Journal of *Xenobiotics*

MDPI

Review

Dissociative Substances in Forensic Toxicology: Pharmacology, Toxicokinetics, and Analytical Detection

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Abstract

Dissociative substances are xenobiotics that can cause clinically meaningful disruption to the integration of perception, cognition, bodily awareness, and environmental awareness. This narrative review evaluates eight primary substances grouped across distinct functional and pharmacological classes: arylcyclohexylamines (phencyclidine [PCP] and ketamine), morphinans (dextromethorphan [DXM]), volatile inhalants (nitrous oxide [N_2O]), kappa-opioid receptor agonists (salvinorin A from Salvia divinorum), aminoadamantanes (memantine and amantadine), and experimental research compounds (dizocilpine [MK-801]). This is a phenomenological and toxicological grouping rather than a single chemical class or receptor-defined category. PCP and ketamine are included as prototypical dissociative anesthetics; DXM is included because dissociative effects emerge at supratherapeutic doses through DXM and dextrorphan-mediated NMDA-receptor antagonism. Nitrous oxide and salvinorin A are included because they can produce short-lived dissociative phenomenology through distinct mechanisms. Memantine and amantadine are included as therapeutically used aminoadamantane NMDA-channel blockers with uncommon, dose- and context-dependent dissociative or psychotomimetic effects, whereas dizocilpine (MK-801) is included solely as an experimental comparator with strong preclinical relevance and no routine human forensic role. A literature search across PubMed, Scopus, Web of Science, and Google Scholar through June 2026 evaluated analytical methods for biological specimens, seized exhibits, and specialized research applications. LC-MS/MS and GC-MS remain central to biological toxicology, but analytical performance cannot be generalized across matrices or compounds; LOD, LOQ, calibration range, sample preparation, validation status, and intended use must be interpreted separately. SFC, NMR, and XRD are presented as specialized or supplementary techniques rather than routine platforms in most forensic toxicology laboratories. Analytical findings require contextual interpretation because blood, plasma, urine, hair, and postmortem specimens are not interchangeable, and a measured concentration alone cannot establish dose, time of administration, impairment, or contribution to death. Parent/metabolite patterns, specimen timing, stability, postmortem redistribution, tolerance, co-exposures, and therapeutic versus non-medical use must be considered.

Keywords: dissociative substances; forensic toxicology; analytical workflows; chromatography; mass spectrometry; toxicokinetics; new psychoactive substances (NPSs)

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Academic Editors: Ngee Sing Chong and Yong Foo Wong

Received: 6 September 2026
Revised: 16 October 2026
Accepted: 20 October 2026
Published: 26 October 2026

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1. Introduction

The historical development of surgical anesthesia sought agents capable of providing reliable analgesia and immobility while maintaining cardiovascular and respiratory stability. The synthesis of dissociative anesthetics in the mid-twentieth century introduced a unique pharmacological profile characterized by profound analgesia, amnesia, and a cataleptic state wherein sensory inputs are functionally uncoupled from conscious processing [1,2]. These clinical advantages facilitated operative and veterinary procedures without inducing the profound cardiorespiratory depression typically associated with halogenated volatile anesthetics or high-dose opioids.

However, the subjective psychological effects of these substances—including depersonalization, derealization, visual distortions, and perceptual indifference—have contributed to their non-medical use in recreational venues [3,4]. In unsupervised settings, the cognitive disorientation, motor incoordination, and sedation induced by dissociative substances significantly impair individual judgment and physical autonomy, leading to risks of accidental injury, acute behavioral agitation, and potential involvement in drug-facilitated crimes [5].

For this review, a 'dissociative substance' is defined operationally by its capacity, under specified dose and exposure conditions, to disrupt the integration of perception, cognition, bodily awareness, and environmental awareness. The term therefore describes a phenomenological toxicological effect rather than a uniform chemical class or a mechanism limited to NMDA-receptor antagonism. PCP and ketamine are prototypical dissociative anesthetics, and DXM is widely recognized as dissociative at supratherapeutic doses. Nitrous oxide and salvinorin A can produce dissociative phenomenology through distinct mechanisms. Memantine and amantadine were included as clinically used aminoadamantane NMDA-channel blockers for which psychotomimetic or dissociative effects are uncommon and strongly dose- and context-dependent. MK-801 was included only as an experimental comparator because of its importance in NMDA-antagonist research; it is not a routine human drug or a common forensic toxicant. This inclusive scope is intended to compare analytical consequences of mechanistically diverse agents, not to imply equivalent abuse liability, prevalence, or evidentiary significance.

This review evaluates eight primary dissociative substances across their chemical classification, pharmacological targets, toxicokinetics, and forensic detection strategies. By transitioning from a narrative descriptive format toward an evidence-calibrated comparative synthesis, this manuscript establishes practical analytical considerations across biological specimens, seized exhibits, and specialized research applications.

2. Literature-Search Strategy and Scope

A narrative literature search was conducted to identify peer-reviewed studies addressing the pharmacology, toxicokinetics, forensic significance, and analytical detection of the substances included in this review. PubMed, Scopus, Web of Science, and Google Scholar were searched for articles published from January 2015 to June 2026. The name of each substance was searched individually and in combination with relevant analytical terms, such as "LC-MS/MS," "GC-MS," "FTIR," "Raman spectroscopy," "SFC," "NMR," "XRD," "forensic toxicology," "biological matrix," "metabolite," and "toxicokinetics." Articles were selected according to their relevance to the review scope, scientific quality, and recency. Because the search strategy was developed and updated iteratively, no prospective systematic-review protocol, formal deduplication log, or PRISMA-style study-selection record was maintained. Thus, the precise numbers of records retrieved, excluded, and ultimately included cannot be reconstructed reliably.

Records were screened for direct relevance to the eight named substances and to pharmacology, toxicokinetics, analytical detection, or forensic interpretation. For comparative

analytical tables, preference was given to primary studies reporting the specimen or exhibit type, sample volume or mass, preparation procedure, target analytes, instrumentation, calibration model or range, sensitivity metric as defined by the original authors, validation characteristics, and intended application. Review articles and official standards were used for context but not as substitutes for primary method-performance data when a primary source was available. Studies lacking sufficiently verifiable methods or bibliographic information were excluded from quantitative method comparison. Because this was not a systematic review, selection was purposive rather than exhaustive.

