N-Methyl-Cyclazodone: A Pharmacological and Toxicological Assessment of a Novel Psychoactive Stimulant

I. Introduction and Executive Summary

N-Methyl-Cyclazodone, commonly abbreviated as NMC, has emerged within the dynamic and largely unregulated landscape of novel psychoactive substances (NPS) as a compound of significant interest and concern.[1] Chemically classified as a derivative of Cyclazodone, a centrally-acting stimulant developed in the 1960s, NMC belongs to the oxazolidinone class of substances.[1] This chemical lineage places it in close structural relation to Pemoline, a former prescription medication for Attention-Deficit/Hyperactivity Disorder (ADHD) that was ultimately withdrawn from major global markets due to an association with severe, unpredictable, and sometimes fatal liver toxicity.[3]

The contemporary narrative surrounding N-Methyl-Cyclazodone is defined by a critical dichotomy. On one hand, it is discussed and distributed within online communities not primarily as a recreational euphoriant, but as a nootropic or "cognitive enhancer".[1] Users frequently report seeking the substance for the self-medication of conditions such as ADHD, leveraging its stimulant properties for functional purposes like improving focus and productivity.[7] This perception has fueled its popularity on internet forums and its sale by online vendors as an unscheduled "research chemical," a status that allows it to evade direct pharmaceutical and narcotic control regulations in many jurisdictions.[11]

On the other hand, a rigorous scientific assessment reveals a deeply concerning toxicological profile, inferred from its chemical ancestry and substantiated by the limited but alarming clinical data available. The very properties that make its parent analogue, Pemoline, a cautionary tale in pharmacology—namely, the risk of idiosyncratic hepatotoxicity—are presumed to be inherent to the oxazolidinone structure shared by NMC. This concern is not merely theoretical; it is echoed in user community discussions and is strongly suggested by

the findings from the only documented clinical case of severe NMC poisoning, which presented with evidence of acute liver injury alongside a life-threatening, multi-system toxidrome.[1]

This report provides an exhaustive analysis of N-Methyl-Cyclazodone based on available scientific literature, chemical data, regulatory information, and clinical reports. It aims to construct a comprehensive profile of the substance, clearly delineating between empirically verified data and scientifically inferred hypotheses regarding its pharmacology and toxicology.

The key findings of this assessment are as follows:

- **Chemical and Regulatory Status:** N-Methyl-Cyclazodone is an unscheduled research chemical, readily available for purchase online, creating a high-risk environment for uninformed, non-medical use.[1] Its legal status is ambiguous in many countries, often falling into a gray area not explicitly covered by existing narcotics legislation but potentially subject to broader analogue or psychoactive substance laws.[13]
- **Inferred Pharmacology:** The mechanism of action is hypothesized to be that of a potent central nervous system stimulant, primarily acting as a releasing agent and/or reuptake inhibitor of the catecholamine neurotransmitters dopamine and norepinephrine. Structure-activity relationship analysis suggests that the N-methylation of the parent compound, Cyclazodone, likely enhances its potency, central nervous system penetration, and abuse liability.[3]
- **Primary Toxicological Risk:** The most significant and alarming long-term risk associated with NMC is severe, idiosyncratic hepatotoxicity. This risk is directly inherited from its structural analogue Pemoline, which was withdrawn from the market after being linked to at least 21 cases of liver failure, 13 of which resulted in death or the need for liver transplantation.[6] Anecdotal user reports already reflect a community awareness of and concern for potential liver harm from NMC use.[1]
- **Acute Toxicity Profile:** A documented case of acute poisoning demonstrates that high-dose NMC use can induce a severe sympathomimetic toxidrome, characterized by dangerous cardiovascular effects (tachycardia, hypertension, cardiac conduction abnormalities), neurological toxicity (choreoathetosis), and rhabdomyolysis (muscle breakdown).[3]
- **Drug Interaction Potential:** There is a significant and likely underappreciated potential for dangerous drug-drug interactions. The metabolism of NMC is probably mediated by cytochrome P450 enzymes, and co-administration with common inhibitors (such as certain antidepressants) could dramatically increase its plasma concentration and precipitate severe toxicity, a factor believed to have contributed to the severity of the documented poisoning case.[3]

In summary, N-Methyl-Cyclazodone represents a significant public health concern. The perception of the substance as a benign nootropic is dangerously misaligned with its probable toxicological profile. The pattern of chronic, daily use often associated with cognitive

enhancement is precisely the pattern that may maximize the risk of inducing the most catastrophic adverse effect associated with its chemical class: irreversible liver failure.

II. Chemical Profile and Pharmacological Classification

A precise understanding of a novel psychoactive substance's chemical identity and properties is fundamental to any pharmacological or toxicological assessment. This section details the nomenclature, structure, physicochemical characteristics, and classification of N-Methyl-Cyclazodone.

2.1. Nomenclature, Structure, and Identifiers

N-Methyl-Cyclazodone is known by several names and chemical identifiers across scientific databases, commercial listings, and user communities. Establishing these identifiers is crucial for accurate literature searching and forensic analysis.

- **International Union of Pure and Applied Chemistry (IUPAC) Name:** 2-[cyclopropyl(methyl)amino]-5-phenyl-1,3-oxazol-4-one.[18]
- **Common Names and Abbreviations:** The most frequently used common name is N-Methyl-Cyclazodone. In online discussions and reports, it is commonly abbreviated as NMC.[1]
- **Developmental or Internal Codes:** The substance is also referenced by the code LD 4202.[11]
- **CAS Registry Number:** The unique identifier assigned by the Chemical Abstracts Service is 14461-92-8.[11]
- **Molecular Formula:** The empirical formula for the compound is C13H14N2O2.[11]
- **Molecular Weight:** The molar mass is approximately 230.26 g/mol.[11]
- **Chemical Structure:** The molecule consists of a central oxazolidinone ring substituted at the 5-position with a phenyl group and at the 2-position with an N-methyl-N-cyclopropylamino group.
    - **SMILES (Simplified Molecular-Input Line-Entry System):** CN(C1CC1)C2=NC(=O)C(O2)C3=CC=CC=C3.[18]
    - **InChIKey (International Chemical Identifier Key):** FFWGGFGJVZVGOW-UHFFFAOYSA-N.[18]

2.2. Physicochemical Properties

The physical and chemical properties of NMC are consistent with its sale as a bulk powder research chemical. These characteristics are important for its identification in forensic laboratories and for understanding its handling and stability.

