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Review Article

Toxicological Assessment of Barbiturates: Analytical Methods, Metabolism, and Forensic Implications in Drug-related Fatalities

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Abstract

Barbiturates, once commonly prescribed for their sedative and anticonvulsant properties, have since fallen out of widespread therapeutic use due to their narrow therapeutic index and high risk of fatal overdose. Despite this decline, they remain critical in forensic toxicology, particularly in drug-related fatalities. This review explores the toxicological assessment of barbiturates, focusing on their mechanisms of action, metabolism, and the forensic implications in cases of overdose. The paper delves into the pharmacodynamics of barbiturates, highlighting their central nervous system (CNS) depressant effects through GABAergic modulation, dose-dependent toxicity, and the resulting cardiovascular and respiratory depression that often leads to fatal outcomes. Furthermore, the review discusses both historical and modern analytical methods employed in forensic toxicology for barbiturate detection, including gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-tandem mass spectrometry (LC-MS/MS). Special attention is given to challenges in interpreting toxicological data, such as postmortem redistribution and polydrug interactions, which complicate forensic investigations. By examining the role of barbiturates in modern forensic toxicology, this paper underscores their ongoing relevance in forensic cases involving drug-induced fatalities.

Introduction

Barbiturates are a class of central nervous system (CNS) depressants that have historically been used for a variety of therapeutic purposes, including as sedatives, hypnotics, anticonvulsants, and anesthetics. Introduced in the early 20th century, barbiturates were widely prescribed for insomnia and anxiety before their addictive potential and high risk for overdose led to the development of safer alternatives, such as benzodiazepines. Despite their decline in medical use, barbiturates still play a critical role in forensic toxicology, particularly in cases of drug-related fatalities due to their potent CNS depressant effects.

Classification of barbiturates

A practical way to classify barbiturates is by duration of action (onset and length of hypnotic/sedative effect).

1. **Ultra-short acting:** These act very rapidly (often via intravenous route) and their effect is very short-lived (minutes). Example: Thiopental (also called thiopentone) and Methohexital.
2. **Short acting:** Onset is relatively fast, but the effect lasts a few hours (often 2-4h or slightly longer). Example: Secobarbital.
3. **Intermediate acting:** Duration typically in the order of several hours (4-8h or somewhat variable). Example: Amobarbital.
4. **Long acting:** These have the longest duration (up to 12h or more, occasionally 24h) and are used in indications such as anticonvulsant therapy rather than as hypnotics. Example: Phenobarbital.

Structural/physicochemical basis of classification

The duration of action is influenced by factors such as lipid solubility, redistribution rate, metabolic rate, and the nature of substituents at the C5 position of the barbituric acid moiety.

More lipid-soluble compounds enter the CNS quickly but also redistribute promptly to other tissues, giving a faster onset but shorter duration.

Conversely, less lipophilic or more slowly metabolised compounds will have a longer duration of action (hence the "long-acting" barbiturates).

Summary table (for forensic reference)			
Duration category	Approximate duration*	Example(s)	Common uses
Ultra-short	Minutes (often < 30 min)	Thiopental, Methohexital	IV induction of anaesthesia
Short-acting	~ 2-4 h or several hours(historical)	Secobarbital Hypnotic/ sedative uses	
Intermediate-acting	~4-8 h	Amobarbital Hypnotic, Sedation	
Long-acting	> 8 h up to ~24 h	Phenobarbital	

Mechanism of Action

Understanding the mechanism of action (MOA) of barbiturates is crucial, especially when interpreting toxicology, overdose cases, or forensic scenarios.

Primary MOA at GABA_A receptor

Barbiturates bind to the (the main inhibitory neurotransmitter receptor in the CNS) at a site distinct from the benzodiazepine binding site. They act as positive allosteric modulators: at therapeutic doses, they prolong the duration of chloride-channel opening when GABA is bound, thereby enhancing inhibitory neurotransmission (hyperpolarising neurons, making them less excitable) [1].

Barbiturate-related overdoses are of significant forensic interest, as these drugs can cause death by respiratory depression, hypotension, and coma, especially when used in conjunction with other depressants like alcohol or opioids. The toxicological assessment of barbiturates in forensic cases involves a deep understanding of their pharmacokinetics, metabolism, and the analytical techniques used for detection in biological samples. Given their narrow therapeutic index and the potential for fatal outcomes even with small dosage errors, barbiturates remain a focus in postmortem toxicological investigations [2].

