~18 h after he was found (autopsy	b, ur, liver	LLE	GC-MS	PB: 58 ng/mL HB: 97 ng/mL L: 320 ng/g	C/P = 1.7 L/P = 5.5	Acetyl-Fentanyl: 38 ng/mL Benzoylecgonine: 0.08 mg/L Levamisole: positive	McIntyre I.M. et al. (2016) [244]
	Butyrfentanyl	8.8	4.3	53-year-old female	Fatal intoxication by butyrfentanyl	Unknown	b, vh, ur, gc, bile, liver, brain	LLE	GC/MS LC–MS/MS	PB: 99 ng/mL HB: 220 ng/mL L: 41 ng/g	C/P = 2.2 L/P = 0.4	---	Poklis J. et al. (2016) [248]
				45-year-old female	Intoxication by the combined effects of butyrylfentanyl, acetylfentanyl, alprazolam, and ethanol,					PB: 3.7 ng/mL HB: 9.2 ng/mL L: 39 ng/g	C/P = 2.5 L/P = 10.5	Acetylfentanyl: 21 ng/mL Acetylnorfentanyl: <1 ng/mL Alprazolam: 40 ng/mL Ethanol: 1.1 g/L	
	Butyrfentanyl	8.8	4.3	23-year-old male	Most probably intoxication with butyrfentanyl	9 h after death	b, ur, gc, liver, brain, hair, muscle, spleen	LLE	LC–MS/MS	FB: 66 ng/mL HB: 39 ng/mL L: 57 ng/g	C/P = 0.6 L/P = 0.8	Benzoylecgonine: <LoQ (1.25 ng/mL) Midazolam: <LoQ (11 ng/mL) Hydroxymidazolam: 1.0 ng/mL	Staeheli S.N. et al. (2016) [249]
	4-Fluoro butyryl-fentanyl	8.7	4.0	26-year-old man	Acute intoxication	Unknown	b, ur, gc, liver, kidney, brain	SPE	LC-MS/MS	B (unspecific): 91 ng/mL L: 902 ng/g	L/P = 9.9	---	Rojkiewicz M. et al. (2017) [250]
				25-year-old woman	Acute intoxication		b, ur, liver, kidney			B (unspecific): 112 ng/mL L: 136 ng/g	L/P = 1.2	---	

Table 3. *Cont.*

Classification	NPS	pKa	logP	Age and Sex	Cause of Death	PMI	Samples Collected	Extraction Method	Analytical Technique	Results	C/P or L/P Ratios	Other Toxicological Findings	Classification
Synthethic Opioids	Carfentanyl	8.0	3.7	31-year-old female	Acute intoxication by the combined effects of carfentanil, heroin, benzodiazepinas, and cyclobenzaprine	Unknown	b	SPE	LC–MS/MS	FB: 0.36 ng/mL HB: 1.9 ng/mL	C/P = 5.3	Fentanyl: <1 ng/mL, morphine: 88 ng/mL, codeine: <10 ng/mL, 6-acetylmorphine: <4 ng/mL, clonazepam: 19 ng/mL, oxazepam: 22 ng/mL, temazepam: 110 ng/mL, cyclobenzaprine: 100 ng/mL	Sofalvi S. et al. (2017) [235]
	Carfentanyl	8.0	3.7	37-year-old male	Unknown	Unknown	b	LLE	LC–MS/MS	FB: 0.50 ng/mL HB (right): 0.57 ng/mL CB (aorta): 1.05 ng/mL	C/P = 2.1	Noscapine:positive, cannabinoids: positive, sertraline:positive, paracetamol:positive	Elliott S.P. et al. (2018) [251]
	Cyclopropyl fentanyl	9.0 *	3.86 *	29-year-old man	Polyintoxication	Unknown	b, ur	PP	LC–MS/MS	FB: 0.10 ng/mL HB: 0.15 ng/mL	C/P = 1.5	Alprazolam, quetiapine, gabapentin, duloxetine, methoxyacetyl, fentanyl: 14 ng/mL, *p*-fluoroisobutyrylfentanyl (FIBF): 27 ng/mL, 4-ANPP: 9.7 ng/mL	Garneau B. et al. (2020) [252]
	Fluoro-fentanyl	8.7 *	4.0 *	34-year-old man	Poisoning by fluorofentanyl: suicide	Unknown	b, vh, ur, gc, bile, liver	SPE	GC/MS LC–MS/MS	FB: 30 ng/mL HB: 30 ng/mL L: 80 ng/g	C/P = 1.0 L/P = 2.7	Amitriptyline:positive, opipramol:positive, nordiazepam:positive, amphetamine: positive, THC-COOH:positive	Strehmel N. et al. (2017) [63]
				33-year-old woman	Poisoning by fluorofentanyl: suicide	Unknown	b, ur			FB: 30 ng/mL HB: 40 ng/mL L: 20 ng/g	C/P = 1.3 L/P = 0.7	nicotine:positive, caffeine: positive, amitriptyline:positive, opipramol:positive	
	p-Fluoro iso butyryl fentanyl (FiBF)	9.0 *	4.0	29-year-old man	Polyintoxication	Unknown	b, ur	PP	LC–MS/MS	FB: 27 ng/mL HB: 31 ng/mL	C/P = 1.1	Alprazolam, quetiapine, gabapentin, duloxetine, methoxyacetyl, fentanyl: 14 ng/mL, cyclopropylfentanyl: 0.10 ng/mL, 4-ANPP: 9.7 ng/mL	Garneau B. et al. (2020) [252]
	p-Fluoro iso butyryl fentanyl (FiBF)	9.0 *	4.0	33-year-old man	Unknown	Unknown	b, vh, ur, gc, bile, liver, brain, kidney	LLE	LC–MS/MS	B (unspecific): 109 ng/mL L: 1400 ng/g	L/P = 12.8	*N*-Ethylpentylone: 64.7 ng/mL, amphetamine: 4.1 ng/mL	Zawadzki M. et al. (2021) [253]
		9.0 *	4.0	38-year-old man	Unknown	Unknown	b, vh, ur, gc, bile, liver, brain, kidney	LLE	LC–MS/MS	B (unspecific): 76.1 ng/mL L: 1620 ng/ g	L/P = 21.3	*N*-Ethylpentylone: 95.7 ng/mL, amphetamine: 3.0 ng/mL	
		9.0 *	4.0	38-year-old man	Unknown	Unknown	b, vh, ur, bile, liver, brain, kidney	LLE	LC–MS/MS	B (unspecific): 257 ng/mL L: 2040 ng/g	L/P = 7.9	*N*-Ethylpentylone: 20.1 ng/mL, amphetamine: 1.9 ng/mL	
		9.0 *	4.0	22-year-old woman	Unknown	Unknown	b, vh, ur, liver, brain	LLE	LC–MS/MS	B (unspecific): 119 ng/mL L: 1540 ng/g	L/P = 12.9	4-CMC: 4.2 ng/mL, alpha-PiHP: 6.1 ng/mL, tramadol: 1.2 ng/mL	

Table 3. *Cont.*

Classification	NPS	pKa	logP	Age and Sex	Cause of Death	PMI	Samples Collected	Extraction Method	Analytical Technique	Results	C/P or L/P Ratios	Other Toxicological Findings	Classification
Synthethic Opioids	*p*-Fluoro iso butyryl fentanyl (FiBF)	9.0 *	4.0	35-year-old man	4-FiBF mono-intoxication	Unknown	blood, vh, urine, gc, liver, kidney, brain	SPE	GC/MS, HPLC-DAD LC–MS/MS	FB: 30 ng/mL HB: 120 ng/mL L: 440 ng/g	C/P = 4.0 L/P = 14.7	---	Roosendaal J. et al. (2023) [254]
	Furanyl fentanyl	9.0 *	3.6 *	53-year-old woman	Acute intoxication due to the combined effects of heroin, fentanyl, diphenydramine and furanylfentanyl	Unknown	b, vh	SPE	GC/MS LC–MS/MS	FB: 5.5 ng/mL HB: 8.7 ng/mL	C/P = 1.6	Fentanyl: 1.3 ng/mL, norfentanyl: 0.34 ng/mL, morphine: <10 ng/mL, 4-ANPP: positive, nicotine: positive, cotinine: positive, diphenhydramine: <50 ng/mL	Sofalvi S. et al. (2017) [235]
	Furanyl fentanyl	9.0 *	3.6 *	30-year-old man	Multiple intoxication	Unknown	b, ur	PP	LC–MS/MS	FB: 0.89 ng/mL HB: 2.4 ng/mL	C/P = 2.7	Clonazepam: 94 ng/mL, mehylphenidate: 15 ng/mL, THC: 18 ng/mL,THCCOOH: 32 ng/mL, THC-OH: 3.3 ng/mL, naproxen: 2.12 ng/mL, nortriptyline: 14 ng/mL, diazepam: 11 ng/mL, 4-ANPP: 18 ng/mL and U-47700: 26 ng/mL	Garneau B. et al. (2020) [252]
	Furanyl fentanyl	9.0 *	3.6 *	23-year-old man	Acute furanylfentanyl toxicty	Unknown	b, vh, ur, gc, liver	LLE	GC/MS LC–MS/MS	FB: 1.9 ng/mL HB: 2.8 ng/mL L: negative	C/P = 1.5	Codeine: <50 ng/mL, amphetamine: <20 ng/mL, methamphetamine: <50 ng/mL, THC: 4 ng/mL, THC-COOH: 17 ng/mL, nicotine: positive, cotinine: positive, caffeine: positive	Martucci H.F.H. et al. (2018) [255]
	4-ANPP	9.4 *	3.5 *							FB: 4.3 ng/mL HB: 5.8 ng/mL L: negative	C/P = 1.3		
	Furanyl fentanyl	9.0 *	3.6 *	53-year-old man	Acute intoxication Furanylfentanyl	48 h after he was found (autopsy)	b, ur, gc, bile, CSF	SPE	LC–MS/MS	FB: 2.7 ng/mL HB: 11.8 ng/mL	C/P = 4.4	---	Freni F. et al. (2019) [256]
	4-ANPP	9.4 *	3.5 *							FB: 50.4 ng/mL HB: 93.5 ng/mL	C/P = 1.8		
Synthethic Opioids	Methoxy acetyl fentanyl	8.9 *	2.8 *	29-year-old man	Pneumonia secondary to drug intoxication	Unknown	b, ur	PP	LC–MS/MS	FB: 14 ng/mL HB: 70 ng/mL	C/P = 5	Alprazolam, quetiapine, gabapentin, duloxetine, FIBF: 27 ng/mL, Cyclopropylfentanyl: 0.10 ng/mL, 4-ANPP: 9.7 ng/mL	Garneau B. et al. (2020) [252]
	Methoxy acetyl fentanyl	8.9 *	2.8 *	20-year-old man	Novel synthethic opioid toxicity	2–5 days after the death	b, gc, liver, brain, kidney	PP	LC-MS/MS	FB: 266 ng/mL CB: 450 ng/mL L: 85 ng/g	C/P = 1.7 L/P = 0.3	Furanylfentanyl 4.3 ng/mL, 4-ANPP: 15 ng/mL, alprazolam 69 ng/mL and alpha hydroxyalprazolam: 3.2 ng/mL as well as traces of diazepam and nordazepam	Giorgetti A. et al. (2024) [257]
	Octfentanil	8.9 *	3.6 *	30-year-old woman	Asphysxia syndrome likely related to toxic origin	Unknown	b, vh, gc bile	Toxivial A®	LC–QTOF-MS	PB: 3.7 ng/mL HB:3.9 ng/mL	C/P =1	Ethanol: 200 mg/mL Acetaminophen: 3 mg/mL Caffeine: 0.7 mg/mL Morphine: <5 ng/mL	Allibe N. et al. (2018) [258]

Table 3. *Cont.*

Classification	NPS	pKa	logP	Age and Sex	Cause of Death	PMI	Samples Collected	Extraction Method	Analytical Technique	Results	C/P or L/P Ratios	Other Toxicological Findings	Classification
Synthethic Opioids	Octfentanil	8.9 *	3.6 *	17-year-old man	Acute intoxication with ocfentanil	Unknown	b, ur, gc, kidney, liver, brain, bile	LLE	GC-MS HPLC-DAD LC-MS/MS	FB: 15.3 ng/mL HB: 23.3 ng/mL L: 31.2 ng/g	C/P = 1.5 L/P = 2.0	Acetaminophen: 45 mg/mL Caffeine: 0.23 mg/mL	Coopman V. et al. (2016) [259]
	Octfentanil	8.9 *	3.6 *	24-year-old man	Acute ocfentanil intoxication	Autopsy 3 days after discovering the corpse	b, ur	LLE	LC-MS/MS	PB: 9.1 ng/mL HB: 27.9 ng/mL	C/P =3.0	Citalopram: 130 ng/mL Quetiapine: <10 ng/mL THC: 2.8 ng/mL, THC-COOH: <5 ng/mL	Dussy F.E. et al. (2016) [260]
	p-Fluoro furanyl fentanyl (p-FFF)	8.99 *	3.81 *	52-year-old man	Synthetic opioid toxicity	Unknown	b	LLE	LC-QTOF LC-MS/MS	PB:2.2 ng/mL CB: 6.1 ng/mL	C/P =2.8	Naloxone, nicotine, caffeine, trazodone, lidocaine, hydroxyzine	Rodriguez Salas J. et al. (2022) [261]
	F-4-ANPP	9.36 *	3.65 *							PB: 0.86 ng/mL CB: 1.8 ng/mL	C/P =2.09		
	p-FFF	8.99 *	3.81 *	37-year-old man	Multidrug toxicity	Unknown	b	LLE	LC-QTOF LC-MS/MS	PB: 2.2 ng/mL CB: 16 ng/mL	C/P =7.3	Morphine, cocaine, BZE, cocaethylene, levamisole, nicotine, ibuprofen, lidocaine	
	F-4-ANPP	9.36 *	3.65 *							PB:1.3 ng/mL CB: 4.1 ng/mL	C/P =3.1		
	p-FFF	8.99 *	3.81 *	27-year-old man	Synthetic opioid toxicity: oxycodone and ethanol toxicity	Unknown	b	LLE	LC-QTOF LC-MS/MS	PB:3.0 ng/mL CB: 2.2 ng/mL	C/P = 0.7	Oxycodone, oxymorphone, noroxycodone, ethanol (0.143 g/dL)	
	F-4-ANPP	9.36 *	3.65 *							PB:2.3 ng/mL CB: 4.7 ng/mL	C/P =2.04		
	p-FFF	8.99 *	3.81 *	36-year-old woman	Multidrug toxicity	Unknown	b	LLE	LC-QTOF LC-MS/MS	PB: 0.88 ng/mL CB: 1.5 ng/mL	C/P = 1.7	Morphine, amphetamine, methamphetamine, ibuprofen	
	F-4-ANPP	9.36 *	3.65 *							PB: 2.3 ng/mL CB: 3.7 ng/mL	C/P =1.61		
	p-FFF	8.99 *	3.81 *	40-year-old man	Synthetic opioid Toxicity: acute and chronic ethanolism	Unknown	b	LLE	LC-QTOF LC-MS/MS	PB: 19 ng/mL CB: 10 ng/mL	C/P = 0.5	ortho-Methyl-4-ANPP, ethanol (0.258 g/dL), caffeine, ibuprofen	
	F-4-ANPP	9.36 *	3.65 *							PB: 32 ng/mL CB: 12 ng/mL	C/P =0.37		
	p-FFF	8.99 *	3.81 *	40-year-old man	Synthetic opioid toxicity: cocaine toxicity	Unknown	b	LLE	LC-QTOF LC-MS/MS	PB: 1.8 ng/mL CB: 10 ng/mL	C/P = 5.6	Naloxone, cocaine, cocaethy lene, alprazolam, ethanol (0.048 g/dL), caffeine, levamisole, lidocaine	
	F-4-ANPP	9.36 *	3.65 *							PB: 1.3 ng/mL CB: 2.3 ng/mL	C/P =1.77		
	p-FFF	8.99 *	3.81 *	31-year-old woman	Synthetic opioid toxicity	Unknown	b	LLE	LC-QTOF LC-MS/MS	PB: 1.3 ng/mL CB: 1 ng/mL	C/P = 0.77	Naloxone, sertraline	
	F-4-ANPP	9.36 *	3.65 *							PB: positive CB: positive	---		
	p-FFF	8.99 *	3.81 *	36-year-old man	Synthetic opioid toxicity	Unknown	b	LLE	LC-QTOF LC-MS/MS	PB: 0.61 ng/mL CB: 1.3 ng/mL	C/P = 2.1	Naloxone, 7-aminoclonazepam, ethanol (0.061 g/dL), caffeine, quinine	
	F-4-ANPP	9.36 *	3.65 *							PB: positive CB: 0.56 ng/mL	---		
	p-FFF	8.99 *	3.81 *	28-year-old man	Synthetic opioid toxicity	Unknown	b	LLE	LC-QTOF LC-MS/MS	PB: 7.6 ng/mL CB: 12 ng/mL	C/P =1.6	Morphine, noscapine, nor buprenorphine, THC, THC-OH, THC-CCOH, lidocaine	
	F-4-ANPP	9.36 *	3.65 *							PB: 14 ng/mL CB: 16 ng/mL	C/P = 1.1		

Table 3. *Cont.*

Classification	NPS	pKa	logP	Age and Sex	Cause of Death	PMI	Samples Collected	Extraction Method	Analytical Technique	Results	C/P or L/P Ratios	Other Toxicological Findings	Classification
Synthethic Opioids	p-FFF	8.99 *	3.81 *	35-year-old man	Synthetic opioid toxicity: Morphine and ethanol intoxication	Unknown	b	LLE	LC-QTOF LC-MS/MS	PB: 6.6 ng/mL CB: 11 ng/mL	C/P =1.6	Morphine, naloxone, cocaine, benzoilecgonine,cocaethylene, phenacetin,levamisole, lidocaine,diphenhydramine, gabapentin	Rodriguez Salas J. et al. (2022) [261]
	F-4-ANPP	9.36 *	3.65 *							PB:0.88 ng/mL CB: 1.1 ng/mL	C/P = 1.2		
	p-FFF	8.99 *	3.81 *	45-year-old woman	Synthetic opioid toxicity: multidrug toxicity	Unknown	b	LLE	LC-QTOF LC-MS/MS	PB: 2.7 ng/mL CB: 16 ng/mL	C/P = 5.9	Naloxone, tramadol, *o*-desmethyltramadol, cocaine, cocaethylene, norcocaine, levamisole, lidocaine, sertra line, trazodone, hydroxyzine, gabapentin, bupropion, lam otrigine, *m*CPP, ethanol (0.011 g/dL)	
	F-4-ANPP	9.36 *	3.65 *							PB: 3.8 ng/mL CB: 6.8 ng/mL	C/P = 1.8		
	p-FFF	8.99 *	3.81 *	53-year-old man	Multidrug toxicity: arteriosclerotic cardiovascular disease	Unknown	b	LLE	LC-QTOF LC-MS/MS	PB: 14 ng/mL CB: 22 ng/mL	C/P =1.6	Methamphetamine, cocaine, cocaethylene, ethanol (0.309 g/dL), caffeine, lidocaine	
	F-4-ANPP	9.36 *	3.65 *							PB: 3.8 ng/mL CB: 6.8 ng/mL	C/P = 1.79		
	p-FFF	8.99 *	3.81 *	24-year-old man	Opioid toxicity: clonazepam intoxication	Unknown	b	LLE	LC-QTOF LC-MS/MS	PB: 2.3 ng/mL CB: 12 ng/mL	C/P =5.2	Hydrocodone, hydro morphone, clonazepam, 7-aminoclonazepam, acetaminophen, quinine, THC, THC-COOH	
	F-4-ANPP	9.36 *	3.65 *							PB: 3.6 ng/mL CB: 7.8 ng/mL	C/P = 2.2		
	p-FFF	8.99 *	3.81 *	47-year-old man	Synthetic opioid toxicity: alprazolam intoxication	Unknown	b	LLE	LC-QTOF LC-MS/MS	PB: 6.2 ng/mL CB: 73 ng/mL	C/P =11.8	Alprazolam, clindamycin	
	F-4-ANPP	9.36 *	3.65 *							PB: 5.8 ng/mL CB: 46 ng/mL	C/P = 7.9		
	p-FFF	8.99 *	3.81 *	40-year-old man	Synthetic opioid toxicity	Unknown	b	LLE	LC-QTOF LC-MS/MS	PB: 23 ng/mL CB: 36 ng/mL	C/P =1.6	Methamphetamine, lidocaine	
	F-4-ANPP	9.36 *	3.65 *							PB: 7.4 ng/mL CB: 13 ng/mL	C/P = 1.7		
	p-FFF	8.99 *	3.81 *	62-year-old man	Synthetic opioid toxicity: cocaine and heroin intoxication, hypertensive cardiovascular disease	Unknown	b	LLE	LC-QTOF LC-MS/MS	PB: 10 ng/mL CB: 6.6 ng/mL	C/P =0.7	6-AM, morphine, cocaine, BZE, Norcocaine, cocaethylene, levamisole, lidocaine, MEGX	
	F-4-ANPP	9.36 *	3.65 *							PB: 2.3 ng/mL CB: 0.71 ng/mL	C/P = 0.3		
	p-FFF	8.99 *	3.81 *	48-year-old man	Synthetic opioid toxicity	Unknown	b	LLE	LC-QTOF LC-MS/MS	PB: 2.7 ng/mL CB: 6.6 ng/mL	C/P =2.4	Naloxone, hydromorphone, alprazolam, caffeine, cyclobenzaprine, levetiracetam	
	F-4-ANPP	9.36 *	3.65 *							PB: 0.56 ng/mL CB: positive	---		
	p-FFF	8.99 *	3.81 *	42-year-old man	Synthetic opioid toxicity	Unknown	b	LLE	LC-QTOF LC-MS/MS	PB: 0.53 ng/mL CB: 16 ng/mL	C/P =30	Ethanol (0.267 g/dL)	
	F-4-ANPP	9.36 *	3.65 *							PB: positive CB: 6.8 ng/mL	---		

Table 3. *Cont.*

Classification	NPS	pKa	logP	Age and Sex	Cause of Death	PMI	Samples Collected	Extraction Method	Analytical Technique	Results	C/P or L/P Ratios	Other Toxicological Findings	Classification
Synthethic Opioids	p-FFF	8.99 *	3.81 *	49-year-old woman	Synthetic opioid toxicity: Multidrug toxicity	Unknown	b	LLE	LC-QTOF LC-MS/MS	PB: 2.9 ng/mL CB: 2.6 ng/mL	C/P = 0.9	Naloxone, 6-MAM, codeine, methamphetamine, cocaine, BZE, lidocaine	Rodriguez Salas J. et al. (2022) [261]
	F-4-ANPP	9.36 *	3.65 *							PB: positive CB: positive	---		
	U-47700	9.2 *	4.0 *	30-year-old man	Polyintoxication with the likely contribution of coronary atherosclerosis.	Unknown	b, ur	SPE	LC–MS/MS	FB: 26 ng/mL HB: 45 ng/mL	C/P = 1.7	Clonazepam: 94 ng/mL, mehylphenidate: 15 ng/mL, THC: 18 ng/mL, THCCOOH: 32 ng/mL, THC-OH: 3.3 ng/mL, naproxen: 2.12 ng/mL, nortriptyline: 14 ng/mL, diazepam: 11 ng/mL, 4-ANPP: 18 ng/mL and furanylfentanyl: 0.89 ng/mL	Garneau B. et al. (2020) [252]
		9.2 *	4.0 *	31-year-old man	U-47700 toxicity, in the setting of a combined intake of multiple drugs	Unknown	b, gc, liver, brain, kidney	PP	LC-MS/MS	FB: 204 ng/mL CB: 470 ng/mL L: 198 ng/g	C/P = 2.3 L/P = 1.0	Methadone: 290 ng/mL, EDDP: 14 ng/mL, flubromazepam: 480 ng/mL and hydroxyflu bromazepam: 85 ng/mL, diazepam: 300 ng/mLL, nordazepam: 100 ng/mL, temazepam: 10 ng/mL, oxazepam and duloxetine (<LOQ), ethanol (1.64 g/kg)	Giorgetti A. et al. (2024) [257]
		9.2 *	4.0 *	46-year-old man	Acute U-47700 and alprazolam abuse	~28 h after he was found (autopsy)	b, vh, ur, gc liver	LLE	GC-MS	PB (iliac): 190 ng/mL HB: 340 ng/mL L: 1700 ng/g	C/P = 1.8 L/P = 8.9	Alprazolam:0.12 mg/ L, nordiazepam: <0.05 mg/ L, doxylamine: 0.30 mg/L, diphenhydramine: 0.14 mg/L, ibuprofen: 2.4 mg/L, salicylicacid: <20 mg/L THC-COOH: 2.4 ng/mL	McIntyre IM et al. (2017) [262]
		9.2 *	4.0 *	Unknown	U-47700 consumption	Unknown	b, ur, liver, lung, brain, kidney	LLE	LC-MS/MS	FB: 525 ng/mL HB: 1347 ng/mL L: 4300 ng/g	C/P = 2.6 L/P = 8.2	Unknown matrix: diphenidine: approx. 1.7 ng/mL, methoxphenidine: approx. 26 ng/mL	Dziadosz M. et al. (2017) [263]
				Unknown	U-47700 consumption	Unknown	b, ur, liver, lung, brain, kidney			FB: 819 ng/mL HB: 1043 ng/mL L: 3100 ng/g	C/P = 1.3 L/P = 3.8	Ibuprofen: approx. 1.8 mg/mL Naloxone: 1.9 ng/mL	
		9.2 *	4.0 *	26-year-old man	Acute U-47700 intoxication	~24 h after he was found (autopsy)	b, vh, ur, liver, brain	SPE	GC/MS GC-NPD	FB: 400 ng/mL HB: 260 ng/mL L: 280 ng/g	C/P = 0.6 L/P = 0.7	THC: 19 ng/mL	Rohrig T.P. et al. (2017) [264]

