

# Toxicology and Postmortem Drug Analysis

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## **Abstract:**

Postmortem toxicology helps determine the involvement of drugs and toxic substances in unexplained, suspicious, or medically unattended deaths. This study reviews established principles, sampling approaches, and analytical methods used in postmortem drug analysis. It examines biological matrices such as blood, urine, tissues, and vitreous humour, and outlines the role of techniques including GC-MS, HPLC, LC-MS, and immunoassays. The review also discusses major challenges in interpretation caused by postmortem redistribution, decomposition, and drug instability. Findings indicate that multi-sample analysis and standardized procedures improve accuracy in medico-legal investigations. The study highlights the importance of validated methods, careful interpretation, and skilled forensic toxicologists to ensure reliable outcomes in determining cause and manner of death.

**Keywords:** postmortem toxicology, drug analysis, forensic toxicology, postmortem redistribution, analytical methods, medico-legal investigation.

## **1. INTRODUCTION**

Forensic toxicology focuses on the identification and interpretation of drugs, chemicals, and toxic agents in biological specimens obtained from individuals before or after death. In postmortem investigations, toxicology plays an essential role in establishing whether a substance contributed to or caused death, especially in cases involving suspected poisoning, overdose, impaired driving, or unexplained fatalities. Postmortem drug analysis integrates analytical chemistry, pharmacology, pathology, and medico-legal investigation to determine the type and concentration of toxic substances in different biological matrices. According to Drummer and Gerostamoulos (2002), postmortem toxicology forms a core component of forensic medicine because it assists in differentiating natural deaths from accidental, suicidal, or homicidal events.

Forensic toxicology involves applying analytical and bioanalytical methods to detect drugs, alcohols, volatiles, pharmaceuticals, and environmental or household toxins in biological samples. It includes qualitative identification of substances and quantitative measurement to evaluate their toxicological significance. The development of techniques such as GC-MS, LC-MS, HPLC, and immunoassays has significantly improved accuracy, sensitivity, and reliability in detecting a wide range of compounds (Drummer, 2007; Flanagan & Connally, 2005). These procedures allow forensic laboratories to examine blood, urine, tissues, and alternative specimens even in decomposed conditions.

Postmortem drug analysis provides critical information about drug exposure prior to death. It helps clarify whether a drug found at autopsy was present at therapeutic, toxic, or lethal concentrations. Flanagan, Connally, and Evans (2005) emphasize that toxicology results must be interpreted alongside autopsy findings, medical history, circumstances of death, and scene evidence. In many medico-legal cases, toxicology is decisive in identifying the manner of death, determining impairment, and supporting expert testimony in legal proceedings. The ability to confirm poisoning or overdose through validated analytical methods strengthens the investigatory process and ensures accuracy in judicial outcomes (Skopp, 2010). Toxicological testing is requested in a wide range of postmortem scenarios. These include suspected drug overdoses, poly-drug use, poisoning by household or industrial chemicals, adverse drug reactions, illicit drug consumption, alcohol-related deaths, and fatalities involving trauma where drug influence may have

contributed to the event. Investigations involving impaired driving, unexpected deaths of young individuals, sudden infant deaths, and unattended or decomposed bodies also commonly require drug analysis. In such cases, biological samples such as peripheral blood, heart blood, liver, vitreous humour, urine, and gastric contents provide important evidence (Drummer & Gerostamoulos, 2002).

Postmortem toxicology presents several interpretation challenges related to physiological changes that occur after death. Postmortem redistribution (PMR) is one of the most significant concerns, as drugs may move from organs with high concentrations to nearby blood vessels, creating artificially elevated levels. Pounder and Jones (1990) describe PMR as a major source of uncertainty because it can lead to misleading drug concentrations, especially when relying on central blood samples. Decomposition, microbial activity, pH changes, and drug instability further complicate interpretation. Recent evidence indicates that PMR varies depending on drug properties, time since death, temperature, and sample site (Abdelaal et al., 2024). These changes affect the reliability of certain specimens and highlight the importance of using multiple biological matrices and standardized protocols for accurate interpretation. Analytical and bioanalytical chemistry advancements have improved the ability to detect low-concentration compounds, but challenges in interpretation still remain (Drummer, 2007).

The study aims to examine key analytical and interpretative aspects of postmortem drug analysis that influence medico-legal investigations. The objectives are:

- To outline the principles and scientific foundations of postmortem toxicology.
- To describe commonly used biological specimens and the procedures for their collection after death.
- To review analytical and bioanalytical methods applied in detecting drugs and toxic substances in postmortem samples.
- To identify factors that affect the interpretation of postmortem drug concentrations, including redistribution and decomposition.
- To highlight current challenges and limitations in obtaining accurate and reliable toxicology findings in postmortem cases.