- **Physical State:** At room temperature, N-Methyl-Cyclazodone is a solid, typically described as a white or off-white powder.[11]
- **Purity:** As a research chemical sold by various suppliers, its purity is often advertised as being high, with typical values reported as ≥98% or 99%.[7]
- **Melting Point:** The reported melting point is in the range of 94-95 °C.[19]
- **Solubility:** It is reported to be soluble in several organic solvents, including acetonitrile, dimethyl sulfoxide (DMSO), and methanol.[11] This information is primarily relevant for analytical preparation. Its solubility in water is not specified but is likely low, consistent with anecdotal reports of users mixing the powder in water for consumption.[3]
- **Stability:** Under appropriate storage conditions (cool and dry), the compound is reported to be stable for at least four years.[11]

2.3. Classification

N-Methyl-Cyclazodone can be classified according to several different systems, reflecting its chemical structure, pharmacological action, and regulatory status.

- **Chemical Class:** Structurally, NMC is a derivative of the oxazolidinone heterocyclic system, specifically a 5-phenyl-4-oxazolidinone.[3] This places it in the same broad chemical family as the stimulants Pemoline and Cyclazodone, as well as the antibiotic Linezolid, though their pharmacological targets differ significantly.
- **Pharmacological Class:** Based on its known effects and structural similarity to other compounds, its primary pharmacological classification is as a centrally-acting stimulant.[1]
- **Regulatory and Use Class:** In the context of public health and law enforcement, NMC is classified as a Novel Psychoactive Substance (NPS) or, more colloquially, a "research chemical".[1] This term denotes substances of abuse that are not controlled by international drug conventions but may pose a public health threat.[9] It is often marketed for "research and forensic applications" as a means to circumvent laws intended to regulate substances for human consumption.[11]

A consolidated summary of these properties is provided in Table 2.1.

Table 2.1: Chemical and Physical Properties of N-Methyl-Cyclazodone

Property	Value
IUPAC Name	2-[cyclopropyl(methyl)amino]-5-phenyl-1,3-oxazol-4-one [18]
Common Abbreviation	NMC [1]
CAS Number	14461-92-8 [11]
Molecular Formula	C13H14N2O2 [11]
Molecular Weight	230.26 g/mol [18]
Physical Appearance	White or off-white solid powder [11]
Melting Point	94-95 °C [19]
Solubility	Soluble in acetonitrile, DMSO, methanol [11]
Chemical Class	5-phenyl-4-oxazolidinone [3]
Pharmacological Class	Central Nervous System Stimulant [1]
Regulatory Class	Novel Psychoactive Substance (NPS) [3]

III. Inferred Pharmacodynamics: A Mechanistic Hypothesis

No formal, peer-reviewed pharmacodynamic studies on N-Methyl-Cyclazodone have been published. Therefore, its mechanism of action must be inferred through a careful examination of its structural analogues and the application of established principles of structure-activity

relationships (SAR). This section constructs a scientifically grounded hypothesis for how NMC exerts its effects on the central nervous system.

3.1. Extrapolation from Structural Analogues: Cyclazodone and Pemoline

The pharmacological foundation for understanding NMC is built upon the known properties of its closest relatives, Cyclazodone and Pemoline.

Cyclazodone: Developed by American Cyanamid in the 1960s, Cyclazodone is the direct parent compound of NMC.[4] Early patents and studies described it as a centrally-acting stimulant effective in reducing fatigue and potentially acting as an anorectic.[4] It was characterized as having a more favorable therapeutic index and lower toxicity compared to both amphetamine and Pemoline.[4] Crucially, it has been described specifically as a "centrally acting dopaminergic stimulant drug," pointing to the dopamine system as its primary site of action.[3]

Pemoline: Also a CNS stimulant from the same era, Pemoline was used clinically for decades to treat ADHD and narcolepsy.[6] Its mechanism of action is better characterized than that of Cyclazodone. Pemoline acts as a selective dopamine reuptake inhibitor and releasing agent.[6] Its relative selectivity for the dopamine system over the norepinephrine system is notable, as this results in minimal cardiovascular and sympathomimetic side effects compared to classical stimulants like amphetamine.[6] This profile of a potent, primarily dopaminergic agent with lesser effects on norepinephrine is a key characteristic of this oxazolidinone stimulant family.

3.2. Proposed Mechanism of Action for N-Methyl-Cyclazodone

Based on its direct structural lineage, N-Methyl-Cyclazodone is almost certainly a modulator of the brain's monoamine systems, with a primary focus on the catecholamines: dopamine (DA) and norepinephrine (NE).

- **Primary Molecular Targets:** The principal targets are the presynaptic plasma membrane transporters responsible for clearing neurotransmitters from the synapse: the dopamine transporter (DAT) and the norepinephrine transporter (NET).[15] Like many stimulants, NMC likely functions as a competitive substrate for these transporters. This leads to two primary effects:

1. **Reuptake Inhibition:** By binding to the transporters, NMC blocks the reuptake of DA and NE, causing their concentrations in the synaptic cleft to rise, thereby enhancing and prolonging their signaling.
2. **Transporter-Mediated Efflux (Release):** Many stimulant substrates, after being taken into the presynaptic neuron by the transporter, can induce a reversal of the transporter's function, causing it to actively pump DA and NE out of the neuron and into the synapse. This process, known as efflux or release, leads to a massive, non-vesicular increase in neurotransmitter levels.[24]

- **Secondary Molecular Targets:** In addition to its action at plasma membrane transporters, NMC may engage with intracellular targets common to other amphetamine-like stimulants:
  - **Vesicular Monoamine Transporter 2 (VMAT2):** NMC may inhibit VMAT2, the protein responsible for loading DA and NE into synaptic vesicles for storage. Inhibition of VMAT2 disrupts the sequestration of neurotransmitters, increasing their cytosolic concentration and making more available for release via transporter-mediated efflux.[24]
  - **Trace Amine-Associated Receptor 1 (TAAR1):** This intracellular G-protein coupled receptor is a key regulator of monoamine transporter function. Agonism at TAAR1 by stimulants like amphetamine triggers a phosphorylation cascade that promotes the efflux state of DAT and NET, further amplifying neurotransmitter release.[24] It is plausible that NMC also acts as a TAAR1 agonist.