Table 3. *Cont.*

Classification	NPS	pKa	logP	Age and Sex	Cause of Death	PMI	Samples Collected	Extraction Method	Analytical Technique	Results	C/P or L/P Ratios	Other Toxicological Findings	Classification
Synthethic Opioids	U-47700	9.2 *	4.0 *	26-year-old man	Combined use of U-47700 with new stimulant drugs	Unknown	b, vh, ur, gc, liver, pericardial fluid	SPE	LC-QTOF-MS LC-MS/MS	FB: 580 ng/mL HB: 860 ng/mL L: 2200 ng/g	C/P = 1.5 L/P = 3.9	MDPPP: ca. 1.9 ng/mL, α-PVP ca. 270 ng/mL, α-PHP ca. 18 ng/mL, α-PVT: detected, butane: detected	Fels H. et al. (2019) [265]
		9.2 *	4.0 *	30-year-old man	Combined use of U-47700 with new stimulant drugs	Unknown	b, vh, ur, gc, liver, pericardial fluid	SPE	LC-QTOF-MS LC-MS/MS	FB: 1000 ng/mL HB: 2000 ng/mL L: 3900 ng/g	C/P = 2.0 L/P = 3.9	Diazepam: 240 ng/mL, nordazepam: 210 ng/mL, oxazepam: 14 ng/mL, temazepam 17 ng/mL, diphenhydramine: 160 ng/mL, amphetamine: trace amounts, MDMA: trace amounts, MDAI ca. 520 ng/mL, 3-FPM: ca. 440 ng/mL, 4-Methyl-*N*-ethyl norpentedrone: ca. 120 ng/mL, *N*-ethylpentylone ca. 330 ng/mL, 4-BMC: ca. 10 ng/mL	
		9.2 *	4.0 *	29-year-old man	Combined use of U-47700 with new stimulant drugs	Unknown	b, vh, ur, gc, liver, pericardial fluid	SPE	LC-QTOF-MS LC-MS/MS	FB: 490 ng/mL HB: 880 ng/mL L: 6000 ng/g	C/P = 1.8 L/P = 12.2	Pregabalin: 6200 ng/mL, quetiapine: 95 ng/mL, *N*-ethylhexedrone ca. 120 ng/mL (heart blood)	
		9.2 *	4.0 *	31-year-old man	Combined use of U-47700 with new stimulant drugs	Unknown	b, vh, ur, gc, liver, pericardial fluid	SPE	LC-QTOF-MS LC-MS/MS	FB: 500 ng/mL HB: 590 ng/mL L: 1500 ng/g	C/P = 1.2 L/P = 3	Pregabalin: 2800 ng/mL, doxepin: 42 ng/mL, nordoxepin: 39 ng/mL, amitriptyline: 8.1 ng/mL, nortriptyline: 4.6 ng/mL, 4F-MPH: ca. 110 ng/mL, PV8 ca. 100 ng/mL.	
		9.2 *	4.0 *	49-year-old man	Monointoxication with U-47700	Unknown	b, vh, ur, gc, liver, pericardial fluid	SPE	LC-QTOF-MS LC-MS/MS	FB: 1500 ng/mL HB: 4600 ng/mL L: 8400 ng/g	C/P = 3.1 L/P = 5.6	Morphine: 5.6 ng/mL, codeine: 1.9 ng/mL, doxepin: 23 ng/mL, nordoxepin: 38 ng/mL, metoprolol: 130 ng/mL, 3-FPM ca.: 90 ng/mL (heart blood), methiopropamine; ca. 1.1 ng/mL (heart blood), methoxphenidine: ca. 5.9 ng/mL (heart blood), 3-MeO-PCP: detected	
		9.2 *	4.0 *	45-year-old man	Combined use of U-47700 with new stimulant drugs	Unknown	b, vh, ur, gc, liver, pericardial fluid	SPE	LC-QTOF-MS LC-MS/MS	FB: 420 ng/mL HB: 440 ng/mL L: 3000 ng/g	C/P = 1.05 L/P = 7.1	Citalopram: 67 ng/mL, diclofenac: 25 ng/mL, α-PNP: ca. 7.0 ng/mL, *N*-ethylhexedrone: ca. 160 ng/mL, *N*-ethylpentylone: ca. 900 ng/mL, etanol: 0.23%.	
		9.2 *	4.0 *	33-year-old man	Monointoxication with U-47700	Unknown	b, vh, ur, gc, liver, pericardial fluid	SPE	LC-QTOF-MS LC-MS/MS	FB: 2100 ng/mL HB: 2500 ng/mL L: 4100 ng/g	C/P = 1.2 L/P = 1.9	Doxepin: 110 ng/mL, nordoxepin: 86 ng/mL, venlafaxine: 1400 ng/mL, *N*-desmethylvenlafaxine: 540 ng/mL, *N*-ethylhexedrone: ca. 7.4 ng/mL	

Table 3. *Cont.*

Classification	NPS	pKa	logP	Age and Sex	Cause of Death	PMI	Samples Collected	Extraction Method	Analytical Technique	Results	C/P or L/P Ratios	Other Toxicological Findings	Classification
Synthethic Opioids	U-47700	9.2 *	4.0 *	23-year-old man	Combined use of U-47700 along with synthetic cannabinoids	Unknown	b, vh, ur, gc, liver, pericardial fluid	SPE	LC-QTOF-MS LC-MS/MS	FB: 490 ng/mL HB: 870 ng/mL L: 5800 ng/g	C/P = 1.8 L/P = 11.8	5F-ADBICA: ca. 0.14 ng/mL, 5F-MDMB-PICA: ca. 0.70 ng/mL, AMB-CHMICA: <0.1 ng/mL, MDMB-CHMICA: <0.1 ng/mL, MDMB-FUBICA: <0.1 ng/ mL	Fels H. et al. (2019) [265]
		9.2 *	4.0 *	31-year-old man	Monointoxication with U-47700	Unknown	b, vh, ur, gc, liver, pericardial fluid	SPE	LC-QTOF-MS LC-MS/MS	FB: 1000 ng/mL HB: 1100 ng/mL L: 1400 ng/g	C/P = 1.1 L/P = 1.4	Amphetamine: 61 ng/mL, MDMA: 100 ng/mL, MDA 1.5 ng/mL, clonazolam: trace amounts, 8-aminoclonazolam:+	
		9.2 *	4.0 *	56-year-old man	Combined use of U-47700 along with other NPS	Unknown	b, vh, ur, gc, liver, pericardial fluid	SPE	LC-QTOF-MS LC-MS/MS	FB: 1600 ng/mL HB: 4900 ng/mL L: 7200 ng/g	C/P = 3.0 L/P = 4.5	Trimipramine: 680 ng/mL, diphenhydramine: 99 ng/mL, fluoxetine: 290 g/mL, mitragynine: 8.4 ng/mL, butylone: ca. 3.5 ng/mL, sildenafil: 42 ng/mL, amlodipine: 4.3 ng/mL, 3,4-DMMC: ca. 1.8 ng/mL, 5F-ADB < 0.1 ng/mL, ADB-FUBINACA: ca. 4.7 ng/mL, AM-2201: ca. 0.12 ng/mL, AMB-CHMICA: ca. 0.1 ng/mL, EG-018: ca. 4.7 ng/mL	
		9.2 *	4.0 *	31-year-old man	Monointoxication with U-47700	Unknown	b, vh, ur, gc, liver, pericardial fluid	SPE	LC-QTOF-MS LC-MS/MS	FB: 400 ng/mL HB: 890 ng/mL L: 1600 ng/g	C/P = 1.8 L/P = 4.0	Ethanol: 0.67%	
		9.2 *	4.0 *	42-year-old man	Monointoxication with U-47700	Unknown	b, vh, ur, gc, liver, pericardial fluid	SPE	LC-QTOF-MS LC-MS/MS	FB: 2000 ng/mL HB: 1200 ng/mL L: 2200 ng/g	C/P = 0.6 L/P = 1.1	Amitriptyline: 340 ng/mL, nortriptyline: 300 ng/mL, diphenhydramine: ca. 28 ng/mL	
		9.2 *	4.0 *	29-year-old man	Intoxication with fentanyl accompanied by U-47700 and alcohol	Unknown	b, vh, ur, gc, liver, pericardial fluid	SPE	LC-QTOF-MS LC-MS/MS	FB: 56 ng/mL HB: 39 ng/mL L: 72 ng/g	C/P = 0.7 L/P = 1.3	Methadone: 24 ng/mL (serum), EDDP: trace amounts (serum), pregabalin: 15,000 ng/mL (serum), fentanyl 1.4 ng/mL (serum), norfentanyl: 2.0 ng/mL (serum), diazepam: traces (serum), nordazepam: traces (serum), ethanol: ca. 2%	
		9.2 *	4.0 *	30-year-old man	Combined use of U-47700 with new stimulant drugs	Unknown	b, vh, ur, gc, liver, pericardial fluid	SPE	LC-QTOF-MS LC-MS/MS	FB: 540 ng/mL HB: 610 ng/mL L: 2500 ng/g	C/P = 1.1 L/P = 4.6	Amitriptyline: 260 ng/mL, nortriptyline 280 ng/mL, methoxphenidine: ca. 200 ng/mL, bromazepam: 5.8 ng/mL, diazepam: traces, nordazepam: traces, lorazepam: traces, carbamazepine 35 ng/mL	

Table 3. *Cont.*

Classification	NPS	pKa	logP	Age and Sex	Cause of Death	PMI	Samples Collected	Extraction Method	Analytical Technique	Results	C/P or L/P Ratios	Other Toxicological Findings	Classification
Synthethic Opioids	U-47700	9.2 *	4.0 *	26-year-old man	Intoxication with both fentanyl and U-47700	Unknown	b, vh, ur, gc, liver, pericardial fluid	SPE	LC-QTOF-MS LC-MS/MS	FB: 1000 ng/mL HB: 990 ng/mL L: 2800 ng/g	C/P = 1.0 L/P = 2.8	Fentanyl: 2.4 ng/mL, norfentanyl: 0.67 ng/mL, diazepam: traces, nordazepam: 1.7 ng/mL, tilidine: traces, nortilidine: traces, fluoxetina: 9.8 ng/mL	Fels H. et al. (2019) [265]
		9.2 *	4.0 *	25-year-old man	Monointoxication with U-47700	Unknown	b, vh, ur, gc, liver, pericardial fluid	SPE	LC-QTOF-MS LC-MS/MS	FB: 2100 ng/mL HB: 2600 ng/mL L: 4200 ng/g	C/P = 1.2 L/P = 2.0	Methamphetamine: 31 ng/mL, amphetamine: 34 ng/mL, ephedrine: 19 ng/mL, benzoylecgonine: traces, morphine: 14 ng/mL, hydromorphone: traces, buprenorphine: ca. 0.3 ng/mL, α-PVP: 34 ng/mL, acetaminophen: traces	
		9.2 *	4.0 *	36-year-old woman	Monointoxication with U-47700	Unknown	b, vh, ur, gc, liver, pericardial fluid	SPE	LC-QTOF-MS LC-MS/MS	FB: 2200 ng/mL HB: 4400 ng/mL L: 4300 ng/g	C/P = 2.0 L/P = 1.9	Venlafaxine: 1600 ng/mL, *N*-desmethylvenlafaxine: 1200 ng/mL, pipamperone: 96 ng/mL, promethazine: 15 ng/mL, diazepam: traces, nordazepam: 26 ng/mL, oxazepam: traces, temazepam: traces, oxycodone: 1.8 ng/mL, noroxycodone: ca. 13 ng/mL	
		9.2 *	4.0 *	40-year-old man	Monointoxication with U-47700	Unknown	b, vh, ur, gc, liver	SPE	LC-QTOF-MS LC-MS/MS	FB: 330 ng/mL HB: 2400 ng/mL L: 5200 ng/g	C/P = 7.3 L/P = 15.8	Quetiapine: 570 ng/mL, doxylamine: 2.3 ng/mL	
	AH-7921	9.1 *	3.7 *	19-year-old man	Opioid in toxication	Unknown	b, ur, gc, bile liver, kidney, lung, brain, spleen, heart	LLE	GC-MS	PB: 9100 ng/mL HB: 3900 ng/mL L: 6000 ng/g	C/P = 0.4 L/P = 0.6	MPHP: 0.10 mg/L Dextrometorphane: positive	Vorce S.P. et al. (2014) [266]
	AH-7921	9.1 *	3.7 *	22-year-old woman	Consumption of an overdose of AH-7921	Unknown	b, vh, ur, gc, liver, pericardial fluid	PP	LC–QTOF-MS	PB: 450 ng/mL CB: 480 ng/mL L: 530 ng/g	C/P = 1.1 L/P = 1.2	Methadone: positive Diphenhydramine: positive Tetrazepam: positive Methamphetamine: traces Amphetamine: traces Mirtazapine: 43.2 ng/mL	Fels H. et al. (2017) [267]
	MT-45	8.94 *	5.27 *	24-year-old man	Death attributed to consumption of an MT-45 overdose	Unknown	b, vh, ur, gc, liver, pericardial fluid	PP	LC–QTOF-MS	PB: 660 ng/mL CB: 1300 ng/mL L: 24,000 ng/g	C/P = 1.9 L/P = 8.3	Lidocaine: positive PB-22: <0.1 ng/mL 5F-AKB-48 (5F-APINACA): <0.1 ng/mL Methoxetamine: positive	Fels H. et al. (2017) [267]

Table 3. *Cont.*

Classification	NPS	pKa	logP	Age and Sex	Cause of Death	PMI	Samples Collected	Extraction Method	Analytical Technique	Results	C/P or L/P Ratios	Other Toxicological Findings	Classification
Nitazenes	*N*-Pyrrolidino protonitazene	8.5	≥4	29-year-old man	Multiple drug intoxication	Date collected: 07/02/2023 Date received: 10/02/2023	b	LLE	LC-QTOF-MS LC-MS/MS	PB: 0.1 ng/mL CB: 0.4 ng/mL	C/P = 4	4-ANPP: 3.9 ng/mL, benzoylecgonine: 620 ng/mL, chlordiazepoxide, cotinine, diphenhydramine: 310 ng/mL, fentanyl: 24 ng/mL, hydroxyzine: 100 ng/mL, naloxone, nordiazepam, norfentanyl: 5.7 ng/mL, quetiapine, quinine, xylazine: 28 ng/mL. In cardiac blood also: protonitazene, metonitazene: 0.63 ng/mL, *N*-desethyl protonitazene: 0.12 ng/mL	De Vrieze L.M. et al. (2024) [268]
	Metonitazene	8.79 *	≥4	47-year-old man	Multiple drug intoxication	Unknown	b, ur	LLE	LC-QTOF-MS LC-MS/MS	PB: 5 ng/mL CB: 12 ng/mL	C/P = 2.4	8-aminoclonazolam, flualprazolam,fentanyl: 3.0 ng/mL, norfentanyl: 0.44 ng/mL, 4-ANPP, THC: 0.52 ng/mL, THCCOOH: 12 ng/mL, caffeine, nicotine, bupropion: 300 ng/mL, hydroxybupropion: 290 ng/mL, 10-OH-carbazepine: 9500 ng/mL,quetiapine: 590 ng/mL, gabapentin: 34,000 ng/mL. 5-aminometonitazene (352%), *N*-desethyl metonitazene (<5%), 4′-hydroxy nitazene (<5%)	Krotulski AJ. et al. (2021) [269]
	Flunitazene	8.79 *	≥4							PB: 2.1 ng/mL CB: 4.8 ng/mL	C/P = 2.3		
	Isotonitazene	8.79	≥4	41-year-old man	Acute intoxication with isotonitazene	Approximately 72 h after death	b, vh, ur, gc, CSF, pericardial fluid, liver, lung, kidney, splee, heart, muscle, hair	SPE	GC/MS LC-MS/MS	FB: 2.28 ng/mL HB: 1.70 ng/mL L: <0.05 ng/g	C/P = 0.7	Diazepam: 29 ng/mL, nordiazepam: 71 ng/mL, oxazepam: 4.8 ng/mL, mefenamic acid <5.0 µg/mL, domperidone: 6.0 ng/mL, acetaminophen: 4.8 µg/mL	Mueller F. et al. (2021) [270]
		8.79	≥4	47-year-old man		Approximately 48 h after death				FB: 0.59 ng/mL HB: 1.13 ng/mL L: <0.05 ng/g	C/P = 1.9	Lorazepam: 12 ng/mL, THC: 56 ng/mL, THC-OH: 1.8 ng/mL, THC-COOH: 6.5 ng/mL, CBN: 2.9 ng/mL	
		8.79	≥4	47-year-old man		Approximately 96 h after death				FB: 0.74 ng/mL HB: 0.70 ng/mL L: < 0.05 ng/g	C/P = 0.9	Ethanol 57 mg/dL	
		8.79	≥4	39-year-old man	Intoxication with isotonitazene	Unknown	b, vh, ur, gc, bile, spleen, liver, brain, lung, heart, kidney, muscle, SF, and presumed IS	LLE	LC-MS/MS	FB: 1.17 ng/mL HB: 1.76 ng/mL	C/P = 1.5	Cetirizine, PB: 28 ng/mL, 4-OH-Nitazene (bile and ur), *N*-desethyl-isotonitazene: CB, 0.1 ng/mL, positive in ur, lung, heart and gc	Bendjilali-Sabiani J.J. et al. (2024) [271,272]

Table 3. *Cont.*

Classification	NPS	pKa	logP	Age and Sex	Cause of Death	PMI	Samples Collected	Extraction Method	Analytical Technique	Results	C/P or L/P Ratios	Other Toxicological Findings	Classification
Synthetic cannabinoids	5F-ADB	---	3.6 *	39-year-old man	Multiple drug toxicity	Unknown	b	SPE	LC-MS/MS	PB: 0.37 ng/mL CB: 0.37 ng/mL	C/P = 1.0	Ethanol and cocaine	Boland D.M. et al. [273]
	5F-ADB (COOH)	3.84 *	3.34 *							PB: 2.4 ng/mL CB: 2.5 ng/mL	C/P = 1.0		
	5F-ADB	---	3.6 *	50-year-old man	Acute 5-fluoro-ADB toxicity	Unknown	b	SPE	LC-MS/MS	PB: 0.05 ng/mL CB: 0.31 ng/mL	C/P = 6.2	---	
	5F-ADB (COOH)	3.84 *	3.34 *							PB: 4.6 ng/mL CB: 81 ng/mL	C/P = 17.6		
	5F-ADB	---	3.6 *	37-year-old man	Acute 5-fluoro-ADB toxicity	Unknown	b	SPE	LC-MS/MS	PB: 0.03 ng/mL CB: 0.01 ng/mL	C/P = 0.3	---	
	5F-ADB (COOH)	3.84 *	3.34 *							PB: 34 ng/mL PB: 64 ng/mL	C/P = 1.9		
	5F-ADB	---	3.6 *	48-year-old man	Acute 5-fluoro-ADB toxicity	Unknown	b	SPE	LC-MS/MS	PB: 0.02 ng/mL CB: 0.04 ng/mL	C/P = 2.0	---	
	5F-ADB (COOH)	3.84 *	3.34 *							PB: 11 ng/mL PB: 18 ng/mL	C/P = 1.6		
	5F-ADB	---	3.6 *	62-year-old man	Acute 5-fluoro-ADB toxicity	Unknown	b	SPE	LC-MS/MS	PB: 0.27 ng/mL CB: 0.11 ng/mL	C/P = 0.4	---	
	5F-ADB (COOH)	3.84 *	3.34 *							PB: 21 ng/mL CB: 41 ng/mL	C/P = 1.9		
	5F-ADB	---	3.6 *	37-year-old man	Acute poly-drug toxicity	Unknown	b	SPE	LC-MS/MS	PB: 0.08 ng/mL CB: 0.15 ng/mL	C/P = 1.9	Cocaine, heroin	
	5F-ADB (COOH)	3.84 *	3.34 *							PB: 15 ng/mL CB: 73 ng/mL	C/P = 4.9		
	5F-ADB	---	3.6 *	34-year-old man	Acute 5-fluoro-ADB toxicity	Unknown	b	SPE	LC-MS/MS	PB: 0.19 ng/mL CB: 0.11 ng/mL	C/P = 0.6	---	
	5F-ADB (COOH)	3.84 *	3.34 *							PB: 31 ng/mL CB: 41 ng/mL	C/P = 1.3		
	5F-ADB	---	3.6 *	44-year-old man	Aspiration associated with 5-fluoro-ADB toxicity, Part II: cardiomegaly, hypertensive type	Unknown	b	SPE	LC-MS/MS	PB: 0.12 ng/mL CB: 0.01 ng/mL	C/P = 0.08	---	
	5F-ADB (COOH)	3.84 *	3.34 *							PB: 14 ng/mL CB: 21 ng/mL	C/P = 1.5		
	5F-ADB	---	3.6 *	49-year-old man	Acute combined drug toxicity	Unknown	b	SPE	LC-MS/MS	PB: 0.56 ng/mL CB: 0.66 ng/mL	C/P = 1.2	MMB-2201, and *N*-ethylpentylone	
	5F-ADB (COOH)	3.84 *	3.34 *							PB: 10 ng/mL CB: 10 ng/mL	C/P = 1.0		
	5F-ADB	---	3.6 *	50-year-old man	5-fluoro-ADB toxicity	Unknown	b	SPE	LC-MS/MS	PB: 0.77 ng/mL CB: 0.76 ng/mL	C/P = 1.0	---	
	5F-ADB (COOH)	3.84 *	3.34 *							PB: 12 ng/mL CB: 6.8 ng/mL	C/P = 0.6		
	5F-ADB	---	3.6 *	56-year-old man	Acute 5-Fluoro-ADB Toxicity	Unknown	b	SPE	LC-MS/MS	PB: 0.15 ng/mL CB: 0.64 ng/mL	C/P = 4.2	---	
	5F-ADB (COOH)	3.84 *	3.34 *							PB: 4.9 ng/mL CB: 2.4 ng/mL	C/P = 0.5		

Table 3. *Cont.*

Classification	NPS	pKa	logP	Age and Sex	Cause of Death	PMI	Samples Collected	Extraction Method	Analytical Technique	Results	C/P or L/P Ratios	Other Toxicological Findings	Classification
Synthetic cannabinoids	5F-ADB	---	3.6 *	20-year-old man	5-fluoro-ADB toxicity	Unknown	b	SPE	LC-MS/MS	PB: 0.09 ng/mL CB: 1.9 ng/mL	C/P = 21.1	---	Boland D.M. et al. [273]
	5F-ADB (COOH)	3.84 *	3.34 *							PB: 14 ng/mL CB: 39 ng/mL	C/P = 2.8		
	5F-ADB	---	3.6 *	29-year-old man	5-fluoro-ADB toxicity	Unknown	b	SPE	LC-MS/MS	PB: 0.07 ng/mL CB: 0.10 ng/mL	C/P = 1.4	---	
	5F-ADB (COOH)	3.84 *	3.34 *							PB: 15 ng/mL CB: 9.8 ng/mL	C/P = 0.5		
	5F-ADB	---	3.6 *	56-year-old man	5-fluoro-ADB toxicity	Unknown	b	SPE	LC-MS/MS	PB: 0.03 ng/mL CB: 0.23 ng/mL	C/P = 7.7	---	
	5F-ADB (COOH)	3.84 *	3.34 *							PB: 12 ng/mL CB: 23 ng/mL	C/P = 1.9		
	5F-ADB	---	3.6 *	32-year-old man	5-Fluoro-ADB Toxicity	Unknown	b	SPE	LC-MS/MS	PB: 0.01 ng/mL CB: 0.70 ng/mL	C/P = 70	---	
	5F-ADB (COOH)	3.84 *	3.34 *							PB: 15 ng/mL CB: 63 ng/mL	C/P = 4.2		
	5F-ADB	---	3.6 *	50-year-old man	5-fluoro-ADB toxicity	Unknown	b	SPE	LC-MS/MS	PB: 0.05 ng/mL CB: 0.28 ng/mL	C/P = 5.6	---	
	5F-ADB (COOH)	3.84 *	3.34 *							PB: 14 ng/mL CB: 35 ng/mL	C/P = 2.5		
	5F-ADB (COOH)	3.84 *	3.34 *	46-year-old man	Acute 5-fluoro-ADB toxicity	Unknown	b	SPE	LC-MS/MS	PB: 11 ng/mL CB: 43 ng/mL	C/P = 3.9	---	
	5F-ADB (COOH)	3.84 *	3.34 *	59-year-old man	Acute 5-fluoro-ADB and *N*-ethylpentylone toxicity	Unknown	b	SPE	LC-MS/MS	PB: 19 ng/mL CB: 33 ng/mL	C/P = 1.7	*N*-ethylpentylone	
	5F-ADB (COOH)	3.84 *	3.34 *	44-year-old man	Acute combined-drug toxicity (*N*-ethylpentylone and 5-Fluoro-ADB)	Unknown	b	SPE	LC-MS/MS	PB: 11 ng/mL CB: 16 ng/mL	C/P = 1.4	*N*-ethylpentylone	
	5F-ADB (COOH)	3.84 *	3.34 *	46-year-old man	Acute 5-fluoro-ADB toxicity	Unknown	b	SPE	LC-MS/MS	PB: 26 ng/mL CB: 37 g/mL	C/P = 1.4	---	
	5F-ADB (COOH)	3.84 *	3.34 *	28-year-old man	Acute 5-fluoro-ADB toxicity	Unknown	b	SPE	LC-MS/MS	PB: 23 ng/mL CB: 29 ng/mL	C/P = 1.3	---	
	5F-ADB (COOH)	3.84 *	3.34 *	56-year-old man	Acute 5-fluoro-ADB toxicity	Unknown	b	SPE	LC-MS/MS	PB: 41 ng/mL CB: 166 ng/mL	C/P = 4.0	---	
	5F-ADB (COOH)	3.84 *	3.34 *	62-year-old man	Acute 5-fluoro-ADB toxicity	Unknown	b	SPE	LC-MS/MS	PB: 15 ng/mL CB: 80 ng/mL	C/P = 5.3	---	

Table 3. *Cont.*

Classification	NPS	pKa	logP	Age and Sex	Cause of Death	PMI	Samples Collected	Extraction Method	Analytical Technique	Results	C/P or L/P Ratios	Other Toxicological Findings	Classification
Synthetic cannabinoids	5F-ADB	---	3.6 *	male, in his 20s	Acute circulatory failure after drug inhalation	Unknown	b	QuEChERS	LC-MS/MS	IB: 0.12 ng/mL RHB: 0.24 ng/mL LHB: 0.45 ng/mL	C/P = 3.7	---	Usui K. et al. (2018) [274]
	5F-ADB	---	3.6 *	male, in his 50s	Acute circulatory failure after drug inhalation	Unknown	b			IB: 0.23 ng/mL RHB: 1.35 ng/mL LHB: NA	C/P = 5.8 (calculated from RHB)		
	5F-ADB	---	3.6 *	male, in his 20s	Acute circulatory failure after drug inhalation	Unknown	b			IB: 0.16 ng/mL RHB: 0.14 ng/mL LHB: 0.11 ng/mL	C/P = 0.7		
	5F-ADB	---	3.6 *	male, in his 50s	Acute circulatory failure after drug inhalation	Unknown	b			IB: 1.38 ng/mL RHB: 1.92 ng/mL LHB: NA	C/P = 1.4 (calculated from RHB)		
	AB-CHMINACA	---	2.96 *	25-year-old man	Diabetic ketoacidosis	Unknown	b, vh, ur, CSF	SPE	LC-MS/MS	FB: 2.8 ng/mL HB: 1.1 ng/mL	C/P = 0.4	AM-2201: traces <0.1 ng/mL, EAM-2201: traces <0.1 ng/mL, JWH-122: traces <0.1 ng/mL, MAM-2201: traces <0.1 ng/mL	Hess, C. et al. (2015) [275]
	AB-FUBINACA	---	---							FB: 0.97 ng/mL HB: N.D.	---		
	5F-AMB	---	3.06 *							FB: 0.19 ng/mL HB: traces <0.1 ng/mL	---		
	5F-APINACA	---	3.98 *							FB: 0.51 ng/mL HB: traces <0.1 ng/mL	---		
	STS135	---	---							FB: 0.16 ng/mL HB: N.D.	---		
	THJ 2201	---	5.22 *							FB: 0.16 ng/mL HB: N.D.	---		
	AB-CHMINACA	---	2.96 *	23 year-old man	Acute intoxication by AB-CHMINACA" resulting in cardiac arrhythmia	Alive about 5 h before being found dead	b, vh, ur, gc, bile, liver	LLE	LC-MS/MS	FB: 7.0 ng/mL HB: 16.9 ng/mL L: 404 ng/g	C/P = 2.4 L/P = 57.7	Caffeine:positive Cotinine:positive	Lavins, E.S. et al. (2015) [276] (abstract only)
				33 year-old woman	Acute intoxication by the combined effects of AB CHMINACA, methadone and diphenhy-dramine" resulting in cardiac arrhythmia	Found at home in a state of moderate decomposition. She was last known alive two days earlier when leaving a party	b, liver, kidney, brain, hair			FB: 7.1 ng/mL HB: 7.8 ng/mL L: 115 ng/g	C/P = 1.1 L/P = 16.2	Methadone: 167 ng/mL EDDP: 29.6 ng/mL Diphenhydramine: <50 ng/mL β-phenethylamine: positive Cotinine: positive	