3. Classification and Chemical Architecture of Dissociative Substances

Because the descriptor 'dissociative' denotes clinical and perceptual outcomes rather than chemical structure, dividing these xenobiotics into distinct functional and chemical classes is essential for meaningful toxicological and analytical evaluation:

1. Arylcyclohexylamines: These are structurally characterized by an aryl group attached to a cyclohexane ring carrying an amine nitrogen center. Prototypical representatives include phencyclidine (1-(1-phenylcyclohexyl)piperidine, PCP) and ketamine (2-(2-chlorophenyl)-2-(methylamino)cyclohexan-1-one). These compounds serve as templates for emerging designer analogues (e.g., 2-fluorodeschloroketamine [2-FDCK], methoxetamine [MXE], 3-methoxy-PCP [3-MeO-PCP]) [2,6].
2. Morphinan Dissociatives: Dextromethorphan (DXM; (+)-3-methoxy-N-methylmorphinan) is the dextrorotatory enantiomer of the methyl ether of levorphanol. While levomethorphan is a potent opioid receptor agonist, DXM does not exhibit significant mu-opioid activity but acts as an antitussive and, at elevated doses, a dissociative via its metabolite dextrorphan [7,8].
3. Volatile Inhalants: Nitrous oxide (N_2O; dinitrogen monoxide) is a low-molecular-weight inorganic gas possessing high volatility, low blood:gas solubility (partition coefficient 0.47), and rapid pulmonary uptake and elimination [9,10].
4. Kappa-Opioid Receptor Agonists: Salvia divinorum is a psychoactive mint endemic to Mexico whose primary active constituent is salvinorin A ((2S,4aR,6aR,7R,9S,10aS,10bR)-9-(acetyloxy)-2-(furan-3-yl)-6a,10b-dimethyl-4,10-dioxododecahydro-2H-benzo[f] isochromene-7-carboxylate). Unlike typical central nervous system xenobiotics, salvinorin A is a non-nitrogenous, lipophilic neoclerodane diterpenoid lacking basic amine properties [11].
5. Aminoadamantanes: These have symmetrical, cage-like tricyclic bridgehead amines including amantadine (adamantan-1-amine) and memantine (3,5-dimethyladamantan-1-amine). Developed and approved for neurodegenerative conditions (Parkinson's disease and Alzheimer's disease), these compounds act as low-affinity, uncompetitive NMDA channel blockers with negligible recreational misuse liability [12,13].
6. Experimental Research Compounds: Dizocilpine ((5R,10S)-(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine; MK-801) is a potent, non-competitive NMDA receptor open-channel antagonist. Due to marked psychotomimetic effects and preclinical neurotoxicity (vacuolization in cortical neurons), MK-801 was abandoned for human therapeutics and remains strictly a laboratory reference compound [14,15].

4. Mechanisms of Action and Toxicological Effects

The molecular pharmacology of dissociative substances involves diverse neurochemical pathways, ranging from open-channel ionotropic glutamate receptor blockade to G-protein-coupled opioid signaling and ion channel modulation.

For arylcyclohexylamines (PCP, ketamine), morphinans (dextrorphan), aminoadamantanes (memantine, amantadine), and dibenzocycloheptenes (MK-801), the primary shared

pharmacodynamic mechanism involves uncompetitive, open-channel antagonism at the N-methyl-D-aspartate (NMDA) receptor complex [1,12,16]. The NMDA receptor is a heterotetrameric ligand-gated cation channel (typically comprising GluN1 and GluN2 subunits) permeable to Ca^{2+} and Na^{+}. Uncompetitive antagonists bind selectively to a site located within the channel pore (the phencyclidine binding pocket), requiring prior channel activation by co-agonists (glutamate and glycine) for access [1,16]. Blockade of this pore attenuates excitatory calcium influx, disrupting synchronized corticothalamic neurotransmission and producing the sensory and cognitive dissociation characteristic of these agents [16].

In addition to generalized NMDA receptor blockade, several complementary neurobiological mechanisms have been proposed to explain specific clinical and toxicological manifestations. In preclinical models of depression, subanesthetic doses of ketamine are hypothesized to preferentially antagonize NMDA receptors located on GABAergic inhibitory interneurons within the prefrontal cortex [1,17]. The resulting disinhibition leads to a transient elevation in extracellular glutamate, secondary activation of postsynaptic AMPA receptors, and subsequent stimulation of brain-derived neurotrophic factor (BDNF) release and downstream mammalian target of rapamycin complex 1 (mTORC1) signaling [17,18]. However, clinical translation indicates that antidepressant response involves multifactorial pathways, including monoaminergic modulation and active metabolites such as (2R,6R)-hydroxynorketamine (HNK) [17,19].

At elevated or supratherapeutic concentrations, PCP and ketamine modulate dopaminergic transmission through indirect mechanisms, including inhibition of dopamine reuptake transporters and partial agonism at dopamine D2 receptors, which may contribute to acute behavioral agitation, paranoia, and psychotomimetic symptoms [5,16]. In contrast, salvinorin A exhibits a distinct pharmacodynamic profile. It is a potent and selective agonist at the kappa-opioid receptor rather than an NMDA-receptor antagonist, and available receptor-screening studies indicate little or no appreciable activity at most other tested molecular targets, including the mu-opioid receptor [20,21]. Preclinical studies indicate that salvinorin A-mediated kappa-opioid receptor activation reduces dopamine release in the dorsal striatum and nucleus accumbens. In controlled human studies, salvinorin A produced intense, dose-dependent dissociative effects characterized by elaborate visual phenomena, altered somatic and interoceptive sensations, disruption of body ownership, and detachment from external reality [22–24].

The mechanisms underlying nitrous oxide include low-affinity uncompetitive antagonism at NMDA receptors alongside activation of background two-pore domain potassium channels (TREK-1) and inhibition of nicotinic acetylcholine receptors [9]. Chronic, high-frequency inhalation of N_2O produces a recognized neurotoxicological complication: N_2O oxidizes the monovalent cobalt core of cob(I)alamin (vitamin B12), thereby inactivating the enzyme methionine synthase [9,10]. This disruption impairs the remethylation of homocysteine to methionine and arrests the synthesis of S-adenosylmethionine, leading to impaired myelin sheath maintenance and clinical subacute combined degeneration of the spinal cord (SCDSC) [10].

The comparative receptor pharmacology, characteristic clinical effects, and acute and chronic toxicological manifestations of the selected dissociative substances are summarized in Table 1.

Table 1. Comparative Receptor Pharmacology and Toxicological Manifestations of Dissociative Substances.

Substance	Chemical Class	Primary Molecular Target	Secondary/Proposed Targets	Intended/Therapeutic or Characteristic Effects	Acute Adverse Effects; Chronic Complications; Evidence Context	Ref.
Ketamine	Arylcyclohexylamine	NMDA receptor channel pore (uncompetitive antagonist)	AMPA activation (downstream), DAT/NET inhibition, D2 partial agonism	Analgesia, anesthesia, rapid antidepressant effects (subanesthetic)	Acute: emergence reactions, confusion, hypertension. Chronic/repeated exposure: ulcerative cystitis and cognitive effects	[17,18,25]
Phencyclidine (PCP)	Arylcyclohexylamine	NMDA receptor channel pore (uncompetitive antagonist)	Dopamine transporter inhibition, sigma receptor binding, D2 agonism	Analgesia, profound sensory dissociation, cataleptic immobility	Severe psychomotor agitation, paranoia, violent delirium, hyperthermia	[26–28]
Dextromethorphan (DXM)	Morphinan derivative	Low-affinity NMDA block (parent); high-affinity NMDA block (dextrorphan)	Sigma-1 receptor agonism, SERT inhibition, NET inhibition	Antitussive action (therapeutic doses); perceptual distortion (high doses)	Serotonin toxicity/syndrome, motor ataxia, tachycardia, psychotomimetic crises	[7,8,29]
Nitrous Oxide (N_2O)	Inorganic volatile gas	NMDA receptor inhibition; TREK-1 potassium channel activation	Inhibition of alpha-4/beta-2 nACh receptors; endogenous opioid release	Analgesia, mild sedation, anxiolysis, transient euphoria	Acute: hypoxia/asphyxial risk and impaired coordination. Repeated/substantial exposure: functional cobalamin inactivation and myeloneuropathy	[9,10]
Salvinorin A (Salvia)	Neoclerodane diterpene	Kappa-opioid receptor (KOR, Gi/o-coupled agonist)	Zero direct affinity for NMDA or classical monoamine receptors	Intense depersonalization, spatial disorientation, visual distortions	Acute dysphoria, profound perceptual panic, motor incapacitation	[11,30]
Memantine	Aminoadamantane	Low-to-moderate affinity uncompetitive NMDA antagonist	5-HT3 receptor antagonism, alpha-7 nACh receptor antagonism	Cognitive stabilization in Alzheimer's disease; neuroprotection	Dizziness, confusion, headache (therapeutic misuse potential negligible)	[12,13]
Amantadine	Aminoadamantane	Low-affinity uncompetitive NMDA channel blocker	Indirect dopamine release stimulation; dopamine reuptake inhibition	Antiparkinsonian symptom control; antiviral activity (historical)	Livedo reticularis, orthostatic hypotension, visual hallucinations (at high doses)	[12]
MK-801 (Dizocilpine)	Dibenzocycloheptene	High-affinity, uncompetitive NMDA receptor open-channel blocker	High-affinity binding inside the ionophore pore; non-selective sigma sites	Experimental anesthesia, potent anticonvulsant activity (preclinical)	Preclinical evidence: hyperlocomotion, behavioral toxicity, and Olney-type neuronal vacuolization; not established as routine human clinical toxicity	[14,15,31]