This review provides a comprehensive examination of barbiturates from a forensic toxicology perspective, focusing on their mechanisms of action, metabolism, and the toxic effects associated with overdose. The paper also discusses the analytical methods used to detect barbiturates in forensic cases, the challenges faced in interpretation, and the implications for drug-related fatalities. By exploring both historical and modern forensic cases, this review aims to highlight the ongoing relevance of barbiturates in forensic toxicology despite their diminished medical use [3].

Pharmacokinetics and metabolism of barbiturates

Pharmacokinetics (PK) is the study of how the body interacts with administered substances for the entire duration of exposure (medications for the sake of this article). This is closely related to but distinctly different from pharmacodynamics, which examines the drug's effect on the body more closely [4].

Barbiturates are metabolized in the liver through oxidation, which produces alcohols, ketones, phenols, or carboxylic acids. These metabolites are then excreted in urine, either as is or as glucuronic acid conjugates [5]. The pharmacokinetics of different barbiturates have been studied extensively, and the relationship of their duration of action to their clinical use has been known for decades. While these particular compounds have largely been displaced by agents with better therapeutic indices, barbiturate use remains relatively common and important in both inpatient and outpatient settings. Their mechanism of action is to bind to inhibitory GABAA receptors in the CNS, causing and potentiating the opening of neuronal chloride ion channels, thus having a sedative and CNS depressant effect. All psychotropic barbiturates feature di-substitution at the C5 position of the barbituric acid prototype. This is also the primary factor by which physiologically active barbiturates differ from one another and a major mediator of lipophilicity and duration of action. However, in this review, inconsistencies in certain commonly held notions about the structure-activity relationship of barbiturates were found [6].

- **Elimination:** About 25% – 50% of barbiturates are eliminated in urine unchanged.
- **Enzyme activity:** Chronic use of barbiturates increases the activity of hepatic microsomal enzymes.
- **Half-life:** The half-life of barbiturates varies by category [7].
- **Metabolism pathways:** Other metabolic pathways include N-demethylation, desulfuration, and N-methylation.
- **Binding:** Barbiturates may bind to P450 enzymes and interfere with the metabolism of other compounds.
- **Metabolism in animals:** The Metabolism of barbiturates may be slow in very young or very old animals or those with hepatic disease.

Metabolism of barbiturates occurs by oxidation in the liver, resulting in the formation of alcohols, ketones, phenols, or carboxylic acids, which are excreted in urine as such or in the form of glucuronic acid conjugates. Approximately 25% of phenobarbitone is excreted unchanged in urine. Barbiturates, which are central nervous system depressants, distribute throughout the body based on their lipid solubility, protein binding, and tissue blood flow. Here's a general overview of their distribution in body tissues [8].

Mechanism of absorption of barbiturates: ADME (absorption, distribution, metabolism, and excretion

Absorption: Absorption is the process that brings a drug from the administration, eg, tablet or capsule, into the systemic circulation. Absorption affects the speed and concentration at which a drug may arrive at its desired location of effect, eg, plasma [9].

Distribution: Drug distribution is the process by which a drug moves through the body's blood and tissues. It is the second stage of pharmacokinetics.

Metabolism: Metabolism of barbiturates occurs by oxidation in the liver, resulting in the formation of alcohols, ketones, phenols, or carboxylic acids, which are excreted in urine as such or in the form of glucuronic acid conjugates. Approximately 25% of phenobarbitone is excreted unchanged in urine.

Excretion: Excretion is the process by which the drug is eliminated from the body. The kidneys most commonly conduct excretion, but for certain drugs, it may be via the lungs, skin, or gastrointestinal tract [10].

Mechanism of Absorption of barbiturates

Oral route: Barbiturates are released from the dosage form and dissolve in the dosage form and dissolve in the gastrointestinal tract. Barbiturates are weak acids, and their absorption is influenced by the PH of the stomach and intestines. After absorption, barbiturates enter the portal circulation and may undergo first-pass metabolism in the liver, which can reduce metabolism in the liver, which can reduce the bioavailability of the drug [11].