Table 3. *Cont.*

Classification	NPS	pKa	logP	Age and Sex	Cause of Death	PMI	Samples Collected	Extraction Method	Analytical Technique	Results	C/P or L/P Ratios	Other Toxicological Findings	Classification
Synthetic cannabinoids	AB-CHMINACA	---	2.96 *	24 year-old man	AB-CHMINACA use	Unknown	b, vh, ur, liver, heart, spleen	LLE	LC-MS/MS	PB: 10.21 ng/mL L: 47.82 ng/g	L/P = 4.7	---	Knittel J.L. et al. (2015) [277] (abstract only)
	AB—CHMINACA metabolite 4	2.49 *	3.38 *							PB: 1.63 ng/mL L: 12.80 ng/g	L/P = 7.8		
	AKB48	---	4.48 *							PB: 0.36 ng/mL L: 1.03 ng/g	L/P = 2.9		
	UR144-*N*-COOH metabolite	4.67 *	3.7 *							PB: 0.54 ng/mL L: 7.60 ng/g	L/P = 14.0		
	XLR11	---	4.61 *	24 year-old man	Multidrug intoxication	Unknown	b, vh, ur, gc, liver, kidney, lung, spleen, heart, brain, adipose	LLE	LC-MS/MS	PB: 2.10 ng/mL CB: 1.95 ng/mL L: 0.31 ng/g	C/P = 0.9 L/P = 0.1	Hydrocodon: 160 ng/mL, XLR11-*N*-OH	Knittel J.L. et al. (2015) [277] (abstract only)
	UR144-*N*-COOH metabolite	4.67 *	3.7 *							PB: 45.20 ng/mL CB: 48.40 ng/mL	C/P = 1.1		
	UR144-*N*-OH metabolite	14.7 *	3.9 *							PB: 6.11 ng/mL CB: 8.94 ng/mL L: 23.70 ng/g	C/P = 1.5 L/P = 3.9		
	MAB-CHMINACA	---	3.6 *	34-year-old man	Asphyxia due to aspiration of stomach contents into the trachea, which likely took place during vomiting under low-consciousness conditions provoked by inhala tion of the 5-fluoro-ADB smoke	35–40 h	b, ur, gc, pericardial fluid, liver, kidney, lung, brain, spleen, heart muscle, adipose, pancreas	QuEChERS	LC-MS/MS	FB: 6.05 ng/mL HB: 9.30 ng/mL L: 156 ng/g	C/P = 1.5 L/P = 25.8	5F-ADB found in gc, adipose tissue, brain, heart muscle, pancreas	Hasegawa, K. et al. (2015) [278,279]
	5F-MDMB-P7AICA	---	2.97 *	31-year-old man	Lethal multiple trauma	Death 10 h after admission to the hospital. The autopsy was performed 4 days after death.	b, bile, liver, kidney, lung	PP+LLE (blood) SPE (tissues)	GC-MS LC-MS/MS	PB: 1.2 ng/mL HB: 0.69 ng/mL	C/P = 0.6	Subtherapeutic concentration of morphine and a very low concentration of benzoylecgonine in peripheral blood	Walle, N. et al. (2022) [280]
	5F-MDMB-P7AICA dimethyl butanoic acid metabolite	3.8*	2.71 *							PB:5.7 ng/mL HB:46 ng/mL L: 4 ng/ g	C/P = 8.0 L/P = 0.7		

Table 3. *Cont.*

Classification	NPS	pKa	logP	Age and Sex	Cause of Death	PMI	Samples Collected	Extraction Method	Analytical Technique	Results	C/P or L/P Ratios	Other Toxicological Findings	Classification
Synthetic cannabinoids	*N*-1-naphthalenyl-1-pentyl-1H-indole-3-carboxamide (NNEI)	---	---	Aged in his twenties, man	Probablyacutecirculatory disturbance inducedby NNEI poisoning	An autopsy was performed about 3 days after the estimated time of death.	plasma, urine, brain, heart, lung, liver, kidney, adipose, hair	SPE	LC-MS/MS	FB: 0.84 ng/mL HB: 0.64 ng/mL L: 1.31 ng/g	C/P = 0.8 L/P = 1.6	---	Sasaki, C. et al. (2015) [281]
	MAM-2201	---	5.67 *	20-year-old man	Misuse of three synthetic cannabinoids	An autopsy was executed 20 h after the victim's death.	b (plasma), ur	PP	LC–QTOF-MS	FB: 16.3 ng/mL HB: 85.8 ng/mL	C/P = 5.2	----	Zaitsu, K. et al. (2015) [282]
	AM-1220	8.76 *	4.73 *							FB: 140 ng/mL HB: 438 ng/mL	C/P = 3.1		
	AM-2232	---	4.75 *							FB: 0.86 ng/mL HB: 1.95 ng/mL	C/P = 2.2		
	3-Naphtoyl indole metabolite	---	---							FB: 9.19 ng/mL HB: 13.8 ng/mL	C/P = 1.5		
	3-(4-Methyl-1-naphtoyl) indole metabolite	---	---							FB: 1.79 ng/mL HB: 9.76 ng/mL	C/P = 5.4		
	5-OH-pentyl metabolite of MAM-2201	---	---							FB: 116 ng/mL HB: 223 ng/mL	C/P = 1.9		
	MAM-2201-COOH metabolite	4.7 *	4.76 *							FB: 7.30 ng/mL HB: 14.4 ng/mL	C/P = 1.9		
	5F-Cumyl-PEGACLONE	---	4.79 *	29-year-old man	5F-Cumyl-PEGACLONE toxicity	The autopsy was performed 2 days after the retrieval of the corpse.	b, ur, hair	LLE	LC-MS/MS	PB: 0.45 ng/mL CB: 0.07 ng/mL	C/P =0.15	9-OH-risperidone: 18 ng/mL, trimipramine: 250 ng/mL, +cinnarizine, +diphenhydramine	Giorgetti, A. et al. (2020) [283]
				48-year-old woman		The autopsy was performed with a postmortem interval of 7 days.	b, ur			PB: 0.23 ng/mL CB: 0.21 ng/mL	C/P =0.9	Morphine: 297 ng/mL, 6-MAM: 20 ng/mL, codeine: 21 ng/mL, oxazepam: 450 ng/mL, alprazolam: 10 ng/mL and paroxetine: <10 ng/mL	
				36-year-old man		The autopsy was performed the same day of the death.	b, ur			PB: 0.12 ng/mL CB: 0.22 ng/mL	C/P =1.8	Pregabalin: 6000 ng/mL, temazepa: 230 ng/mL, oxazepam: 12 ng/mL, alprazolam: 16 ng/mL, lorazepam <5 ng/mL	
				33-year-old man		The autopsy was performed with a PMI of 4 days.	b, ur, hair			PB: 0.09 ng/mL CB: 0.35 ng/mL	C/P =3.9	Benzoilecgonine: 107 ng/mL, ecgonine methyl ester: 11 ng/mL, +cocaine, +THC-COOH	

Table 3. *Cont.*

Classification	NPS	pKa	logP	Age and Sex	Cause of Death	PMI	Samples Collected	Extraction Method	Analytical Technique	Results	C/P or L/P Ratios	Other Toxicological Findings	Classification
Synthetic cannabinoids	AB-PINACA	---	2.64 *	Unknown	Polydrug toxicity	Case from 2013 reanalysed in 2018 (blood and solid tissues preserved at −80 °C for five years)	b, liver, kidney, lung	LLE	LC-MS/MS	PB: 12.6 pg/mL RHB: 19.6 pg/mL LHB: 20.6 pg/mL L: 169 pg/g	C/P = 1.6 L/P = 13.4	AB-FUBINACA, α-PVP (detected but <LOQ)	Yamagishi I. et al. [284]
	EAM-2201	---	6.09 *							PB: 56.6 pg/mL RHB: 28.7 pg/mL LHB: 31.0 pg/mL L: 126 pg/g	C/P = 0.5 L/P = 2.2		
	Mepirapim	8.09 *	2.6 *	60-year-old man	Acute poisoning by intravenous injection of mepiramim and acetylfentanyl	Unknown	b, ur	LLE	GC–MS GC-MS/MS LC-MS/MS	PB: 554 ng/mL HB: 587 ng/mL L: 6300 ng/g	C/P = 1.0 L/P = 11.4	Acetylfentanyl: 125 ng/mL	Mochizuki A. et al. [285,286]

Samples:PB: peripheral blood, FB: femoral blood, IB: iliac blood, SB: subclavian blood, CB: central blood, HB: heart blood, RHB: right heart blood, LHB: left heart blood, AB: aorta blood, L: liver, ur: urine, vh: vitreous humor, gc: gastric content, SA: serum antemortem, SC: serum cardiac, SF: subcutaneous fat, IS: injection site. **Analytical techniques:** GC-NPD: gas chromatography coupled to nitrogen–phosphorus detector, GC-MS: gas chromatography coupled to mass spectrometry; GC-MS/MS: gas chromatography coupled to tandem mass spectrometry, HPLC-DAD: High performance liquid chromatography–diode-array detector, LC-Q-TOF-MS: liquid chromatography quadrupole–time of flight mass spectrometry, LC-MS/MS: liquid chromatography–tandem mass spectrometry, LC-LIT-MS: liquid chromatography–linear ion trap mass spectrometry. **Extraction methods:** LLE: liquid–liquid extraction, SPE: solid-phase extraction, QuEChERS: quick, easy, cheap, effective, rugged, and safe, PP: protein precipitation. **Substances:**4-ANPP: 4-Aminophenyl-1-phenethylpiperidine, 5F-ADB: *N*-[[1-(5-fluoropentyl)-1H-indazol-3-yl]carbonyl]-3-methyl-L-valine, methyl ester, 5F-APINACA: *N*-(1-Amino-3-methyl-1-oxobutan-2-yl)-1-(5-fluoropentyl)-1H-indazole-3-carboxamide, 5F-Cumyl-PEGACLONE: 5-(5-fluoropentyl)-2,5-dihydro-2-(1-methyl-1-phenylethyl)-1H-pyrido [4,3-b]indol-1-one, 5F-MDMB-PICA: Methyl 2-(1-(5-fluoropentyl)-1H-indazole-3-carboxamido)-3,3-dimethylbutanoate, AB-CHMINACA: *N*-(1-Amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1H-indazole-3-carboxamide, AB-PINACA: *N*-(1-Adamantyl)-1-pentyl-1H-indazole-3-carboxamide, AKB48 (APINACA): *N*-(1-Adamantyl)- 1-pentyl-1H-indazole-3-carboxamide), AM-1220: 1-(2-Methoxyphenyl)-2-(1-pentyl-1H-indol-3-yl)ethanone, AM-2232: 1-(4-Fluorophenyl)-2-(1-pentyl-1H-indol-3-yl)ethanone, EAM-2201: 5-Fluoro-*N*-ethyl-*N*-(1-pentyl)indole-3-carboxamide, F-4-ANPP: 1-(4-Fluorophenyl)-*N*-phenylpiperidin-4-amine, AH-7921: 3,4-Dichloro-*N*-((1-(dimethylamino)cyclohexyl)-methylbenzamide, FiBF: *p*-Fluoroisobutyrylfentanyl, p-FFF: *p*-fluorofuranylfentanyl, MT-45: 1-Cyclohexyl-4-(1,2-diphenylethyl)piperazine, MAM-2201: 1-(5-Fluoropentyl)-3-(2,2,3,3-tetramethylcyclopropyl)indole, STS135: (5-fluoro-APICA): 1-(5-fluoropentyl)-*N*-tricyclo[3.3.1.13,7]dec-1-yl-1H-indole-3-carboxamide, THJ 2201: [1-(5-fluoropentyl)-1H-indazol-3-yl]-1-naphthalenyl-methanone, U-47700: 3,4-Dichloro-*N*-[2-(dimethylamino)cyclohexyl]-*N*-methylbenzamide, XLR11 (5-Fluoro-UR-144): ((1-(5-fluoropentyl)-1H-indol-3-yl)(2,2,3,3- tetramethylcyclopropyl)methanone. * Values of pKa and logP predicted using ChemDraw Professional 15.0 © Copyright 1998-2015 Perkin-Elmer Informatics Inc.

N-Pyrrolidino etonitazene and protonitazene are approximately 43 and 25 times more potent than fentanyl, respectively. In comparison, *N*-Pyrrolidino metonitazene is twice as potent as fentanyl [268]. Meanwhile, *N*,*N*-diethyl derivatives such as isotonitazene, protonitazene, and metonitazene are 9, 4, and 2 times more potent than fentanyl, respectively. Butonitazene and etodesnitazene are 2 and 4 times less potent than fentanyl [287].

Nitazenes exhibit both acidic and basic properties, with the basic properties being more pronounced due to the presence of two basic groups: the benzimidazole ring and the tertiary amine in the side chain. However, analogs lacking a nitrogen substituent can still form anions in the presence of strong bases [288]. The electron-withdrawing NO_2 group at position 5 reduces the basicity of the heteroaromatic ring [289]. Despite this, nitazenes generally have higher basic pKa values compared to acidic ones. Predicted pKa values are 9.90 and 9.60 for metonitazene and etonitazene, respectively, 8.5 for both *N*-pyrrolidino metonitazene and *N*-pyrrolidino etonitazene, and 8.9 for metodesnitazene and etodesnitazene [49,189]. Nitazenes are also lipophilic compounds. Although experimental n-octanol-water partition coefficient (log P) values have not been reported, calculated values are available. With log P values of $\geq$4 [49,189], nitazenes, similar to fentanyl (log P = 4.28), are about a thousand times more lipophilic than morphine (log P = 1.07). These chemical properties suggest that, in principle, these compounds may undergo PMR.

The metabolism of metonitazene, etonitazene, and protonitazene has been studied in vitro using human hepatocyte incubations. In the hydrolyzed culture medium, phase I metabolites such as *N*-desethyl, *N*,*N*-di-desethyl, *O*-desalkyl, *N*-desethyl-*O*-desalkyl, *N*,*N*-di-desethyl-*O*-desalkyl, and *N*-oxidized metabolites were identified. In the unhydrolyzed culture medium, *O*-glucuronides of the phase I metabolites with *O*-dealkylation were observed as phase II metabolites [290]. Another study [291] compared in vitro results with real postmortem samples, finding that in urine samples for isotonitazene, metonitazene, etodesnitazene, and metodesnitazene, *O*-dealkyl and *N*-deethyl-*O*-dealkyl metabolites, as well as glucuronides, were predominant. The *O*-dealkyl metabolites of isotonitazene and metonitazene were identical molecules, likely produced through the metabolism of structural analogs like etonitazene, protonitazene, or butonitazene, which differ from isotonitazene and metonitazene only in the composition of their alkoxy side chains. Similarly, the *O*-dealkyl metabolites of etodesnitazene and metodesnitazene were identical molecules and may result from the metabolism of isotodesnitazene or protodesnitazene. Reduction in the nitro group to form 5-amino-nitazene has been documented in nitro derivatives like metonitazene and isotonitazene [269,292] and probably in the rest of nitro derivatives but is less common than de-alkylation metabolites. This reduction may occur due to microbial degradation, similar to the process observed with nitro-benzodiazepines. Degradation of metonitazene into its metabolites, 5-aminometonitazene and 5-acetamidometonitazene, has been observed in unpreserved postmortem blood. However, no such degradation was detected in preserved blood samples treated with fluoride/oxalate [293]. Regarding isotonitazene, the reduction in the 5-nitro group led to a >200-fold reduced potency, when compared to isotonitazene [292]. On the other hand, the metabolite *N*-desethylisotonitazene has the same potency as etonitazene and is more potent than isotonitazene itself [287].

In a study [294], clonitazene, etodesnitazene, etonitazene, etonitazepyne, flunitazene, isotonitazene, metodesnitazene, metonitazene, and protonitazene were generally stable in the autosampler after 1 and 3 days, though metodesnitazene and etodesnitazene showed some exceptions. All analytes met freeze–thaw stability requirements, except for etodesnitazene and protonitazene, for which repeated freezing should be avoided.

- **Postmortem Levels in Fatal Case Reports and PMR**

Several studies have reported postmortem concentrations of various nitazenes, but research on their distribution in postmortem tissues remains limited. Metonitazene was detected in 18 postmortem cases, with a median blood concentration of 3.8 ng/mL (ranging from 0.5 to 33 ng/mL). In 30% of these cases, metonitazene was the only opioid present, while in 55%, it was found alongside fentanyl. Additionally, it was detected with other substances such as NPS benzodiazepines, opioids, and hallucinogens in 45% of cases [269].

In one of these reported cases, a 47-year-old man with a history of heroin use was found deceased on his bed at home. His femoral blood and heart blood concentrations yielded a C/P ratio of 2.4. Additionally, flunitazene was detected in both femoral and heart blood, producing a C/P ratio of 2.3.

In another study [292], isotonitazene was found in 18 postmortem cases, with a median blood concentration of 1.0 ng/mL (ranging from 0.4 to 9.5 ng/mL). The lowest concentration observed was 0.4 ng/mL in two cases, where no other opioids were detected. Additionally, a separate study [295] reported that isotonitazene had an average blood concentration of 1.59 ng/mL in 69 deaths, with concentrations ranging from 0.5 to 9 ng/mL. In three documented deaths linked to isotonitazene use, the postmortem concentrations in femoral blood and cardiac blood yielded C/P ratios of 0.7, 1.9, and 0.9 [270]. The distribution of isotonitazene in postmortem analysis was investigated in the first case attributed to this substance in France [271,272], resulting in a C/P ratio of 1.5.

Protonitazene was linked to the cause of death in five male individuals, aged 20 to 35 years, in a French department of the Indian Ocean. Postmortem femoral blood levels of protonitazene in these cases ranged from below LOQ to 0.8 ng/mL [296]. *N*-Desethyl isotonitazene was detected and quantified in nine related deaths, with an average blood concentration of 3.4 ng/mL, ranging from 0.82 to 8.3 ng/mL [268]. Additionally, etodesnitazene was present in 15 deaths, with a median postmortem blood concentration of 4.0 ng/mL, ranging from 0.1 to 120 ng/mL [268].

For *N*-pyrrolidin derivatives, *N*-pyrrolidino metonitazene was present in 11 deaths, with a median blood concentration of 0.47 ng/mL (range, 0.2 to 26) [268]. *N*-pyrrolidino etonitazene had a median concentration of 2.2 ng/mL in 15 deaths, with a range from 0.3 to 8.3 ng/mL [297]. Lastly, *N*-pyrrolidino protonitazene was found in 26 deaths, with a median postmortem blood concentration of 1.2 ng/mL, ranging from 0.3 to 55 ng/mL [268]. In one case [268], a 29-year-old man showed a *N*-pyrrolidino protonitazene was quantified in peripheral and cardiac blood, yielding a C/P ratio of 4. Other nitazenes found were protonitazene metonitazene and *N*-desethyl protonitazene, without specifying the matrix.

According to the initial cases studied, nitazenes are associated with a tendency for PMR, although there were exceptions where the C/P ratio was below 1 in two instances of isotonitazenes [270]. Stability may be a significant factor, as post-mortem concentrations in the body can be affected by microbial degradation of the nitro group.

3.11. Synthetic Cannabinoids

Synthetic cannabinoids are a varied group of compounds designed to mimic the effects of delta-9-tetrahydrocannabinol (Δ^9-THC) by binding to cannabinoid receptors CB1 and CB2. While Δ^9-THC acts as a partial agonist at these receptors, most synthetic cannabinoids serve as full agonists, often demonstrating much greater potency [298,299]. JWH-018 was the first synthetic cannabinoid detected in Spice mixtures in 2008. It is part of a series of compounds synthesized by John W. Huffman (JWH) for studies conducted at NIDA (National Institute on Drug Abuse), which were intended to explore their potential use in the pharmaceutical industry. Since then, the number of new synthetic cannabinoids entering the drug market has systematically and intensively increased. Initially promoted as "safe" alternatives to marijuana due to their comparable pharmacological effects to Δ^9-THC and other phytocannabinoids, numerous in vitro and in vivo studies, as well as multiple reports and warnings, have since highlighted their severe adverse effects and heightened toxicity. Cannabis users may also face the risk of unintentional exposure to synthetic cannabinoids, as adulterated cannabis can closely resemble its unadulterated form and be sold unknowingly. Additionally, the rise of cannabis edibles, often sweets infused with cannabis extract, on the illicit market poses further concerns [300,301].

The use of synthetic cannabinoids is unpredictable and can result in serious health complications, including cardiovascular, neurological, and cognitive disorders, as well as death. Intoxication from synthetic cannabinoids is often linked to cardiovascular events, kidney damage, seizures, and psychiatric symptoms, though many individuals can fully

recover with proper hospital care. However, more severe effects, such as heart attacks or organ failure, may directly or indirectly lead to fatal outcomes [302–304].

A typical structure features a main core (with various side chains), a linker, and a secondary moiety. The linker connects the main core such as indole, indazole, benzimidazole, or carbazole to the secondary moiety, which can include groups like naphthalene, quinoline, valine, or *tert*-leucine. Generally, the linker may be a carbonyl, ester, or amide. Major structural classes of synthetic cannabinoids according to their main core [10] are carbonyl-indoles (JWH-007, JWH-018, JWH-201, AM-1220, AM-2201, 5F-MDMB-PICA, etc.), carbonyl-indazoles (5F-ADB, 5F-NPB-22, FAB-144, THJ-018, MDMB-4en-PINACA, ADB-PINACA, AB-PINACA, MAB-CHMINACA, 5F-CUMYL-PINACA, etc.), carbonyl-benzimidazoles (JWH-018 benzimidazole analog, FUBIMINA, etc.), carbonyl-carbazoles (EG-018, EG-2201, MDMB-CHMCZCA, etc.), and phenyl-carbonyl-pyrazoles (AB-CHMFUPPYCA, 5F-AB-FUPPYCA, etc.), see Figure 16. Recently, dibenzopyran cannabinoids, also known as semi-synthetic cannabinoids, have emerged on the illicit market. This is likely due to the deregulation of cannabidiol (CBD) in several countries and the increased availability of this compound. Examples include Δ^8-THC, the acetate ester of Δ^9-THC (THC-O), and hexahydrocannabinol (HHC), among others.

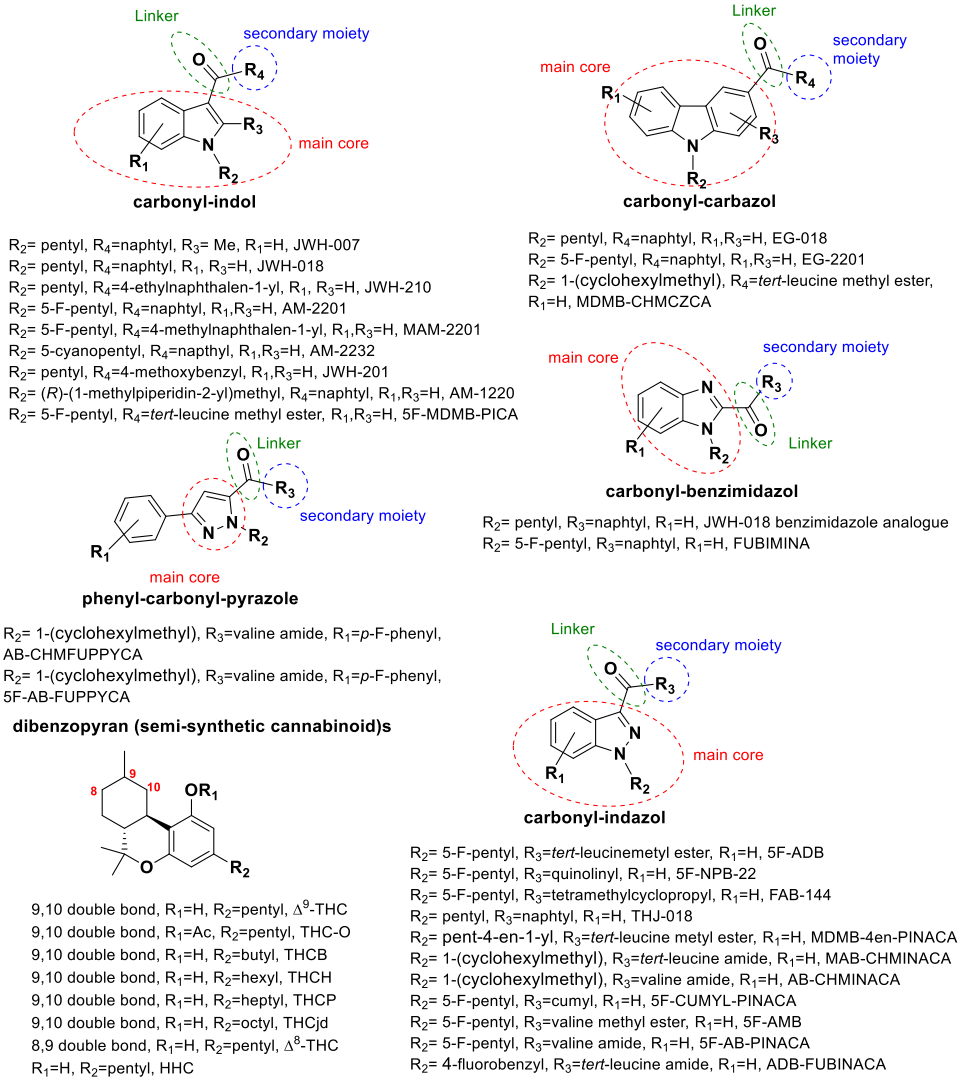


Figure 16. The main cores of synthetic cannabinoids and semi-synthetic cannabinoids and some examples of each core.

The diverse chemical structures of synthetic cannabinoids can greatly influence their pharmacokinetics. Several studies have been conducted to investigate the physicochemical properties of synthetic cannabinoids, including 5F-MDMB-PINACA, 4F-MDMB-BINACA, and their ester hydrolysis metabolites (carboxylic acids). The pKa values for 5F-MDMB-PINACA and its carboxylic acid metabolite are −0.76 and 14.65, and −0.76, 3.86, 14.65, respectively. Similarly, the pKa values for 4F-MDMB-BINACA and its carboxylic acid derivative are −0.76 and 14.65, and −0.76, 3.86, 14.65, respectively. In terms of lipophilicity, the logP values for 5F-MDMB-PINACA, 5F-MDMB-PINACA carboxylic acid, 4F-MDMB-BINACA, and 4F-MDMB-BINACA carboxylic acid are 3.56, 3.42, 3.12, and 2.97, respectively [305]. These values shed light on the acidic and basic characteristics of these compounds and their metabolites and can be approximately applied to other related compounds. In general, there is limited information on their chemical properties and pharmacokinetics, making it difficult to detect synthetic cannabinoids in biological samples and interpret test results accurately. Similar to phytocannabinoids, synthetic cannabinoids are highly lipophilic, meaning they tend to accumulate in fatty tissues. Their logP values, which reflect their lipophilicity, are directly related to their chemical structure. For instance, compounds with more condensed aromatic rings, such as naphthoyl/benzoyl indole/indazole/benzimidazole derivatives (e.g., JWH-018, JWH-210, MAM-2201, AM-2232) or indole-3-carboxylate/carboxamide derivatives with naphthol/quinol groups (e.g., 5F-PB-22, FUB-PB-22, NM-2201), exhibit logP values ranging from 5.01 to 8.14 and 5.80 to 6.74, respectively. In contrast, compounds containing valine/*tert*-leucine derivatives (e.g., 5F-AMB, 5F-AB-PINACA, AB-CHMINACA, ADB-FUBINACA) have logP values between 2.29 and 3.81, indicating lower lipophilicity [306].