5. Pharmacokinetics, Metabolism, and Forensic Biomarkers

In forensic toxicology, an analytical result must be interpreted in relation to the specimen and case context. Whole-blood, plasma, serum, urine, oral-fluid, hair, and tissue concentrations are not interchangeable because partitioning, protein binding, metabolism, excretion, and collection timing differ. A blood concentration does not automatically correspond to a particular clinical effect, and overlap may occur among therapeutic, recreational, toxic, and fatal concentrations. Interpretation should consider parent drug and metabolites, dose and route, elapsed time, tolerance and chronic exposure, co-exposures, specimen stability, storage, analytical uncertainty, and, in death investigations, postmortem redistribution and the sampling site. Urine generally demonstrates prior exposure rather than contemporaneous impairment, while metabolite patterns may support ingestion but rarely establish an exact dose or time of use. The detection windows below are therefore approximate, context-specific ranges rather than universal cutoffs.

Ketamine is rapidly cleared from plasma (elimination half-life ~2 to 3 h) primarily via hepatic N-demethylation catalyzed by CYP2B6 and CYP3A4 to form norketamin [32]. Norketamine undergoes subsequent conversion to dehydronorketamine (DHNK) and hydroxynorketamine (HNK) isomers, which are conjugated and renally excreted [12]. While parent ketamine remains detectable in blood for approximately 12 to 24 h post-administration, its secondary metabolites (notably DHNK) provide extended detection windows in urine (typically 3 to 6 days). In keratinized matrices (scalp hair), parent ketamine and norketamine incorporate into the hair shaft, permitting retrospective detection for months [31].

Phencyclidine (PCP) exhibits substantial lipophilicity and a high apparent volume of distribution (~6 L/kg), resulting in extensive partitioning into adipose tissue [19,33]. Its plasma elimination half-life ranges from 18 to over 48 h. Hepatic clearance proceeds via oxidative hydroxylation to generate 4-phenyl-4-piperidinocyclohexanol (PPC) and 4-hydroxypiperidine derivatives [26]. In single acute exposures, PCP is detectable in urine for 3 to 7 days; however, in individuals with chronic, high-dose exposure, slow redistribution from lipid reservoirs, coupled with urinary pH-dependent reabsorption in the renal tubules, can extend urinary detectability of parent PCP and metabolites to several weeks [27].

Dextromethorphan (DXM) undergoes extensive first-pass metabolism mediated by polymorphic CYP2D6 via O-demethylation to produce dextrorphan, which is subsequently glucuronidated [7,29]. A secondary pathway mediated by CYP3A4 produces 3-methoxymorphinan. In extensive metabolizers, the plasma half-life of DXM is brief (2 to 4 h), whereas in poor metabolizers lacking functional CYP2D6 alleles, clearance is markedly impaired (half-life exceeding 20 h), resulting in prolonged systemic parent drug concentrations [29]. Dextrorphan and its glucuronide conjugates serve as essential urinary biomarkers in toxicology casework [34].

Nitrous oxide (N_2O) presents unique toxicokinetic characteristics. Following inhalation, it rapidly saturates systemic blood and distributes across the blood–brain barrier. Because N_2O is not significantly metabolized (<0.004%), it is eliminated almost entirely unchanged via pulmonary exhalation within minutes of cessation [9,10]. Consequently, detectability in blood is restricted to an exceptionally narrow post-exposure window (typically <1 to 2 h), requiring immediate sealed biological specimen collection without headspace to prevent volatilization [35,36].

Salvinorin A undergoes rapid enzymatic hydrolysis by blood and tissue carboxylesterases at the C-2 acetate position, generating the pharmacologically inactive metabolite salvinorin B [11,30]. The elimination half-life of salvinorin A is exceptionally short (approximately 50 to 75 min in plasma). In clinical and forensic specimens, parent

salvinorin A remains detectable in blood and oral fluid for only 1 to 4 h, and in urine for up to 12 to 24 h, making timely specimen acquisition critical [11,37].

Memantine and amantadine exhibit long terminal elimination half-lives (memantine: 60 to 100 h; amantadine: 12 to 18 h) with predominant renal excretion of the unchanged parent compound [12,38]. Their extended presence in urine and plasma facilitates routine confirmatory detection [32,39].

The pharmacokinetic characteristics and approximate, matrix-specific forensic detection windows of the selected dissociative substances are summarized in Table 2.

Table 2. Pharmacokinetic Parameters and Forensic Detection Windows of Dissociative Substances.

Substance	Common Exposure Routes	Plasma Elimination Half-Life (t1/2)	Principal Metabolites	Primary Excretion Route	Preferred Forensic Matrix	Approximate, Context-Specific Detection Window	Critical Preanalytical Limitations	Ref.
Ketamine	Insufflation, IV/IM, oral	2–3 h (parent ketamine)	Norketamine, DHNK, HNK (glucuronides)	Renal (~90% as metabolites)	Blood (acute); Urine; Hair	Blood: 12–24 h; Urine: 3–6 d; Hair: months	Rapid parent clearance; monitor DHNK/norketamine in urine	[19,40,41]
Phencyclidine (PCP)	Inhalation (smoking), oral, insufflation	18–48 h (variable with pH)	4-Phenyl-4-piperidinocyclohexanol (PPC)	Renal (variable with urinary pH)	Urine; Whole blood; Hair	Blood: 1–3 d; Urine: 3–7 d (acute), up to weeks (chronic)	Urinary pH shifts alter renal reabsorption; fat accumulation	[26,27,42]
Dextromethorphan (DXM)	Oral (syrup, tablets, powder)	2–4 h (EM); >20 h (PM)	Dextrorphan (active), 3-methoxymorphinan	Renal (largely as dextrorphan glucuronide)	Urine; Whole blood	Blood: 6–24 h; Urine: 1–3 d (longer in PM)	CYP2D6 polymorphism creates substantial inter-individual variance	[7,29,34]
Nitrous Oxide (N_2O)	Inhalation (balloons, chargers)	<5–15 min (pulmonary clearance)	Negligible biotransformation (<0.004%)	Pulmonary exhalation (>99.9% unchanged)	Whole blood (sealed); Lung tissue	Blood: <1–2 h; Postmortem lung: variable	Extreme volatility; require zero-headspace crimp-sealed vials	[9,10,35]
Salvinorin A	Inhalation (smoking/vaping), sublingual	50–75 min (plasma clearance)	Salvinorin B (inactive hydrolysis product)	Renal and biliary (as conjugates)	Urine; Whole blood; Oral fluid	Blood: 1–4 h; Urine: 12–24 h	Rapid esterase hydrolysis requires prompt collection/freezing	[11,30,37]
Memantine	Oral (therapeutic tablets/solution)	60–100 h (prolonged clearance)	Minor hydroxylated and glucuronidated forms	Renal (~50–60% unchanged)	Urine; Whole blood	Blood: 3–7 d; Urine: 7–14 d	Basic aliphatic amine requires pH adjustment in extraction	[38,43]
Amantadine	Oral (capsules, tablets)	12–18 h (elderly: 24–30 h)	Minor acetylated conjugates (~5–10%)	Renal (~90% unchanged parent)	Urine; Whole blood	Blood: 1–3 d; Urine: 3–7 d	Highly water-soluble; low extraction recovery if pH unadjusted	[32]
MK-801 (Dizocilpine)	Parenteral (research administration)	~2–4 h (rodent plasma)	Hydroxymethyl and carboxydizocilpine	Renal and biliary excretion	Biological fluids; Liver tissue	Case-dependent (postmortem data)	Rare clinical presentation; requires targeted reference library	[14,31,44]