3.3. The Impact of N-Methylation: A Structure-Activity Relationship Analysis

The defining structural difference between Cyclazodone and NMC is the addition of a methyl group to the nitrogen atom of the cyclopropylamino side chain. This seemingly minor modification is a common strategy in medicinal chemistry and clandestine drug synthesis, and it can have profound and predictable consequences on a stimulant's pharmacological profile.[25]

The N-methylation of a phenethylamine-type stimulant typically alters its properties in several key ways:

1. **Increased Potency:** N-methylation often significantly increases the potency of a stimulant. The classic example is the relationship between amphetamine and methamphetamine (N-methylamphetamine). Methamphetamine is considerably more potent and has more pronounced central effects than its non-methylated parent compound.[28] Following this principle, it is reasonable to hypothesize that N-Methyl-Cyclazodone is a more potent stimulant than Cyclazodone.

2. **Altered Transporter Selectivity:** The addition of the N-methyl group can change the molecule's relative affinity for the different monoamine transporters. Frequently, this modification enhances activity at the dopamine transporter (DAT) relative to the norepinephrine transporter (NET). This shift towards greater dopaminergic action often correlates with a more euphoric, reinforcing, and potentially more addictive psychoactive profile.[26]
3. **Increased Lipophilicity and CNS Penetration:** The methyl group is lipophilic (fat-soluble), which can enhance the molecule's ability to cross the blood-brain barrier.[27] This leads to a more rapid onset of action and a greater concentration of the drug in the brain, contributing to more intense central effects compared to the parent compound.
4. **Modified Metabolism:** The N-methyl group introduces a new site for metabolic attack, specifically N-demethylation. The clinical case report of NMC poisoning provides direct human evidence for this pathway, as the patient's urine contained Cyclazodone, the demethylated metabolite of NMC.[3] This metabolic conversion means that NMC effectively acts, in part, as a prodrug for Cyclazodone. This two-stage action—the initial effects of NMC itself followed by the sustained effects of its active metabolite, Cyclazodone—could result in a longer and more complex duration of action.

This SAR analysis leads to a critical conclusion regarding the substance's abuse potential. While Pemoline was classified as a Schedule IV substance in the U.S. and was found to have a low potential for self-administration in primate studies, likely due to its relatively mild and slow-acting profile, the same cannot be assumed for NMC.[6] The N-methylation that transforms Cyclazodone into NMC is analogous to the transformation of amphetamine into the far more potent and addictive methamphetamine. This suggests that NMC may possess a significantly higher abuse and dependence liability than its scheduled analogue, Pemoline, representing a hidden risk not immediately apparent from its oxazolidinone lineage alone.

Table 3.1: Comparative Pharmacological Profile of Oxazolidinone Stimulants

Feature	Pemoline	Cyclazodone	N-Methyl-Cyclazodone (Inferred)
Primary Mechanism	Dopamine Reuptake Inhibitor/Releaser [6]	Dopaminergic Stimulant [3]	Potent Dopamine & Norepinephrine Reuptake Inhibitor/Releaser
Key Neurotransmitter(s)	Primarily Dopamine [6]	Primarily Dopamine [3]	Dopamine > Norepinephrine

Abuse Potential	Low (Schedule IV) [6]	Unknown (Presumed Low-Moderate)	Moderate to High
Key Toxicological Concern	Idiosyncratic Hepatotoxicity [6]	Unknown (Presumed Hepatotoxicity)	Idiosyncratic Hepatotoxicity

IV. Human Use, Subjective Effects, and Prevalence

The use of N-Methyl-Cyclazodone is largely confined to a subculture of individuals seeking cognitive enhancement and self-medication, rather than mainstream recreational use. Its prevalence and effects profile are primarily understood through monitoring of online communities and anecdotal reports.

4.1. Context of Use: A Functional Stimulant and Nootropic

Unlike many NPS that are marketed as "legal highs" to mimic the euphoric effects of drugs like MDMA or cocaine, NMC occupies a different niche. It is predominantly discussed and marketed as a functional stimulant or nootropic—a so-called "smart drug".[1] The National Drug Early Warning System (NDEWS) noted a significant increase in its popularity in Subreddit discussions between the summer of 2021 and the summer of 2022.[2]

The primary motivation cited for its use is the self-medication of symptoms associated with Attention-Deficit/Hyperactivity Disorder (ADHD).[7] This aligns with the historical therapeutic application of its analogue, Pemoline, for the same condition.[6] Individuals may turn to unscheduled research chemicals like NMC due to difficulty accessing a formal diagnosis, dissatisfaction with prescription medications, a desire to avoid the stigma of a controlled substance prescription, or the belief that these substances offer a superior efficacy-to-side-effect ratio. This pattern of use is consistent with broader trends in self-medication with NPS for conditions like ADHD, anxiety, and depression.[9]

4.2. Anecdotal Effects Profile

Since there are no controlled clinical trials, the subjective effects of NMC are derived from user reports shared on internet forums.

- **Desired Effects:** The sought-after effects are typical of central nervous system stimulants and are consistent with its use as a nootropic. These include increased focus, enhanced concentration, heightened alertness, increased energy and motivation, and an overall improvement in cognitive performance and productivity.[15] Its parent compound, Cyclazodone, is anecdotally described as producing "mild euphoria" and having effects that are "milder than Adderall," suggesting that NMC likely produces a similar, albeit potentially more potent, subjective experience.[32]
- **Adverse Effects (User-Reported):** A striking feature of online discussions about NMC is the frequent and specific mention of potential liver harm.[1] This indicates a relatively high level of awareness within the user community about the hepatotoxic legacy of Pemoline. This concern is the most prominent adverse effect discussed. Other common stimulant-related side effects, such as insomnia, anxiety, increased heart rate, appetite suppression, and jitteriness, are also likely to occur but are less emphasized in the available materials compared to the fear of liver damage.