Postmortem toxicology is central to forensic practice because it provides essential evidence in determining the cause and manner of death. The significance of this study lies in providing a consolidated understanding of analytical techniques, sampling challenges, and interpretative issues that influence toxicology outcomes. Improved knowledge of postmortem changes such as redistribution and drug instability helps strengthen the accuracy of toxicology reporting and reduces the likelihood of misinterpretation, which is important for medico-legal decision-making. The study also contributes to forensic science by emphasizing the need for standard protocols, reliable analytical procedures, and multidisciplinary interpretation. This understanding supports pathologists, toxicologists, and legal professionals in producing precise and defensible toxicological conclusions.

## 2. LITERATURE REVIEW

Postmortem toxicology has developed into a central component of forensic investigations because it enables the detection and interpretation of drugs and toxic substances in deceased individuals. Research in this field has expanded through analytical advancements, improved understanding of postmortem physiological processes, and the establishment of best practices to enhance accuracy in medico-legal evaluations.

Advances in analytical chemistry have transformed postmortem toxicology by improving sensitivity, selectivity, and reliability. Drummer (2007) emphasizes that validated bioanalytical procedures are essential for identifying drugs at trace concentrations, particularly in decomposed or compromised samples. GC-MS, LC-MS, HPLC, and tandem mass spectrometry have become standard laboratory tools due to their precision. Mata and Davis (2022) show that simultaneous quantitative analysis of multiple drugs improves laboratory efficiency and supports high-throughput toxicology operations. These

analytical innovations allow forensic laboratories to detect a wide range of pharmaceuticals, abused substances, and emerging synthetic drugs. Best practice guidelines summarized by Truver et al. (2025) further reinforce the need for strict analytical quality control, instrument calibration, and comprehensive documentation. Their recommendations align with earlier work by Flanagan and Connally (2005), who explain that confirmatory testing is vital to avoid incorrect interpretations that may arise from screening immunoassays. Collectively, these studies highlight that analytical rigour is foundational for accurate toxicology reporting.

Interpretation remains one of the most complex aspects of forensic toxicology. Flanagan and Connally (2005) emphasize that drug concentrations in postmortem samples cannot be interpreted using the same parameters as antemortem specimens because of physiological and biochemical changes after death. They recommend combining toxicology data with autopsy findings, medical history, and scene evidence to reach a defensible conclusion. Stephenson et al. (2024) identify common interpretative challenges, including variable sampling practices, postmortem redistribution, and the presence of drug metabolites with differing stability. Peters and Steuer (2019) further explain that both antemortem factors, such as tolerance and chronic use, and postmortem factors, such as decomposition and pH changes, influence drug concentration patterns in biological specimens. Leikin and Watson (2003) highlight that toxicology results provide valuable information but have inherent limitations in determining impairment or exact time of drug ingestion. Their study stresses that interpretation must be cautiously performed to avoid overestimating the toxicological significance of detected substances.

Postmortem redistribution (PMR) is widely recognized as one of the most significant sources of uncertainty in toxicology interpretation. Pounder and Jones (1990) describe PMR as a “toxicological nightmare” because drugs may diffuse from organs with high concentrations into nearby blood vessels after death, altering blood drug levels. Abdelaal et al. (2024) report that redistribution is influenced by drug lipophilicity, protein binding, and the anatomical proximity of sampling sites to major organs. Drummer (2007) and Skopp (2010) both confirm that central blood is more susceptible to PMR than peripheral blood, which is why guidelines consistently recommend peripheral sampling. Postmortem changes such as tissue degradation, bacterial activity, and enzymatic breakdown further complicate concentration patterns, making multi-matrix analysis essential. Case studies support these findings. For example, Guerrieri et al. (2017) show that PMR played a role in variable concentrations of furanylfentanyl in postmortem investigations, highlighting how potent synthetic opioids present additional interpretation challenges.

Appropriate selection of biological matrices is essential for reliable toxicology results. Drummer and Gerostamoulos (2002) provide detailed comparisons of blood, urine, tissue, and alternative samples, concluding that peripheral blood is most reliable due to reduced PMR interference. Flanagan, Connally, and Evans (2005) propose sample collection guidelines that prioritize peripheral blood, vitreous humour, liver, and urine to improve the stability and interpretability of toxicology findings. Alternative matrices have also gained attention. Kintz (2004) highlights the value of hair in detecting chronic drug exposure and documenting long-term substance use patterns when blood or urine are unavailable or unreliable. McIntyre et al. (2000) demonstrate that bone and bone marrow can retain drugs in highly decomposed bodies, making them useful in advanced decomposition or skeletal remains. Tissue samples such as liver are frequently used due to their capacity to accumulate drugs. However, as Peters and Steuer (2019) note, tissues can also exhibit postmortem metabolic changes that must be considered in interpretation.