6. Occurrence, Use Patterns, and Regulatory Frameworks

Understanding how dissociative substances enter forensic casework requires examining their approved therapeutic applications, patterns of recreational misuse, and prevailing jurisdictional controls. The regulatory classification of these substances reflects differing legal evaluations of medical utility and abuse liability. In the United States, control status is governed by the Controlled Substances Act (CSA, Title 21 United States Code) [45].

Regulatory status is jurisdiction-specific and was verified against official sources current to 11 October 2026. In the United States, ketamine is listed in Schedule III and phencyclidine (PCP) in Schedule II of the federal Controlled Substances Act schedules [45]. Nitrous oxide is not listed as a federally controlled substance; 21 CFR §184.1545 affirms food-grade nitrous oxide as GRAS for specified food uses under current good manufacturing practice, a status that should not be conflated with authorization for intoxicating use [46]. Dextromethorphan is regulated federally as an over-the-counter antitussive under the FDA monograph framework and is not federally scheduled; purchaser-age restrictions, where enacted, are state-specific and should not be summarized by an unsupported national count [47]. Neither Salvia divinorum nor salvinorin A is controlled under the federal CSA, although the DEA notes that some states control the plant or constituent [21]. Because state provisions differ in whether they regulate the plant, extracts, salvinorin A, possession, sale, or age of purchase, this review does not claim that more than 30 states impose equivalent prohibitions. International examples are also non-equivalent: nitrous oxide became a Class C drug throughout the United Kingdom on 8 November 2023, subject to regulations preserving legitimate access [48]. In Canada, Salvia divinorum and its preparations and derivatives are controlled under Schedule IV of the Controlled Drugs and Substances

Act framework [49]. These examples are illustrative rather than a comprehensive global legal survey.

The jurisdiction-specific regulatory classifications, approved uses, and legal controls applicable to the selected dissociative substances are summarized in Table 3.

Table 3. Jurisdictional Regulatory Frameworks and Legal Status of Dissociative Substances.

Substance	Verified US Federal Status	Approved/Recognized Use	Selected Non-US Comparison	Official Source Primary Regulatory Source
Ketamine	Schedule III, 21 CFR §1308.13	FDA-approved anesthetic; esketamine has an approved nasal-spray indication	National controls vary; do not infer international status from US scheduling	[45]
Phencyclidine (PCP)	Schedule II, 21 CFR §1308.12	No current FDA-approved human medical use identified in this review	Listed under international psychotropic-control materials; verify the current INCB Green List when making treaty-level claims	[45]
Dextromethorphan	Not listed in federal CSA schedules; OTC antitussive under FDA monograph framework	OTC cough suppressant when marketed in conformity with the applicable monograph	Retail age restrictions are jurisdiction-specific; no national state-count claim is made	[47]
Nitrous oxide	Not listed in federal CSA schedules; food use addressed by 21 CFR §184.1545	Food propellant/aerating agent under stated GRAS conditions; medical uses are regulated separately	United Kingdom: Class C drug from 8 November 2023, with legitimate-use provisions	[46,50]
Salvia divinorum/salvinorin A	Not controlled under the federal CSA as of the verification date	No approved medical use in the United States	Canada: controlled under Schedule IV framework. US state laws vary and are not reduced to a single count	[21,49]
Memantine	Not identified in federal CSA schedules; prescription drug	FDA-approved for moderate-to-severe dementia of the Alzheimer type	Prescription status and indications vary by jurisdiction	[13]
Amantadine	Not identified in federal CSA schedules; prescription drug	FDA labeling describes antiparkinsonian use; current product labeling should be consulted	Prescription status and indications vary by jurisdiction	[51]
MK-801 (dizocilpine)	Not identified in federal CSA schedules	No approved human or veterinary use identified; research compound	No broad international "unscheduled" claim is made without jurisdiction-specific verification	[14]

7. Forensic Analytical Methodologies and Identification Schemes

Seized-drug analysis and biological toxicology address different evidentiary questions and require separate analytical and interpretive frameworks. SWGDRUG recommendations apply primarily to the identification of seized materials and are not a general confirmation framework for xenobiotics in biological specimens [52]. Seized-material examination focuses on defensible substance identification and, when relevant, purity or form. Biological toxicology instead addresses screening, confirmation, quantification, and interpretation in a validated matrix, with attention to calibration, matrix effects, stability, metabolites, uncertainty, and case context. The SWGDRUG categories below are therefore used only for

seized-drug identification. Biological methods should follow the laboratory's applicable accreditation requirements and matrix-specific consensus or standards documents.

- Category A (maximum discriminatory capability): Infrared spectroscopy (FTIR), Raman spectroscopy, Nuclear Magnetic Resonance (NMR) spectroscopy, mass spectrometry (MS), and X-ray diffractometry (XRD).
- Category B (intermediate discriminatory capability): Gas chromatography (GC), liquid chromatography (LC), supercritical fluid chromatography (SFC), thin-layer chromatography (TLC), and capillary electrophoresis (CE).
- Category C (presumptive/screening capability): Colorimetric chemical tests, ultraviolet–visible spectrophotometry (UV-Vis), and immunoassay screening.

Under SWGDRUG recommendations, when a validated Category A technique is incorporated, the minimum identification scheme requires pairing with at least one other independent technique from Category A, B, or C. When a Category A technique is not used, a minimum of three independent and validated techniques must be employed, at least two of which must be Category B. Crucially, forensic identification differs between seized bulk materials and biological toxicology: seized drug chemistry focuses on qualitative identification and purity profiling of active ingredients, whereas biological toxicology requires sensitive, quantitative confirmation of parent drugs and metabolites within complex matrices subject to strict matrix-effect validation.