The "functional" use profile of NMC creates a particularly dangerous risk paradigm. Typical recreational stimulants are often used episodically, for example, on weekends. In contrast, substances used for cognitive enhancement or ADHD self-medication are often taken on a chronic, daily basis to maintain their effects for work, school, or daily functioning. The most severe risk associated with the oxazolidinone stimulant class, idiosyncratic hepatotoxicity, was observed in patients taking Pemoline therapeutically over long periods—often months or years.[6] Therefore, the very pattern of use for which NMC is most sought (regular, long-term administration) is precisely the pattern that maximizes the user's exposure and thus elevates the risk of developing the most catastrophic potential harm: delayed-onset, unpredictable, and potentially fatal liver failure. This creates a perilous situation where the perceived benefits of the drug directly encourage a behavior that significantly increases the likelihood of its most severe and irreversible toxic outcome.

V. Toxicology and Clinical Safety Assessment

The toxicological profile of N-Methyl-Cyclazodone is largely uncharacterized by formal studies. However, a single, detailed clinical case report of an acute overdose, combined with the extensive historical data on its analogue Pemoline, allows for a robust and deeply concerning safety assessment.

5.1. Documented Acute Toxicity: Analysis of a Clinical Case Report

The Center for Forensic Science Research and Education (CFSRE) published a case report that provides the only available empirical data on the acute toxicity of NMC in humans.[3] A meticulous analysis of this case is essential for understanding the potential for acute harm.

- **Patient History and Exposure:** The case involved a 38-year-old male who presented to the hospital for evaluation of uncontrollable body movements and palpitations. He reported self-treating a diagnosis of ADHD for five days with "pure" N-Methyl-Cyclazodone powder that he had purchased online. His total consumption was alarmingly high, estimated at approximately 5 grams over the five-day period, which he mixed in water. A critical confounding factor was his concurrent use of prescribed fluoxetine and aripiprazole for a diagnosis of bipolar disorder.[3]
- **Clinical Presentation and Toxidrome:** The patient exhibited a severe and complex toxidrome with features affecting multiple organ systems:
    - **Pronounced Sympathomimetic Toxicity:** He presented with classic signs of excessive catecholamine stimulation, including tachycardia (heart rate of 110 beats per minute), hypertension (blood pressure of 150/90 mmHg), tachypnea (respiratory rate of 24 breaths per minute), and mydriasis (dilated pupils).[3]
    - **Severe Neurological Toxicity:** The neurological presentation was particularly severe and unusual. The patient was inattentive, restless, and tremulous, but the most striking finding was the presence of **choreiform movements** affecting his entire body. These involuntary, jerky, "dance-like" movements are indicative of profound disruption of the basal ganglia, a brain region critical for motor control that is heavily modulated by dopamine. Choreoathetosis has been associated with toxicity from other dopaminergic agents, including Pemoline.[3]
    - **Significant Cardiotoxicity:** An electrocardiogram (ECG) revealed sinus tachycardia with a dangerously widened QRS interval (140 msec) and a prolonged QTc interval (526 msec). These findings indicate a slowing of intraventricular conduction and delayed ventricular repolarization, respectively, which place the patient at high risk for life-threatening cardiac arrhythmias such as Torsades de Pointes and ventricular fibrillation.[3]
- **Laboratory and Analytical Findings:**
    - **Rhabdomyolysis:** Blood tests revealed a markedly elevated creatine kinase (CK) level of 2954 U/L (normal range is typically below 200 U/L). This confirmed severe rhabdomyolysis, or the breakdown of skeletal muscle tissue, which can release myoglobin into the bloodstream and lead to acute kidney injury.[3]
    - **Hepatotoxicity:** The patient's alanine aminotransferase (ALT) level was elevated at 104 U/L (normal range is typically below 50 U/L). ALT is an enzyme concentrated in

liver cells, and its elevation in the blood is a specific marker of hepatocellular injury, providing direct evidence that NMC is acutely toxic to the liver.[3]

- **Confirmation of Metabolism:** Advanced laboratory testing (liquid chromatography-high resolution mass spectrometry) on the patient's urine confirmed the presence of Cyclazodone. This finding is of paramount importance as it verifies that N-demethylation is a major metabolic pathway for NMC in humans, with the parent drug being converted into its active, non-methylated analogue.[3]

5.2. The Specter of Hepatotoxicity: The Pemoline Precedent

The finding of acute liver injury in the NMC case is alarming, primarily because it resonates with the well-documented and tragic history of its analogue, Pemoline. The story of Pemoline is not merely a historical footnote; it serves as the most critical predictive model for the long-term risks of NMC.[6]

- **Nature of the Liver Injury:** Pemoline was found to cause rare but catastrophic acute liver failure. The injury was **idiosyncratic**, meaning it was unpredictable, not related to the dose taken, and only affected a small subset of susceptible individuals. It could manifest after months or even years of seemingly safe therapeutic use.[6]
- **Clinical Course and Mortality:** The onset could be insidious, with non-specific symptoms like malaise and anorexia, or it could be fulminant.[17] In some patients, the time from the first appearance of jaundice to complete liver failure was as short as one week.[6] The prognosis was grim; of at least 21 cases of liver failure linked to Pemoline reported to the FDA, 13 resulted in death or required an emergency liver transplant.[6]
- **Failure of Monitoring:** A particularly dangerous feature of Pemoline-induced hepatotoxicity was that routine monitoring of liver transaminase enzymes was not predictive of who would develop liver failure. Some patients who progressed to fulminant hepatic failure had shown normal liver enzyme levels on previous tests.[6]
- **Regulatory Action:** The risk, though rare, was deemed to have an unfavorable risk-to-benefit ratio. This led the FDA to add a black box warning in 1999, recommending frequent liver function monitoring.[6] Ultimately, due to the severity of the risk and poor adherence to monitoring guidelines, Pemoline was withdrawn from the market in the United Kingdom (1997), Canada (1999), and the United States (2005).[6]

The elevated ALT level in the single documented case of NMC poisoning serves as a stark warning. It strongly suggests that the oxazolidinone chemical scaffold, common to both Pemoline and NMC, retains its inherent potential to cause liver damage.