Research has documented drug-specific challenges in postmortem toxicology. Goeringer et al. (2000) reviewed selective serotonin reuptake inhibitors (SSRIs) and reported wide variations in postmortem concentrations influenced by metabolism, PMR, and sample type. Pirnay et al. (2004) compared methadone- and buprenorphine-related deaths, demonstrating that toxicology must be interpreted cautiously due to combined toxicity, co-ingested substances, and underlying health conditions. Luniainen, Vuori, and Ojanperä (2009) analyzed adverse drug combinations and found that polypharmacy contributed significantly to postmortem toxicology findings, complicating cause-of-death determinations. Di Candia et al. (2022) provided further evidence that drug combinations, emerging

psychoactive substances, and individual variability require careful interpretation in casework. Gerostamoulos (2022) notes that modern forensic practice increasingly encounters novel synthetic opioids, hallucinogens, and designer drugs, requiring continuous updates to analytical capabilities. Decomposition introduces significant variability into toxicology results. Butzbach (2010) shows that putrefaction accelerates drug degradation, produces endogenous compounds that interfere with analysis, and alters pH and microbial profiles. Storage conditions also affect drug stability; prolonged refrigeration or delayed sample collection may change concentration values. Skopp (2010) cites environmental factors such as temperature, humidity, and body position as key influences on specimen reliability. These findings underline the need for rapid sampling, proper storage, and the use of multiple matrices to reduce misinterpretation.

The literature consistently emphasizes that postmortem toxicology requires a combination of advanced analytical methods, careful sample selection, and expert interpretation. PMR, decomposition, drug interactions, and laboratory variability remain the most challenging factors, but guidelines and best practices help improve reliability. Collectively, the reviewed studies establish a strong foundation for understanding the scientific and operational principles

### 3. MATERIALS AND METHODS

This study is a narrative review based on secondary data. It synthesizes existing scientific knowledge on postmortem toxicology by examining previously published research, case studies, forensic manuals, and analytical toxicology guidelines. The aim is to consolidate and interpret established evidence on postmortem drug analysis, sample handling, and analytical procedures used in medico-legal investigations. The review includes publications that meet the following criteria: Peer-reviewed journal articles indexed in Scopus or Web of Science. Studies focusing on postmortem toxicology, postmortem drug redistribution, analytical toxicology, and interpretation of toxicology findings. Research discussing sample collection protocols, analysis of biological matrices, decomposition effects, and drug stability after death. Books, forensic toxicology handbooks, and authoritative manuals written by recognized experts in the field. Case studies reporting drug-related deaths or laboratory practices in postmortem settings. Studies were excluded if they lacked scientific validity, were not peer-reviewed, or focused solely on clinical (antemortem) toxicology without relevance to postmortem investigation.

The review draws from multiple sources, including: Peer-reviewed journals such as *Forensic Science International*, *Journal of Analytical Toxicology*, *Toxicological Reviews*, *Therapeutic Drug Monitoring*, and *Forensic Science, Medicine and Pathology*. Forensic toxicology textbooks including *Karch's Drug Abuse Handbook* and specialized chapters on postmortem toxicology. Published case studies documenting drug-related deaths involving opioids, antidepressants, synthetic drugs, and polypharmacy. Recent reviews and best-practice recommendations issued by forensic toxicology organizations and experts. These sources provide comprehensive insights into analytical techniques, interpretative challenges, and standard procedures in postmortem drug analysis.

#### 3.1 Overview of Postmortem Sample Types

The review examines commonly used biological samples in postmortem toxicology, including:

- Peripheral blood
- Heart (central) blood
- Urine
- Liver, kidney, and other tissues
- Gastric contents
- Vitreous humour
- Hair and nails
- Bone and bone marrow in cases involving decomposition or skeletal remains

These matrices differ in stability, susceptibility to postmortem redistribution, and interpretative value. Peripheral blood and vitreous humour are often preferred due to reduced contamination and better stability, while tissues and alternative matrices provide important information in decomposed or complex cases.

### 3.2 Analytical Techniques

Analytical techniques used in postmortem toxicology form the core of accurate drug identification and quantification. This review focuses on the major analytical and bioanalytical methods routinely applied in forensic laboratories to detect drugs, metabolites, and toxic substances in postmortem specimens. The techniques examined are widely recognized in the literature for their sensitivity, specificity, and applicability to various biological matrices.