7.1. Bioanalytical Methods for Biological Specimens

In biological specimens (whole blood, plasma, urine, oral fluid, and keratinized matrices), LC-MS/MS is commonly used for targeted confirmation and quantification when a matrix-appropriate method has been validated. No universal sensitivity threshold applies to this heterogeneous group. Reported LODs and LOQs vary with analyte, matrix, sample amount, extraction, instrument configuration, calibration model, and the authors' definitions. In the cited studies, some targeted assays reach sub-ng/mL performance for selected analytes, whereas other methods report higher limits or use different units. LOD, LOQ or LLOQ, cutoff concentration, and calibration range are therefore presented as distinct metrics and should not be used interchangeably. Appropriate validation should address selectivity, calibration performance, precision, accuracy or bias, recovery, matrix effects, carryover, dilution integrity, stability, and, where applicable, measurement uncertainty.

Gas chromatography–mass spectrometry (GC-MS) with electron ionization provides highly reproducible, library-searchable fragmentation spectra (e.g., NIST, SWGDRUG). For thermally stable, sufficiently volatile analytes like PCP and DXM, GC-MS operating in full-scan or selected-ion monitoring (SIM) mode provides robust confirmatory analysis [34,42]. However, polar basic amines (ketamine, norketamine, amantadine) are prone to peak tailing on standard capillary columns unless subjected to chemical derivatization (e.g., acylation with heptafluorobutyric anhydride, HFBA) to improve chromatographic peak shape and volatility [53]. For nitrous oxide, headspace gas chromatography (HS-GC-MS) coupled with porous-layer open-tubular (PLOT) columns represents the primary viable analytical technique for blood and tissue analysis [35,36].

The validated bioanalytical methods used for the detection and quantification of dissociative substances in biological specimens are summarized in Table 4.

Table 4. Validated Bioanalytical Methods for Dissociative Substances in Biological Specimens.

Analytical Platform	Biological Matrix	Target Analyte(s)	Extraction & Sample Preparation	Instrumental Parameters & Mode	Analytical Sensitivity (LOD/LOQ)	Calibration Range	Validation Status & Applicability	Key Analytical Limitations	Ref.
LC-MS/MS (QqQ)	Human plasma	Ketamine, norketamine, DHNK, HNK	Protein precipitation (ACN) with deuterated ISTDs	C18 column; ESI(+)-MRM transitions	LOQ: 0.5–2.0 ng/mL	0.5–500 ng/mL	Fully validated bioanalytical method	Matrix effects require stable labeled ISTDs	[19]
LC-MS/MS (QqQ)	Human plasma	Amantadine	Liquid–liquid extraction (MTBE); no derivatization	C18 column; ESI(+)-MRM (m/z 152.1 → 135.1)	LOD: 0.18 ng/mL; LOQ: 0.50 ng/mL	0.5–1000 ng/mL	Validated pharmacokinetic bioassay	Basic pH extraction optimization required	[32]
LC-MS/MS (QqQ)	Human urine	PCP & multi-drug panel	Solid-phase extraction (mixed-mode SPE)	Reversed-phase LC-ESI(+)-MRM	LOD: 0.30 ng/mL	1.0–500 ng/mL	Validated clinical & forensic urine assay	Instrument maintenance from urine salts	[54]
LC-MS/MS (QqQ)	Human urine	Ketamine, PCP, psilocin, mitragynine	Enzymatic beta-glucuronidase hydrolysis + dilute	LC-ESI(+)-MRM with matrix-matched calibrators	LOD: 0.30 ng/mL	1.0–250 ng/mL	Validated forensic screening & confirmation	Dilution approach reduces sensitivity for trace levels	[55]
LC-MS/MS (QqQ)	Human urine	Ketamine and reported co-analytes/metabolites	SPE as described in the primary source	C18; positive electrospray ionization MRM	LOD: 1 ng/mL; LOQ: 5 ng/mL	50–1000 ng/mL	Validated urine method; not a postmortem blood method	Applicability is limited to the matrix and analytes validated in the source	[41]
UPLC-MS/MS (QqQ)	Human hair (20 mg)	36 PCP-type analogues	Decontamination, pulverization, methanolic extraction	Acquity UPLC BEH C18; ESI(+)-MRM	LOD: 0.25–2.0 pg/mg; LOQ: 0.5–5.0 pg/mg	0.5–500 pg/mg	Validated forensic hair analysis	Extensive sample preparation (18 h extraction)	[56]
GC-MS (EI, SIM)	Human hair (10 mg)	Ketamine & amphetamines	Decontamination, HCl/MeOH extraction, HFBA derivatization	HP-5MS (30 m); 70 eV EI, SIM mode	LOD: <0.10 ng/mg	0.5–40 ng/mg	Validated hair bioassay	Mandatory chemical derivatization step	[55]
GC-MS (EI)	Human urine (1.0 mL)	Ketamine, norketamine, DHNK	Alkaline LLE with ketamine-d4; direct injection	Capillary GC-EI-MS; SIM confirmation	LOD: 10 ng/mL	20–2000 ng/mL	Validated clinical & forensic screening	Lower sensitivity than modern LC-MS/MS	[57]
GC-MS (EI, SIM)	Plasma, urine & saliva	Salvinorin A (Salvia)	LLE (chloroform/IPA); 17α-methyltestosterone ISTD	HP-5MS column; 70 eV EI, SIM	LOD: 0.005 µg/mL; LOQ: 0.015 µg/mL	0.015–5.0 µg/mL	Validated pharmacokinetic bioassay	Narrow biological detection window (hours)	[37]
HS-GC-MS (PLOT)	Forensic whole blood	Nitrous oxide (N_2O)	Static headspace (500 µL blood) in crimp vial; Xe ISTD	HP-PLOT/Q (30 m × 0.32 mm); SIM mode (m/z 30, 44)	LOD: not reported; LOQ: 0.10 mL/L	0.10–10.0 mL/L	Validated forensic blood toxicology	Extreme volatility; zero vial headspace required	[36]
HS-GC-MS (PLOT)	Postmortem fluids	Nitrous oxide (N_2O)	Headspace incubation at 60 °C; fluorobenzene ISTD	5 Å Molecular Sieve & Porabond Q capillary	LOD: not reported; LOQ: 0.05 mL/L	0.05–5.0 mL/L	Forensic fatal intoxication confirmation	Specialized PLOT columns and gas standards	[35]

7.2. Analytical Methods for Seized Materials and Pharmaceutical Products

For seized powders, crystalline exhibits, and solid dosage forms, analytical priorities center on non-destructive screening, rapid identification, and purity quantitation [52]. As detailed in Table 5, portable attenuated total reflectance FTIR (ATR-FTIR) and handheld Raman spectroscopy provide rapid screening without chemical reagents [58,59]. Handheld Raman offers the specific practical advantage of interrogating suspected exhibits directly through transparent plastic baggies or glass vials, reducing direct chemical handling hazards for field personnel [59]. However, vibrational spectroscopy possesses limited capability for resolving target analytes present at low concentrations (<5–10% *w*/*w*) in complex mixtures or heavily cut exhibits, requiring laboratory confirmation via GC-MS, LC-UV, or LC-MS [52,58].

Table 5. Analytical Methods for Seized Drug Materials, Herbal Exhibits, and Pharmaceutical Products.