All synthetic cannabinoids studied so far are extensively metabolized, resulting in minimal to no unchanged parent drug detectable in human urine, which typically has higher drug concentrations and a longer detection window than blood or oral fluid. Generally, phase I metabolites are the most effective biomarkers for documenting intake because they yield higher mass spectrometry responses and are more stable over time than phase II metabolites [307]. Some hydroxylated urinary metabolites are even more toxic than their parent drugs. For instance, the major metabolites of JWH-018, 4′-OH-JWH-018, and 5′-OH-JWH-018, as well as the AM-2201 metabolite, 4′-OH-AM-2201, continue to act as full agonists at nanomolar concentrations [308,309].

In general, synthetic cannabinoids with ester linkages are susceptible to hydrolysis, resulting in the formation of carboxylic acids, while those with carbonyl and amide linkages do not undergo hydrolysis. For carbonyl derivatives, the main core often experiences either aromatic or aliphatic hydroxylation within the alkyl chain. The oxidation of ω-hydroxyl-alkyl and ω-1-hydroxyl-alkyl intermediates leads to the production of carboxylic acids and ω-1-carbonylated metabolites. These alkyl chain oxidations are observed in synthetic cannabinoids with ester and amide linkages. Synthetic cannabinoids containing an amide linker and a secondary moiety of valine or tert-leucine amide typically undergo hydrolysis of the terminal amide, producing a carboxylic acid. This process is frequently accompanied by carbonylation, which usually targets the ω-1 carbon of the alkyl chain or the terminal methyl groups of the secondary moiety [307].

The stability of 84 synthetic cannabinoids was examined [310] in fortified serum samples stored at −20 °C, 4 °C, and room temperature for 150 days, including the impact of three freeze/thaw cycles. The study revealed that 51 analytes remained stable at −20 °C throughout the study period. The most unstable analytes were 3-CAF and MAM-2201, which lost 49.3% and 24.2% of their concentration, respectively, after one month at −20 °C. The research concluded that AMB- and SBD-type cannabinoids were the least stable. It was also observed that hydrolysis of the ester group in the valinate residue of AMB, 5F-AMB, or FUB-AMB occurred rapidly at elevated temperatures. In a separate study [311], the stability of MMB-FUBINACA, 5F-MDMB-PINACA, 5F-MDMB-PICA, and ADB-FUBINACA, along with their metabolites, was assessed in blood samples stored at 22 °C, 4 °C, and −20 °C. Analyzed over a 35-day period, the metabolite-only samples remained stable, while all

parent compounds, except ADB-FUBINACA, showed degradation. MMB-FUBINACA was found to be the least stable parent compound, degrading into MMB-FUBINACA 3-methylbutanoic acid within one day at room temperature.

Like Δ^9-THC, lipophilic synthetic cannabinoids can adsorb to polypropylene tubes [312]; so, it is advisable to store them in glass containers. Although this group of compounds is relatively stable, for long-term storage of samples containing these drugs, refrigeration or freezing is recommended.

- **Postmortem Levels in Fatal Case Reports**

There is considerable literature documenting synthetic cannabinoid concentrations linked to fatal events. However, many reported cases encounter the issue of unquantified or unidentified metabolites. Similar to Δ^9-THC, synthetic cannabinoids are rapidly distributed throughout various organs and tissues, accumulating in fatty tissues from which they can later enter the bloodstream. Additionally, they undergo extensive hepatic metabolism and may exhibit instability in postmortem samples. These factors can result in low or undetectable levels in postmortem blood. Therefore, analyzing metabolites in blood and especially in urine is an effective approach to confirm intake. There is frequently an overlap between toxic levels observed in non-fatal and fatal cases. Alternative matrices, such as adipose tissue or hair, can be analyzed as specific reservoirs for detecting their use. For instance, in three reported deaths in Germany, femoral blood samples revealed the presence of 5F-PB-22, AB-CHMINACA, and 5F-ADB at concentrations of 0.37 ng/mL, 4.1 ng/mL, and 0.38 ng/mL, respectively [313]. These concentrations are relatively low compared to other published cases. However, when considering the death scene, forensic autopsy findings, and comprehensive toxicological analysis, the deaths were determined to be a direct result of synthetic cannabinoid consumption. In the case of 5F-ADB, the low concentration can be attributed to its instability in blood samples, as it undergoes cleavage by carboxylesterases [314]. Nevertheless, despite this, a series of cases with postmortem concentrations of certain synthetic cannabinoids are referred below.

A recent study [315] provided a comprehensive report on 98 fatalities related to synthetic cannabinoids. The most commonly detected compound was 5F-ADB (n = 21), followed by 5F-MDMB-PICA (n = 13), AB-CHMINACA (n = 10), ADB-CHMINACA (n = 9), and MDMB-CHMICA (n = 9). Due to the rapid distribution and metabolism of synthetic cannabinoids after use, it has been noticed that a longer interval between consumption and death (ranging in the study from 1.5 h to approximately 47 days) may lead to lower concentrations in postmortem blood. The average femoral postmortem concentrations for 5F-ADB, 5F-MDMB-PICA, AB-CHMINACA, ADB-CHMINACA, and MDMB-CHMICA were 1.61 ng/mL (range, <0.1 to 14), 1.44 ng/mL (range, <0.1 to 7.2), 7.40 ng/mL (range, 0.2 to 28), 5.95 ng/mL (range, 0.26 to 22), and 0.91 ng/mL (range, <0.1 to 1.8), respectively. In a different study [273], 5F-ADB was involved in 43 fatalities. The peripheral blood concentrations ranged from 0.010 to 0.77 ng/mL for 5F-ADB and from 2.0 to 110 ng/mL for its carboxylic acid metabolite. A 26-year-old man with a long history of abusing NPS and multiple previous drug-related offenses was found unconscious in his room while wearing an electronic tagging device. Resuscitation attempts were unsuccessful. The autopsy revealed brain edema, internal congestion, petechial hemorrhages, pleural ecchymoses, and increased blood fluidity. Toxicological analysis identified 7.2 ng/mL of MDMB-4en-PINACA and 9.1 ng/mL of 4F-ABUTINACA in the peripheral blood [316].

In a recent case report [317], a 33-year-old man lost consciousness after smoking an unidentified substance. At the scene, a glass pipe and lumps containing 5F-MDMB-PICA and 4F-MDMB-BINACA were found. Blood, urine, and cerebrospinal fluid samples were analyzed, with 5F-MDMB-PICA detected in all samples at 0.9 ng/mL in blood and 3.2 ng/mL in cerebrospinal fluid. 4F-MDMB-BINACA was found only in cerebrospinal fluid at 0.1 ng/mL. The rapid elimination of parent drugs and the prolonged presence of their metabolites make these metabolites useful for identifying substance intake. The literature describes a case involving a 35-year-old man found kneeling over a bucket with his head just above the water. Despite emergency medical services' efforts, resuscitation

was unsuccessful [318]. The autopsy revealed coronary artery disease and liver congestion but no acute myocardial ischemia. Femoral blood concentrations were 14 ng/mL of fentanyl and 3200 ng/mL of pregabalin. Additionally, 2.7 ng/mL of 5F-ADB and 13 ng/mL of 5F-MDMB-P7AICA were found in cardiac blood, along with lower levels of five other synthetic cannabinoids. In total, up to 17 synthetic cannabinoids were detected in the kidney, liver, urine, and hair.

Reported postmortem blood concentrations for the JWH series of synthetic cannabinoids are as follows: JWH-018 ranges from 0.1 to 199 ng/mL, JWH-073 from 0.1 to 68.3 ng/ mL, JWH-122 from 0.12 to 17 ng/mL, and JWH-210 from 0.18 to 15 ng/ mL [319]. For AM-1220, AM-2201, and AM-2232, postmortem blood concentrations in fatalities ranged from 140 to 438 ng/mL, 0.1 to 17 ng/mL, and 0.86 to 1.95 ng/mL, respectively [282,319]. Lastly, UR-144 and XLR-11 had postmortem blood concentrations ranging from 1.4 to 12.3 ng/mL and 0.6 to 2.1 ng/mL, respectively [319].

- **Tissue Distribution and PMR**

Semi-synthetic cannabinoids like THC-O, HHC, THCH, THCB, etc., are expected to exhibit a postmortem distribution similar to that of Δ^9-THC. However, the PMR of Δ9-THC remains a subject of debate. In one study [320], Δ^9-THC blood concentrations were analyzed in 14 postmortem cases, comparing antemortem (AM) blood, blood at admission to the morgue (AD), and blood during autopsy (PM). The median concentrations were 4.0 ng/mL (range: LOQ–48) for AM, 15.5 ng/ mL (range: 4.0–176) for AD, and 4.4 ng/ mL (range: LOQ–56) for PM. The median elapsed times from AM to AD and AD to PM were 33 and 97.5 h, respectively. These findings indicate a significant increase in Δ^9-THC concentration in the early postmortem period, followed by a decrease, although the median blood concentrations at autopsy were similar to those observed antemortem. In a recent study [321] on the PMR of cannabis, data from antemortem and postmortem cases positive for cannabinoids were compiled into a database. The analysis revealed significantly higher concentrations of Δ^9-THC in postmortem blood compared to antemortem blood. PMR of Δ^9-THC can be suspected when the following indicators are observed: (i) Δ^9-THC blood concentration exceeding 50 ng/mL, (ii) a Δ^9-THC central-to-peripheral (C/P) ratio lower than 1.0, (iii) a blood Δ^9-THC to THCCOOH concentration ratio greater than 1.0, and (iv) the absence of detectable THCCOOH in urine. Some researchers argue that due to site-specific variations and substantial fluctuations in Δ^9-THC concentrations during the postmortem interval and storage, along with the limited relevance of cannabinoid levels in living individuals, measuring cannabinoid concentrations in postmortem blood (even peripheral blood) to determine levels at the time of death or impairment is not advisable. The presence of Δ^9-THC in postmortem blood merely suggests prior drug use at an undetermined time, and such concentrations should not be regarded as forensically reliable [322]. Drawing a parallel with Δ^9-THC and pending research to confirm this assertion, semi-synthetic cannabinoids are expected to exhibit similar behavior due to their structural similarity. On the other hand, synthetic cannabinoids do not seem to show a consistent or predictable postmortem distribution.

In a previously cited study [273], 5F-ADB and its metabolite, 5F-ADB carboxylic acid (metabolite 7), were analyzed in samples from 24 cases of peripheral and central blood. For 5F-ADB, the average C/P ratio was 7.8, with a median of 1.7 and a range from 0.1 to 70. Out of 24 cases, 14 (58%) showed a C/P ratio greater than 1 for 5F-ADB. In contrast, the 5F-ADB carboxylic acid had an average C/P ratio of 2.7, with a median of 1.7 and a range of 0.5 to 17.6. In this case, 17 out of 24 cases (71%) demonstrated a C/P ratio greater than 1 for metabolite 7. These results suggest that they both undergo postmortem redistribution to some extent. Additionally, in another study [274] involving four reported deaths, 5F-ADB was quantified in both postmortem iliac and cardiac blood samples. The median C/P ratio was 2.5, with a range of 0.7 to 5.8, supporting the hypothesis that 5F-ADB may exhibit PMR.

According to Table 3, carbonyl indazole AB-CHMINACA was detected in the femoral and cardiac blood of a man suffering from diabetic ketoacidosis, likely due to synthetic cannabinoid use [275]. This resulted in a C/P ratio of 0.4. Other synthetic cannabinoids,

including AB-FUBINACA, 5F-AMB, 5F-APINACA, STS135, and THJ 2201, were detected only in femoral blood and not in heart blood. AB-CHMINACA was identified and quantified in another two related deaths [276]. The C/P ratios were 2.4 and 1.1. The L/P ratios were 57.7 and 16.2. In another reported case of a 24-year-old man who died following AB-CHMINACA use, the L/P ratios were 4.7 for AB-CHMINACA, 7.8 for its metabolite 4 (carboxylic acid), 2.9 for AKB48, and 14.0 for the UR144-N-COOH metabolite [277].

A 24-year-old man who died from multidrug intoxication, XLR11 and the UR144 metabolites, UR144-*N*-COOH and UR144-*N*-OH, were detected and quantified in peripheral and central blood, resulting in C/P ratios of 0.9, 1.1, and 1.5, respectively [275]. Additionally, hydrocodone was found at a toxic level. In another case report [278,279], MAB-CHMINACA was detected in a man with a history of synthetic cannabinoid use. The postmortem concentrations in femoral and cardiac blood, along with the liver concentration, resulted in C/P and L/P ratios of 1.5 and 25.8, respectively. Furthermore, 5F-ADB was present in the gastric contents, adipose tissue, brain, heart muscle, and pancreas. 5F-MDMB-P7AICA and its metabolite, dimethyl butanoic acid, were identified in postmortem samples from a 31-year-old man who died after jumping from a roof [280]. The concentrations of 5F-MDMB-P7AICA and metabolite in peripheral and heart blood resulted in C/P ratios of 0.8 for the parent drug and 8.0 for the metabolite.

N-1-Naphthalenyl-1-pentyl-1H-indole-3-carboxamide (NNEI), a synthetic cannabinoid, was identified in a man in his twenties who likely died from acute circulatory disturbance caused by NNEI poisoning [281]. The C/P and L/P ratios were 0.8 and 1.6, respectively. In another case, MAM-2201, AM-1220, AM-2232, and some metabolites were identified and quantified in plasma from femoral blood. The concentrations of parent drugs and their metabolites in heart blood (right and left ventricles) were 1.5–5.5 times greater than in femoral blood, indicating postmortem redistribution. Additionally, the levels of parent drugs in the left ventricle were 1.1–2.8 times higher than in the right ventricle, suggesting drug accumulation in the myocardium. This accumulation may explain the cardiotoxic effects of this synthetic cannabinoids.

The gamma-carboline-based synthetic cannabinoid 5F-cumyl-PEGACLONE was reported in four deaths [283]. The calculated C/P ratios were 0.15, 0.9, 1.8, and 3.9.

In 2018, AB-PINACA and EAM-2201 were reanalyzed from postmortem samples related to an unresolved case from 2013, with the samples having been stored at −80 °C [284]. The postmortem concentrations found in peripheral blood and left heart blood for AB-PINACA and EAM-2201, led to C/P ratios of 1.6 and 0.5 for the two compounds. Given the low levels detected, it is important to consider the potential degradation of these compounds over the storage period.

Finally, mepirapim was detected in an incident involving two individuals, one fatal and the other non-fatal [285,286]. The survivor inhaled the substance, while the deceased self-administered approximately 50–60 mg via intravenous injection. Postmortem concentrations of mepirapim in peripheral blood, heart blood, and liver yield C/P and L/P ratios of 1.0 and 11.4, respectively.

As noted, there is currently inadequate literature to make definitive conclusions about the PMR of synthetic cannabinoids. Evidence suggests that some compounds, such as 5F-ADB [273,274], AB-CHMINACA [274], MAM-2201, AM-1220, and AM-2232 [282], along with their metabolites, may exhibit PMR, as indicated by observed C/P ratios in certain cases. Data regarding metabolite PMR supports this hypothesis. Their lipophilic structures imply a susceptibility to this phenomenon. However, challenges such as instability in biological matrices and frequent difficulties in accurately quantifying metabolites—often due to the unavailability of reference standards—complicate efforts to gather adequate data on potential PMR.

4. Conclusions

Although qualitative analysis of NPS is commonly considered adequate for routine forensic work [323], quantification data from specialized forensic laboratories and exam-

ination of various postmortem tissues can offer crucial insights into the PMR of these substances. While many studies report NPS-related fatalities, fewer investigate the postmortem distribution of NPS in tissues and quantify their levels in peripheral blood, central blood, and liver to assess potential PMR. A review of 94 studies (peer-reviewed papers and communications for congresses), all of which provided data on fatal cases involving NPS in different tissues, was conducted.

Based on the chemical properties of the 11 NPS groups studied (phenylethylamines (alpha and phenyl-substituted/β-oxo-substituted, cathinones)/phenmetrazines/piperazines/phenidates/arylcyclohexylamines (phencyclidines)/lysergamides/tryptamines/designer benzodiazepines/synthetic opioids/nitazenes/synthetic cannabinoids) and insights from previous research on the PMR of classical related parent drugs, we have attempted to predict whether these substances are likely to undergo PMR. Additionally, we reviewed various studies on the stability of each NPS group, as this can significantly affect the detectable concentrations in a corpse, particularly if the postmortem interval is prolonged.

New synthetic opioids, synthetic cathinones, phenethylamines/amphetamines, and synthetic cannabinoids were the most commonly found NPS in postmortem samples. Polydrug use was prevalent, increasing overdose risks due to potential drug interactions. Substances like synthetic cannabinoids, fentanyl analogs, and nitazenes can be lethal even at low doses, making detection and toxicological analysis challenging. For synthetic cannabinoids, their rapid metabolism and tissue distribution result in low blood concentrations, making alternative matrices, such as adipose tissue useful for detection. It is also highly recommended to study the metabolic profile of synthetic cannabinoids [324].

Based on the reviewed papers, the NPS groups most likely to exhibit PMR include phenylethylamines (excluding NBOMe or 2C-X derivatives, potentially due to their instability), certain synthetic cathinones like *N*-alkylcathinones (e.g., mephedrone, 3-MMC, 3,4-DMMC), some pyrrolidin cathinones (e.g., MPHP, MDPV), tryptamine derivatives such as 5-API (5-IT), and some synthetic opioids (e.g., acetylfentanyl, furanylfentanyl, *p*-fluorofuranylfentanyl, U-47700). Nitazenes and synthetic cannabinoids may also be prone to PMR, although further case reports are needed to confirm these findings.

In terms of instability, groups such as synthetic cathinones are particularly unstable in postmortem samples, especially those with halogen atoms, which leads to the recommendation to look for dihydrometabolites as biomarkers of exposure. Nitazenes and others NPS compounds with a nitro groups, such as new nitrobenzodiazepines clonazolam, are unstable by nitroreduction. The chemical instability of NPS with labile ester functions (e.g., mytragynine, acrylfentanyl, remifentanil, and some synthetic cannabinoids (e.g., ADB, MDMB, EMB derivations in secondary moieties)) may hinder their detection through the formation of their carboxylic acid by heat and changes in and liberation of enzimes carboxylesterases released postmortem into the bloodstream.

LC-MS/MS (LC-QQQ) methods were the most commonly employed for quantification analysis, while GC-MS and LC–HRMS/MS techniques were frequently used for screening and confirmation. Additionally, LC–HRMS/MS was the preferred method for identifying metabolites.

Establishing the cause of death based solely on concentration levels is difficult and requires a holistic approach, including clinical history, autopsy, and histopathological findings for each case. This compilation of postmortem concentrations, along with C/P and L/P ratios, is intended as a reference to identify relevant studies on specific NPS or substance groups and should be used as a guide to determine if the detected substance may be prone or not to PMR.

The review findings highlight the need for continual updates and reassessment of our understanding of the metabolism, stability, and PMR of NPS. It is essential for routine toxicological screening methods to evolve continuously, integrating new strategies to analyze emerging NPS and their metabolites [325].

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/psychoactives3040033/s1. Table S1: Classification of reviewed NPS families based on chemical structure; Figure S1 Common metabolite mCPP of trazodone, nefazodone and mepiprazol; Figure S2. *N*-dealkylation of aripiprazol and formation of 2,3-DCPP.

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Glossary

11-hydroxy-THC	11-Hydroxy-Δ9-tetrahydrocannabinol
1-BZP	1-Benzylpiperazine
1B-LSD	1-Butanoyl-lysergic acid diethylamide
1cP-LSD	1-Cyclopropanoyl-lysergic acid diethylamide
1P-LSD	1-Propanoyl-lysergic acid diethylamide
1V-LSD	1-Valeroyl-lysergic acid diethylamide
25B-NBOMe	2-(4-Bromo-2,5-dimethoxyphenyl)-*N*-(2-methoxyphenyl)methyl-ethanamine
25C-NBOMe	2-(4-Chloro-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl] ethanamine
25H-NBOMe	2-(2,5-Dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine
25I-NBOMe	2-(4-Iodo-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl] ethanamine
2-AI	2-Aminoindane
2-Cl-DPH	2-Chloro-diphenidine
2C-T-7	2-(2,5-Dimethoxy-4-(n)-propylthio)phenylethylamine
2F-DCK	2-Fluorodeschloroketamine
2-FMA	2-Fluoromethamphetamine
2-MAPB	1-(1-Benzofuran-2-yl)-*N*-methylpropan-2-amine
2-FMP	2-Fluorophenmetrazine
2-MXP	2-Methoxyphenidine
2-oxo-PCE	2-(Ethylamino)-2-phenylcyclohexanone
3,4-DMMC	2-(Methylamino)-1-(3,4-dimethylphenyl)propan-1-one
3,6-DMPM	2-Phenyl-3,6-dimethylmorpholine
3-FPM	3-Fluorophenmetrazine
3-MeO-PCP	3-Methoxyphencyclidine
3-Methyl-4-fluoro-PVP	(RS)-1-(3-Methyl-4-fluorophenyl)-2-(pyrrolidin-1-yl)pentan-1-one
3-MMC	3-Methylmethcathinone
3-MPM	3-Methylphenmetrazine
3-MXP	3-Methoxyphenidine
3-OH-PCP	3-Hydroxyphencyclidine
4-CEC	4-Chloro-ethcathinone
4-Cl-α-PPP	4-Chloro-alpha-pyrrolidinopropiophenone
4-CEC	4-Chloro-ethcathinone
4-Cl-α-PVP	4-Chloro-alpha-pyrrolidinovalerophenone
4F-ANPP	1-(4-Fluorophenyl)-*N*-phenylpiperidin-4-amine
4F-EPH	4-Fluoroethylphenidate
4-Fluorobutyryl-fentanyl	N-[1-(2-Phenylethyl)-4-piperidinyl]-*N*-phenyl-4-fluorobutanamide
4-FMC	1-(4-Fluorophenyl)-2-(methylamino)propan-1-one
4F-MPH	4-Fluoromethylphenidate
4-F-PHP	4-Fluoro-pyrrolidinohexanophenone

4-FPM	4-Fluorophenmetrazine
4-F-α-PVP	1-(4-Fluorophenyl)-2-(pyrrolidin-1-yl)pentan-1-one
4-MA	4-Methylamphetamine
4-MEAP	*N*-Ethyl-4′-methylnorpentedrone
4-MEC	4-Methylmethcathinone
4-MeO-PCP	4-Methoxyphencyclidine
4-MeO-α-PVP	1-(4-Methoxyphenyl)-2-(pyrrolidin-1-yl)pentan-1-one
4-Methoxy-PV8	1-(4-Methoxyphenyl)-2-(pyrrolidin-1-yl)heptan-1-one
4-Methoxy-PV9	1-(4-Methoxyphenyl)-2-(pyrrolidin-1-yl)octan-1-one
4-MMC (mephedrone)	4-methylmethcathinone
4M-MPH	4-Methylmethylphenidate
4-MPD	4-Methylpentedrone
4-MTA	4-Methylthioamphetamine
4-PV8	4-Methoxy-PV8
5-APB	5-(2-Aminopropyl)benzofuran
5-API	5-(2-Aminopropyl)indole
5-APINACA	N-(1-Amino-3-methyl-1-oxobutan-2-yl)-1-(5-fluoropentyl)-1H-indazole-3-carboxamide
5-EAPB	5-(2-Ethylaminopropyl)benzofuran
5F-ADB(COOH)	1-(5-Fluoropentyl)-1H-indazole-3-carboxylic aci
5F-ADB	Methyl 2-(1-(5-fluoropentyl)-1H-indazole-3-carboxamido)-3-methylbutanoate
5F-AMB	Methyl 2-(1-(5-fluoropentyl)-1H-indazole-3-carboxamido)-3-methylbutanoate
5F-MDMB-PICA	Methyl 2-(1-(5-fluoropentyl)-1H-indazole-3-carboxamido)-3,3-dimethylbutanoate
5F-NPB-22	1-(5-Fluoropentyl)-8-quinolinyl ester-1H-indole-3-carboxylic acid
5-HT	Serotonin
5-IAI	5-Iodo-2-aminoindane
5-MAPB	5-(2-Aminomethylpropyl)benzofuran
5-MeO-DiPT	5-Methoxy-*N*,*N*-diisopropyltryptamine
5-MeO-NiPT	5-Methoxy-*N*-isopropyltryptamine
5-OH-DiPT	5-Hydroxy-*N*,*N*-diisopropyltryptamine
6-APB	1-(1-Benzofuran-6-yl)-2-(aminopropane)
6-APDB	6-(2-Aminopropyl)-2,3-dihydrobenzofuran
AB	Aorta blood
AB-CHMINACA	*N*-(1-Amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1H-indazole-3-carboxamide
AB-FUBINACA	N-(1-Amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1H-indazole-3-carboxamide
AB-PINACA	*N*-(1-Adamantyl)-1-pentyl-1H-indazole-3-carboxamide
AB-PINACA	*N*-(1-Amino-3-methyl-1-oxobutan-2-yl)-1-pentyl-1H-indazole-3-carboxamide
Acetyl-fentanyl	N-(1-Phenethylpiperidin-4-yl)-*N*-phenylacetamide
ADB-PINACA	*N*-(1-Amino-3,3-dimethylbutan-2-yl)-1-pentyl-1H-indazole-3-carboxamide
AET	Alpha-Ethyltryptamine
AH-7921	3,4-Dichloro-*N*-((1-(dimethylamino)cyclohexyl)-methylbenzamide
AKB48 (APINACA)	*N*-(1-Adamantyl)- 1-pentyl-1H-indazole-3-carboxamide)
ALD-52	1-Acetyl- lysergic acid diethylamide
ALDH	Aldehyde dehydrogenase
AM-1220	1-(2-Methoxyphenyl)-2-(1-pentyl-1H-indol-3-yl)ethanone
AM-2201	1-(5-Fluoropentyl)-3-(1-naphthoyl)indole
AM-2232	1-(4-Fluorophenyl)-2-(1-pentyl-1H-indol-3-yl)ethanone
AMT	Alpha-Methyltryptamine
AM	Antemortem
ADHD	attention deficit hyperactivity disorder
BZDs	Benzodiazepines