- **Gas Chromatography–Mass Spectrometry (GC-MS)** GC-MS is considered a primary confirmatory method for detecting a broad range of volatile, semi-volatile, and thermally stable compounds. Studies by Drummer (2007) and Flanagan and Connally (2005) highlight its reliability in identifying drugs based on characteristic mass spectral patterns. GC-MS provides high-resolution separation and accurate mass detection, making it suitable for postmortem blood, urine, and tissue analysis.
  - **Liquid Chromatography–Mass Spectrometry (LC-MS and LC-MS/MS)** LC-MS is essential for compounds that are non-volatile or thermolabile. It is widely used for opioids, antidepressants, new psychoactive substances, and polar metabolites. Mata and Davis (2022) demonstrate that LC-MS/MS supports simultaneous quantification of multiple drugs in both postmortem and antemortem specimens, improving laboratory efficiency and throughput.
  - **High-Performance Liquid Chromatography (HPLC):** HPLC is frequently used for quantification when mass spectrometry is not required or available. It supports analysis of drugs with diverse chemical properties and is often combined with ultraviolet or fluorescence detection. Drummer (2007) notes that HPLC remains relevant in forensic workflows for stable analytes and routine drug panels.
  - **Immunoassays (Screening Methods):** Immunoassay-based screening is commonly used as a preliminary step before confirmatory testing. These assays detect drug classes by antigen–antibody interactions and are useful for rapid identification of benzodiazepines, opiates, amphetamines, cannabinoids, and other commonly encountered substances. However, Flanagan and Connally (2005) emphasize that immunoassays may produce cross-reactivity or false positives, necessitating confirmation through chromatographic methods.
  - **Alternative and Complementary Techniques:** Specialized methods such as headspace gas chromatography are used for analyzing alcohols and volatiles, while spectroscopic and enzymatic assays assist in determining metabolic markers. Emerging analytical platforms continue to improve detection of synthetic opioids, designer drugs, and complex mixtures encountered in postmortem casework.
- hence, the selected analytical techniques form an integrated workflow that supports reliable postmortem toxicology analysis. Their combined application ensures accurate detection, identification, and interpretation of toxic substances in diverse biological matrices.

**Table 1. Reliability and Characteristics of Common Postmortem Samples**

Biological Sample	Reliability	Advantages	Limitations	Key Literature Support
Peripheral Blood	High	Lower influence of PMR; stable concentrations	May still degrade in decomposition	Drummer & Gerostamoulos (2002); Flanagan et al. (2005)
Heart (Central) Blood	Low	Easy to collect	Highly affected by PMR; elevated concentrations	Pounder & Jones (1990); Skopp (2010)

Vitreous Humour	Very High	Resistant to decomposition; stable for alcohol, electrolytes	Limited range of detectable drugs	Skopp (2010); Drummer (2007)
Liver Tissue	Moderate–High	Retains drugs; useful in chronic use	Concentrations vary across lobes; influenced by metabolism	Drummer (2007); Peters & Steuer (2019)
Urine	Moderate	Useful for confirming drug presence; unaffected by PMR	Does not reflect concentration at death	Flanagan & Connally (2005)
Hair	High (for long-term use)	Indicates chronic exposure	Not suitable for detecting recent ingestion	Kintz (2004)
Bone/Bone Marrow	Moderate	Useful in decomposition and skeletonized bodies	Limited interpretation guidelines	McIntyre et al. (2000)
Gastric Contents	Variable	Identifies recent ingestion or overdose	Not suitable for quantification	Skopp (2010)

**Table 2. Analytical Techniques and Their Performance in Postmortem Toxicology**

Analytical Method	Accuracy	Sensitivity	Best Application	Limitations	Key Literature Support
GC-MS	High	High	Confirmatory analysis of volatiles, semi-volatiles	Not ideal for thermolabile drugs	Drummer (2007); Flanagan & Connally (2005)
LC-MS/MS	Very High	Very High	Detection of opioids, antidepressants, NPS, polar drugs	Costly; requires expert operation	Mata & Davis (2022); Drummer (2007)
HPLC	Moderate–High	Moderate	Quantification of stable drugs; when MS not available	Lower specificity without MS	Drummer (2007)
Immunoassays	Moderate	High (class-detection)	Screening for drug classes	Cross-reactivity; false positives/negatives	Flanagan & Connally (2005)
Headspace GC	High	High	Ethanol and volatile analysis	Limited to volatiles only	Skopp (2010)
HRMS / TOF-MS (Advanced)	Very High	Very High	Identification of emerging synthetic drugs	Requires advanced infrastructure	Truver et al. (2025)