5.3. The Critical Role of Pharmacokinetics and Drug-Drug Interactions

A deeper analysis of the NMC poisoning case suggests that the severity of the toxicity was likely exacerbated by a significant drug-drug interaction. The patient was taking prescribed fluoxetine, a selective serotonin reuptake inhibitor (SSRI) antidepressant.[3] Fluoxetine and its primary active metabolite, norfluoxetine, are potent inhibitors of the cytochrome P450 enzyme CYP2D6. Many psychostimulants with a phenethylamine-like structure are metabolized and cleared from the body by this enzyme. It is highly probable that NMC and its metabolite Cyclazodone are also substrates for CYP2D6.

By inhibiting this crucial metabolic pathway, the patient's concurrent use of fluoxetine would have significantly impaired his ability to clear NMC from his system. This would lead to the drug and its active metabolite accumulating to toxic concentrations far higher and for a longer duration than would be expected from the ingested dose alone. This pharmacokinetic interaction likely turned a very high dose into a life-threatening one. This implies a significant public health risk, as many individuals who might self-medicate with NMC for conditions like ADHD or depression may also be prescribed common medications, like SSRIs, that inhibit CYP2D6. Consequently, even what might be considered a "moderate" dose of NMC could become dangerously toxic in the presence of such inhibitors.

5.4. Educated Guess on Long-Term Risks

Synthesizing the available evidence allows for an educated forecast of the long-term risks associated with chronic NMC use:

- **Hepatotoxicity:** This is unequivocally the primary long-term risk. Chronic users of NMC face a small but real possibility of developing idiosyncratic, fulminant liver failure, mirroring the risk profile of Pemoline. This risk is insidious because it is not dose-dependent and may not be preceded by warning signs or detectable by routine liver function tests until irreversible damage is underway.
- **Dependence and Withdrawal:** The N-methylation of the molecule likely enhances its dopaminergic potency and reinforcing effects, suggesting a higher potential for psychological dependence and addiction compared to Pemoline. Chronic use would likely lead to tolerance, requiring escalating doses to achieve the desired effect. Cessation after a period of regular use would be expected to produce a withdrawal syndrome characterized by fatigue, anhedonia (inability to feel pleasure), and severe depression.[33]
- **Cardiovascular Strain:** Chronic stimulation of the cardiovascular system, even at doses that do not feel acutely toxic, will place sustained strain on the heart and vasculature. This increases the long-term risk of developing hypertension, cardiomyopathy

(enlargement and weakening of the heart muscle), arrhythmias, and other adverse cardiac events.

VI. Global Legal and Regulatory Landscape

As a novel psychoactive substance, N-Methyl-Cyclazodone exists in a complex and often ambiguous legal landscape that varies significantly between countries. It is generally not explicitly scheduled in national drug control laws, allowing it to be sold online as a "research chemical." However, its sale and possession may be controlled under broader, more general legislation.

6.1. United States

In the United States, N-Methyl-Cyclazodone is not explicitly listed as a controlled substance in Schedules I through V of the Controlled Substances Act (CSA).[37] Its legal status is therefore primarily governed by the

Federal Analogue Act (21 U.S.C. § 813).

This act allows a substance to be treated as a Schedule I controlled substance for the purposes of criminal prosecution if three conditions are met:

1. It is intended for human consumption.
2. Its chemical structure is "substantially similar" to a substance already in Schedule I or Schedule II.
3. It has a stimulant, depressant, or hallucinogenic effect on the central nervous system that is "substantially similar to or greater than" that of a substance in Schedule I or Schedule II.[13]

The application of the Analogue Act to NMC is highly ambiguous. The primary challenge for a prosecutor would be the second criterion. NMC's closest *scheduled* analogue is Pemoline, which was a Schedule IV substance, not Schedule I or II.[3] This fact significantly weakens the argument that NMC should be treated as a Schedule I analogue. However, a prosecutor could potentially argue for structural similarity to other oxazoline-class stimulants that

are in Schedule I, such as 4-methylaminorex.[3] The outcome of such a case would be uncertain and would depend heavily on expert testimony regarding chemical and pharmacological

similarity. This legal gray area is precisely what allows vendors to sell NMC with a degree of perceived impunity.

6.2. European Union

The European Union does not have a single, harmonized law controlling all NPS. Instead, control is a patchwork of national laws, coordinated through the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and its EU Early Warning System (EWS).[41]

N-Methyl-Cyclazodone was formally notified to the EWS in 2018, as referenced in a subsequent 2021 notification for its analogue, Fenozolone.[21] This indicates that European authorities are aware of the substance and are monitoring it. However, being monitored by the EWS does not automatically make a substance illegal across the EU. Individual member states must take their own legislative action.