Analytical Platform	Sample Matrix/Exhibit	Target Analyte(s)	Sample Preparation & Extraction	Instrumental Parameters & Mode	Analytical Sensitivity (LOD/LOQ)	Key Analytical Capabilities	Primary Limitations	Ref.
Portable ATR-FTIR	Street powders & tablets	Ketamine & adulterants	Direct solid presentation to diamond ATR crystal	Mid-IR spectral acquisition (4000–400 cm^{-1})	LOD: ~5–10% *w*/*w* (matrix-dependent)	Rapid presumptive field screening (<1 min)	Poor sensitivity for minor active adulterants	[58]
Handheld Raman (785 nm)	Seized baggies & vials	Ketamine, cocaine, MDMA	Non-invasive laser interrogation through packaging	785 nm diode laser; spectral library matching	LOD: ~5% *w*/*w* (matrix-dependent)	Direct container penetration; reduces officer exposure	Fluorescence interference from colored diluents	[59]
LC-UV (DAD)	Dissolved seized exhibits	Ketamine class drugs	Methanol dissolution and 0.22 µm filtration	C18 column; isocratic elution, UV λ = 215 nm	LOD: 1.0 µg/mL; LOQ: 3.0 µg/mL	Quantitative purity profiling in drug checking	Lacks structural specificity for novel isomers	[60]
GC-FID & GC-MS	Seized designer exhibits	PCP analogues (POXP, PTHP)	Methanol extraction; retention index calculation	DB-35 (MS) & DB-5 (FID) capillary columns	LOD: not reported; LOQ: ~0.05 mg/mL	High-precision quantitation paired with EI confirmation	Requires authentic reference materials for retention index	[61]
DART-HRMS	Commercial herbal products	Salvinorin A (Salvia)	Rapid methanol swab presentation in heated plasma	Direct Analysis in Real Time coupled to Orbitrap HRMS	LOD: not reported; LOQ: 5.0 mg/L	High-throughput quantitation (<15 s per sample)	Matrix suppression; lack of chromatographic separation	[33]
Benchtop 1H-qNMR (43 MHz)	Seized night-time exhibits	Ketamine & illicit mixtures	Dissolution in DMSO-d6; no internal standard	Low-field permanent magnet NMR; chemometrics	LOD: ~1–2% *w*/*w* (qualitative threshold)	Simultaneous identification and purity quantification	Lower sensitivity compared to high-field NMR or MS	[62]
GC-FID & GC-MS	Bulk pharmaceutical tablets	Memantine hydrochloride	Methanolic extraction of pulverized tablets	DB-1701 & HP-5 columns; split injection	LOD: 1.98 µg/mL; LOQ: 5.98 µg/mL	Stability-indicating pharmaceutical assay	Non-biological; applies to bulk tablets	[39]
LC-UV (HPLC)	Nanoparticle formulations	Memantine hydrochloride	Pre-column derivatization with FMOC-Cl	C18 column; gradient elution, UV λ = 265 nm	LOD: 0.36 µg/mL; LOQ: 1.08 µg/mL	UV active tagging of non-chromophoric amine	Derivatization required; pharmaceutical matrix	[19]

In community drug checking and seized drug chemistry, LC-UV provides reliable, cost-effective quantitative profiling for active chromophoric substances such as ketamine (LOD ~1 µg/mL) [60]. However, non-chromophoric aminoadamantanes (memantine, amantadine) require pre-column derivatization (e.g., FMOC-Cl) to introduce a UV chromophore [38]. Gas chromatography coupled to flame ionization detection (GC-FID) paired with GC-MS provides quantitative determination and structural confirmation of designer phencyclidine analogues (e.g., POXP, PTHP) based on retention index matching and electron ionization mass spectra [61].

7.3. Specialized, Structural, Chiral, and Environmental Research Applications

Beyond routine bioanalysis and seized-drug casework, specialized platforms address stereochemical, structural, solid-state, and research questions. SFC is valuable for chiral or

isomeric separations but is not routinely available in many forensic toxicology laboratories. NMR and XRD can provide orthogonal structural information for sufficiently concentrated or crystalline material; they are generally supplementary methods for novel-compound characterization, seized exhibits, reference-material characterization, or research rather than routine biological toxicology. Their inclusion here should not be interpreted as a recommendation that every case requires these platforms.

Nuclear magnetic resonance (NMR) spectroscopy and X-ray diffraction (XRD) provide definitive Category A structural elucidation for novel psychoactive substances and solid-state materials [63,64]. While high-field NMR (400–600 MHz) affords structural characterization of emerging analogues without requiring an authentic target standard, its sensitivity is limited to the milligram-to-microgram scale, restricting its application to seized exhibits or concentrated extracts [63,65]. Single-crystal X-ray diffraction (SC-XRD) provided absolute stereochemical confirmation of the novel urinary ketamine analogue 2-fluorodeschloro-N-ethyl-ketamine (2-FDCNEK) [66], whereas powder XRD (PXRD) confirmed crystalline lattice integrity in pharmaceutical solid forms [67,68].

Specialized instrumental applications for the structural, chiral, and research characterization of dissociative substances are summarized in Table 6.

Table 6. Specialized Instrumental Applications for Structural, Chiral, and Research Characterization.

Analytical Platform	Sample Matrix/System	Target Analyte/Purpose	Sample Preparation & Conditions	Instrumental Parameters	Primary Analytical Outcome	Key Research Limitation	Ref.
Chiral SFC-SQD	Analytical standards	DXM vs. Levomethorphan (LVM)	Direct methanolic dissolution; no derivatization	Trefoil AMY1 (2.1 × 150 mm); $scCO_2$/MeOH + CHA	Baseline chiral resolution (LOD: 10 ng/mL)	Specialized chiral stationary phase	[69]
Chiral SFC-MS	Methanolic standards	Chiral ketamine metabolites (HNK/DHNK)	Dissolution in methanol; stored at −20 °C	Lux Amylose-2, i-Cellulose-5; $scCO_2$/MeOH gradient	Stereospecific baseline separation of enantiomers	Sub-ambient temperature control required	[70]
SFC-MS/MS	Environmental wastewater	Ketamine & emerging pharmaceuticals	Solid-phase extraction (Oasis HLB clean-up)	Chiral SFC coupled to triple quadrupole MS	Trace environmental quantitation (LOD: 33 ng/L)	Environmental monitoring; non-forensic casework	[71]
SFC-UV (Method study)	Alcoholic solutions	Nitrous oxide (hold-up volume marker)	Direct injection of dissolved N_2O in methanol	Spherisorb Silica, C18, BEH; $scCO_2$/MeOH mobile phase	Verification of N_2O as unretained dead-time tracer	Fundamental chromatography research application	[72]
Single-Crystal XRD	Purified urine extract	Ketamine analogue (2-FDCNEK)	Methanolic extraction followed by recrystallization	SC-XRD, crystal-to-detector 40 mm, 2θ scan 10–360°	Absolute stereochemical structural confirmation	Requires single high-quality crystal specimen	[66]
Powder XRD (PXRD)	Pure crystalline powder	Dextromethorphan HBr	Direct dry powder presentation; zero solvent prep	Scintillation detector, Cu-Kα, 2θ scan 5–50°	Crystallinity and inclusion complex confirmation	Cannot evaluate amorphous or dissolved matrices	[67]
Powder XRD + DSC	Authentic/counterfeit pills	Active pharmaceutical ingredients	Direct solid tablet presentation without extraction	Coupled PXRD phase diffraction + thermal calorimetry	Discrimination of authentic active APIs from counterfeits	Qualitative solid-phase screening; non-biological	[73]
1H-qNMR (600 MHz)	Postmortem blood/urine/hair	PCP & designer cathinones	Liquid extraction; dissolution in CD3CN and CD3OD	High-field 600 MHz 1H-NMR coupled with GC-MS/LC-MS	Definitive structural verification in fatal intoxication	Requires high analyte mass (~µg–mg); high cost	[65]

8. Comparative Evaluation of Forensic Analytical Platforms

To provide direct decision-oriented guidance for forensic practitioners, Table 7 compares the primary analytical platforms across analytical role, sensitivity, matrix versatility, and major operational limitations.