Intravenous route: here we consider two processes for direct entry into circulation where barbiturates are delivered directly into the bloodstream, bypassing the GI tract and first-pass metabolism. After this, they rapidly distribute to highly perfused tissues, leading to a quick onset of action.

Lipid solubility: Barbiturates are lipophilic (fat-soluble) drugs. This property allows them to easily cross cellular membranes by passive diffusion. The higher the lipid solubility, the faster the absorption.

Stomach and small intestine: After oral administration, barbiturates can be absorbed from the stomach, but most absorption occurs in the small intestine due to its larger surface area and higher permeability.

pH and ionization: The absorption of barbiturates depends on the pH of the environment and the drug's pKa. In the acidic environment of the stomach (pH ~1.5 to 3.5), barbiturates, being weak acids, exist largely in their non-ionized form, which facilitates absorption. However, due to the prolonged transit time in the intestine and the neutral to alkaline pH (~6-7.5), the absorption primarily occurs in the small intestine [12,13].

Factors affecting barbiturate toxicity

Dosage and administration route: Increased dosages significantly raise the risk of toxicity.

Individual patient factors: Older adults may have altered pharmacokinetics, leading to increased sensitivity. Body weight and composition can affect drug distribution and metabolism.

Drug interactions: medications that induce or inhibit CYP enzymes can affect barbiturate metabolism, increasing toxicity risk.

Liver function: Liver diseases can reduce the metabolism of barbiturates, increasing serum levels and toxicity risk.

Chronic use and dependence: Chronic use can lead to tolerance, requiring higher doses for the same effect, increasing toxicity risk if doses are escalated suddenly. Withdrawal Symptoms: Abrupt cessation after long-term use can lead to withdrawal symptoms, which may be mistaken for toxicity.

Environment and physiological factors: Hypoxia, Hypercapnia, acidosis, hypothermia, stress.

Clinical signs of barbiturate toxicity: respiratory depression, coma, hypotension, bradycardia, Hypothermia, confusion, agitation

Patient-specific factors:

Age: Elderly infants and young children are more susceptible.

Body weight: overweight/obese individuals may experience increased toxicity.

Renal function: Impaired kidney function slows elimination.

Cardiovascular disease: Increases risk of cardiovascular complications [14-20].

Dose-response relationship

The dose–response relationship, or exposure–response relationship, describes the magnitude of the response of an organism as a function of exposure (or doses) to a stimulus or stressor (usually a chemical) after a certain exposure time. Dose–response relationships can be described by dose–response curves. This is explained further in the following sections. A stimulus response function or stimulus response curve is defined more broadly as the response from any type of stimulus, not limited to chemicals. Barbiturates are medications that cause you to relax or feel drowsy. They can also stop or prevent convulsions and seizures. The most common uses are for anesthesia reasons, treating epilepsy

and non-epileptic seizures, insomnia, and other conditions. Barbiturates belong to the sedative-hypnotic class of medications. The dose-response relationship of barbiturates is complex and varies depending on the specific barbiturate, individual characteristics, and other factors [21, 22].

Symptoms of acute and chronic toxicity

Signs of overdose: In cases of acute barbiturate toxicity, the hallmark signs include respiratory failure, loss of consciousness, and hypotension. As CNS depression deepens, individuals may present with shallow or absent breathing, hypothermia, and cyanosis. Reflexes such as the gag reflex can be suppressed, increasing the risk of aspiration and airway obstruction. Without prompt medical intervention, these symptoms can progress to coma, irreversible brain damage, or death [28].

Long-term effects of chronic barbiturate use: Chronic use of barbiturates can lead to physical dependence and tolerance, requiring progressively higher doses to achieve the desired sedative effects. Long-term users are at a higher risk for cognitive impairments, mood disturbances, and coordination problems due to sustained CNS depression. Additionally, chronic use can exacerbate the risk of overdose, particularly when barbiturates are combined with other CNS depressants like alcohol or benzodiazepines, which can have synergistic effects [29]. Chronic barbiturate users may also suffer from liver and kidney damage due to the long-term burden of metabolizing the drug, leading to further health complications.