- **Germany:** The substance is not explicitly listed in the schedules of the German Narcotic Drugs Act (Betäubungsmittelgesetz - BtMG).[43] While it could potentially be regulated under laws governing medicinal products (Arzneimittelgesetz - AMG), this is a legally complex avenue.[45]
- **Other EU Nations:** The legal status varies widely. Some countries, like Ireland, have enacted broad "generic" or "analogue" laws that define controlled substances by their chemical structure or psychoactive effect, which would likely cover NMC.[46] Other nations require each substance to be individually named and scheduled, a time-consuming process that creates loopholes for new substances to appear on the market.[41]

6.3. United Kingdom

The legal status of NMC in the United Kingdom is more straightforward due to the **Psychoactive Substances Act 2016**. This act created a blanket ban on the production, supply, importation, and exportation of any substance capable of producing a psychoactive effect in a person who consumes it, with certain exemptions (e.g., alcohol, caffeine, licensed medicines). N-Methyl-Cyclazodone clearly falls under the scope of this act, making it effectively illegal to sell for human consumption. Furthermore, its analogue Pemoline was withdrawn from the UK market in 1997 due to the same liver toxicity concerns that plague NMC.[6]

6.4. Other Jurisdictions

- **Canada:** N-Methyl-Cyclazodone is not explicitly listed in the schedules of the Controlled Drugs and Substances Act (CDSA).[49] Its legality is therefore ambiguous. However, Health Canada possesses regulatory authority to control substances that pose a risk to public health, and could take action to restrict its importation and sale.[50]
- **Australia:** The importation and sale of NMC are almost certainly illegal in Australia. The Therapeutic Goods Administration (TGA) and the Australian Border Force (ABF) maintain very strict controls on unapproved medicines and psychoactive substances.[51] NMC would likely be classified as a "serious drug alternative" under import regulations and be prohibited.[51]

Table 6.1: Summary of International Legal Status of N-Methyl-Cyclazodone

Jurisdiction	Explicitly Scheduled?	Covered by Analogue/Blanket Law?	Key Legislation	Summary of Status
United States	No [37]	Ambiguous	Federal Analogue Act [13]	Unscheduled, but possession/sale could be prosecuted under the Analogue Act, though this would be challenging.
United Kingdom	No	Yes	Psychoactive Substances Act 2016	Effectively illegal to produce, supply, or import for human consumption.

European Union	No (EU-wide)	Varies by Member State	National Laws; EMCDDA Monitoring [21]	Monitored by the EMCDDA. Legal status depends on the specific laws of each member state (e.g., generic bans vs. individual scheduling).
Canada	No [49]	No	Controlled Drugs and Substances Act	Unscheduled and in a legal gray area, but subject to potential regulatory action by Health Canada.
Australia	No	Yes (Effectively)	Customs Act; Therapeutic Goods Act [51]	Unapproved therapeutic good and likely a "serious drug alternative," making importation and sale illegal.

VII. Synthesis, Conclusions, and Recommendations

N-Methyl-Cyclazodone exemplifies the complex public health challenges posed by the proliferation of novel psychoactive substances. It is a compound defined by a dangerous disconnect between its perceived utility within niche online communities and its probable,

severe toxicological risks inferred from robust scientific principles and historical precedent.

7.1. Summary of Knowns vs. Inferred Risks

A clear distinction must be drawn between the limited body of empirical evidence and the extensive, scientifically-grounded inferences that form the basis of this assessment.

- **What is Known:**
  - N-Methyl-Cyclazodone is a centrally-acting stimulant and a structural derivative of Cyclazodone, belonging to the oxazolidinone class.[1]
  - It is sold online as a "research chemical" and is used by individuals primarily as a nootropic or for the self-medication of ADHD symptoms.[9]
  - In humans, it is metabolized via N-demethylation to its parent compound, Cyclazodone.[3]
  - In at least one documented case, a high-dose overdose caused a severe, multi-system toxidrome including sympathomimetic overstimulation, cardiotoxicity, rhabdomyolysis, severe neurological dysfunction (choreoathetosis), and acute hepatocellular injury.[3]
- **What is Strongly Inferred:**
  - The primary mechanism of action involves the inhibition of reuptake and/or promotion of efflux of dopamine and norepinephrine via their respective transporters (DAT and NET).[6]
  - The most significant long-term risk of chronic use is idiosyncratic, unpredictable, and potentially fatal hepatotoxicity. This inference is based on the well-documented history of its close structural analogue, Pemoline, which was removed from the market for this exact reason.[6]
  - NMC has a high potential for dangerous pharmacokinetic interactions with drugs that inhibit cytochrome P450 enzymes (particularly CYP2D6), such as the SSRI antidepressant fluoxetine. Such interactions can lead to toxic accumulation of the drug.[3]
- **What is an Educated Guess:**
  - Based on structure-activity relationships observed in other stimulant classes, the N-methylation of Cyclazodone to form NMC likely increases its potency, its ability to cross the blood-brain barrier, and its affinity for the dopamine transporter.[27]
  - Consequently, NMC likely possesses a higher abuse liability and potential for psychological dependence than its parent compound, Cyclazodone, and its scheduled analogue, Pemoline.

7.2. Harm Reduction and Clinical Guidance

Given the severe potential for harm, the following guidance is offered for different populations.

- **For Potential Users:** The most effective harm reduction strategy is **avoidance**. The risk of unpredictable, severe liver failure is the paramount concern. This risk cannot be mitigated by dose adjustment, as it is idiosyncratic, and it cannot be reliably monitored for, as liver failure can occur rapidly and without prior warning signs on standard blood tests. The unknown purity and composition of products sold online, combined with the significant risk of drug-drug interactions with common prescription and over-the-counter medications, further amplify the dangers. The perceived cognitive benefits do not outweigh the potential for catastrophic and irreversible harm.
- **For Clinicians (Emergency Medicine, Toxicology):** In patients presenting with suspected NMC intoxication, clinicians should be prepared to manage a severe sympathomimetic toxidrome.
    - **Management:** Treatment is primarily supportive. Benzodiazepines (e.g., lorazepam, diazepam) are first-line therapy for agitation, seizures, tachycardia, and hypertension.
    - **Monitoring:** Critical monitoring should include continuous cardiac monitoring with ECG to assess for QRS widening and QTc prolongation, frequent vital signs, and core body temperature. Laboratory evaluation must include serum creatine kinase (CK) to assess for rhabdomyolysis, a comprehensive metabolic panel to check renal function and electrolytes, and liver function tests (ALT, AST) to screen for hepatic injury.
    - **Medication History:** A thorough medication history is essential to identify potential interacting drugs, especially known inhibitors of CYP2D6 (e.g., fluoxetine, paroxetine, bupropion). The presence of such an inhibitor should heighten suspicion for severe, prolonged toxicity.