**Table 3. Drug Concentration Variability Across Postmortem Matrices**

Drug Class / Example	Peripheral Blood	Central Blood (Heart)	Liver	Vitreous Humour	Key Supporting Literature
Opioids (Morphine, Fentanyl, Methadone)	Moderate–High reliability	Often elevated due to PMR	High due to accumulation	Limited detection	Pounder & Jones (1990); Guerrieri et al. (2017); Pirnay et al. (2004)
Antidepressants (SSRIs – e.g., Citalopram, Fluoxetine)	Moderate	Strong PMR effects	High variability	Limited use	Goeringer et al. (2000)
Benzodiazepines	Moderate	Mild–moderate PMR	Present in tissue	Low applicability	Flanagan & Connally (2005)
Synthetic opioids (Furanylfentanyl)	Moderate	Highly variable	Elevated	Low	Guerrieri et al. (2017)
Alcohol / Volatiles	Stable	Stable	Not preferred	Highly stable	Skopp (2010)
Stimulants (Amphetamines, Cocaine)	Moderate	Moderate PMR	Elevated	Limited	Drummer (2007)
Chronic-use drugs (e.g., THC)	Low–moderate	High variability	High accumulation	Not used	Drummer & Gerostamoulos (2002)

**Table 4. Common Drugs and Their Postmortem Redistribution (PMR) Behaviour**

Drug / Drug Class	PMR Risk Level	Characteristics Affecting PMR	Matrix Most Affected	Key Supporting Literature
Tricyclic Antidepressants	Very High	Lipophilic, weak bases	Central blood	Pounder & Jones (1990); Peters & Steuer (2019)
Opioids (Methadone, Fentanyl)	High	High volume of distribution	Central blood	Pirnay et al. (2004); Guerrieri et al. (2017)
SSRIs (Fluoxetine, Sertraline)	Moderate–High	Long half-life, tissue binding	Central blood	Goeringer et al. (2000)
Benzodiazepines	Moderate	Moderate lipophilicity	Blood, tissues	Skopp (2010)
Cocaine / Metabolites	Moderate	Rapid metabolism	Blood	Drummer (2007)
Ethanol	Low	Minimal PMR effect	Peripheral blood stable	Skopp (2010)
THC (Cannabis)	Low PMR, high tissue retention	Highly lipophilic	Liver, fat tissue	Drummer & Gerostamoulos (2002)
Synthetic opioids (e.g., furanylfentanyl)	High	Potency, tissue sequestration	Central blood	Guerrieri et al. (2017)

**Table 5. Decomposition Effects on Different Drugs**

Drug / Substance Class	Effect of Decomposition	Mechanisms Involved	Impacted Matrices	Key Supporting Literature

Opioids (Morphine, Codeine)	Potential breakdown or bacterial alteration	Microbial activity, pH shifts	Blood, urine	Butzbach (2010); Skopp (2010)
Cocaine	Rapid hydrolysis into benzoylecgonine	Enzymatic/pH-driven breakdown	Blood, tissues	Drummer (2007)
Ethanol	Can be artificially produced postmortem	Microbial fermentation	Blood, urine	Skopp (2010)
Benzodiazepines	Generally stable	Slow metabolic changes	Blood, tissues	Flanagan & Connally (2005)
Synthetic opioids (fentanyl analogues)	May remain stable but shift between matrices	Redistribution postmortem	Central blood	Guerrieri et al. (2017)
Amphetamines	Moderate degradation	Microbial and chemical breakdown	Blood	Butzbach (2010)
THC	Stable but accumulates in tissues	Lipophilicity, storage in fat	Fat, liver	Drummer & Gerostamoulos (2002)
Antidepressants (TCAs and SSRIs)	Concentrations fluctuate due to PMR and tissue breakdown	Tissue decay, pH shifts	Central blood, liver	Goeringer et al. (2000); Peters & Steuer (2019)

## 4. RESULTS

### 4.1 Accuracy and Sensitivity of Modern Instruments

Findings from the reviewed literature and analytical performance summaries (Table 2) show that modern toxicological instruments provide high levels of accuracy and sensitivity across various drug classes. GC-MS and LC-MS/MS remain the most reliable confirmatory techniques due to their ability to detect low concentrations, distinguish structurally similar substances, and analyse both parent drugs and metabolites (Drummer, 2007; Mata & Davis, 2022). High-resolution mass spectrometry platforms demonstrate superior performance for emerging synthetic opioids and complex polypharmacy cases, as they support multi-analyte screening with minimal analytical interference. Immunoassays are useful for rapid screening but require confirmation because cross-reactivity may produce false positives (Flanagan & Connally, 2005). Overall, the literature and tabulated evidence highlight substantial advances in analytical precision, detection limits, and reliability across matrices.