Recent advancements in analytical methods: GC-MS and LC-MS in toxicological analysis

Analytical methods

Analytical toxicology has witnessed remarkable progress with the advent of advanced instrumental techniques such as Gas Chromatography–Mass Spectrometry (GC-MS) and Liquid Chromatography–Mass Spectrometry (LC-MS). These methods have transformed the detection, identification, and quantification of toxic substances in biological and environmental samples, providing enhanced sensitivity, specificity, and reliability.

GC-MS has long been a cornerstone in toxicology, especially for analyzing volatile and semi-volatile compounds such as drugs, alcohols, and pesticides. Recent advancements include high-resolution mass spectrometry (HRMS) and tandem mass spectrometry (MS/MS), which enable more accurate molecular identification and structural elucidation. Automated sample preparation systems and miniaturized GC columns have also improved analytical throughput, reducing analysis time and solvent use. Furthermore, software-driven spectral libraries and data processing algorithms have enhanced compound identification, allowing rapid screening of complex mixtures.

LC-MS, on the other hand, has become the preferred method for detecting thermally labile, polar, and non-volatile compounds that are unsuitable for GC analysis. Innovations like ultra-high-performance liquid chromatography (UHPLC) coupled with triple quadrupole or time-of-flight (TOF) mass analyzers have significantly improved sensitivity and dynamic range. LC-MS/MS allows simultaneous quantification of multiple analytes at trace levels, making it invaluable in forensic toxicology, therapeutic drug monitoring, and environmental testing.

The integration of GC-MS and LC-MS with advanced data analytics, metabolomics, and high-throughput screening platforms has further expanded their applicability. These methods now offer real-time monitoring, lower detection limits, and improved reproducibility.

Overall, the recent advancements in GC-MS and LC-MS have revolutionized toxicological analysis by offering unparalleled analytical power. They ensure accurate detection of a wide array of toxins and drugs, supporting forensic investigations, clinical diagnostics, and public health safety with greater efficiency and confidence [30-34].

Benefits

High sensitivity and specificity: Both LC-MS and GC-MS offer excellent sensitivity, allowing detection of trace levels of toxic substances even in complex biological matrices like blood, urine, and tissues. Their high specificity ensures accurate identification of compounds based on unique mass-to-charge (m/z) ratios and retention times.

Broad range of detectable compounds: GC-MS is ideal for analyzing volatile and thermally stable substances such as alcohols, hydrocarbons, and pesticides. LC-MS, on the other hand, can detect non-volatile, polar, and thermally labile compounds like pharmaceuticals and metabolites. Together, they provide a comprehensive approach to screening a wide range of toxic agents.

Structural elucidation and confirmation: Mass spectrometry provides valuable molecular fragmentation data that helps in determining the structure and identity of unknown substances. This is particularly important in forensic toxicology for confirming the presence of specific drugs or poisons.

Rapid and reliable results: Modern LC-MS/MS and GC-MS/MS systems allow simultaneous analysis of multiple compounds in a single run, reducing turnaround time while maintaining reliability [35-38].

Forensic interpretation: challenges in toxicological evaluation of barbiturates

The forensic interpretation of barbiturate findings in biological specimens remains a complex process influenced by several confounding factors. Accurate determination of the

cause of death or impairment requires careful consideration of variables such as poly-drug overdose, postmortem redistribution, and individual variability. These factors often complicate the correlation between detected concentrations and toxic effects, leading to interpretative uncertainties in forensic casework [39].

Poly-drug overdose

Barbiturates are frequently encountered in combination with other central nervous system (CNS) depressants such as benzodiazepines, opioids, and alcohol. The synergistic or additive depressant effects of these substances can significantly enhance toxicity, even when individual drug levels fall within therapeutic ranges. This overlap complicates interpretation, as it becomes difficult to attribute fatality to a single agent. In forensic toxicology, distinguishing the relative contribution of barbiturates in mixed drug intoxications demands a comprehensive toxicological screening and clinical correlation.

Postmortem Redistribution (PMR)

Postmortem changes in drug concentration are another critical challenge. Barbiturates, particularly the lipophilic long-acting compounds, may undergo significant redistribution from tissues to the central blood after death. This phenomenon can lead to falsely elevated postmortem blood levels, potentially misleading the interpretation of overdose. Therefore, forensic analysts often compare concentrations from multiple sites (e.g., femoral versus cardiac blood) and consider tissue levels to minimize misinterpretation caused by PMR.