Table 7. Comparative Capabilities, Forensic Applicability, and Operational Limitations of Analytical Platforms.

Platform	SWGDRUG Category	Primary Forensic Role	Analytical Sensitivity	Selectivity/Structural Specificity	Preferred Matrices	Key Operational Limitations
LC-MS/MS (QqQ)	Category A (MS) + B (LC)	Targeted quantitative confirmation	High (sub-ng/mL to ng/mL)	High (retention time + multiple MRM ion transitions)	Whole blood, plasma, urine, oral fluid, hair	Requires certified standards; susceptible to matrix effects
LC-Q-TOF-MS	Category A (MS) + B (LC)	Non-targeted screening & unknown NPS	High (low ng/mL range)	Very High (accurate mass <5 ppm, isotopic ratios, MS/MS)	Blood, urine, seized novel designer exhibits	Higher instrumental cost; complex data processing pipelines
GC-MS (EI, SIM/Scan)	Category A (MS) + B (GC)	Confirmatory analysis & library search	Moderate-to-High (low ng/mL in SIM)	High (standard 70 eV reproducible fragmentation spectra)	Seized powders, blood, urine, hair (after extraction)	Polar amines require derivatization; thermal degradation risk
HS-GC-MS	Category A (MS) + B (GC)	Volatile gas detection & quantitation	High for gas phase (mL/L blood)	High (retention time + diagnostic EI fragments)	Whole blood (sealed zero-headspace), postmortem lung	Strict preanalytical seal requirements; specialized PLOT columns
LC-UV/HPLC-DAD	Category B (LC) + C (UV)	Screening & quantitation in drug checking	Moderate (~1 µg/mL)	Moderate (retention time + UV spectrum match)	Dissolved seized powders, pharmaceutical formulations	Insufficient sensitivity for blood; cannot resolve co-eluting isomers
SFC-MS	Category A (MS) + B (SFC)	Chiral separation & isomer resolution	High (ng/mL range)	Very High (chiral stationary phase + MS confirmation)	Stereoisomeric seized drugs, chiral metabolite extracts	Limited presence in routine casework; specialized methodology
ATR-FTIR	Category A (IR)	Non-destructive screening of bulk exhibits	Low (requires >5–10% *w*/*w*)	Moderate-to-High for pure compounds (infrared fingerprint)	Solid seized powders, bulk crystalline materials, tablets	Poor sensitivity for minor active adulterants; matrix masking
Handheld Raman	Category A (Raman)	Non-destructive field screening	Low (requires >5% *w*/*w*)	Moderate-to-High for pure solids (molecular vibrations)	Seized exhibits interrogated through transparent containers	Fluorescence emission from colored cuts can obscure signals
1H-qNMR	Category A (NMR)	Primary structural elucidation & purity	Low (µg to mg required)	Very High (independent primary structural elucidation)	Seized bulk exhibits, concentrated purified extracts	Low inherent sensitivity; high capital and cryogen operating costs
PXRD/SC-XRD	Category A (XRD)	Solid-state phase & crystalline analysis	Moderate for crystalline solids	Very High (crystal lattice unit cell dimensions)	Solid crystalline powders, polymorphs, counterfeit tablets	Inapplicable to amorphous solids, liquids, solutions, or volatile gases

Analytical performance values are method- and matrix-specific. LOD, LOQ/LLOQ, cutoff, and calibration range are distinct quantities and retain the definitions used by the cited primary studies. Cross-method comparisons must account for specimen type, sample amount, extraction, validation design, intended use, and unit conventions. SFC, NMR, and XRD entries describe specialized or supplementary applications unless otherwise indicated.

9. Forensic Decision Roadmap and Analytical Recommendations

Figure 1 is an illustrative, case-dependent framework rather than a prescriptive protocol. The appropriate strategy depends on the evidentiary question, specimen or exhibit type, collection history, expected analytes, available instrumentation, reference materials, applicable regulations, and the validation scope of the laboratory. An immunoassay is not necessarily the preferred first-line test for this chemically heterogeneous group; high-resolution MS screening does not by itself guarantee definitive identification; and preliminary GC-FID or LC-UV profiling is not mandatory before confirmation. Orthogonal or structural techniques should be selected only when they add information required by the case.