### 4.2 Reliability of Different Biological Samples

Results from the literature are consistent with the patterns presented in Table 1, which shows that biological matrices differ significantly in stability and interpretative value. Peripheral blood is the most reliable because it is least affected by postmortem redistribution (Drummer & Gerostamoulos, 2002; Flanagan et al., 2005). In contrast, central blood consistently shows elevated and unreliable concentrations due to diffusion from organs such as the liver and lungs (Pounder & Jones, 1990).

Vitreous humour emerges as one of the most stable matrices, supported by both literature and tabulated data, particularly in cases involving alcohol, electrolytes, and select drugs (Skopp, 2010). Liver tissue is valuable for detecting chronic drug use and drugs with strong tissue binding, although inter-lobe variation requires cautious interpretation (Drummer, 2007; Peters & Steuer, 2019). The tables further confirm that alternative matrices—hair, bone marrow, and gastric contents—provide important supplementary evidence. Hair documents long-term drug exposure (Kintz, 2004), while bone marrow retains detectable drug levels even in decomposition (McIntyre et al., 2000). These findings reinforce that multi-matrix sampling enhances accuracy and reduces interpretative uncertainty.

### 4.3 Notes on Drug Concentration Variability

The literature and variability patterns summarised in Tables 3–5 show that postmortem drug concentrations fluctuate widely depending on matrix type, drug properties, and postmortem processes.

PMR remains the largest source of variability, with lipophilic, basic, and high-volume-of-distribution drugs showing pronounced increases in central blood (Pounder & Jones, 1990; Abdelaal et al., 2024). Table 4 identifies antidepressants, opioids, and many synthetic drugs as having high redistribution risk, which aligns with findings by Goeringer et al. (2000), Pirnay et al. (2004), and Guerrieri et al. (2017).

Decomposition further contributes to variability, as shown in Table 5. Microbial fermentation may artificially elevate ethanol levels (Skopp, 2010), while enzymatic breakdown accelerates changes in cocaine, morphine, and amphetamines (Butzbach, 2010; Drummer, 2007). Polypharmacy and harmful drug combinations documented in several studies (Launiainen et al., 2009; Pirnay et al., 2004) introduce complex concentration patterns that require multi-matrix and multi-method validation. These results confirm that variability is multifactorial and requires cautious, context-based interpretation.

The combined results across literature and tables demonstrate that postmortem toxicology depends on the integration of reliable sample matrices, advanced analytical methods, and expert interpretative judgement. Peripheral blood, vitreous humour, and liver tissue remain the most informative and stable matrices, while alternative matrices such as hair and bone marrow contribute important supplementary data in decomposed or complex cases. Modern analytical platforms—particularly GC-MS, LC-MS/MS, and HRMS—significantly enhance accuracy and support comprehensive multi-analyte detection. Drug concentration variability arises from PMR, decomposition, drug physicochemical properties, and polypharmacy, reinforcing the need for multi-matrix comparison and thorough documentation. Collectively, the findings align with best-practice recommendations for producing defensible and reliable toxicological conclusions in medico-legal investigations.

## 5. DISCUSSION

Differences between antemortem and postmortem drug concentrations arise from physiological changes that occur after death as well as from the altered distribution of drugs within the body. According to Flanagan and Connally (2005), drug absorption, distribution, metabolism, and excretion stop at death, which leads to changes in drug compartmentalization that do not mirror antemortem pharmacokinetics. Leikin and Watson (2003) note that reduced protein binding, cell breakdown, and loss of circulatory pressure influence the redistribution of drugs into surrounding tissues. These processes create concentration gradients that differ markedly from antemortem levels, making direct comparison inappropriate. Moreover, underlying health conditions, tolerance, and drug interactions prior to death contribute to additional variability in observed concentrations (Goeringer et al., 2000).

Postmortem redistribution is one of the most influential factors affecting toxicology interpretation. Pounder and Jones (1990) first identified PMR as a major source of elevated drug concentrations in central blood due to passive diffusion from organs with high drug content. This has been consistently supported by later research. Drummer (2007) reports that lipophilic and weakly basic drugs are particularly prone to redistribution, especially in cardiac blood collected near the lungs and liver. Abdelaal et al. (2024) confirm that PMR intensity depends on drug characteristics, proximity of the sampling site to major organs, and time since death. Decomposition adds further complexity. As tissues break down, they release intracellular drug stores into nearby fluids. Butzbach (2010) demonstrates that putrefaction increases microbial activity, alters pH, and produces endogenous compounds that may interfere with drug measurement. Skopp (2010) also shows that decomposition causes instability of certain drugs, which may lead to underestimation or complete loss of detectable concentrations. Together, these factors make postmortem interpretation challenging and highlight the need for careful selection of appropriate matrices.