Individual variability

Pharmacokinetic and pharmacodynamic differences among individuals further complicate interpretation. Factors such as age, genetic polymorphisms of metabolic enzymes (notably CYP450 isoenzymes), tolerance, liver function, and concurrent diseases influence both the metabolism and sensitivity to barbiturates. Chronic users may exhibit higher tolerance levels, while naïve individuals may succumb to lower concentrations. Consequently, "toxic" and "lethal" concentration ranges must be interpreted cautiously, taking into account the subject's drug history and physiological condition.

In conclusion, the forensic interpretation of barbiturate toxicology requires a holistic approach that integrates analytical findings with case history, autopsy results, and pharmacological understanding. Addressing these interpretative challenges is essential for achieving reliable conclusions in medico-legal investigations [40-43].

Future research directions: Metabolomic and toxicogenomic approaches

The integration of metabolomic and toxicogenomic technologies represents a promising frontier in forensic toxicology and toxicological research. While current analytical methods, such as GC–MS and LC, have enhanced the detection and quantification of toxicants, understanding the underlying biological responses to toxic exposure requires more comprehensive molecular-level insight.

Metabolomics, the systematic study of small-molecule metabolites, offers an advanced platform to elucidate biochemical alterations induced by toxic agents. Future studies should focus on developing metabolite biomarkers that can differentiate between acute and chronic exposure, elucidate mechanisms of toxicity, and assist in postmortem interval estimation. Expanding metabolomic databases and integrating high-resolution mass spectrometry with bioinformatics pipelines will improve compound identification and pathway mapping. Moreover, real-time and non-invasive metabolomic profiling, such as through biofluids like sweat or saliva, could revolutionize field-based toxicological screening.

Toxicogenomics, on the other hand, aims to correlate gene expression profiles with toxicant exposure, offering predictive insights into individual susceptibility and molecular mechanisms of toxicity. Future research should emphasize multi-omics integration, combining transcriptomic, proteomic, and epigenomic data to establish holistic toxicological signatures. Advances in next-generation sequencing and machine learning can facilitate the identification of gene networks and regulatory pathways involved in toxicant response. Additionally, population-specific toxicogenomic studies may help understand genetic variability influencing drug metabolism and toxicity. Overall, the convergence of metabolomic and toxicogenomic approaches will enable a systems biology perspective, improving risk assessment, biomarker discovery, and personalized toxicology. Future directions should prioritize data standardization, inter-laboratory validation, and the development of robust bioinformatics frameworks to translate omics-based findings into practical forensic and clinical applications [44-46].

Metabolomic approach in toxicological analysis: Metabolomics refers to the comprehensive study of small-molecule metabolites within a biological system under specific physiological or pathological conditions. Metabolites are the end products of cellular processes and provide a direct reflection of the organism's biochemical state. In toxicology, metabolomics helps in identifying metabolic alterations that occur following exposure to toxic substances such as drugs, pesticides, heavy metals, or environmental pollutants. Modern metabolomic studies rely on analytical platforms like Nuclear Magnetic Resonance (NMR) spectroscopy, LC–MS, and GC–MS, which allow the detection, quantification, and structural elucidation of a wide range of metabolites. By comparing metabolomic profiles of exposed and unexposed individuals, researchers can pinpoint specific biomarkers of exposure and effect.

For instance, toxicant-induced changes in amino acid metabolism, lipid peroxidation products, or energy metabolism intermediates can reveal the affected biochemical pathways and organ systems. Such insights are invaluable in understanding mechanisms of toxicity, differentiating between acute and chronic exposure, and evaluating dose–response relationships.

Moreover, metabolomic fingerprinting aids in postmortem toxicological studies by distinguishing between ante-mortem metabolic disturbances and postmortem artifacts. With the integration of bioinformatics and statistical modeling, metabolomics can also assist in predicting toxic outcomes and assessing the impact of mixtures of toxicants, a common real-world scenario [47-49].

Toxicogenomic approach in toxicological analysis: Toxicogenomics combines genomics, transcriptomics, and bioinformatics to study the influence of toxicants on gene expression and genetic regulation. It provides a molecular understanding of how organisms respond to chemical exposure at the genetic level. This approach focuses on identifying gene expression signatures, regulatory networks, and pathways that are altered upon exposure to toxic substances [50].