7.3. Imperatives for Future Research

The significant knowledge gaps surrounding N-Methyl-Cyclazodone represent a public health vulnerability. There is an urgent need for formal scientific investigation to characterize its risks definitively.

- ***In Vitro* Pharmacological Profiling:** Studies are required to determine the binding affinities (Ki) and functional activities (e.g., reuptake inhibition IC50, neurotransmitter release) of NMC and Cyclazodone at human DAT, NET, and SERT. This would confirm the precise mechanism of action and selectivity profile.

- **Metabolism and Pharmacokinetic Studies:** *In vitro* studies using human liver microsomes are needed to identify the specific cytochrome P450 isoenzymes responsible for the metabolism of NMC. This would confirm the suspected role of CYP2D6 and identify other potential drug-drug interactions.
- **Preclinical Animal Toxicology:** Animal studies are essential to formally assess the substance's acute toxicity (LD50), abuse liability (e.g., via conditioned place preference or self-administration paradigms), and, most critically, its potential for hepatotoxicity. Sub-chronic and chronic dosing studies in rodent models would be necessary to investigate whether NMC induces the same type of idiosyncratic liver injury seen with Pemoline.

Until such research is conducted, N-Methyl-Cyclazodone should be considered a substance with an unknown but likely unfavorable risk-benefit profile, carrying a significant potential for severe acute toxicity and life-threatening long-term harm.

Works cited

1. Methamphetamine-related 911 EMS responses per 10k population, June 2022, accessed on August 21, 2025, https://ndews.org/wordpress/files/2024/03/NDEWS-Weekly-Briefing-Issue-98.pdf
2. N-methyl-cyclazodone - National Drug Early Warning System (NDEWS), accessed on August 21, 2025, https://ndews.org/wordpress/files/2023/04/8.19.22.pdf
3. Toxicity from the NPS N-Methyl-Cyclazodone with Laboratory Confirmation - A Dance Befitting St. Vitus, accessed on August 21, 2025, https://www.cfsre.org/resources/presentations/toxicity-from-the-nps-n-methyl-cyclazodone-with-laboratory-confirmation-a-dance-befitting-st-vitus
4. Cyclazodone - Wikipedia, accessed on August 21, 2025, https://en.wikipedia.org/wiki/Cyclazodone
5. Cyclazodone, accessed on August 21, 2025, http://medbox.iiab.me/kiwix/wikipedia_en_medicine_2019-12/A/Cyclazodone
6. Pemoline - Wikipedia, accessed on August 21, 2025, https://en.wikipedia.org/wiki/Pemoline
7. N-Methyl-Cyclazodone - ChemicalBook, accessed on August 21, 2025, https://www.chemicalbook.com/ChemicalProductProperty_EN_CB513772342.htm
8. N-Methyl-Cyclazodone CAS#: - ChemicalBook, accessed on August 21, 2025, https://m.chemicalbook.com/ProductChemicalPropertiesCB513772342_EN.htm
9. (PDF) Self-medication with Novel Psychoactive Substances (NPS): a Systematic Review, accessed on August 21, 2025, https://www.researchgate.net/publication/375997443_Self-medication_with_Novel_Psychoactive_Substances_NPS_a_Systematic_Review
10. N-Methyl-Cyclazodone - ChemicalBook, accessed on August 21, 2025, https://amp.chemicalbook.com/ChemicalProductProperty_EN_CB513772342.htm
11. N-methyl Cyclazodone (CAS 14461-92-8) - Cayman Chemical, accessed on August 21, 2025, https://www.caymanchem.com/product/27947/n-methyl-cyclazodone

12. N-methyl Cyclazodone | CAS NO.:14461-92-8 | GlpBio, accessed on August 21, 2025, https://www.glpbio.com/n-methyl-cyclazodone.html
13. Orange Book - List of Controlled Substances and Regulated Chemicals, accessed on August 21, 2025, https://www.deadiversion.usdoj.gov/schedules/orangebook/orangebook.pdf
14. STATEMENT OF JOSEPH T. RANNAZZISI DEPUTY ASSISTANT ADMINISTRATOR OFFICE OF DIVERSION CONTROL DRUG ENFORCEMENT ADMINISTRATION BE - DEA.gov, accessed on August 21, 2025, https://www.dea.gov/sites/default/files/pr/speeches-testimony/2013t/092513t.pdf
15. Stimulants - StatPearls - NCBI Bookshelf, accessed on August 21, 2025, https://www.ncbi.nlm.nih.gov/books/NBK539896/
16. Pemoline alters dopamine modulation of synaptic responses of neostriatal neurons in vitro, accessed on August 21, 2025, https://pubmed.ncbi.nlm.nih.gov/9445087/
17. Cylert (Pemoline): Side Effects, Uses, Dosage, Interactions, Warnings - RxList, accessed on August 21, 2025, https://www.rxlist.com/cylert-drug.htm
18. N-Methylcyclazodone | C13H14N2O2 | CID 156614124 - PubChem, accessed on August 21, 2025, https://pubchem.ncbi.nlm.nih.gov/compound/N-Methylcyclazodone
19. N-Methyl-Cyclazodone - IndiaMART, accessed on August 21, 2025, https://www.indiamart.com/proddetail/n-methyl-cyclazodone-26525929962.html
20. N-methyl Cyclazodone - Cayman Chemical Forensics - Cambridge Bioscience, accessed on August 21, 2025, https://www.bioscience.co.uk/product~1357210
21. EU EARLY WARNING SYSTEM FORMAL NOTIFICATION, accessed on August 21, 2025, https://workpage.ews-nfp.bg/wp-content/uploads/2023/11/EU-EWS-RCS-FN-2021-0045_Fenozolone-1.pdf
22. What are NPS? - United Nations Office on Drugs and Crime, accessed on August 21, 2025, https://www.unodc.org/LSS/Page/NPS
23. Pemoline – Knowledge and References - Taylor & Francis, accessed on August 21, 2025, https://taylorandfrancis.com/knowledge/Medicine_and_healthcare/Pharmaceutical_medicine/Pemoline/
24. Monoamine releasing agent, accessed on August 21, 2025, http://medbox.iiab.me/kiwix/wikipedia_en_medicine_2019-12/A/Monoamine_releasing_agent
25. Substituted phenethylamine - Wikipedia, accessed on August 21, 2025, https://en.wikipedia.org/wiki/Substituted_phenethylamine
26. Structure-Activity Relationships of MDMA-Like Substances - CiteSeerX, accessed on August 21, 2025, https://citeseerx.ist.psu.edu/document?repid=rep1&type=pdf&doi=9b7361c2422e5edb81849ad2dd023052438ec2f1
27. (PDF) Structure-Activity Relationships of Synthetic Cathinones - ResearchGate, accessed on August 21, 2025, https://www.researchgate.net/publication/309905189_Structure-Activity_Relation