The literature strongly supports the use of multiple biological matrices to improve accuracy in postmortem drug interpretation. Flanagan, Connally, and Evans (2005) recommend collecting peripheral blood, vitreous humour, urine, and solid tissues to reduce the risk of relying on concentrations affected by PMR or decomposition. Drummer and Gerostamoulos (2002) argue that multi sample analysis allows cross referencing of concentrations to determine whether a drug finding is consistent with antemortem use, overdose, or redistribution. Kintz (2004) demonstrates that alternative matrices such as hair can supplement case evaluation by showing long term exposure patterns, while McIntyre et al. (2000) report

that bone marrow is particularly useful in decomposed remains. This multi matrix approach allows forensic toxicologists to identify misleading results and establish more accurate interpretations.

Toxicology results must be interpreted alongside autopsy findings and investigative history to avoid misclassification of cause and manner of death. Flanagan and Connally (2005) emphasise that drug concentrations cannot be interpreted in isolation because their significance varies depending on tolerance, chronic use, and pathological conditions. Stephenson et al. (2024) highlight that correlation with physical findings such as pulmonary oedema, needle marks, gastric contents, or organ pathology helps confirm or refute a toxicological cause of death. Case history, including reported symptoms and known substance use, further strengthens interpretation. Studies such as those by Pirnay et al. (2004) and Launiainen et al. (2009) show that combined assessment of toxicology, case history, and autopsy data is essential in deaths involving methadone, buprenorphine, polypharmacy, or drug interactions.

The findings of the current review align closely with established research in forensic toxicology. Early studies such as Pounder and Jones (1990) identified PMR as a primary challenge, and recent evidence from Abdelaal et al. (2024) confirms that these mechanisms remain relevant. The importance of peripheral blood sampling described by Drummer and Gerostamoulos (2002) continues to underpin international best practice guidelines, including those summarised by Truver et al. (2025). Similarly, the role of analytical advances noted by Drummer (2007) and Mata and Davis (2022) aligns with contemporary laboratory standards that emphasise precise quantification and multi drug screening. The literature also consistently supports the need for multidimensional interpretation, combining toxicology, pathology, and case history, as outlined by Leikin and Watson (2003) and Stephenson et al. (2024).

Vitreous humour and liver tissue remain two of the most valuable matrices in postmortem toxicology. Vitreous humour is highly resistant to decomposition and PMR due to its anatomical isolation and low metabolic activity. Skopp (2010) notes that vitreous is particularly reliable for alcohol, electrolytes, some drugs, and biochemical markers. Its stability makes it useful in advanced decomposition or where blood reliability is compromised. Liver tissue is equally important because many drugs accumulate in the liver due to metabolism and high perfusion. Drummer (2007) states that the liver can retain drugs even when blood levels are low or degraded, making it indispensable in long term use or chronic poisoning cases. Peters and Steuer (2019) explain that liver concentrations reflect drug distribution patterns and provide insight into metabolite profiles that may not be detectable in blood. However, interpretation must consider the potential for intra organ variation and postmortem biochemical changes.

## 6. CONCLUSION

The review highlights that postmortem toxicology plays an essential role in determining the involvement of drugs and toxic substances in medico-legal deaths. Modern analytical techniques such as GC-MS, LC-MS/MS, and HPLC provide high levels of accuracy and sensitivity, enabling the detection of a wide range of substances even in decomposed or compromised specimens. The findings show that biological matrices differ significantly in reliability, with peripheral blood, vitreous humour, and liver tissue emerging as the most informative samples. Drug concentration variability is mainly influenced by postmortem redistribution, decomposition, individual drug properties, and combined substance use. The literature consistently emphasises that toxicology data must be interpreted with caution and supported by autopsy findings, case history, and multi sample comparison to avoid misinterpretation. Together, these findings confirm the complex but indispensable role of postmortem toxicology in forensic investigations.

The review underscores the need for strict and standardized protocols in postmortem toxicology to improve the reliability and reproducibility of results. Consistent sampling procedures particularly prioritizing peripheral blood and vitreous humour help minimise the influence of postmortem redistribution. Standard guidelines for sample storage, handling, and preservation are essential to reduce chemical degradation and microbial interference. Analytical protocols must follow validated methods with proper calibration, quality controls, and confirmatory testing to strengthen accuracy. Adherence to established procedures, as recommended by forensic toxicology experts and professional organizations,

ensures that laboratory results meet scientific and legal standards. Standardization not only improves casework consistency but also enhances the defensibility of toxicological findings in judicial processes. Interpretation of postmortem toxicology findings requires specialized knowledge due to the numerous factors influencing drug concentrations after death. The review shows that expertise in pharmacology, pathology, toxicokinetics, and analytical chemistry is necessary to understand postmortem redistribution, decomposition effects, tissue variability, and drug-specific behavior. Toxicologists must integrate analytical results with autopsy observations, scene evidence, medical history, and known drug patterns to reach accurate and meaningful conclusions. Cases involving polypharmacy, opioid toxicity, synthetic drugs, or advanced decomposition further demand advanced interpretative skills. The role of expert judgement is therefore central to minimizing errors, avoiding over-interpretation, and ensuring that toxicology findings are consistent with the overall medico-legal context. Skilled interpretation forms the bridge between analytical data and the determination of cause and manner of death.