High-throughput techniques such as DNA microarrays, RNA sequencing (RNA-seq), and quantitative PCR enable the simultaneous analysis of thousands of genes to identify molecular biomarkers of toxicity. These tools can help determine whether a toxicant activates pathways associated with apoptosis, oxidative stress, or inflammation [51].

Toxicogenomic data also contribute to risk assessment by revealing dose-dependent gene expression changes, which help in establishing No Observable Adverse Effect Levels (NOAELs) and Lowest Observable Adverse Effect Levels (LOAELs). Additionally, toxicogenomics supports personalized toxicology, as genetic variations among individuals can influence their susceptibility to toxins and drugs [52].

Understanding these genetic differences allows for better prediction of adverse effects and supports safer drug and chemical development. Integration of toxicogenomic data with other omics disciplines (proteomics and metabolomics) provides a comprehensive view of cellular responses, enabling the identification of key molecular pathways involved in toxicity. This systems biology approach bridges the gap between molecular mechanisms and observable toxic effects [53].

Case studies and forensic case reports

Barbiturates, which were frequently prescribed for anxiety, insomnia, and seizure disorders, act as depressants on the central nervous system and have a small range within which they are effective before becoming toxic, making overdoses quite common. Barbiturates have been implicated in a large number of poisoning deaths (mostly suicides), which peaked in the 1970s 's [50-53]. In forensic inquiries, instances of barbiturate overdose typically revolve around unintentional fatalities, suicides, and, on rare occasions, homicides. The lethal dose of barbiturate is 10-15gm g. The following are some notable forensic cases involving barbiturate overdoses:

A) Marilyn Monroe (1962)

Marilyn Monroe was one of the famous actresses in Los Angeles at that time. The death of actress Marilyn Monroe was due to an overdose of barbiturates. She was found dead in her home due to an apparent overdose of barbiturates, specifically pentobarbital and chloral hydrate. Her death was ruled a probable suicide due to the high levels of the drugs in her system. The forensic examination showed no signs of foul play, though the case has remained the subject of conspiracy theories due to her high-profile relationships and abrupt death. This case underscores how barbiturates, particularly when combined, can cause lethal respiratory depression [54].

A total of 10.4 g of barbiturate was found in her body after postmortem.

Lethal concentration of barbiturate found:

1. Phenobarbital = 107 mg
2. Secobarbital = 27 mg
3. Pentobarbital = 53 mg
4. Amobarbital = 52 mg

Pointing to the dangers of combining barbiturates with other depressants. This case exemplifies the risks of polypharmacy, particularly in individuals with a history of such 13.2 g of barbiturate was found in her body after postmortem

B) Lethal concentration of barbiturate found:

1. Phenobarbital = 136 mg
2. Secobarbital = 42 mg
3. Pentobarbital = 61 mg
4. Amobarbital = 63 mg

Forensic investigations into barbiturate overdoses require careful toxicological analysis, consideration of the individual's medical and psychological history, and attention to potential complicating factors like drug interactions. These cases illustrate the thin line between therapeutic and lethal doses and the broader implications for criminal investigations, especially in cases where intentional overdose or foul play is suspected [55].

The legal implications of barbiturate overdose cases vary significantly depending on the circumstances surrounding the overdose, the intent of the deceased or others involved,

and the findings from forensic investigations. These cases can result in different legal classifications, including suicide, accidental death, or homicide, each of which carries unique legal considerations and potential verdicts [56].

Conclusion

Barbiturates continue to pose significant challenges in forensic toxicology despite their reduced clinical use. Their powerful CNS depressant properties, narrow therapeutic window, and propensity to cause fatal respiratory and cardiovascular depression, particularly in combination with other central depressants, make them a critical focus in drug-related death investigations. This review highlights the importance of advanced analytical methods in detecting and interpreting barbiturate toxicity in forensic cases. The complexities surrounding postmortem redistribution, metabolism, and the influence of polydrug use underscore the need for careful forensic interpretation. As drug abuse patterns evolve, the forensic community must remain vigilant in addressing the ongoing implications of barbiturate toxicity, ensuring that both classic and contemporary approaches to toxicological screening are employed to provide accurate and reliable data in forensic investigations.

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