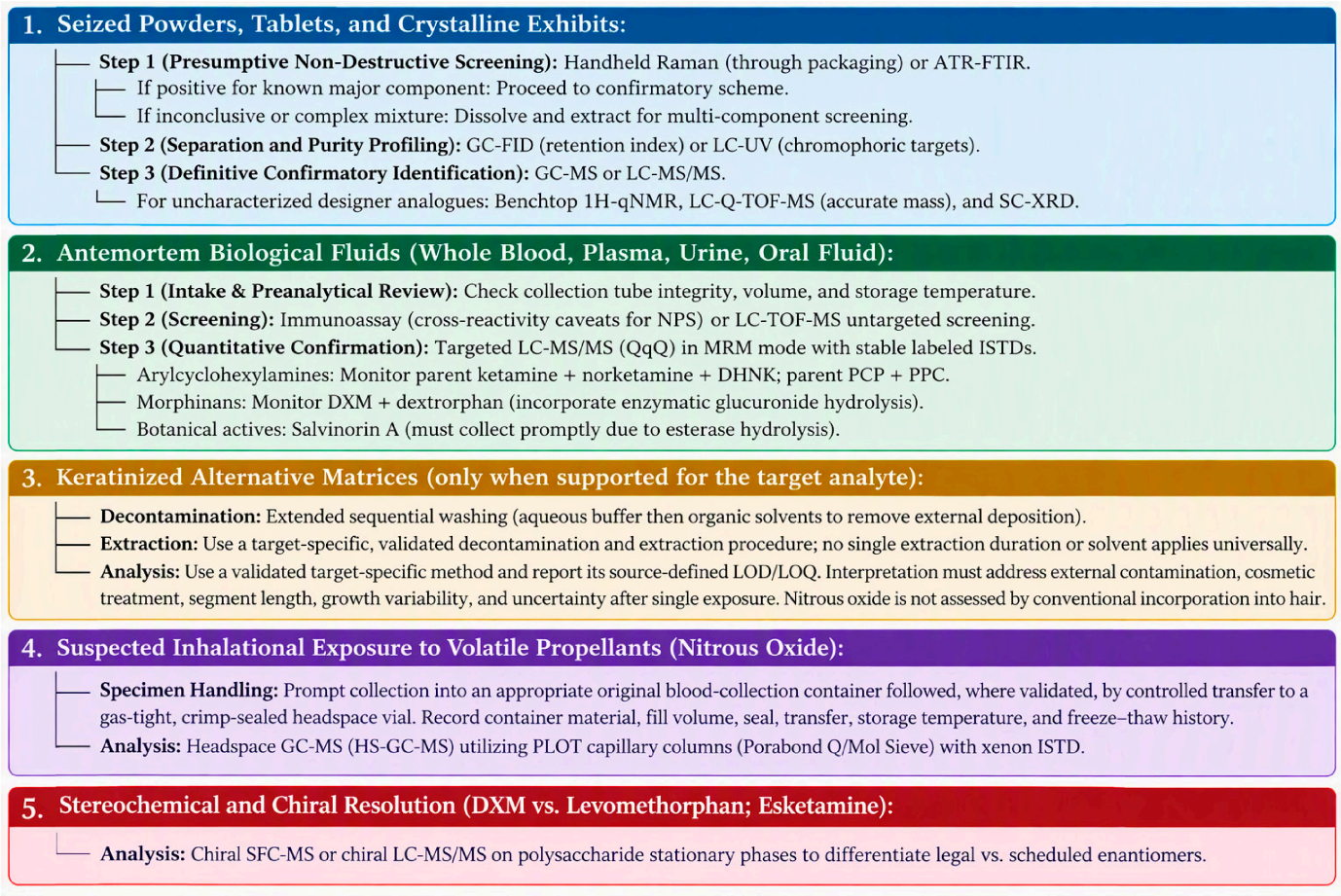


Figure 1. Strategic Analytical Decision Roadmap for Forensic Dissociative Investigations.

Practical Analytical Considerations: Critical practical insights derived from this roadmap include the following:

1. Derivatization Requirements: Uncompetitive aliphatic amines such as memantine and amantadine, as well as ketamine metabolites in GC workflows, benefit significantly from acylation (HFBA) or silylation to prevent column peak tailing [53]. Conversely, LC-MS/MS with electrospray ionization completely eliminates the need for chemical derivatization of polar amines [32].
2. Metabolite Targeting for Extended Detection: Due to rapid parent clearance (ketamine t1/2 ~2–3 h; salvinorin A t1/2 ~1 h), assays that measure only parent compounds incur severe false-negative risks. Monitoring dehydronorketamine (DHNK) in urine extends the diagnostic window to 3–6 days [19,41], while detecting dextrorphan glucuronide confirms true systemic metabolism of DXM [34].
3. Enantiomeric Discrimination: Classical achiral screening cannot differentiate over-the-counter antitussive dextromethorphan (DXM) from its federal Schedule II opioid isomer levomethorphan (LVM). Chiral SFC-MS or chiral LC-MS/MS is required when legal status depends on stereochemistry [69].

10. Discussion: Diagnostic Challenges, NPS Proliferation, and Operational Realities

The practical implementation of forensic detection schemes faces substantial technical and institutional challenges that require ongoing adaptation by toxicology laboratories.

Proliferation of Designer Arylcyclohexylamine Analogues: Clandestine synthesis of novel psychoactive substances (NPSs) frequently modifies the aromatic, cyclohexyl, or

alkylamino substituents of PCP and ketamine to create novel dissociative analogues (e.g., 2-FDCK, methoxetamine, 3-MeO-PCP, deschloroketamine) [2,74]. Because commercial screening immunoassays are configured with antibodies targeted against parent PCP or ketamine, they display variable and unpredictable cross-reactivity toward designer derivatives, creating risks of false-negative screening outcomes [74]. Similarly, targeted MRM workflows on triple-quadrupole LC-MS/MS platforms cannot detect newly introduced analogues whose precursor and product ion transitions are absent from the acquisition method. To overcome this limitation, forensic laboratories are increasingly incorporating untargeted high-resolution mass spectrometry (LC-Q-TOF-MS or Orbitrap) utilizing data-independent acquisition (DIA) coupled with continuously updated spectral repositories [61,74].

Narrow toxicokinetic windows and interpretive limitations: Several included substances undergo rapid clearance or are unstable or volatile. Delayed sampling can therefore produce a negative result despite prior exposure, particularly for nitrous oxide and salvinorin A. Hair or nails may extend the detection window for some stable organic analytes, but performance is compound-specific and cannot be generalized to nitrous oxide or to every dissociative substance. Incorporation, decontamination, extraction, sensitivity, cosmetic treatment, external contamination, and segment length all affect interpretation. A single exposure may not be reliably localized in time, and a negative segment does not exclude an isolated or recent event. Nitrous oxide requires prompt, gas-tight collection and validated headspace analysis; the original blood-collection container should be distinguished from the sealed vial used for headspace measurement, and transfer, fill volume, closure, storage temperature, and freeze–thaw effects should be controlled. Post-collection loss and delayed sampling substantially limit the meaning of negative findings.

Quality assurance and reporting: Biological toxicology and seized-drug laboratories should operate within their applicable accreditation scope and documented quality system. Chain of custody, method validation and verification, calibration, quality-control acceptance, technical review, and reporting requirements should be supported by the specific normative or discipline-specific documents adopted by the laboratory. ISO/IEC 17025 alone should not be cited as the sole source for every procedural detail. Rapid techniques such as DART-HRMS or benchtop NMR may support efficient screening or characterization of appropriate exhibits, but their role, validation status, and limitations must be stated and they do not automatically replace confirmatory workflows.

11. Conclusions and Future Directions

Dissociative drugs represent a structurally and pharmacologically diverse group of xenobiotics that share the phenomenological ability to uncouple conscious perception from environmental and somatic sensory inputs. While arylcyclohexylamines (PCP, ketamine), morphinans (DXM), and aminoadamantanes (memantine, amantadine) act primarily through uncompetitive blockade of the NMDA receptor channel, salvinorin A functions as a selective kappa-opioid receptor agonist, and nitrous oxide modulates NMDA receptors, potassium channels, and cobalamin-dependent enzymes.

Analytical workflows should be matched to the evidentiary question. In biological toxicology, LC-MS/MS and GC-MS are commonly used for matrix-validated screening, confirmation, and quantification of parent drugs and metabolites. In seized-material analysis, vibrational spectroscopy and chromatographic–mass-spectrometric methods may provide complementary identification. SFC, NMR, and XRD are specialized or supplementary tools for chiral, structural, or solid-state questions rather than routine requirements. Regardless of platform, the reported result must remain linked to the matrix, sampling time, analyte stability, parent–metabolite relationship, validation characteristics, and measurement limitations.

Future work should prioritize updated high-resolution mass-spectral libraries for emerging arylcyclohexylamines, substance-specific validation of alternative-matrix methods, and robust preanalytical studies for volatile or unstable analytes. Interpretation frameworks should better characterize concentration overlap, tolerance, chronic exposure, postmortem redistribution, degradation, and specimen-specific limitations. A single concentration generally cannot establish administered dose, exact time of intake, impairment, or causal contribution to death without clinical, investigative, pathological, and analytical context.

Author Contributions: Conceptualization, M.S.; methodology, writing—original draft preparation, S.C. (Stacey Cuyuche), S.M., A.V., E.L., K.S.H., S.C. (Sam Charlie) and S.S.; writing—review and editing, M.S.; supervision, M.S. All authors have read and agreed to the published version of the manuscript.

Funding: Work on this project was supported by the National Science Foundation IUSE-HIS program (award ID 2247157); the National Science Foundation Major Research Instrumentation (MRI) Program (award ID 2409248); and NIH Undergraduate Research Training Initiative for Student Enhancement (U-RISE) Program (award ID: 5T34GM149448-03). Any opinions, findings, and conclusions or recommendations expressed in this material are those of the author and do not necessarily reflect the views of the National Institutes of Health and National Science Foundation.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest.

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