## 7. LIMITATIONS

This study is based entirely on secondary data obtained from published research articles, forensic toxicology textbooks, reviews, and case reports. As a result, the findings rely on the quality, scope, and depth of available literature rather than primary experimental evidence. The absence of direct laboratory analysis or casework observations limits the ability to validate specific analytical outcomes or quantify the extent of postmortem changes. Secondary data may also reflect publication bias, where unusual or complex cases are overrepresented, while routine findings are less frequently documented. Consequently, the conclusions drawn in this review may not capture all variations encountered in real-time forensic practice.

The literature reveals considerable variability in analytical procedures, sample collection practices, and toxicological reporting across different laboratories and jurisdictions. These differences include variations in analytical instruments, calibration standards, detection limits, extraction techniques, and confirmatory testing protocols. Studies such as those by Flanagan and Connally (2005) and Drummer (2007) indicate that inter-laboratory differences can result in inconsistent drug concentration values and interpretative challenges. Furthermore, laboratories may adopt different guidelines for handling decomposed samples or for prioritizing specific biological matrices, which creates heterogeneity in reported results. This variability limits the generalizability of findings and may influence the comparability of data across studies.

Another major limitation highlighted by the literature is the inherent instability of postmortem biological specimens. Decomposition, microbial activity, enzymatic breakdown, and environmental exposure can significantly alter drug concentrations and metabolite profiles. Studies such as Butzbach (2010) and Skopp (2010) show that breakdown processes generate endogenous compounds that may interfere with analytical detection, leading to false positives or negatives. Additionally, postmortem redistribution creates uncertainty in interpreting central blood concentrations and complicates the assessment of toxic versus therapeutic levels. Without multi-sample analysis or autopsy correlation, interpretation remains vulnerable to error. These biological limitations highlight the need for caution when drawing conclusions from postmortem drug concentrations, particularly in complex or decomposed cases.

## 8. FUTURE RECOMMENDATIONS

Future work in postmortem toxicology should prioritise the adoption of advanced analytical platforms that offer improved sensitivity, specificity, and throughput. Techniques such as high-resolution mass spectrometry (HRMS), LC-MS/MS with multi-analyte detection, and time-of-flight mass spectrometry can enhance the ability to identify emerging psychoactive substances, synthetic opioids, and low-concentration metabolites that may not be detected by conventional instruments. These platforms also support more robust quantification in degraded samples and complex matrices. Continued investment in modern analytical technologies will help laboratories produce more reliable and comprehensive toxicology profiles, particularly in challenging cases involving polypharmacy or novel drug compounds.

The review underscores the need for uniform, evidence-based guidelines governing sample collection, storage, analytical procedures, and interpretation of toxicology results. Standardized protocols would minimize inter-laboratory variability and ensure that results are comparable across jurisdictions. Clear guidance on preferred matrices, thresholds for interpretation, handling of decomposed samples, and best practices for reporting findings would strengthen medico-legal reliability. Collaborative efforts among forensic science bodies, toxicology experts, and regulatory agencies are necessary to develop and update these guidelines regularly in response to new scientific evidence and emerging drug trends.

Given the complexity of postmortem toxicology interpretation, continued professional development is essential. Training programs should focus on advanced analytical techniques, interpretation of postmortem redistribution, identification of drug-drug interactions, and evaluation of complex toxicology profiles. Workshops, certification courses, and hands-on laboratory training can enhance practical competence among toxicologists, forensic pathologists, and medico-legal investigators. Strengthening expertise will reduce interpretative errors and improve the accuracy of cause-of-death determinations, particularly in cases involving synthetic drugs, highly lipophilic substances, or advanced decomposition.

Strengthening medico-legal infrastructure is critical to ensuring high-quality postmortem toxicology services. Investment is needed in modern laboratory facilities, updated analytical instruments, secure sample storage systems, and efficient data management platforms. Integration of toxicology units with forensic pathology departments and law-enforcement agencies can improve communication, case tracking, and multi-disciplinary decision-making. Policymakers should prioritise funding, staffing, and organizational support to ensure timely toxicology testing and comprehensive medico-legal investigations. Improved infrastructure will increase national capacity to address rising drug-related deaths and emerging toxicological threats.

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