BZP	1-Benzylpiperazine
COMT	catechol-*O*-methyltransferase
CB	Central blood
C/P	Central Blood/Peripheral Blood
DA	Dopamine
DBZP	1,4-Dibenzylpiperazine
DCK	Deschloroketamine
DCPP	2,3-Dichlorophenylpiperazine
DET	Diethyltryptamine
DHC	dihydrocodeine
DiPT	*N*,*N*-diisopropyltryptamine
DMT	*N*,*N*-Dimethyltryptamine
DOB	2,5-Dimethoxy-4-bromoamphetamine
DPH (diphenidine)	1-(1,2-Diphenylethyl)piperidine
DPT	*N*,*N*-Dipropyltryptamine
EAM-2201	5-Fluoro-*N*-ethyl-*N*-(1-pentyl)indole-3-carboxamide
EMCDDA	European Monitoring Center for Drugs and Drug Addiction
EPE (ephenidine)	*N*-Ethyl-(1,2-diphenyl)ethanamine
EPH	Ethylphenidate
EUDA	The European Union Drugs Agency
FAB-144	1-Pentyl-3-(2,2,3,3-tetramethylcyclopropoyl)indole
FB	Femoral blood
FBZP	1-(4-Fluorobenzyl)piperazine
p-FFF	*p*-Fluorofuranylfentanyl
p-FiBF	Fluoroisobutyrfentanyl
FMC	Fluoromethcathinone
Fb	fraction bound to plasma proteins
GI	gastrointestinal tract
GC-MS	Gas Chromatography—Mass Spectrometry
HB	Heart blood
IB	Iliac blood
IIPH	Isopropylphenidate
IS	Injection site
JWH	John W. Huffman
JWH-007	1-Pentyl-3-(2-chlorophenylacetyl)indole
JWH-018	1-Pentyl-3-(1-naphthoyl)indole
JWH-201	1-(5-Fluoropentyl)-3-(4-methyl-1-naphthoyl)indole
L	Liver
LC–HRMS/MS	Liquid Chromatography—High-Resolution Tandem Mass Spectrometry
LC-MS/MS	Liquid Chromatography—Tandem Mass Spectrometry
LC-QQQ	Liquid Chromatography—Triple Quadrupole Mass Spectrometry
LHB	Left heart blood
L/P	Liver/Blood
LLE	Liquid–Liquid Extraction
logP	log of the partition coefficient of a solute between octanol and water
LSD	Lysergic acid diethylamide
m/p-CPP	1-(3/4-Chlorophenyl)piperazine
m/p-MPP	1-(3/4-Methylphenyl)piperazine
MAB-CHMINACA	Methyl 2-(1-(cyclohexylmethyl)-1H-indazole-3-carboxamido)-3-methylbutanoate
MAM-2201	1-(5-Fluoropentyl)-3-(2,2,3,3-tetramethylcyclopropyl)indole
MAO	monoaminoxydase
MBDB	*N*-Methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine
MBZP	1-Benzyl-4-methylpiperazine
mCPCPP	1-(3-Chlorophenyl)-4-(3-chloropropyl)piperazine
MDAI	5,6-Methylenedioxy-2-aminoindane
MDAT	6,7-Methylenedioxy-2-aminotetralin

MDDM	5,6-Methylenedioxy-*N*,*N*-dimethyl-2-aminoindane
MDMAI	5,6-Methylenedioxy-*N*-methyl-2-aminoindane
MDMB-4en-PINACA	Methyl-2-(1-(4-methoxyphenyl)-3-indazole-carboxamido)-3,3-dimethylbutanoate
MDPV	3,4-Methylenedioxypyrovalerone
MEAI	5-Methoxy-2-aminoindane
MMAI	5-Methoxy-6-methyl-2-aminoindane
MPA	Methiopropamine
MPH	Methylphenidate
MPHP	4′-Methyl-α-pyrrolidinohexiophenone
mMPP	1-(3-methylphenyl)pyperazine
MT-45	1-Cyclohexyl-4-(1,2-diphenylethyl)piperazine
MXE (methoxetamine)	2-(ethylamino)-2-(3-methoxyphenyl)-cyclohexanone
MXPr (methoxpropamine)	2-(3-methoxyphenyl)-2-(propylamino)cyclohexan-1-one
NA	Not available
NBOMes	*N*-methoxybenzyl derivatives
NE	Noradrenaline
NPS	New Psychoactive Substances
NIDA	National Institute on Drug Abuse
NM-2-AI	*N*-Methyl-2-aminoindane
NPD	*N*-Propylpentedrone
o/p-MeOPP	1-(2/4Methoxyphenyl)piperazine
PB	Peripheral Blood
PCE	Ethylphencyclidine
PCP	1-(1-Phenylcyclohexyl)piperidine
pFPP	1-(4-Fluorophenyl) piperazine
PEAs	Phenylethylamines
PMEA	*para*-Methoxyethylamphetamine
PMMA	*para*-Methoxymethamphetamine
PM	Postmortem
PMR	Postmortem redistribution
PP	Protein Precipitation
PV8	1-phenyl-2-(1-pyrrolidinyl)-1-heptanone
PV9	1-phenyl-2-(1-pyrrolidinyl)-1-octanone
QuEChERS	Quick, Easy, Cheap, Effective, Rugged, and Safe
Rasagiline	*N*-Propargyl-1(*R*)-aminoindane
RHB	Right heart blood
SA	Serum antemortem
SB	Subclavian blood
SC	Serum cardiac
STS135 (5-fluoro-APICA)	1-(5-fluoropentyl)-*N*-tricyclo[3.3.1.13,7]dec-1-yl-1H-indole-3-carboxamide
SF	Subcutaneous fat
SPE	Solid-Phase Extraction
TFMPP	1-(3-Trifluoromethylphenyl)piperazine
THC	Δ^9-Tetrahydrocannabinol
THC-COOH	11-Nor-9-carboxy-Δ^9-tetrahydrocannabinol
THH	Tetrahydroharmine
THJ-018	1-Naphthoyl-3-(1-pentylindazole)
THJ 2201	1-(5-fluoropentyl)-1H-indazol-3-yl]-1-naphthalenyl-methanone
U-47700	3,4-Dichloro-*N*-[2-(dimethylamino)cyclohexyl]-*N*-methylbenzamide
UNODC	United Nations Office on Drugs and Crime
Ur	Urine
Vd	Volume of distribution
XLR11	(5-Fluoro-UR-144) ((1-(5-fluoropentyl)-1H-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone
vh	Vitreous humor
α-PBP	Alpha-pyrrolidinobutiophenone

α-PiHP	Alpha-pyrrolidinoisohexanophenone
α-PVP	Alpha-pyrrolidinovalerophenone
Δ^9-THC	(-)-Δ9-trans-Tetrahydrocannabinol

References

1. Han, E.; Kim, E.; Hong, H.; Jeong, S.; Kim, J.; In, S.; Chung, H.; Lee, S. Evaluation of postmortem redistribution phenomena for commonly encountered drugs. *Forensic Sci. Int.* **2012**, *219*, 265–271. [CrossRef] [PubMed]
2. Stephenson, L.; Heuvel, C.V.D.; Scott, T.; Byard, R.W. Difficulties associated with the interpretation of postmortem toxicology. *J. Anal. Toxicol.* **2024**, *48*, 405–412. [CrossRef] [PubMed] [PubMed Central]
3. Glicksberg, L.; Kartick, C.; Gangadhar, J.; Vijayachari, P. Postmortem distribution and redistribution of synthetic cathinones. *Forensic Toxicol.* **2018**, *36*, 291–303. [CrossRef]
4. Dalpe-Scott, M.; Degouffe, M.; Garbutt, D.; Drost, M. A Comparison of drug concentrations in postmortem cardiac and peripheral blood in 320 cases. *Can. Soc. Forensic Sci. J.* **1995**, *28*, 113–121. [CrossRef]
5. Gerostamoulos, D.; Beyer, J.; Staikos, V.; Tayler, P.; Woodford, N.; Drummer, O.H. The effect of the postmortem interval on the redistribution of drugs: A comparison of mortuary admission and autopsy blood specimens. *Forensic Sci. Med. Pathol.* **2012**, *8*, 373–379. [CrossRef]
6. McIntyre, I.M. Analytical data supporting the "theoretical" postmortem redistribution factor (Ft): A new model to evaluate postmortem redistribution. *Forensic Sci. Res.* **2016**, *1*, 33–37. [CrossRef]
7. Pélissier-Alicot, A.-L.; Gaulier, J.-M.; Champsaur, P.; Marquet, P. Mechanisms underlying postmortem redistribution of drugs: A review. *J. Anal. Toxicol.* **2003**, *27*, 533–544. [CrossRef]
8. Drummer, O.H. Postmortem toxicology of drugs of abuse. *Forensic Sci. Int.* **2004**, *142*, 101–113. [CrossRef]
9. Júnior, E.F.; Leite, B.H.M.; Gomes, E.B.; Vieira, T.M.; Sepulveda, P.; Caldas, E.D. Fatal cases involving new psychoactive substances and trends in analytical techniques. *Front. Toxicol.* **2022**, *4*, 1033733. [CrossRef] [PubMed] [PubMed Central]
10. Zapata, F.; Matey, J.M.; Montalvo, G.; García-Ruiz, C. Chemical classification of new psychoactive substances (NPS). *Microchem. J.* **2021**, *163*, 105877. [CrossRef]
11. UNODC. United Nations Office on Drugs and Crime NPS Substance Groups. Available online: www.unodc.org (accessed on 20 July 2024).
12. EMCDDA. European Monitoring Centre for Drugs and Drug Addiction. Available online: www.euda.europa.eu/topics/nps_en (accessed on 20 July 2024).
13. Dinis-Oliveira, R.J.; Vieira, D.N.; Magalhães, T. Guidelines for Collection of Biological Samples for Clinical and Forensic Toxicological Analysis. *Forensic Sci. Res.* **2017**, *1*, 42–51. [CrossRef] [PubMed] [PubMed Central]
14. Baselt, R.C. *Disposition of Toxic Drugs and Chemicals in Man*, 12th ed.; Biomedical Publications: Seal Beach, CA, USA, 2020.
15. Barnhart, F.; Fogacci, J.; Reed, D. Methamphetamine—A study of postmortem redistribution. *J. Anal. Toxicol.* **1999**, *23*, 69–70. [CrossRef] [PubMed]
16. de Groot, A.D.E.; Borra, L.C.P.; van der Hulst, R.; Etsouli, O.; Kloos, D.-P.; Rijken, D.J.; Elsinga, P.H.; Boersma, H.H.; Bosman, I.J.; Touw, D.J. Postmortem redistribution of amphetamines and benzodiazepines in humans: Important variables that might be influencing the central blood/peripheral blood ratio. *Forensic Sci. Int.* **2023**, *353*, 111876. [CrossRef] [PubMed]
17. Prouty, R.; Anderson, W. The Forensic Science Implications of Site and Temporal Influences on Postmortem Blood-Drug Concentrations. *J. Forensic Sci.* **1990**, *35*, 243–270. [CrossRef] [PubMed]
18. Elliott, S.P. MDMA and MDA Concentrations in Antemortem and Postmortem Specimens in Fatalities Following Hospital Admission. *J. Anal. Toxicol.* **2005**, *29*, 296–300. [CrossRef] [PubMed]
19. McIntyre, I.M.; Nelson, C.L.; Schaber, B.; Hamm, C.E. Antemortem and Postmortem Methamphetamine Blood Concentrations: Three Case Reports. *J. Anal. Toxicol.* **2013**, *37*, 386–389. [CrossRef] [PubMed]
20. Clauwaert, K.M.; Van Bocxlaer, J.F.; De Leenheer, A.P. Stability study of the designer drugs "MDA, MDMA and MDEA" in water, serum, whole blood, and urine under various storage temperatures. *Forensic Sci. Int.* **2001**, *124*, 36–42. [CrossRef]
21. Alsenedi, K.A.; Morrison, C. Determination of amphetamine-type stimulants (ATSs) and synthetic cathinones in urine using solid phase micro-extraction fibre tips and gas chromatography-mass spectrometry. *Anal. Methods* **2018**, *10*, 1431–1440. [CrossRef]
22. da Cunha, K.F.; Eberlin, M.N.; Huestis, M.A.; Costa, J.L. NBOMe instability in whole blood. *Forensic Toxicol.* **2019**, *37*, 82–89. [CrossRef]
23. Caspar, A.T.; Kollas, A.B.; Maurer, H.H.; Meyer, M.R. Development of a quantitative approach in blood plasma for low-dosed hallucinogens and opioids using LC-high resolution mass spectrometry. *Talanta* **2018**, *176*, 635–645. [CrossRef]
24. Gerostamoulos, D.; Glowacki, L.; Pricone, M.; Crump, K.; Di Rago, M.; Joubert, S.; Lynch, M.J.; Woodford, N.W.; Drummer, O.H. Fatal Intoxications from a Combination of 4-Fluoroamphetamine and 25C-NBOMe. *J. Anal. Toxicol.* **2023**, *47*, 191–196. [CrossRef] [PubMed]
25. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), AH7921: EMCDDA–Europol Joint Report on a New Psychoactive Substance: AH7921 3,4-dichloro-N-{[1-(dimethylamino)cyclohexyl]methyl} benzamide. 2014. Available online: www.emcdda.europa.eu/system/files/publications/816/AH-7921_465209.pdf (accessed on 16 July 2024).

26. World Health Organization (WHO). AH-7921 Critical Review Report Agenda item 4.21: Expert Committee on Drug Dependence. In Proceedings of the Thirty-Sixth Meeting, Geneva, Switzerland, 16–20 June 2014. Available online: http://www.who.int/medicines/areas/quality_safety/4_21_review.pdf (accessed on 19 July 2024).
27. Karinen, R.; Tuv, S.S.; Rogde, S.; Peres, M.D.; Johansen, U.; Frost, J.; Vindenes, V.; Øiestad, M.L. Lethal poisonings with AH-7921 in combination with other substances. *Forensic Sci. Int.* **2014**, *244*, e21–e24. [CrossRef] [PubMed]
28. Elliott, S.P. Fatal Poisoning with a New Phenylethylamine: 4-Methylthioamphetamine (4-MTA). *J. Anal. Toxicol.* **2000**, *24*, 85–89. [CrossRef] [PubMed]
29. De Letter, E.A.; Coopman, V.A.E.; Cordonnier, J.A.C.M.; Piette, M.H.A. One fatal and seven non-fatal cases of 4-methylthioamphetamine (4-MTA) intoxication: Clinico-pathological findings. *Int. J. Leg. Med.* **2001**, *114*, 352–356. [CrossRef] [PubMed]
30. Kueppers, V.B.; Cooke, C.T. 25I-NBOMe related death in Australia: A case report. *Forensic Sci. Int.* **2015**, *249*, e15–e18. [CrossRef] [PubMed]
31. Wiergowski, M.; Aszyk, J.; Kaliszan, M.; Wilczewska, K.; Anand, J.S.; Kot-Wasik, A.; Jankowski, Z. Identification of novel psychoactive substances 25B-NBOMe and 4-CMC in biological material using HPLC-Q-TOF-MS and their quantification in blood using UPLC–MS/MS in case of severe intoxications. *J. Chromatogr. B Analyt Technol Biomed Life Sci.* **2017**, *1041*, 1–10. [CrossRef] [PubMed]
32. Société Française de Toxicologie Analytique (SFTA), Recommandations de la SFTA pour la réalisation des analyses toxicologiques dans les cas de décès impliquant des NPS, SFTA Guidelines for the Achievement of Toxicological Analyzes for Deaths Involving NPS. 2017. Available online: www.RecoSFTApourRCMavecNPS.pdf (accessed on 19 July 2024).
33. Epain, M.; Cartiser, N.; Bevalot, F.; Bottinelli, C.; Chatenay, C.; Fanton, L. Alpha-methyltryptamine and 5-(2-methylaminopropyl)-benzofuran (5-MAPB) fatal co-intoxication: Case report and review of literature. *Int. J. Leg. Med.* **2024**, *138*, 1813–1820. [CrossRef] [PubMed]
34. Elliott, S.; Evans, J. A 3-year review of new psychoactive substances in casework. *Forensic Sci. Int.* **2014**, *243*, 55–60. [CrossRef] [PubMed]
35. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), MT45: Report on the Risk Assessment of MT-45 in the Framework of the Council Decision on New Psychoactive Substances. 2015. Available online: http://www.emcdda.europa.eu/system/files/publications/1865/TDA%20K14006ENN.pdf (accessed on 19 July 2024).
36. Deville, M.; Dubois, N.; Cieckiewicz, E.; De Tullio, P.; Lemaire, E.; Charlier, C. Death following consumption of MDAI and 5-EAPB. *Forensic Sci. Int.* **2019**, *299*, 89–94. [CrossRef] [PubMed]
37. Carter, N.; Rutty, G.N.; Milroy, C.M.; Forrest, A.R.W. Deaths associated with MBDB misuse. *Int. J. Leg. Med.* **2000**, *113*, 168–170. [CrossRef] [PubMed]
38. Zaitsu, K.; Katagi, M.; Kamata, T.; Kamata, H.; Shima, N.; Tsuchihashi, H.; Hayashi, T.; Kuroki, H.; Matoba, R. Determination of a newly encountered designer drug "p-methoxyethylamphetamine" and its metabolites in human urine and blood. *Forensic Sci. Int.* **2008**, *177*, 77–84. [CrossRef] [PubMed]
39. Balíková, M. Nonfatal and fatal DOB (2,5-dimethoxy-4-bromamphetamine) overdose. *Forensic Sci. Int.* **2005**, *153*, 85–91. [CrossRef] [PubMed]
40. De Letter, E.A.; Lambert, W.E.; Bouche, M.-P.L.A.; Cordonnier, J.A.C.M.; Van Bocxlaer, J.F.; Piette, M.H.A. Postmortem distribution of 3,4-methylenedioxy-N,N-dimethyl-amphetamine (MDDM or MDDA) in a fatal MDMA overdose. *Int. J. Leg. Med.* **2007**, *121*, 303–307. [CrossRef] [PubMed]
41. Morini, L.; Bernini, M.; Vezzoli, S.; Restori, M.; Moretti, M.; Crenna, S.; Papa, P.; Locatelli, C.; Osculati, A.M.M.; Vignali, C.; et al. Death after 25C-NBOMe and 25H-NBOMe consumption. *Forensic Sci. Int.* **2017**, *279*, e1–e6. [CrossRef] [PubMed]
42. Poklis, J.L.; Devers, K.G.; Arbefeville, E.F.; Pearson, J.M.; Houston, E.; Poklis, A. Postmortem detection of 25I-NBOMe [2-(4-iodo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine] in fluids and tissues determined by high performance liquid chromatography with tandem mass spectrometry from a traumatic death. *Forensic Sci. Int.* **2014**, *234*, e14–e20. [CrossRef] [PubMed] [PubMed Central]
43. Andreasen, M.F.; Telving, R.; Rosendal, I.; Eg, M.B.; Hasselstrøm, J.B.; Andersen, L.V. A fatal poisoning involving 25C-NBOMe. *Forensic Sci. Int.* **2015**, *251*, e1–e8. [CrossRef] [PubMed]
44. Curtis, B.; Kemp, P.; Harty, L.; Choi, C.; Christensen, D. Postmortem identification and quantitation of 2,5-dimethoxy-4-n-propylthiophenethylamine using GC-MSD and GC-NPD. *J. Anal. Toxicol.* **2003**, *27*, 493–498. [CrossRef] [PubMed]
45. Hofmann, V.; Sundermann, T.R.; Landmann, A.; Rechtsteiner, S.; Schmitt, G.; Bartel, M. Simultaneous Determination of 5- and 6-APB in Blood, Other Body Fluids, Hair and Various Tissues by HPLC--MS-MS. *J. Anal. Toxicol.* **2022**, *46*, 264–269. [CrossRef] [PubMed]
46. McIntyre, I.M.; Gary, R.D.; Trochta, A.; Stolberg, S.; Stabley, R. Acute 5-(2-aminopropyl)benzofuran (5-APB) intoxication and fatality: A case report with postmortem concentrations. *J. Anal. Toxicol.* **2015**, *39*, 156–159. [CrossRef] [PubMed]
47. Theofel, N.; Budach, D.; Vejmelka, E.; Scholtis, S.; Tsokos, M. Toxicological investigations in a death involving 2-MAPB. *Forensic Sci. Med. Pathol.* **2021**, *17*, 317–321. [CrossRef] [PubMed]
48. Shintani-Ishida, K.; Saka, K.; Nakamura, M.; Yoshida, K.; Ikegaya, H. Experimental Study on the Postmortem Redistribution of the Substituted Phenethylamine, 25B-NBOMe. *J. Forensic Sci.* **2018**, *63*, 588–591. [CrossRef] [PubMed]
49. Dearden, J.C. Prediction of physicochemical properties. *Methods Mol. Biol.* **2012**, *929*, 93–138. [CrossRef] [PubMed]

50. Shimshoni, J.A.; Sobol, E.; Golan, E.; Ben Ari, Y.; Gal, O. Pharmacokinetic and pharmacodynamic evaluation of 5-methoxy-2-aminoindane (MEAI): A new binge-mitigating agent. *Toxicol. Appl. Pharmacol.* **2018**, *343*, 29–39. [CrossRef] [PubMed]
51. Mestria, S.; Odoardi, S.; Federici, S.; Bilel, S.; Tirri, M.; Marti, M.; Rossi, S.S. Metabolism Study of N-Methyl 2-Aminoindane (NM2AI) and Determination of Metabolites in Biological Samples by LC–HRMS. *J. Anal. Toxicol.* **2020**, *45*, 475–483. [CrossRef] [PubMed]
52. Manier, S.K.; Felske, C.; Eckstein, N.; Meyer, M.R. The metabolic fate of two new psychoactive substances − 2-aminoindane and *N*-methyl-2-aminoindane—Studied in vitro and in vivo to support drug testing. *Drug Test. Anal.* **2019**, *12*, 145–151. [CrossRef] [PubMed]
53. Soh, Y.N.A.; Elliott, S. An investigation of the stability of emerging new psychoactive substances. *Drug Test. Anal.* **2014**, *6*, 696–704. [CrossRef] [PubMed]
54. Maskell, P.; Smith, P.; Cole, R.; Hikin, L.; Morley, S. Seven fatalities associated with ethylphenidate. *Forensic Sci. Int.* **2016**, *265*, 70–74. [CrossRef] [PubMed]
55. Corkery, J.M.; Elliott, S.; Schifano, F.; Corazza, O.; Ghodse, A.H. MDAI (5,6-methylenedioxy-2-aminoindane; 6,7-dihydro-5H-cyclopenta[f][1,3]benzodioxol-6-amine; 'sparkle'; 'mindy') toxicity: A brief overview and update. *Hum. Psychopharmacol. Clin. Exp.* **2013**, *28*, 345–355. [CrossRef] [PubMed]
56. Staeheli, S.N.; Boxler, M.I.; Oestreich, A.; Marti, M.; Gascho, D.; Bolliger, S.A.; Kraemer, T.; Steuer, A.E. Postmortem distribution and redistribution of MDAI and 2-MAPB in blood and alternative matrices. *Forensic Sci. Int.* **2017**, *279*, 83–87. [CrossRef] [PubMed]
57. Hasegawa, K.; Wurita, A.; Minakata, K.; Gonmori, K.; Nozawa, H.; Yamagishi, I.; Watanabe, K.; Suzuki, O. Postmortem distribution of AB-CHMINACA, 5-fluoro-AMB, and diphenidine in body fluids and solid tissues in a fatal poisoning case: Usefulness of adipose tissue for detection of the drugs in unchanged forms. *Forensic Toxicol.* **2015**, *33*, 45–53. [CrossRef]
58. Kudo, K.; Usumoto, Y.; Kikura-Hanajiri, R.; Sameshima, N.; Tsuji, A.; Ikeda, N. A fatal case of poisoning related to new cathinone designer drugs, 4-methoxy PV8, PV9, and 4-methoxy PV9, and a dissociative agent, diphenidine. *Leg. Med.* **2015**, *17*, 421–426. [CrossRef] [PubMed]
59. Bottinelli, C.; Cartiser, N.; Gaillard, Y.; Boyer, B.; Bévalot, F. A fatal case of 3-methylmethcathinone (3-MMC) poisoning. *Toxicol. Anal. Clin.* **2017**, *29*, 123–129. [CrossRef]
60. Palazzoli, F.; Santunione, A.; Verri, P.; Vandelli, D.; Silingardi, E. Post-mortem distribution of mephedrone and its metabolites in body fluids and organ tissues of an intoxication case. *J. Pharm. Biomed. Anal.* **2021**, *201*, 114093. [CrossRef] [PubMed]
61. Braham, M.Y.; Franchi, A.; Cartiser, N.; Bévalot, F.; Bottinelli, C.M.; Fabrizi, H.; Fanton, L. Fatal 4-MEC Intoxication: Case Report and Review of Literature. *Am. J. Forensic Med. Pathol.* **2020**, *42*, 57–61. [CrossRef] [PubMed]
62. Benedicte, L.; Camille, R.; Audrey, C.; Deborah, I.; Morgan, B.; Marie, D.; David, B.; Delphine, A.; Severine, F.; Guillaume, D.; et al. Case report on two-cathinones abuse: MPHP and *N*-ethyl-4′methylnorpentedrone, with a fatal outcome. *Forensic Toxicol.* **2020**, *38*, 243–254. [CrossRef]
63. Marinetti, L.J.; Antonides, H.M. Analysis of synthetic cathinones commonly found in bath salts in human performance and postmortem toxicology: Method development, drug distribution and interpretation of results. *J. Anal. Toxicol.* **2013**, *37*, 135–146. [CrossRef] [PubMed]
64. Strehmel, N.; Vejmelka, E.; Kastner, K.; Roscher, S.; Tsokos, M.; Scholtis, S. NPS-findings in forensic toxicology—Three case reports. *Toxichem. Krimtech.* **2017**, *84*, 199–204.
65. Yonemitsu, K.; Sasao, A.; Mishima, S.; Ohtsu, Y.; Nishitani, Y. A fatal poisoning case by intravenous injection of "bath salts" containing acetyl fentanyl and 4-methoxy PV8. *Forensic Sci. Int.* **2016**, *267*, e6–e9. [CrossRef] [PubMed]
66. Pearson, J.M.; Hargraves, T.L.; Hair, L.S.; Massucci, C.J.; Frazee, C.C.; Garg, U.; Pietak, B.R. Three fatal intoxications due to methylone. *J. Anal. Toxicol.* **2012**, *36*, 444–451. [CrossRef] [PubMed]
67. Shimomura, E.T.; Briones, A.J.; Warren, W.S.; Addison, J.W.; Knittel, J.L.; Shoemaker, S.A.; King, T.D.; Bosy, T.Z. Case Report of Methylone, Oxymorphone and Ethanol in a Fatality Case with Tissue Distribution. *J. Anal. Toxicol.* **2016**, *40*, 543–545. [CrossRef] [PubMed]
68. Cawrse, B.M.; Levine, B.; Jufer, R.A.; Fowler, D.R.; Vorce, S.P.; Dickson, A.J.; Holler, J.M. Distribution of methylone in four postmortem cases. *J. Anal. Toxicol.* **2012**, *36*, 434–439. [CrossRef] [PubMed]
69. Corey; Lightfoot, A.; Lavins, E.S.; Niblo, C.A.; Wyman, J.F.; Meditz, C.M.; Mazzola, C.D.; Schueler, H.E.; Gilson, T.P. Methylone Induced Death: Distribution of Methylone in Postmortem fluids ad Tissues. 2014 SOFT-TIAFT Meeting, Boca Raton, FL. Programme book, P-70. 2014; Available online: https://www.soft-tox.org/assets/docs/SOFT_2014_meeting_abstracts.pdf (accessed on 21 September 2024).
70. Rojek, S.; Kłys, M.; Strona, M.; Maciów, M.; Kula, K. "Legal highs"—Toxicity in the clinical and medico-legal aspect as exemplified by suicide with bk-MBDB administration. *Forensic Sci. Int.* **2012**, *222*, e1–e6. [CrossRef] [PubMed]
71. McIntyre, I.M.; Hamm, C.E.; Sherrard, J.L.; Gary, R.D.; Burton, C.G.; Mena, O. Acute 3,4-methylenedioxy-N-ethylcathinone (Ethylone) intoxication and related fatality: A case report with postmortem concentrations. *J. Anal. Toxicol.* **2015**, *39*, 225–228. [CrossRef] [PubMed]
72. Poston, A.; Jufer-Phipps, R.A.; Levine, B.S. Postmortem distribution of N ethylpentylone. In Proceedings of the 2017 SOFT-TIAFT Meeting, Grand Rapids, MI, USA, 9–14 September 2017; pp. 460–461. Available online: https://www.soft-tox.org/assets/docs/SOFT_2017_meeting_abstracts.pdf (accessed on 21 September 2024).