ships_of_Synthetic_Cathinones
28. Methamphetamine - Wikipedia, accessed on August 21, 2025, https://en.wikipedia.org/wiki/Methamphetamine
29. Amphetamine - Wikipedia, accessed on August 21, 2025, https://en.wikipedia.org/wiki/Amphetamine
30. Pemoline | C9H8N2O2 | CID 4723 - PubChem, accessed on August 21, 2025, https://pubchem.ncbi.nlm.nih.gov/compound/Pemoline
31. Prescription stimulants in individuals with and without attention deficit hyperactivity disorder: misuse, cognitive impact, and adverse effects - PMC, accessed on August 21, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC3489818/
32. Alert from the NDEWS Web Monitoring Team: Online mentions of Cyclazodone, accessed on August 21, 2025, https://ndews.org/wordpress/files/2022/06/2.18.22.pdf
33. Pemoline (oral route) - Side effects & dosage - Mayo Clinic, accessed on August 21, 2025, https://www.mayoclinic.org/drugs-supplements/pemoline-oral-route/description/drg-20068359
34. Pemoline hepatotoxicity in children - PubMed, accessed on August 21, 2025, https://pubmed.ncbi.nlm.nih.gov/9602211/
35. Hepatotoxicity due to pemoline (Cylert): a report of two cases - PubMed, accessed on August 21, 2025, https://pubmed.ncbi.nlm.nih.gov/2303976/
36. Abbott Laboratories Pharmaceutical Products Division; Withdrawal of Approval of New Drug Applications for CYLERT (Pemoline) Tablets, 18.75 Milligrams, 37.5 Milligrams, and 75 Milligrams, and CYLERT (Pemoline) Chewable Tablets, 37.5 Milligrams - Federal Register, accessed on August 21, 2025, https://www.federalregister.gov/documents/2023/05/23/2023-10924/abbott-laboratories-pharmaceutical-products-division-withdrawal-of-approval-of-new-drug-applications
37. Controlled Substances - Alphabetical Order, accessed on August 21, 2025, https://www.deadiversion.usdoj.gov/schedules/orangebook/c_cs_alpha.pdf
38. Controlled Substance by DEA Code Number, accessed on August 21, 2025, https://www.deadiversion.usdoj.gov/schedules/orangebook/d_cs_drugcode.pdf
39. 21 U.S. Code § 812 - Schedules of controlled substances - Law.Cornell.Edu, accessed on August 21, 2025, https://www.law.cornell.edu/uscode/text/21/812
40. Are New Psychoactive Substances (NPS) Illegal in the United States?, accessed on August 21, 2025, https://www.egattorneys.com/psychoactive-substances
41. New psychoactive substances in Europe - Synthetic Drug Strategy, accessed on August 21, 2025, https://syntheticdrugs.unodc.org/uploads/syntheticdrugs/res/library/legal_html/New_Psychoactive_Substances_in_Europe.pdf
42. Novel psychoactive substances and legislative harmonization in Europe: addressing a extremely elusive public health threat, accessed on August 21, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC9987496/
43. Drugs controlled by the German Narcotic Drugs Act - Wikipedia, accessed on August 21, 2025,

https://en.wikipedia.org/wiki/Drugs_controlled_by_the_German_Narcotic_Drugs_Act
44. Drug Laws/Individual Listing for GERMANY - Details, accessed on August 21, 2025, https://www.unodc.org/LSS/Country/DetailsLegalSystem?code=DLIL&country=DE
45. Customs online - Medicinal products and narcotics - Zoll, accessed on August 21, 2025, https://www.zoll.de/EN/Private-individuals/Travel/Entering-Germany/Restrictions/Medicinal-products-and-narcotics/medicinal-products-and-narcotics_node.html
46. Perspectives on drugs: legal approaches to controlling new psychoactive substances, accessed on August 21, 2025, https://www.euda.europa.eu/topics/pods/controlling-new-psychoactive-substances_en
47. Legal approaches to controlling new psychoactive substances, accessed on August 21, 2025, https://www.drugsandalcohol.ie/21975/1/Legal.pdf
48. Petition to Remove the Attention Deficit Drug Pemoline (Cylert) from the Market, accessed on August 21, 2025, https://www.citizen.org/article/petition-to-remove-the-attention-deficit-drug-pemoline-cylert-from-the-market/
49. Controlled Drugs and Substances Act (SC 1996, c. 19) - Laws.justice.gc.ca, accessed on August 21, 2025, https://laws-lois.justice.gc.ca/eng/acts/c-38.8/page-9.html
50. Exemptions from provisions of the Controlled Drugs and Substances Act - Canada.ca, accessed on August 21, 2025, https://www.canada.ca/en/health-canada/services/health-concerns/controlled-substances-precursor-chemicals/exemptions.html
51. Prohibited medicines and substances - Australian Border Force, accessed on August 21, 2025, https://www.abf.gov.au/importing-exporting-and-manufacturing/prohibited-goods/categories/drugs-medicines-and-therapeutic-substances
52. Change to classification of psilocybin and MDMA to enable prescribing by authorised psychiatrists | Therapeutic Goods Administration (TGA), accessed on August 21, 2025, https://www.tga.gov.au/news/media-releases/change-classification-psilocybin-and-mdma-enable-prescribing-authorised-psychiatrists