73. Sykutera, M.; Cychowska, M.; Bloch-Boguslawska, E. A Fatal Case of Pentedrone and -Pyrrolidinovalerophenone Poisoning. *J. Anal. Toxicol.* **2015**, *39*, 324–329. [CrossRef] [PubMed]
74. Cartiser, N.; Sahy, A.; Advenier, A.-S.; Franchi, A.; Revelut, K.; Bottinelli, C.; Bévalot, F.; Fanton, L. Fatal intoxication involving 4-methylpentedrone (4-MPD) in a context of chemsex. *Forensic Sci. Int.* **2021**, *319*, 110659. [CrossRef] [PubMed]
75. Majchrzak, M.; Celiński, R.; Kowalska, T.; Sajewicz, M. Fatal case of poisoning with a new cathinone derivative: α-propylaminopentiophenone (N-PP). *Forensic Toxicol.* **2018**, *36*, 525–533. [CrossRef] [PubMed] [PubMed Central]
76. Wurita, A.; Hasegawa, K.; Minakata, K.; Gonmori, K.; Nozawa, H.; Yamagishi, I.; Suzuki, O.; Watanabe, K. Postmortem distribution of α-pyrrolidinobutiophenone in body fluids and solid tissues of a human cadaver. *Leg. Med.* **2014**, *16*, 241–246. [CrossRef] [PubMed]
77. Potocka-Banaś, B.; Janus, T.; Majdanik, S.; Banaś, T.; Dembińska, T.; Borowiak, K. Fatal Intoxication with α-PVP, a Synthetic Cathinone Derivative. *J. Forensic Sci.* **2017**, *62*, 553–556. [CrossRef] [PubMed]
78. Hasegawa, K.; Suzuki, O.; Wurita, A.; Minakata, K.; Yamagishi, I.; Nozawa, H.; Gonmori, K.; Watanabe, K. Postmortem distribution of α-pyrrolidinovalerophenone and its metabolite in body fluids and solid tissues in a fatal poisoning case measured by LC–MS–MS with the standard addition method. *Forensic Toxicol.* **2014**, *32*, 225–234. [CrossRef]
79. Wachholz, P.; Celiński, R.; Bujak-Giżycka, B.; Skowronek, R.; Pawlas, N. A fatal case of poisoning with a cathinone derivative: α-PiHP and its postmortem distribution in body fluids and organ tissues. *J Anal Toxicol.* **2023**, *47*, 547–551. [CrossRef]
80. Hobbs, J.M.; DeRienz, R.T.; Baker, D.D.; Shuttleworth, M.R.; Pandey, M. Fatal Intoxication by the Novel Cathinone 4-Fluoro-3-methyl-α-PVP. *J. Anal. Toxicol.* **2022**, *46*, e101–e104. [CrossRef] [PubMed]
81. Mochizuki, A.; Adachi, N.; Shojo, H. Detection of 4-FMC, 4-MeO-α-PVP, 4-F-α-PVP, and PV8 in blood in a forensic case using liquid chromatography–electrospray ionization linear ion trap mass spectrometry. *Forensic Sci. Int.* **2021**, *325*, 110888. [CrossRef] [PubMed]
82. Wink, C.S.D.; Michely, J.A.; Jacobsen-Bauer, A.; Zapp, J.; Maurer, H.H. Diphenidine, a new psychoactive substance: Metabolic fate elucidated with rat urine and human liver preparations and detectability in urine using GC-MS, LC-MS^n, and LC-HR-MS^n. *Drug Test. Anal.* **2016**, *8*, 1005–1014. [CrossRef] [PubMed]
83. Helander, A.; Beck, O.; Bäckberg, M. Intoxications by the dissociative new psychoactive substances diphenidine and methoxphenidine. *Clin. Toxicol.* **2015**, *53*, 446–453. [CrossRef] [PubMed]
84. Kusano, M.; Zaitsu, K.; Taki, K.; Hisatsune, K.; Nakajima, J.; Moriyasu, T.; Asano, T.; Hayashi, Y.; Tsuchihashi, H.; Ishii, A. 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.* **2018**, *10*, 284–293. [CrossRef] [PubMed]
85. Ferec, S.; Gegu, C.; Bruneau, C.; Leroux, G.; Abbara, C.; Lelievre, B.; Boels, D.; Bretaudeau, M.; Turcant, A. Méthiopropamine, méthoxphénidine, diphénidine, D2PM, 5-MeO-DALT: À propos de nouveaux cas d'exposition unique ou en polyconsommation. *Toxicol. Anal. Clin.* **2015**, *27*, 2. [CrossRef]
86. Elliott, S.P.; Brandt, S.D.; Wallach, J.; Morris, H.; Kavanagh, P.V. First Reported Fatalities Associated with the 'Research Chemical' 2-Methoxydiphenidine. *J. Anal. Toxicol.* **2015**, *39*, 287–293. [CrossRef]
87. Shimshoni, J.A.; Britzi, M.; Sobol, E.; Willenz, U.; Nutt, D.; Edery, N. 3-Methyl-methcathinone: Pharmacokinetic profile evaluation in pigs in relation to pharmacodynamics. *J. Psychopharmacol.* **2015**, *29*, 734–743. [CrossRef]
88. López-Arnau, R.; Martínez-Clemente, J.; Carbó; M l Pubill, D.; Escubedo, E.; Camarasa, J. An integrated pharmacokinetic and pharmacodynamic study of a new drug of abuse, methylone, a synthetic cathinone sold as "bath salts". *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2013**, *45*, 64–72. [CrossRef]
89. Martínez-Clemente, J.; López-Arnau, R.; Carbó, M.; Pubill, D.; Camarasa, J.; Escubedo, E. Mephedrone pharmacokinetics after intravenous and oral administration in rats: Relation to pharmacodynamics. *Psychopharmacology* **2013**, *229*, 295–306. [CrossRef]
90. Dams, R.; De Letter, E.; Mortier, K.; Cordonnier, J.; Lambert, W.; Piette, M.; Van Calenbergh, S.; De Leenheer, A. Fatality due to combined use of the designer drugs MDMA and PMA: A distribution study. *J. Anal. Toxicol.* **2003**, *27*, 318–323. [CrossRef] [PubMed]
91. A De Letter, E.; Bouche, M.-P.L.; Van Bocxlaer, J.F.; E Lambert, W.; Piette, M.H. Interpretation of a 3,4-methylenedioxymethamphetamine (MDMA) blood level: Discussion by means of a distribution study in two fatalities. *Forensic Sci. Int.* **2004**, *141*, 85–90. [CrossRef] [PubMed]
92. De Letter, E.A.; Clauwaert, K.M.; Lambert, W.E.; Van Bocxlaer, J.F.; De Leenheer, A.P.; Piette, M.H.A. Distribution study of 3,4-methylenedioxymethamphetamine and 3,4-methylenedioxyamphetamine in a fatal overdose. *J. Anal. Toxicol.* **2002**, *26*, 113–118. [CrossRef] [PubMed]
93. Logan, B.; Weiss, E.; Harruff, R. Case report: Distribution of methamphetamine in a massive fatal ingestion. *J. Forensic Sci.* **1996**, *41*, 322–323. [CrossRef] [PubMed]
94. Tsujikawa, K.; Mikuma, T.; Kuwayama, K.; Miyaguchi, H.; Kanamori, T.; Iwata, Y.T.; Inoue, H. Degradation pathways of 4-methylmethcathinone in alkaline solution and stability of methcathinone analogs in various pH solutions. *Forensic Sci. Int.* **2012**, *220*, 103–110. [CrossRef] [PubMed]
95. Glicksberg, L.; Kerrigan, S. Stability of Synthetic Cathinones in Blood. *J. Anal. Toxicol.* **2017**, *41*, 711–719. [CrossRef] [PubMed]
96. Sørensen, L.K. Determination of cathinones and related ephedrines in forensic whole-blood samples by liquid-chromatography–electrospray tandem mass spectrometry. *J. Chromatogr. B Analyt. Technol. Biomed. Life Sci.* **2011**, *879*, 727–736. [CrossRef]

97. Adamowicz, P.; Malczyk, A. Stability of synthetic cathinones in blood and urine. *Forensic Sci. Int.* **2019**, *295*, 36–45. [CrossRef] [PubMed]
98. López-Arnau, R.; Martínez-Clemente, J.; Carbó; M l Pubill, D.; Escubedo, E.; Camarasa, J. Extended Stability Evaluation of Selected Cathinones. *Front. Chem.* **2020**, *8*, 597726. [CrossRef] [PubMed]
99. Glicksberg, L.; Rana, S.; Kerrigan, S. Cathinone stability in authentic urine specimens. *Forensic Sci. Int.* **2018**, *286*, 54–60. [CrossRef] [PubMed]
100. Lopes, R.P.; Ferro, R.A.; Milhazes, M.; Figueira, M.; Caldeira, M.J.; Antunes, A.M.M.; Gaspar, H. Metabolic stability and metabolite profiling of emerging synthetic cathinones. *Front. Pharmacol.* **2023**, *14*, 1145140. [CrossRef] [PubMed] [PubMed Central]
101. Aldubayyan, A.A.; Castrignanò, E.; Elliott, S.; Abbate, V. Influence of long-term storage temperatures and sodium fluoride preservation on the stability of synthetic cathinones and dihydro-metabolites in human whole blood. *Forensic Toxicol.* **2023**, *41*, 81–93. [CrossRef] [PubMed] [PubMed Central]
102. Aldubayyan, A.A.; Castrignanò, E.; Elliott, S.; Abbate, V. Short- and long-term stability of synthetic cathinones and dihydro-metabolites in human urine samples. *Forensic Toxicol.* **2024**, *42*, 172–180. [CrossRef] [PubMed]
103. Adamowicz, P. Blood concentrations of synthetic cathinones. *Clin. Toxicol.* **2021**, *59*, 648–654. [CrossRef] [PubMed]
104. Woźniak, M.K.; Banaszkiewicz, L.; Wiergowski, M.; Tomczak, E.; Kata, M.; Szpiech, B.; Biziuk, M. Development and validation of a GC–MS/MS method for the determination of 11 amphetamines and 34 synthetic cathinones in whole blood. *Forensic Toxicol.* **2020**, *38*, 42–58. [CrossRef]
105. Kubo, S.-I.; Waters, B.; Hara, K.; Fukunaga, T.; Ikematsu, K. A report of novel psychoactive substances in forensic autopsy cases and a review of fatal cases in the literature. *Leg. Med.* **2017**, *26*, 79–85. [CrossRef] [PubMed]
106. Namera, A.; Urabe, S.; Saito, T.; Torikoshi-Hatano, A.; Shiraishi, H.; Arima, Y.; Nagao, M. A fatal case of 3,4-methylenedioxypyrovalerone poisoning: Coexistence of α-pyrrolidinobutiophenone and α-pyrrolidinovalerophenone in blood and/or hair. *Forensic Toxicol.* **2013**, *31*, 338–343. [CrossRef]
107. Zawilska, J.B.; Wojcieszak, J. α-Pyrrolidinophenones: A new wave of designer cathinones. *Forensic Toxicol.* **2017**, *35*, 201–216. [CrossRef]
108. Beck, O.; Bäckberg, M.; Signell, P.; Helander, A. Intoxications in the STRIDA project involving a panorama of psychostimulant pyrovalerone derivatives, MDPV copycats. *Clin. Toxicol.* **2017**, *56*, 256–263. [CrossRef] [PubMed]
109. Pieprzyca, E.; Skowronek, R.; Korczyńska, M.; Kulikowska, J.; Chowaniec, M. A two fatal cases of poisoning involving new cathinone derivative PV8. *Leg. Med.* **2018**, *33*, 42–47. [CrossRef] [PubMed]
110. Kovács, K.; Kereszty, E.; Berkecz, R.; Tiszlavicz, L.; Sija, E.; Körmöczi, T.; Jenei, N.; Révész-Schmehl, H.; Institóris, L. Fatal intoxication of a regular drug user following N-ethyl-hexedrone and ADB-FUBINACA consumption. *J. Forensic Leg. Med.* **2019**, *65*, 92–100. [CrossRef] [PubMed]
111. Krotulski, A.J.; Papsun, D.M.; De Martinis, B.S.; A Mohr, A.L.; Logan, B.K. N-Ethyl Pentylone (Ephylone) Intoxications: Quantitative Confirmation and Metabolite Identification in Authentic Human Biological Specimens. *J. Anal. Toxicol.* **2018**, *42*, 467–475. [CrossRef] [PubMed]
112. Mercieca, G.; Odoardi, S.; Cassar, M.; Rossi, S.S. 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. Pharm. Biomed. Anal.* **2018**, *149*, 494–501. [CrossRef] [PubMed]
113. Adamowicz, P.; Hydzik, P. Fetal death associated with the use of 3,4-MDPHP and α-PHP. *Clin. Toxicol.* **2018**, *57*, 112–116. [CrossRef] [PubMed]
114. Di Candia, D.; Boracchi, M.; Ciprandi, B.; Giordano, G.; Zoja, R. A unique case of death by MDPHP with no other co-ingestion: A forensic toxicology case. *Int. J. Leg. Med.* **2022**, *136*, 1291–1296. [CrossRef] [PubMed] [PubMed Central]
115. Grumann, C.; Huppertz, L.M.; Bisel, P.; Angerer, V.; Auwärter, V. Method validation and preliminary pharmacokinetic studies on the new designer stimulant 3-fluorophenmetrazine (3-FPM). *Drug Test. Anal.* **2019**, *11*, 1009–1017. [CrossRef] [PubMed]
116. Raisi, A.; Beckett, A.H. Identification and quantitative analysis of phendimetrazine and some of its metabolites in biological fluids. *Monatshefte Fuer Chemie/Chemical Mon.* **1986**, *117*, 1047–1055. [CrossRef]
117. Rossi, S.S.; de la Torre, X.; Botrè, F. A fast gas chromatography/mass spectrometry method for the determination of stimulants and narcotics in urine. *Rapid Commun. Mass Spectrom.* **2010**, *24*, 1475–1480. [CrossRef] [PubMed]
118. Norheim, G. A Fatal Case of Phenmetrazine Poisoning. *J. Forensic Sci. Soc.* **1973**, *13*, 287–289. [CrossRef] [PubMed]
119. Bäckberg, M.; Westerbergh, J.; Beck, O.; Helander, A. Adverse events related to the new psychoactive substance 3-fluorophenmetrazine—Results from the Swedish STRIDA project. *Clin. Toxicol.* **2016**, *54*, 819–825. [CrossRef] [PubMed]
120. Bonnichsen, R.; Maehly, A.C.; Ryhage, R.; Schubert, B. Determination and identification of sympathomimetic amines in blood samples from drivers by a combination of gas chromatography and mass spectrometry. Zeitschrift fur Rechtsmedizin. *J. Leg. Med.* **1970**, *67*, 19–26.
121. Musshoff, F.; Padosch, S.; Steinborn, S.; Madea, B. Fatal blood and tissue concentrations of more than 200 drugs. *Forensic Sci. Int.* **2004**, *142*, 161–210. [CrossRef] [PubMed]
122. Gottschalk, L.; Cravey, R.H. *Toxicological and Pathological Studies on Psychoactive Drug-Induced Deaths*; Biomedical Publications: Irving, CA, USA, 1980.
123. Hood, I.; Monforte, J.; Gault, R.; Mirchandani, H. Fatality from illicit phendimetrazine use. *J. Toxicol. Clin. Toxicol.* **1988**, *26*, 249–255. [CrossRef] [PubMed]

124. Ellefsen, K.N.; A Taylor, E.; Simmons, P.; Willoughby, V.; Hall, B.J. Multiple Drug-Toxicity Involving Novel Psychoactive Substances, 3-Fluorophenmetrazine and U-47700. *J. Anal. Toxicol.* **2017**, *41*, 765–770. [CrossRef] [PubMed]
125. Lehmann, S.; Sczyslo, A.; Froch-Cortis, J.; Rothschild, M.A.; Thevis, M.; Andresen-Streichert, H.; Mercer-Chalmers-Bender, K. Organ distribution of diclazepam, pyrazolam and 3-fluorophenmetrazine. *Forensic Sci. Int.* **2019**, *303*, 109959. [CrossRef] [PubMed]
126. Souto, C.; Göethel, G.; Peruzzi, C.P.; Cestonaro, L.V.; Garcia, I.; Ávila, D.S.; Eifler-Lima, V.; Carmo, H.; Bastos, M.d.L.; Garcia, S.C.; et al. Piperazine designer drugs elicit toxicity in the alternative in vivo model *Caenorhabditis elegans*. *J. Appl. Toxicol.* **2020**, *40*, 363–372. [CrossRef]
127. Cantrell, F.L.; Ogera, P.; Mallett, P.; McIntyre, I.M. Fatal oral methylphenidate intoxication with postmortem concentrations. *J. Forensic Sci.* **2014**, *59*, 847–849. [CrossRef] [PubMed]
128. Theofel, N.; Möller, P.; Vejmelka, E.; Kastner, K.; Roscher, S.; Scholtis, S.; Tsokos, M. A Fatal Case Involving *N*-Ethyldeschloroketamine (2-Oxo-PCE) and Venlafaxine. *J. Anal. Toxicol.* **2019**, *43*, e2–e6. [CrossRef] [PubMed]
129. McIntyre, I.M.; Trochta, A.; Gary, R.D.; Storey, A.; Corneal, J.; Schaber, B. A Fatality Related to Two Novel Hallucinogenic Compounds: 4-Methoxyphencyclidine and 4-Hydroxy-*N*-methyl-*N*-ethyltryptamine. *J. Anal. Toxicol.* **2015**, *39*, 751–755. [CrossRef] [PubMed]
130. Seetohul, L.N.; Pounder, D.J. Four Fatalities Involving 5-IT. *J. Anal. Toxicol.* **2013**, *37*, 447–451. [CrossRef] [PubMed]
131. Timko, C.; Phipps, R.J.; Southall, P.; Fowler, D. Postmortem Distribution of N,N-Dipropyltryptamine in an Intoxication Case. 2019 SOFT Anual Meeting, San Antonio, TX, USA, 2019; p. 85. Available online: https://www.SOFT_2019_meeting_abstracts.pdf (accessed on 21 September 2024).
132. McIntyre, I.M.; Trochta, A.; Stolberg, S.; Campman, S.C. Mitragynine 'kratom' related fatality: A case report with postmortem concentrations. *J. Anal. Toxicol.* **2015**, *39*, 152–155. [CrossRef] [PubMed]
133. Mata, D.C.; Chang, H.H. Postmortem Mitragynine Distribution in a Single Drug Fatality Case. *Acad. Forensic Pathol.* **2023**, *13*, 34–40. [CrossRef] [PubMed] [PubMed Central]
134. Crichton, M.L.; Shenton, C.F.; Drummond, G.; Beer, L.J.; Seetohul, L.N.; Maskell, P.D. Analysis of phenazepam and 3-hydroxyphenazepam in post-mortem fluids and tissues. *Drug Test. Anal.* **2015**, *7*, 926–936. [CrossRef] [PubMed]
135. Giorgetti, A.; Sommer, M.J.; Wilde, M.; Perdekamp, M.G.; Auwärter, V. A case of fatal multidrug intoxication involving flualprazolam: Distribution in body fluids and solid tissues. *Forensic Toxicol.* **2023**, *40*, 180–188. [CrossRef] [PubMed] [PubMed Central]
136. Kolbe, V.; Rentsch, D.; Boy, D.; Schmidt, B.; Kegler, R.; Büttner, A. The adulterated XANAX pill: A fatal intoxication with etizolam and caffeine. *Int. J. Leg. Med.* **2020**, *134*, 1727–1731. [CrossRef] [PubMed] [PubMed Central]
137. Gevorkyan, J.; Kinyua, J.; Pearring, S.; Rodda, L.N. A Case Series of Etizolam in Opioid-Related Deaths. *J. Anal. Toxicol.* **2021**, *45*, E4–E17. [CrossRef] [PubMed]
138. Miller, C.; Lintemoot, J.; Montero, T.; Anderson, D. Etizolam: There's a New Benzodiazepine in Town. 2014 SOFT-TIAFT Meeting, Grand Rapids, MI, USA, S-29. 2014. Available online: http://www.soft-tox.org/assets/docs/SOFT_2014_meeting_abstracts.pdf (accessed on 21 September 2024).
139. Staack, R.F.; Maurer, H.H. Metabolism of Designer Drugs of Abuse. *Curr. Drug Metab.* **2005**, *6*, 259–274. [CrossRef] [PubMed]
140. Antia, U.; Tingle, M.D.; Russell, B.R. Validation of an LC–MS method for the detection and quantification of BZP and TFMPP and their hydroxylated metabolites in human plasma and its application to the pharmacokinetic study of TFMPP in humans*. *J. Forensic Sci.* **2010**, *55*, 1311–1318. [CrossRef] [PubMed]
141. Peters, F.T.; Schaefer, S.; Staack, R.F.; Kraemer, T.; Maurer, H.H. Screening for and validated quantification of amphetamines and of amphetamine- and piperazine-derived designer drugs in human blood plasma by gas chromatography/mass spectrometry. *J. Mass Spectrom.* **2003**, *38*, 659–676. [CrossRef] [PubMed]
142. Al-Saffar, Y.; Stephanson, N.N.; Beck, O. Multicomponent LC–MS/MS screening method for detection of new psychoactive drugs, legal highs, in urine—Experience from the Swedish population. *J. Chromatogr. B Analyt. Technol. Biomed. Life Sci.* **2013**, *930*, 112–120. [CrossRef] [PubMed]
143. Lau, T.; LeBlanc, R.; Botch-Jones, S. Stability of Synthetic Piperazines in Human Whole Blood. *J. Anal. Toxicol.* **2018**, *42*, 88–98. [CrossRef] [PubMed]
144. Lehmann, S.; Kieliba, T.; Thevis, M.; Rothschild, M.A.; Mercer-Chalmers-Bender, K. Fatalities associated with NPS stimulants in the Greater Cologne area. *Int. J. Leg. Med.* **2020**, *134*, 229–241. [CrossRef] [PubMed]
145. Elliott, S.; Smith, C. Investigation of the first deaths in the United Kingdom involving the detection and quantitation of the piperazines BZP and 3-TFMPP. *J. Anal. Toxicol.* **2008**, *32*, 172–177. [CrossRef] [PubMed]
146. Dinis-Oliveira, R.J. Metabolomics of Methylphenidate and Ethylphenidate: Implications in Pharmacological and Toxicological Effects. *Eur. J. Drug Metab. Pharmacokinet.* **2017**, *42*, 11–16. [CrossRef] [PubMed]
147. Josefsson, M.; Rydberg, I. Determination of methylphenidate and ritalinic acid in blood, plasma and oral fluid from adolescents and adults using protein precipitation and liquid chromatography tandem mass spectrometry—A method applied on clinical and forensic investigations. *J. Pharm. Biomed. Anal.* **2011**, *55*, 1050–1059. [CrossRef] [PubMed]
148. Karinen, R.; Øiestad, E.L.; Andresen, W.; Wethe, G.; Smith-Kielland, A.; Christophersen, A. Comparison of ethanol and other drugs of abuse concentrations in whole blood stored in venoject(R) glass and plastic and venosafe plastic evacuated tubes. *J. Anal. Toxicol.* **2010**, *34*, 420–428. [CrossRef] [PubMed]

149. Zhu, H.-J.; Patrick, K.S.; Markowitz, J.S. Enantiospecific determination of DL-methylphenidate and DL-ethylphenidate in plasma by liquid chromatography—Tandem mass spectrometry: Application to human ethanol interactions. *J. Chromatogr. B Analyt. Technol. Biomed. Life Sci.* **2011**, *879*, 783–788. [CrossRef] [PubMed] [PubMed Central]
150. Levine, B.; Caplan, Y.H.; Kauffman, G. Fatality resulting from methylphenidate overdose. *J. Anal. Toxicol.* **1986**, *10*, 209–210. [CrossRef] [PubMed]
151. Thomsen, R.; Rasmussen, H.B.; Linnet, K. The INDICES consortium enantioselective determination of methylphenidate and ritalinic acid in whole blood from forensic cases using automated solid-phase extraction and liquid chromatography-tandem mass spectrometry. *J. Anal. Toxicol.* **2012**, *36*, 560–568. [CrossRef] [PubMed]
152. Roy, S.; Charreteur, R.; Gerardin, M.; Faucherre, V.; Xatart, S.; Eiden, C.; Vigneau, C.; Peyrière, H. Serious Complications Associated With the Injection of Ethylphenidate: 2 Case Reports. *J. Clin. Psychopharmacol.* **2020**, *40*, 87–89. [CrossRef]
153. Parks, C.; McKeown, D.; Torrance, H.J. A review of ethylphenidate in deaths in east and west Scotland. *Forensic Sci. Int.* **2015**, *257*, 203–208. [CrossRef] [PubMed]
154. Shoff, E.N.; Kahl, J.H.; Hime, G.W.; Coburn, M.; Boland, D.M. 4-Fluoromethylphenidate: Fatal Intoxication Involving a Previously Unreported Novel Psychoactive Substance in the USA. *J. Anal. Toxicol.* **2019**, *43*, 666–672. [CrossRef] [PubMed]
155. Corkery, J.M.; Schifano, F. First Death Involving 4-Fluoroethylphenidate (4F-EPH): Case Report, User Experiences, and Review of the Related Literature. *Acad. Forensic Pathol.* **2022**, *12*, 149–166. [CrossRef] [PubMed] [PubMed Central]
156. Pelletier, R.; Le Daré, B.; Le Bouëdec, D.; Kernalléguen, A.; Ferron, P.-J.; Morel, I.; Gicquel, T. Arylcyclohexylamine Derivatives: Pharmacokinetic, Pharmacodynamic, Clinical and Forensic Aspects. *Int. J. Mol. Sci.* **2022**, *23*, 15574. [CrossRef]
157. Hijazi, Y.; Bolon, M.; Boulieu, R. Stability of ketamine and its metabolites norketamine and dehydronorketamine in human biological samples. *Clin. Chem.* **2001**, *47*, 1713–1715. [CrossRef] [PubMed]
158. Grieshaber, A.; Costantino, A.; Lappas, N. Stability of phencyclidine in stored blood samples. *J. Anal. Toxicol.* **1998**, *22*, 515–519. [CrossRef] [PubMed]
159. Kraemer, M.; Boehmer, A.; Madea, B.; Maas, A. Death cases involving certain new psychoactive substances: A review of the literature. *Forensic Sci. Int.* **2019**, *298*, 186–267. [CrossRef] [PubMed]
160. Copeland, C.S.; Hudson, S.; Treble, R.; Hamnett, H.J. The First Fatal Intoxication with 3-MeO-PCP in the UK and a Review of the Literature. *J. Anal. Toxicol.* **2022**, *46*, 461–470. [CrossRef] [PubMed]
161. Gicquel, T.; Richeval, C.; Mesli, V.; Gish, A.; Hakim, F.; Pelletier, R.; Cornez, R.; Balgairies, A.; Allorge, D.; Gaulier, J.-M. Fatal intoxication related to two new arylcyclohexylamine derivatives (2F-DCK and 3-MeO-PCE). *Forensic Sci. Int.* **2021**, *324*, 110852. [CrossRef] [PubMed]
162. Wikström, M.; Thelander, G.; Dahlgren, M.; Kronstrand, R. An Accidental Fatal Intoxication with Methoxetamine. *J. Anal. Toxicol.* **2013**, *37*, 43–46. [CrossRef] [PubMed]
163. Wiergowski, M.; Anand, J.S.; Krzyżanowski, M.; Jankowski, Z. Acute methoxetamine and amphetamine poisoning with fatal outcome: A case report. *Int. J. Occup. Med. Environ. Health* **2014**, *27*, 683–690. [CrossRef] [PubMed]
164. Lalonde, B.R.; Wallage, H.R. Postmortem blood ketamine distribution in two fatalities. *J. Anal. Toxicol.* **2004**, *28*, 71–74. [CrossRef] [PubMed]
165. Brandt, S.D.; Kavanagh, P.V.; Westphal, F.; Stratford, A.; Elliott, S.P.; Hoang, K.; Wallach, J.; Halberstadt, A.L. Return of the lysergamides. Part I: Analytical and behavioural characterization of 1-propionyl-*d*-lysergic acid diethylamide (1P-LSD). *Drug Test. Anal.* **2016**, *8*, 891–902. [CrossRef] [PubMed] [PubMed Central]
166. Brandt, S.D.; Kavanagh, P.V.; Westphal, F.; Elliott, S.P.; Wallach, J.; Colestock, T.; Burrow, T.E.; Chapman, S.J.; Stratford, A.; Nichols, D.E.; et al. Return of the lysergamides. Part II: Analytical and behavioural characterization of N^6-allyl-6-norlysergic acid diethylamide (AL-LAD) and (2′*S*,4′*S*)-lysergic acid 2,4-dimethylazetidide (LSZ). *Drug Test. Anal.* **2016**, *9*, 38–50. [CrossRef] [PubMed] [PubMed Central]
167. Brandt, S.D.; Kavanagh, P.V.; Westphal, F.; Elliott, S.P.; Wallach, J.; Stratford, A.; Nichols, D.E.; Halberstadt, A.L. Return of the lysergamides. Part III: Analytical characterization of N^6-ethyl-6-norlysergic acid diethylamide (ETH-LAD) and 1-propionyl ETH-LAD (1P–ETH-LAD). *Drug Test. Anal.* **2017**, *9*, 1641–1649. [CrossRef] [PubMed] [PubMed Central]
168. Brandt, S.D.; Kavanagh, P.V.; Twamley, B.; Westphal, F.; Elliott, S.P.; Wallach, J.; Stratford, A.; Klein, L.M.; McCorvy, J.D.; Nichols, D.E.; et al. Return of the lysergamides. Part IV: Analytical and pharmacological characterization of lysergic acid morpholide (LSM-775). *Drug Test. Anal.* **2018**, *10*, 310–322. [CrossRef] [PubMed] [PubMed Central]
169. Brandt, S.D.; Kavanagh, P.V.; Westphal, F.; Stratford, A.; Elliott, S.P.; Dowling, G.; Wallach, J.; Halberstadt, A.L. Return of the lysergamides. Part V: Analytical and behavioural characterization of 1-butanoyl-*d*-lysergic acid diethylamide (1B-LSD). *Drug Test. Anal.* **2019**, *11*, 1122–1133. [CrossRef] [PubMed] [PubMed Central]
170. Brandt, S.D.; Kavanagh, P.V.; Westphal, F.; Stratford, A.; Odland, A.U.; Klein, A.K.; Dowling, G.; Dempster, N.M.; Wallach, J.; Passie, T.; et al. Return of the lysergamides. Part VI: Analytical and behavioural characterization of 1-cyclopropanoyl-*d*-lysergic acid diethylamide (1CP-LSD). *Drug Test. Anal.* **2020**, *12*, 812–826. [CrossRef] [PubMed] [PubMed Central]
171. Brandt, S.D.; Kavanagh, P.V.; Westphal, F.; Pulver, B.; Morton, K.; Stratford, A.; Dowling, G.; Halberstadt, A.L. Return of the lysergamides. Part VII: Analytical and behavioural characterization of 1-valeroyl-d-lysergic acid diethylamide (1V-LSD). *Drug Test. Anal.* **2022**, *14*, 733–740. [CrossRef] [PubMed] [PubMed Central]
172. Junior, L.F.N.; Fabris, A.L.; Barbosa, I.L.; Ponce, J.d.C.; Martins, A.F.; Costa, J.L.; Yonamine, M. Lucy is back in Brazil with a new dress. *Forensic Sci. Int.* **2022**, *341*, 111497. [CrossRef] [PubMed]

173. Tanaka, R.; Kawamura, M.; Mizutani, S.; Kikura-Hanajiri, R. Identification of LSD analogs, 1cP-AL-LAD, 1cP-MIPLA, 1V-LSD and LSZ in sheet products. *Forensic Toxicol.* **2023**, *41*, 294–303. [CrossRef] [PubMed] [PubMed Central]
174. Tanaka, R.; Kawamura, M.; Mizutani, S.; Kikura-Hanajiri, R. Characterization of the lysergic acid diethylamide analog, 1-(thiophene-2-carbonyl)-*N*,*N*-diethyllysergamide (1T-LSD) from a blotter product. *Drug Test. Anal.* **2024**, *16*, 482–488. [CrossRef] [PubMed]
175. Okada, Y.; Segawa, H.; Yamamuro, T.; Kuwayama, K.; Tsujikawa, K.; Kanamori, T.; Iwata, Y.T. Synthesis and analytical characterization of 1-(2-thienoyl)-6-allyl-nor-*d*-lysergic acid diethylamide (1T-AL-LAD). *Drug Test. Anal.* **2024**. [CrossRef] [PubMed]
176. Halberstadt, A.L.; Chatha, M.; Klein, A.K.; McCorvy, J.D.; Meyer, M.R.; Wagmann, L.; Stratford, A.; Brandt, S.D. Pharmacological and biotransformation studies of 1-acyl-substituted derivatives of *D*-lysergic acid diethylamide (LSD). *Neuropharmacology* **2019**, *172*, 107856. [CrossRef] [PubMed] [PubMed Central]
177. Martin, R.; Schürenkamp, J.; Gasse, A.; Pfeiffer, H.; Köhler, H. Determination of psilocin, bufotenine, LSD and its metabolites in serum, plasma and urine by SPE-LC-MS/MS. *Int. J. Leg. Med.* **2013**, *127*, 593–601. [CrossRef] [PubMed]
178. Francom, P.; Andrenyak, D.; Lim, H.-K.; Bridges, R.R.; Foltz, R.L.; Jones, R.T. Determination of LSD in urine by capillary column gas chromatography and electron impact mass spectrometry. *J. Anal. Toxicol.* **1988**, *12*, 1–8. [CrossRef] [PubMed]
179. Wagmann, L.; Richter, L.H.J.; Kehl, T.; Wack, F.; Bergstrand, M.P.; Brandt, S.D.; Stratford, A.; Maurer, H.H.; Meyer, M.R. In vitro metabolic fate of nine LSD-based new psychoactive substances and their analytical detectability in different urinary screening procedures. *Anal. Bioanal. Chem.* **2019**, *411*, 4751–4763. [CrossRef] [PubMed]
180. Fysh, R.; Oon, M.; Robinson, K.; Smith; White, P.; Whitehouse, M. A fatal poisoning with LSD. *Forensic Sci. Int.* **1985**, *28*, 109–113. [CrossRef] [PubMed]
181. Mardal, M.; Johansen, S.S.; Thomsen, R.; Linnet, K. Advantages of analyzing postmortem brain samples in routine forensic drug screening—Case series of three non-natural deaths tested positive for lysergic acid diethylamide (LSD). *Forensic Sci. Int.* **2017**, *278*, e14–e18. [CrossRef] [PubMed]
182. Dinis-Oliveira, R.J. Metabolism of psilocybin and psilocin: Clinical and forensic toxicological relevance. *Drug Metab. Rev.* **2017**, *49*, 84–91. [CrossRef] [PubMed]
183. Hasler, F.; Bourquin, D.; Brenneisen, R.; Vollenweider, F.X. Renal excretion profiles of psilocin following oral administration of psilocybin: A controlled study in man. *J. Pharm. Biomed. Anal.* **2002**, *30*, 331–339. [CrossRef] [PubMed]
184. Tittarelli, R.; Mannocchi, G.; Pantano, F.; Romolo, F.S. Recreational Use, Analysis and Toxicity of Tryptamines. *Curr. Neuropharmacol.* **2015**, *13*, 26–46. [CrossRef] [PubMed] [PubMed Central]
185. Araújo, A.M.; Carvalho, F.; Bastos, M.d.L.; de Pinho, P.G.; Carvalho, M. The hallucinogenic world of tryptamines: An updated review. *Arch. Toxicol.* **2015**, *89*, 1151–1173. [CrossRef] [PubMed]
186. Malaca, S.; Faro, A.F.L.; Tamborra, A.; Pichini, S.; Busardò, F.P.; Huestis, M.A. Toxicology and Analysis of Psychoactive Tryptamines. *Int. J. Mol. Sci.* **2020**, *21*, 9279. [CrossRef] [PubMed] [PubMed Central]
187. Oliver, J.; Smith, H.; Williams, D. The detection, identification and measurement of indole, tryptamine and 2-phenethylamine in putrefying human tissue. *Forensic Sci.* **1977**, *9*, 195–203. [CrossRef] [PubMed]
188. Brito-Da-Costa, A.M.; Dias-Da-Silva, D.; Gomes, N.G.M.; Dinis-Oliveira, R.J.; Madureira-Carvalho, Á. Toxicokinetics and Toxicodynamics of Ayahuasca Alkaloids *N*,*N*-Dimethyltryptamine (DMT), Harmine, Harmaline and Tetrahydroharmine: Clinical and Forensic Impact. *Pharmaceuticals* **2020**, *13*, 334. [CrossRef] [PubMed] [PubMed Central]
189. Available online: https://www.drugbank.ca/drug (accessed on 27 July 2024).
190. Ramanathan, S.; Parthasarathy, S.; Murugaiyah, V.; Magosso, E.; Tan, S.C.; Mansor, S.M. Understanding the Physicochemical Properties of Mitragynine, a Principal Alkaloid of *Mitragyna speciosa*, for Preclinical Evaluation. *Molecules* **2015**, *20*, 4915–4927. [CrossRef] [PubMed] [PubMed Central]
191. Chen, J.; Li, M.; Yan, X.; Wu, E.; Zhu, H.; Lee, K.J.; Chu, V.M.; Zhan, L.; Lee, W.; Kang, J.S. Determining the pharmacokinetics of psilocin in rat plasma using ultra-performance liquid chromatography coupled with a photodiode array detector after orally administering an extract of Gymnopilus spectabilis. *J. Chromatogr. B* **2011**, *879*, 2669–2672. [CrossRef] [PubMed]
192. Tiscione, N.B.; Vacha, R.E.; Alford, I.; Yeatman, D.T.; Shan, X. Long-Term Blood Alcohol Stability in Forensic Antemortem Whole Blood Samples. *J. Anal. Toxicol.* **2015**, *39*, 419–425. [CrossRef] [PubMed]
193. Martin, R.; Schürenkamp, J.; Pfeiffer, H.; Lehr, M.; Köhler, H. Synthesis, hydrolysis and stability of psilocin glucuronide. *Forensic Sci. Int.* **2014**, *237*, 1–6. [CrossRef] [PubMed]
194. Brown, R.T.; Nicholas, C.R.; Cozzi, N.V.; Gassman, M.C.; Cooper, K.M.; Muller, D.; Thomas, C.D.; Hetzel, S.J.; Henriquez, K.M.; Ribaudo, A.S.; et al. Pharmacokinetics of Escalating Doses of Oral Psilocybin in Healthy Adults. *Clin. Pharmacokinet.* **2017**, *56*, 1543–1554. [CrossRef] [PubMed]
195. Basiliere, S.; Kerrigan, S. Temperature and pH-Dependent Stability of Mitragyna Alkaloids. *J. Anal. Toxicol.* **2020**, *44*, 314–324. [CrossRef] [PubMed]
196. Parthasarathy, S.; Ramanathan, S.; Ismail, S.; Adenan, M.I.; Mansor, S.M.; Murugaiyah, V. Determination of mitragynine in plasma with solid-phase extraction and rapid HPLC–UV analysis, and its application to a pharmacokinetic study in rat. *Anal. Bioanal. Chem.* **2010**, *397*, 2023–2030. [CrossRef] [PubMed]

197. Lu, S.; Tran, B.N.; Nelsen, J.L.; Aldous, K.M. Quantitative analysis of mitragynine in human urine by high performance liquid chromatography-tandem mass spectrometry. *J. Chromatogr. B Analyt. Technol. Biomed. Life Sci.* **2009**, *877*, 2499–2505. [CrossRef] [PubMed]
198. Sklerov, J.; Levine, B.; Moore, K.A.; King, T.; Fowler, D. A fatal intoxication following the ingestion of 5-methoxy-N,N- dimethyltryptamine in an ayahuasca preparation. *J. Anal. Toxicol.* **2005**, *29*, 838–841. [CrossRef] [PubMed]
199. Neukamm, M.A.; Pollak, S.; Thoma, V.; Vogt, S.; Huppertz, L.M.; Auwärter, V. A fatal case of aspiration due to consumption of the hallucinogenic tryptamine derivative dipropyltryptamine (DPT). *J. Pharm. Biomed. Anal.* **2024**, *240*, 115959. [CrossRef] [PubMed]
200. Tanaka, E.; Kamata, T.; Katagi, M.; Tsuchihashi, H.; Honda, K. A fatal poisoning with 5-methoxy-N,N-diisopropyltryptamine, Foxy. *Forensic Sci. Int.* **2006**, *163*, 152–154. [CrossRef] [PubMed]
201. Meatherall, R.; Sharma, P. Foxy, a Designer Tryptamine Hallucinogen*. *J. Anal. Toxicol.* **2003**, *27*, 313–317. [CrossRef] [PubMed]
202. Wilson, J.M.; McGeorge, F.; Smolinske, S.; Meatherall, R. A foxy intoxication. *Forensic Sci. Int.* **2005**, *148*, 31–36. [CrossRef] [PubMed]
203. Honyiglo, E.; Franchi, A.; Cartiser, N.; Bottinelli, C.; Advenier, A.; Bévalot, F.; Fanton, L. Unpredictable Behavior Under the Influence of "Magic Mushrooms": A Case Report and Review of the Literature. *J. Forensic Sci.* **2019**, *64*, 1266–1270. [CrossRef] [PubMed]
204. Boland, D.M.; Andollo, W.; Hime, G.W.; Hearn, W.L. Fatality Due to Acute α-Methyltryptamine Intoxication. *J. Anal. Toxicol.* **2005**, *29*, 394–397. [CrossRef] [PubMed]
205. Daldrup, T.; Heller, C.; Matthiesen, U.; Honus, S.; Bresges, A.; Haarhoff, K. Etryptamin, eine neue Designer-Droge mit fataler Wirkung [Etryptamine, a new designer drug with a fatal effect]. *Z Rechtsmed.* **1986**, *97*, 61–68. [CrossRef] [PubMed]
206. Kronstrand, R.; Roman, M.; Thelander, G.; Eriksson, A. Unintentional fatal intoxications with mitragynine and O-desmethyltramadol from the herbal blend krypton. *J. Anal. Toxicol.* **2011**, *35*, 242–247. [CrossRef] [PubMed]
207. Neerman, M.F.; Frost, R.E.; Deking, J. A Drug Fatality Involving Kratom. *J. Forensic Sci.* **2013**, *58*, S278–S279. [CrossRef] [PubMed]
208. Karinen, R.; Fosen, J.T.; Rogde, S.; Vindenes, V. An accidental poisoning with mitragynine. *Forensic Sci. Int.* **2014**, *245*, e29–e32. [CrossRef] [PubMed]
209. Mata, D.C.; Davis, J.F. Simultaneous quantitative analysis of 39 common toxicological drugs for increased efficiency in an ante- and postmortem laboratory. *Forensic Sci. Int.* **2022**, *334*, 111246. [CrossRef] [PubMed]
210. Manchester, K.R.; Maskell, P.D.; Waters, L. Experimental versus theoretical log $D_{7.4}$, pK_a and plasma protein binding values for benzodiazepines appearing as new psychoactive substances. *Drug Test. Anal.* **2018**, *10*, 1258–1269. [CrossRef] [PubMed]
211. Zilg, B.; Thelander, G.; Giebe, B.; Druid, H. Postmortem blood sampling—Comparison of drug concentrations at different sample sites. *Forensic Sci. Int.* **2017**, *278*, 296–303. [CrossRef]
212. Mantinieks, D.; Gerostamoulos, D.; Glowacki, L.; Di Rago, M.; Schumann, J.; Woodford, N.W.; Drummer, O.H. Postmortem Drug Redistribution: A Compilation of Postmortem/Antemortem Drug Concentration Ratios. *J. Anal. Toxicol.* **2021**, *45*, 368–377. [CrossRef] [PubMed]
213. Oertel, R.; Pietsch, J.; Arenz, N.; Zeitz, S.; Goltz, L.; Kirch, W. Distribution of metoprolol, tramadol, and midazolam in human autopsy material. *J. Chromatogr. A* **2011**, *1218*, 4988–4994. [CrossRef] [PubMed]
214. Mata, D.C. Stability of 26 Sedative Hypnotics in Six Toxicological Matrices at Different Storage Conditions. *J. Anal. Toxicol.* **2016**, *40*, 663–668. [CrossRef] [PubMed]
215. Robertson, M.D.; Drummer, O. Stability of Nitrobenzodiazepines in Postmortem Blood. *J. Forensic Sci.* **1998**, *43*, 5–8. [CrossRef] [PubMed]
216. Robertson, M.D.; Drummer, O. Postmortem distribution and redistribution of nitrobenzodiazepines in man. *J. Forensic Sci.* **1998**, *43*, 9–13. [CrossRef] [PubMed]
217. Casey, B.K.; Papsun, D.M.; Mudd, A. Elucidating the Potential Role of Microorganisms in Postmortem Biotransformation: A Comparison of Clonazolam and Its Metabolite in Postmortem and DUID Cases. *J. Anal. Toxicol.* **2024**, *48*, 550–556. [CrossRef] [PubMed]
218. Bergstrand, M.P.; Helander, A.; Beck, O. Development and application of a multi-component LC–MS/MS method for determination of designer benzodiazepines in urine. *J. Chromatogr. B* **2016**, *1035*, 104–110. [CrossRef]
219. Watson, S.S.K.H.; O'Connor, L.; McKeown, D.A. Determination of the stability of 10 novel benzodiazepines and 3 metabolites in urine using LC-MS/MS. In Proceedings of the 6th Annual Meeting of the United Kingdom and Ireland Association of Forensic Toxicologists (UKIAFT), Manchester, UK, 31 May 2017.
220. Papsun, D.M.; Krotulski, A.J.; Homan, J.; Temporal, K.D.H.; Logan, B.K. Flualprazolam Blood Concentrations in 197 Forensic Investigation Cases. *J. Anal. Toxicol.* **2021**, *45*, 226–232. [CrossRef] [PubMed]
221. Rice, K.; Hikin, L.; Lawson, A.; Smith, P.R.; Morley, S. Quantification of Flualprazolam in Blood by LC–MS-MS: A Case Series of Nine Deaths. *J. Anal. Toxicol.* **2021**, *45*, 410–416. [CrossRef] [PubMed]
222. Abdul, K.; Hikin, L.; Smith, P.; Kurimbokus, H.; Ashong, E.; Couchman, L.; Morley, S.R. Flubromazolam: Detection in five post-mortem cases. *Med. Sci. Law* **2020**, *60*, 266–269. [CrossRef] [PubMed]
223. Hikin, L.J.; Smith, P.R.; Maskell, P.D.; Kurimbokus, H.; Ashong, E.; Couchman, L.; Morley, S.R. Femoral blood concentrations of the designer benzodiazepine etizolam in post-mortem cases. *Med. Sci. Law* **2021**, *61*, 122–129. [CrossRef] [PubMed]
224. Mérette, S.A.M.; Thériault, S.; Piramide, L.E.C.; Davis, M.D.; Shapiro, A.M. Bromazolam Blood Concentrations in Postmortem Cases—A British Columbia Perspective. *J. Anal. Toxicol.* **2023**, *47*, 385–392. [CrossRef] [PubMed]

225. Maskell, P.D.; Wilson, G.; Manchester, K.R. Designer Benzodiazepines Gidazepam and Desalkygidazepam (Bromonordiazepam): What Do We Know? *J. Anal. Toxicol.* **2023**, *47*, 324–331. [CrossRef] [PubMed]
226. Mérette, S.A.M.; Kim, S.; Davis, M.D.; Shapiro, A.M. Desalkylgidazepam blood concentrations in 63 forensic investigation cases. *J. Anal. Toxicol.* **2023**, *47*, 858–866. [CrossRef] [PubMed]
227. PubChem Open Chemistry Database at the National Institutes of Health (NIH), U.S. National Library of Medicine. Available online: https://pubchem.ncbi.nlm.nih.gov/ (accessed on 7 January 2021).
228. Nisbet, L.A.; DiEmma, G.E.; Scott, K.S. Drug stability in forensic toxicology. *WIREs Forensic Sci.* **2023**, *5*, e1481. [CrossRef]
229. Palmquist, K.B.; Swortwood, M.J. Long-Term Stability of 13 Fentanyl Analogs in Blood. *J. Anal. Toxicol.* **2021**, *45*, 870–877. [CrossRef] [PubMed]
230. Jung, J.; Kolodziej, A.; Pape, E.; Bisch, M.; Javot, L.; Gibaja, V.; Jouzeau, J.-Y.; Scala-Bertola, J.; Gambier, N. Multiplex detection of 14 fentanyl analogues and U-47700 in biological samples: Application to a panel of French hospitalized patients. *Forensic Sci. Int.* **2020**, *317*, 110437. [CrossRef] [PubMed]
231. Wang, L.; Bernert, J.T. Analysis of 13 Fentanils, Including Sufentanil and Carfentanil, in Human Urine by Liquid Chromatography-Atmospheric-Pressure Ionization-Tandem Mass Spectrometry. *J. Anal. Toxicol.* **2006**, *30*, 335–341. [CrossRef] [PubMed]
232. Schackmuth, M.; Kerrigan, S. Temperature and pH-dependent stability of fentanyl analogs: Degradation pathways and potential biomarkers. *J. Forensic Sci.* **2024**, *69*, 1799–1814. [CrossRef] [PubMed]
233. Concheiro, M.; Chesser, R.; Pardi, J.; Cooper, G. Postmortem Toxicology of New Synthetic Opioids. *Front. Pharmacol.* **2018**, *9*, 1210. [CrossRef] [PubMed] [PubMed Central]
234. Ojanperä, I.; Gergov, M.; Rasanen, I.; Lunetta, P.; Toivonen, S.; Tiainen, E.; Vuori, E. Blood Levels of 3-Methylfentanyl in 3 Fatal Poisoning Cases. *Am. J. Forensic Med. Pathol.* **2006**, *27*, 328–331. [CrossRef] [PubMed]
235. Sofalvi, S.; Schueler, H.E.; Lavins, E.S.; Kaspar, C.K.; Brooker, I.T.; Mazzola, C.D.; Dolinak, D.; Gilson, T.P.; Perch, S. 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.* **2017**, *41*, 473–483. [CrossRef] [PubMed]
236. Papsun, D.; Krywanczyk, A.; Vose, J.C.; Bundock, E.A.; Logan, B.K. Analysis of MT-45, a Novel Synthetic Opioid, in Human Whole Blood by LC-MS-MS and its Identification in a Drug-Related Death. *J. Anal. Toxicol.* **2016**, *40*, 313–317. [CrossRef] [PubMed]
237. Martinez, J.; Gonyea, J.; Zaney, M.E.; Kahl, J.; Moore, D.M. The evolution of fentanyl-related substances: Prevalence and drug concentrations in postmortem biological specimens at the Miami-Dade Medical Examiner Department. *J. Anal. Toxicol.* **2024**, *48*, 104–110. [CrossRef] [PubMed]
238. Cooper, G. The rise and rise of fentanyl in postmortem casework. *J Forensic Sci* **2023**, *68*, 1675–1685. [CrossRef] [PubMed]
239. Anderson, D.T.; Muto, J.J. Duragesic(R) Transdermal Patch: Postmortem Tissue Distribution of Fentanyl in 25 Cases. *J. Anal. Toxicol.* **2000**, *24*, 627–634. [CrossRef] [PubMed]
240. Dwyer, J.B.; Janssen, J.; Luckasevic, T.M.; Williams, K.E. 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.* **2017**, *63*, 195–200. [CrossRef] [PubMed]
241. Matey, J.M.; Ruíz, C.G.; García, G.M.; Soro, J.C.G.; Delicado, D.G.; Gallardo, J.R.; Martínez, M. Ultraviolet-Visible and High-Resolution Mass Spectrometry for the Identification of Cyclopropyl-Fentanyl in the First Fatal Case in Spain. *J. Anal. Toxicol.* **2020**, *44*, 927–935. [CrossRef] [PubMed]
242. Van Bever, W.F.; Niemegeers, C.J.; Schellekens, K.H.; A Janssen, P. N-4-Substituted 1-(2-arylethyl)-4-piperidinyl-N-phenylpropanamides, a novel series of extremely potent analgesics with unusually high safety margin. *Arzneimittel-Forschung* **1976**, *26*, 1548–1551. [PubMed]
243. McIntyre, I.M.; Trochta, A.; Gary, R.D.; Malamatos, M.; Lucas, J.R. An Acute Acetyl Fentanyl Fatality: A Case Report with Postmortem Concentrations. *J. Anal. Toxicol.* **2015**, *39*, 490–494. [CrossRef]
244. McIntyre, I.M.; Trochta, A.; Gary, R.D.; Wright, J.; Mena, O. An Acute Butyr-Fentanyl Fatality: A Case Report with Postmortem Concentrations. *J. Anal. Toxicol.* **2016**, *40*, 162–166. [CrossRef] [PubMed]
245. Poklis, J.; Poklis, A.; Wolf, C.; Mainland, M.; Hair, L.; Devers, K.; Chrostowski, L.; Arbefeville, E.; Merves, M.; Pearson, J. Postmortem tissue distribution of acetyl fentanyl, fentanyl and their respective nor-metabolites analyzed by ultrahigh performance liquid chromatography with tandem mass spectrometry. *Forensic Sci. Int.* **2015**, *257*, 435–441. [CrossRef] [PubMed] [PubMed Central]
246. Pearson, J.; Poklis, J.; Poklis, A.; Wolf, C.; Mainland, M.; Hair, L.; Devers, K.; Chrostowski, L.; Arbefeville, E.; Merves, M. Postmortem Toxicology Findings of Acetyl Fentanyl, Fentanyl, and Morphine in Heroin Fatalities in Tampa, Florida. *Acad. Forensic Pathol.* **2015**, *5*, 676–689, Erratum in: *Acad Forensic Pathol.* **2017**, *7*, 667–704. [CrossRef] [PubMed] [PubMed Central]
247. Fort, C.; Curtis, B.; Nichols, C.; Niblo, C. Acetyl Fentanyl Toxicity: Two Case Reports. *J. Anal. Toxicol.* **2016**, *40*, 754–757. [CrossRef] [PubMed]
248. Poklis, J.; Poklis, A.; Wolf, C.; Hathaway, C.; Arbefeville, E.; Chrostowski, L.; Devers, K.; Hair, L.; Mainland, M.; Merves, M.; et al. Two Fatal Intoxications Involving Butyryl Fentanyl. *J. Anal. Toxicol.* **2016**, *40*, 703–708. [CrossRef] [PubMed] [PubMed Central]
249. Staeheli, S.N.; Baumgartner, M.R.; Gauthier, S.; Gascho, D.; Jarmer, J.; Kraemer, T.; Steuer, A.E. Time-dependent postmortem redistribution of butyrfentanyl and its metabolites in blood and alternative matrices in a case of butyrfentanyl intoxication. *Forensic Sci. Int.* **2016**, *266*, 170–177. [CrossRef] [PubMed]

250. Rojkiewicz, M.; Majchrzak, M.; Celiński, R.; Kuś, P.; Sajewicz, M. Identification and physicochemical characterization of 4-fluorobutyrfentanyl (1-((4-fluorophenyl)(1-phenethylpiperidin-4-yl)amino)butan-1-one, 4-FBF) in seized materials and post-mortem biological samples. *Drug Test. Anal.* **2017**, *9*, 405–414. [CrossRef] [PubMed]
251. Elliott, S.P.; Lopez, E.H. A Series of Deaths Involving Carfentanil in the UK and Associated Post-mortem Blood Concentrations. *J. Anal. Toxicol.* **2018**, *42*, e41–e45. [CrossRef] [PubMed]
252. Garneau, B.; Desharnais, B.; Beauchamp-Doré, A.; Lavallée, C.; Mireault, P.; Lajeunesse, A. Challenges Related to Three Cases of Fatal Intoxication to Multiple Novel Synthetic Opioids. *J. Anal. Toxicol.* **2020**, *44*, 86–91. [CrossRef] [PubMed]
253. Zawadzki, M.; Wachełko, O.; Chłopaś-Konowałek, A.; Szpot, P. Quantification and distribution of 4-fluoroisobutyryl fentanyl (4-FiBF) in postmortem biological samples using UHPLC–QqQ-MS/MS. *Forensic Toxicol.* **2021**, *39*, 451–463. [CrossRef]
254. Roosendaal, J.; Oosting, R.; Kloos, D.-P.; de Boer, H.H.; Berg, J.D.v.D.; Oldenhof, S.; Bosman, I.J. A fatal mono-intoxication with 4-fluoroisobutyrylfentanyl: Case report with postmortem concentrations. *J. Anal. Toxicol.* **2023**, *47*, 541–546. [CrossRef] [PubMed]
255. Martucci, H.F.; Ingle, E.A.; Hunter, M.D.; Rodda, L.N. Distribution of furanyl fentanyl and 4-ANPP in an accidental acute death: A case report. *Forensic Sci. Int.* **2018**, *283*, e13–e17. [CrossRef] [PubMed]
256. Freni, F.; Pezzella, S.; Vignali, C.; Moretti, M.; Cisini, S.; Rossetti, C.; Ravizza, R.; Motta, M.; Groppi, A.; Morini, L. A case report on potential postmortem redistribution of furanyl fentanyl and 4-ANPP. *Forensic Sci. Int.* **2019**, *304*, 109915. [CrossRef] [PubMed]
257. Giorgetti, A.; Perdekamp, M.G.; Franchetti, G.; Pircher, R.; Pollak, S.; Pelotti, S.; Auwärter, V. Intoxications involving methoxyacetylfentanyl and U-47700: A study of 3 polydrug fatalities. *Int. J. Leg. Med.* **2024**, *138*, 1801–1811. [CrossRef] [PubMed] [PubMed Central]
258. Allibe, N.; Richeval, C.; Phanithavong, M.; Faure, A.; Allorge, D.; Paysant, F.; Stanke-Labesque, F.; Eysseric-Guerin, H.; Gaulier, J. Fatality involving ocfentanil documented by identification of metabolites. *Drug Test. Anal.* **2018**, *10*, 995–1000. [CrossRef] [PubMed]
259. Coopman, V.; Cordonnier, J.; De Leeuw, M.; Cirimele, V. Ocfentanil overdose fatality in the recreational drug scene. *Forensic Sci. Int.* **2016**, *266*, 469–473. [CrossRef] [PubMed]
260. Dussy, F.; Hangartner, S.; Hamberg, C.; Berchtold, C.; Scherer, U.; Schlotterbeck, G.; Wyler, D.; Briellmann, T. An Acute Ocfentanil Fatality: A Case Report with Postmortem Concentrations. *J. Anal. Toxicol.* **2016**, *40*, 761–766. [CrossRef] [PubMed]
261. Salas, J.R.; Krotulski, A.J.; Newman, R.; Thogmartin, J.R.; A Mohr, A.L.; Logan, B.K. Concentrations of *para*-Fluorofuranylfentanyl in Paired Central and Peripheral Blood Collected during Postmortem Death Investigations. *J. Anal. Toxicol.* **2021**, *46*, 358–373. [CrossRef] [PubMed]
262. McIntyre, I.M.; Gary, R.D.; Joseph, S.; Stabley, R. A Fatality Related to the Synthetic Opioid U-47700: Postmortem Concentration Distribution. *J. Anal. Toxicol.* **2017**, *41*, 158–160. [CrossRef] [PubMed]
263. Dziadosz, M.; Klintschar, M.; Teske, J. Postmortem concentration distribution in fatal cases involving the synthetic opioid U-47700. *Int. J. Leg. Med.* **2017**, *131*, 1555–1556. [CrossRef] [PubMed]
264. Rohrig, T.P.; A Miller, S.; Baird, T.R. U-47700: A Not So New Opioid. *J. Anal. Toxicol.* **2018**, *42*, e12–e14. [CrossRef] [PubMed]
265. Fels, H.; Lottner-Nau, S.; Sax, T.; Roider, G.; Graw, M.; Auwärter, V.; Musshoff, F. Postmortem concentrations of the synthetic opioid U-47700 in 26 fatalities associated with the drug. *Forensic Sci. Int.* **2019**, *301*, e20–e28. [CrossRef] [PubMed]
266. Vorce, S.P.; Knittel, J.L.; Holler, J.M.; Magluilo, J.; Levine, B.; Berran, P.; Bosy, T.Z. A Fatality Involving AH-7921. *J. Anal. Toxicol.* **2014**, *38*, 226–230. [CrossRef] [PubMed]
267. Fels, H.; Krueger, J.; Sachs, H.; Musshoff, F.; Graw, M.; Roider, G.; Stoever, A. Two fatalities associated with synthetic opioids: AH-7921 and MT-45. *Forensic Sci. Int.* **2017**, *277*, e30–e35. [CrossRef] [PubMed]
268. De Vrieze, L.M.; Walton, S.E.; Pottie, E.; Papsun, D.; Logan, B.K.; Krotulski, A.J.; Stove, C.P.; Vandeputte, M.M. In vitro structure–activity relationships and forensic case series of emerging 2-benzylbenzimidazole 'nitazene' opioids. *Arch. Toxicol.* **2024**, *98*, 2999–3018. [CrossRef] [PubMed] [PubMed Central]
269. Krotulski, A.J.; Papsun, D.M.; Walton, S.E.; Logan, B.K. Metonitazene in the United States—Forensic toxicology assessment of a potent new synthetic opioid using liquid chromatography mass spectrometry. *Drug Test. Anal.* **2021**, *13*, 1697–1711. [CrossRef] [PubMed]
270. Mueller, F.; Bogdal, C.; Pfeiffer, B.; Andrello, L.; Ceschi, A.; Thomas, A.; Grata, E. Isotonitazene: Fatal intoxication in three cases involving this unreported novel psychoactive substance in Switzerland. *Forensic Sci. Int.* **2021**, *320*, 110686. [CrossRef]
271. Bendjilali-Sabiani, J.-J.; Eiden, C.; Lestienne, M.; Cherki, S.; Gautre, D.; Broek, T.V.D.; Mathieu, O.; Peyrière, H. Isotonitazene, a synthetic opioid from an emerging family: The nitazenes. *Therapies* **2024**. [CrossRef] [PubMed]
272. Bendjilali-Sabiani, J.-J.; Descoeur, J.; Lossois, M.; Eiden, C.; Peyriere, H.; Mathieu, O. Post mortem distribution of isotonitazene and its three metabolites in the first lethal case observed in France. In Proceedings of the Annual Conference, St. Gallen, Switzerland, 6 September 2024; p. 101. Available online: https://www.WEB_KSSG-9258_Programm_TIAFT_A4_ZUSAMMEN_NEU_03_ES.cleaned.pdf (accessed on 21 September 2024).
273. Boland, D.M.; Reidy, L.J.; Seither, J.M.; Radtke, J.M.; Lew, E.O. Forty-Three Fatalities Involving the Synthetic Cannabinoid, 5-Fluoro-ADB: Forensic Pathology and Toxicology Implications. *J. Forensic Sci.* **2020**, *65*, 170–182. [CrossRef] [PubMed]
274. Usui, K.; Fujita, Y.; Kamijo, Y.; Kokaji, T.; Funayama, M. Identification of 5-Fluoro ADB in Human Whole Blood in Four Death Cases. *J. Anal. Toxicol.* **2018**, *42*, E21–E25. [CrossRef] [PubMed]
275. Hess, C.; Stockhausen, S.; Kernbach-Wighton, G.; Madea, B. Death due to diabetic ketoacidosis: Induction by the consumption of synthetic cannabinoids? *Forensic Sci. Int.* **2015**, *257*, e6–e11. [CrossRef] [PubMed]

276. Lavins, E.S.; Shanks, K.G.; Engelhart, D.E.; Schueler, H.E.; Galita, D.; McCollom, A. Postmortem Tissue Distribution of AB-CHMINACA Following Lethal Intoxication Compared with AB-CHMINACA Concentrations in Impaired Drivers. Presented at the annual meeting of Society of Forensic Toxicologists Annual Conference 2015 in Atlanta Abstracts P33. Available online: https://www.soft-tox.org/assets/docs/SOFT_2015_meeting_abstracts.pdf (accessed on 21 September 2024).
277. Knittel, J.L.; Magluilo, J.; Mazuchowski, E.L. The isolation and distribution of synthetic cannabinoids in two postmortem cases. Presented at the annual meeting of Society of Forensic Toxicologists Annual Conference 2015 in Atlanta Abstracts P79. Available online: https://www.soft-tox.org/assets/docs/SOFT_2015_meeting_abstracts.pdf (accessed on 21 September 2024).
278. Hasegawa, K.; Wurita, A.; Minakata, K.; Gonmori, K.; Yamagishi, I.; Nozawa, H.; Watanabe, K.; Suzuki, O. Identification and quantitation of 5-fluoro-ADB, one of the most dangerous synthetic cannabinoids, in the stomach contents and solid tissues of a human cadaver and in some herbal products. *Forensic Toxicol.* **2015**, *33*, 112–121. [CrossRef]
279. Hasegawa, K.; Wurita, A.; Minakata, K.; Gonmori, K.; Nozawa, H.; Yamagishi, I.; Watanabe, K.; Suzuki, O. Postmortem distribution of MAB-CHMINACA in body fluids and solid tissues of a human cadaver. *Forensic Toxicol.* **2015**, *33*, 380–387. [CrossRef] [PubMed]
280. Walle, N.; Doerr, A.A.; Schmidt, P.H.; Schaefer, N. 'Flying high?'—Jump from a height in a 'Spice' high?: A case report on the synthetic cannabinoid 5F-MDMB-P7AICA. *Drug Test. Anal.* **2023**, *15*, 368–373. [CrossRef] [PubMed]
281. Sasaki, C.; Saito, T.; Shinozuka, T.; Irie, W.; Murakami, C.; Maeda, K.; Nakamaru, N.; Oishi, M.; Nakamura, S.; Kurihara, K. A case of death caused by abuse of a synthetic cannabinoid N-1-naphthalenyl-1-pentyl-1H-indole-3-carboxamide. *Forensic Toxicol.* **2014**, *33*, 165–169. [CrossRef]
282. Zaitsu, K.; Nakayama, H.; Yamanaka, M.; Hisatsune, K.; Taki, K.; Asano, T.; Kamata, T.; Katagai, M.; Hayashi, Y.; Kusano, M.; et al. High-resolution mass spectrometric determination of the synthetic cannabinoids MAM-2201, AM-2201, AM-2232, and their metabolites in postmortem plasma and urine by LC/Q-TOFMS. *Int. J. Leg. Med.* **2015**, *129*, 1233–1245. [CrossRef]
283. Giorgetti, A.; Mogler, L.; Halter, S.; Haschimi, B.; Alt, A.; Rentsch, D.; Schmidt, B.; Thoma, V.; Vogt, S.; Auwärter, V. Four cases of death involving the novel synthetic cannabinoid 5F-Cumyl-PEGACLONE. *Forensic Toxicol.* **2020**, *38*, 314–326. [CrossRef]
284. Yamagishi, I.; Minakata, K.; Nozawa, H.; Hasegawa, K.; Suzuki, M.; Kitamoto, T.; Suzuki, O.; Watanabe, K. 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.* **2018**, *35*, 44–49. [CrossRef] [PubMed]
285. Mochizuki, A.; Nakazawa, H.; Adachi, N.; Takekawa, K.; Shojo, H. 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.* **2018**, *36*, 81–87. [CrossRef] [PubMed] [PubMed Central]
286. Mochizuki, A.; Nakazawa, H.; Adachi, N.; Takekawa, K.; Shojo, H. Postmortem distribution of mepirapim and acetyl fentanyl in biological fluid and solid tissue specimens measured by the standard addition method. *Forensic Toxicol.* **2019**, *37*, 27–33. [CrossRef] [PubMed] [PubMed Central]
287. Vandeputte, M.M.; Van Uytfanghe, K.; Layle, N.K.; Germaine, D.M.S.; Iula, D.M.; Stove, C.P. Synthesis, Chemical Characterization, and μ-Opioid Receptor Activity Assessment of the Emerging Group of "Nitazene" 2-Benzylbenzimidazole Synthetic Opioids. *ACS Chem. Neurosci.* **2021**, *12*, 1241–1251. [CrossRef] [PubMed]
288. Grimmett, M.R. *Advances in Imidazole Chemistry*; Elsevier: Amsterdam, The Netherlands, 1970; pp. 103–183.
289. Ujváry, I.; Christie, R.; Evans-Brown, M.; Gallegos, A.; Jorge, R.; de Morais, J.; Sedefov, R. DARK Classics in Chemical Neuroscience: Etonitazene and Related Benzimidazoles. *ACS Chem. Neurosci.* **2021**, *12*, 1072–1092. [CrossRef] [PubMed]
290. Kanamori, T.; Okada, Y.; Segawa, H.; Yamamuro, T.; Kuwayama, K.; Tsujikawa, K.; Iwata, Y.T. Metabolism of highly potent synthetic opioid nitazene analogs: *N*-ethyl-*N*-(1-glucuronyloxyethyl) metabolite formation and degradation to *N*-desethyl metabolites during enzymatic hydrolysis. *Drug Test. Anal.* **2024**. [CrossRef] [PubMed]
291. Taoussi, O.; Berardinelli, D.; Zaami, S.; Tavoletta, F.; Basile, G.; Kronstrand, R.; Auwärter, V.; Busardò, F.P.; Carlier, J. Human metabolism of four synthetic benzimidazole opioids: Isotonitazene, metonitazene, etodesnitazene, and metodesnitazene. *Arch. Toxicol.* **2024**, *98*, 2101–2116. [CrossRef] [PubMed] [PubMed Central]
292. Krotulski, A.J.; Papsun, D.M.; Kacinko, S.L.; Logan, B.K. Isotonitazene Quantitation and Metabolite Discovery in Authentic Forensic Casework. *J. Anal. Toxicol.* **2020**, *44*, 521–530. [CrossRef] [PubMed]
293. Parks, C.; Maskell, P.D.; A McKeown, D.; Couchman, L. Identification of 5-aminometonitazene and 5-acetamidometonitazene in a post-mortem case: Are nitro-nitazenes unstable? *J. Anal. Toxicol.* **2024**, *5*, bkae076. [CrossRef] [PubMed]
294. Schüller, M.; Lucic, I.; Øiestad, Å.M.L.; Pedersen-Bjergaard, S.; Øiestad, E.L. High-throughput quantification of emerging "nitazene" benzimidazole opioid analogs by microextraction and UHPLC–MS-MS. *J. Anal. Toxicol.* **2023**, *47*, 787–796. [CrossRef] [PubMed] [PubMed Central]
295. Available online: https://www.cfsre.org/images/Presentations/WaltonSE_NPS_Quarterly_Webinar_230705SW.pdf (accessed on 15 September 2024). [PubMed]
296. Maruejouls, C.; Ameline, A.; Gheddar, L.; Mazoyer, C.; Teston, K.; Aknouche, F.; Kintz, P. First evidence in an oversea French department of the deadly risk of protonitazene use: About 5 post mortem cases. *Int. J. Leg. Med.* **2024**, 1–7. [CrossRef] [PubMed]
297. Vandeputte, M.M.; Krotulski, A.J.; Walther, D.; Glatfelter, G.C.; Papsun, D.; Walton, S.E.; Logan, B.K.; Baumann, M.H.; Stove, C.P. Pharmacological evaluation and forensic case series of N-pyrrolidino etonitazene (etonitazepyne), a newly emerging 2-benzylbenzimidazole 'nitazene' synthetic opioid. *Arch. Toxicol.* **2022**, *96*, 1845–1863. [CrossRef] [PubMed]

298. Fantegrossi, W.E.; Moran, J.H.; Radominska-Pandya, A.; Prather, P.L. Distinct pharmacology and metabolism of K2 synthetic cannabinoids compared to Δ(9)-THC: Mechanism underlying greater toxicity? *Life Sci.* **2013**, *97*, 45–54. [CrossRef] [PubMed] [PubMed Central]
299. Atwood, B.K.; Huffman, J.; Straiker, A.; Mackie, K. JWH018, a common constituent of 'Spice' herbal blends, is a potent and efficacious cannabinoid CB_1 receptor agonist. *Br. J. Pharmacol.* **2010**, *160*, 585–593. [CrossRef] [PubMed] [PubMed Central]
300. Kasper, A.M.; Ridpath, A.D.; Gerona, R.R.; Cox, R.; Galli, R.; Kyle, P.B.; Parker, C.; Arnold, J.K.; Chatham-Stephens, K.; Morrison, M.A.; et al. Severe illness associated with reported use of synthetic cannabinoids: A public health investigation (Mississippi, 2015). *Clin. Toxicol.* **2018**, *57*, 10–18. [CrossRef] [PubMed] [PubMed Central]
301. New Psychoactive Substances—The Current Situation in Europe (European Drug Report 2024). Available online: https://www.euda.europa.eu/publications/european-drug-report/2024/new-psychoactive-substances_en (accessed on 7 September 2024).
302. Hermanns-Clausen, M.; Kneisel, S.; Szabo, B.; Auwärter, V. Acute toxicity due to the confirmed consumption of synthetic cannabinoids: Clinical and laboratory findings. *Addiction* **2013**, *108*, 534–544. [CrossRef] [PubMed]
303. Cooper, Z.D. Adverse Effects of Synthetic Cannabinoids: Management of Acute Toxicity and Withdrawal. *Curr. Psychiatry Rep.* **2016**, *18*, 1–10. [CrossRef] [PubMed] [PubMed Central]
304. Giorgetti, A.; Busardò, F.P.; Tittarelli, R.; Auwärter, V.; Giorgetti, R. Post-Mortem Toxicology: A Systematic Review of Death Cases Involving Synthetic Cannabinoid Receptor Agonists. *Front. Psychiatry* **2020**, *11*, 464. [CrossRef] [PubMed] [PubMed Central]
305. Lie, W.; Cheong, E.J.Y.; Goh, E.M.L.; Moy, H.Y.; Cannaert, A.; Stove, C.P.; Chan, E.C.Y. Diagnosing intake and rationalizing toxicities associated with 5F-MDMB-PINACA and 4F-MDMB-BINACA abuse. *Arch. Toxicol.* **2022**, *95*, 489–508. [CrossRef] [PubMed]
306. Kakehashi, H.; Shima, N.; Ishikawa, A.; Nitta, A.; Asai, R.; Wada, M.; Nakano, S.; Matsuta, S.; Sasaki, K.; Kamata, H.; et al. Effects of lipophilicity and functional groups of synthetic cannabinoids on their blood concentrations and urinary excretion. *Forensic Sci. Int.* **2020**, *307*, 110106. [CrossRef] [PubMed]
307. Diao, X.; Huestis, M.A. New Synthetic Cannabinoids Metabolism and Strategies to Best Identify Optimal Marker Metabolites. *Front. Chem.* **2019**, *7*, 109. [CrossRef] [PubMed] [PubMed Central]
308. Hutter, M.; Broecker, S.; Kneisel, S.; Franz, F.; Brandt, S.D.; Auwarter, V. 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. Pharm. Biotechnol.* **2018**, *19*, 144–162. [CrossRef] [PubMed]
309. Chimalakonda, K.C.; Seely, K.A.; Bratton, S.M.; Brents, L.K.; Moran, C.L.; Endres, G.W.; James, L.P.; Hollenberg, P.F.; Prather, P.L.; Radominska-Pandya, A.; et al. Cytochrome P450-Mediated Oxidative Metabolism of Abused Synthetic Cannabinoids Found in K2/Spice: Identification of Novel Cannabinoid Receptor Ligands. *Drug Metab. Dispos.* **2012**, *40*, 2174–2184. [CrossRef] [PubMed] [PubMed Central]
310. Hess, C.; Krueger, L.; Unger, M.; Madea, B. Freeze-thaw stability and long-term stability of 84 synthetic cannabinoids in serum. *Drug Test. Anal.* **2017**, *9*, 1506–1511. [CrossRef] [PubMed]
311. Krotulski, A.J.; Bishop-Freeman, S.C.; A Mohr, A.L.; Logan, B.K. Evaluation of Synthetic Cannabinoid Metabolites in Human Blood in the Absence of Parent Compounds: A Stability Assessment. *J. Anal. Toxicol.* **2021**, *45*, 60–68. [CrossRef] [PubMed]
312. Kneisel, S.; Speck, M.; Moosmann, B.; Auwärter, V. Stability of 11 prevalent synthetic cannabinoids in authentic neat oral fluid samples: Glass versus polypropylene containers at different temperatures. *Drug Test. Anal.* **2013**, *5*, 602–606. [CrossRef] [PubMed]
313. Angerer, V.; Jacobi, S.; Franz, F.; Auwärter, V.; Pietsch, J. Three fatalities associated with the synthetic cannabinoids 5F-ADB, 5F-PB-22, and AB-CHMINACA. *Forensic Sci. Int.* **2017**, *281*, e9–e15. [CrossRef] [PubMed]
314. Thomsen, L.R.; Rosengren, R.J.; Glass, M. Potential Implications of Multi-Drug Exposure with Synthetic Cannabinoids: A Scoping Review of Human Case Studies. *Psychoactives* **2024**, *3*, 365–383. [CrossRef]
315. Groth, O.; Roider, G.; Angerer, V.; Schäper, J.; Graw, M.; Musshoff, F.; Auwärter, V. "Spice"-related deaths in and around Munich, Germany: A retrospective look at the role of synthetic cannabinoid receptor agonists in our post-mortem cases over a seven-year period (2014–2020). *Int. J. Leg. Med.* **2023**, *137*, 1059–1069. [CrossRef] [PubMed] [PubMed Central]
316. Simon, G.; Kuzma, M.; Mayer, M.; Petrus, K.; Tóth, D. Fatal Overdose with the Cannabinoid Receptor Agonists MDMB-4en-PINACA and 4F-ABUTINACA: A Case Report and Review of the Literature. *Toxics* **2023**, *11*, 673. [CrossRef] [PubMed] [PubMed Central]
317. Tokarczyk, B.; Jurczyk, A.; Krupińska, J.; Adamowicz, P. Fatal intoxication with new synthetic cannabinoids 5F-MDMB-PICA and 4F-MDMB-BINACA—Parent compounds and metabolite identification in blood, urine and cerebrospinal fluid. *Forensic Sci. Med. Pathol.* **2022**, *18*, 393–402. [CrossRef] [PubMed] [PubMed Central]
318. Neukamm, M.A.; Halter, S.; Auwärter, V.; Schmitt, G.; Giorgetti, A.; Bartel, M. Death after smoking of fentanyl, 5F-ADB, 5F-MDMB-P7AICA and other synthetic cannabinoids with a bucket bong. *Forensic Toxicol.* **2023**, *42*, 82–92. [CrossRef] [PubMed] [PubMed Central]
319. Adamowicz, P. Blood concentrations of synthetic cannabinoids. *Clin. Toxicol.* **2021**, *59*, 246–251. [CrossRef] [PubMed]
320. Chu, M.; Di Rago, M.; Mantinieks, D.; Glowacki, L.; Woodford, N.W.; Gerostamoulos, D.; Drummer, O.H. Time-Dependent Changes in THC Concentrations in Deceased Persons. *J. Anal. Toxicol.* **2021**, *45*, 1–7. [CrossRef] [PubMed]
321. Tascon, I.; Côté, C.; Garneau, B.; Desharnais, B.; Gosselin, V.; Mireault, P. Postmortem redistribution of cannabinoids: Statistical analysis of a novel dataset and meta-analysis. *Forensic Sci. Int.* **2023**, *353*, 111873. [CrossRef] [PubMed]

322. Kacinko, S.L.; Isenschmid, D.S.; Logan, B.K. Are Postmortem Cannabinoid Concentrations Forensically Reliable? *Am. J. Forensic Med. Pathol.* **2024**, *45*, 92–93. [CrossRef] [PubMed]
323. Gerostamoulos, D.; Elliott, S.; Walls, H.C.; Peters, F.T.; Lynch, M.; Drummer, O.H. To Measure or Not to Measure? That is the NPS Question. *J. Anal. Toxicol.* **2016**, *40*, 318–320. [CrossRef] [PubMed]
324. Wille, S.M.R.; Elliott, S. The future of analytical and interpretative toxicology: Where are we going and how do we get there? *J. Anal. Toxicol.* **2021**, *45*, 619–632. [CrossRef] [PubMed]
325. Matey, J.M.; Zapata, F.; Menéndez-Quintanal, L.M.; Montalvo, G.; García-Ruiz, C. Identification of new psychoactive substances and their metabolites using non-targeted detection with high-resolution mass spectrometry through diagnosing fragment ions/neutral loss analysis. *Talanta* **2023**, *265*, 124816. [CrossRef] [PubMed]