



The Abuse Potential of 7-Hydroxymitragynine (7-OH) According to the 8 Factors of the Controlled Substances Act

Developed for Submission to the Drug
Enforcement Administration (DEA), Food
and Drug Administration (FDA), and
National Institute on Drug Abuse (NIDA)

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List of Abbreviations

Abbreviation	Definition
B-arrestin-2	Beta (β)-arrestin-2
7-OH (7-OH-MG, 7-OH-MIT)	7-hydroxymitragynine
8-FA	8-Factor Analysis
CAMU	Commonly Accepted for Medical Use
CNS	Central nervous system
CPP	Conditioned place preference
CSA	Controlled Substances Act
CYP	Cytochrome P450 (i.e., 3A, 2D6, 3A4)
DAWN	Drug Abuse Warning Network
DEA	Drug Enforcement Agency
DHHS	Department of Health and Human Services
DOJ	Department of Justice
DOR	Delta (δ)-opioid receptor
ECDD	World Health Organization's Expert Committee on Drug Dependence
FAERS	Food and Drug Administration Adverse Event Reporting System
FDA	Food and Drug Administration
GI	Gastrointestinal
IC ₅₀	Half-maximal inhibitory concentration
ICSS	Intracranial self-stimulation
IP	intraperitoneal
IQR	Interquartile range
IV	intravenous
K _i	Inhibitor constant
KOR	Kappa (κ)-opioid receptor
LSD	Lysergic acid diethylamide
MOR	Mu (μ)-opioid receptors
NDIN	New Dietary Ingredient Notification
NFLIS	National Forensic Laboratory Information System
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
NFLIS	National Forensic Laboratory Information System
NPDS	National Poison Data System
NSDUH	National Survey on Drug Use and Health
PO	Per oral
TEDS	Treatment Episodes Data Set
UGT	UDP-glucuronosyltransferase (i.e., UGT1A1, UGT1A3, UGT1A9)
UNODC	United Nations Office on Drugs and Crime
U.S.	United States

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1 Introduction

On July 29, 2025, the United States (U.S.) Food and Drug Administration (FDA) presented its assessment of a potential “novel, emerging public health threat”, 7-hydroxymitragynine (also known as 7-OH), a psychoactive substance that naturally occurs as a minor constituent of the kratom plant (*Mitragyna speciosa*) and also forms in the body as a metabolite of mitragynine, the plant's primary alkaloid. This assessment, shared as a news release on the FDA website (FDA, 2025a), was based on epidemiological findings and scientific data on toxicological concerns. FDA's release linked to a summary scientific evaluation developed by FDA scientists titled “Assessment of the Scientific Data and Toxicological Concerns Around an Emerging Opioid Threat” (Reissig et al., 2025), a slide set titled “Preventing the Next Wave of the Opioid Epidemic: What You Need to Know about 7-OH” (FDA, 2025b), and a Dear Colleagues letter by Commissioner Dr. Marty Makary (2025). Additionally, the Secretary of Health and Human Services, Robert F. Kennedy, Jr., hosted a press conference described as “measures to safeguard American public from dangerous opioid 7-OH (DHHS, 2025b). Participants included Secretary Kennedy, Department of Health and Human Services (DHHS) Deputy Secretary Jim O'Neill, FDA Commissioner Dr. Marty Makary, U.S. Senator Markwayne Mullin (R-OK), and Melody Woolf (chronic pain survivor) (DHHS, 2025a).

These scientific analyses and announcements summarized FDA's findings that 7-OH binds to morphine opioid receptors (also referred to as “mu (μ)- opioid receptors or MOR”) with potentially strong effects similar to those that can be produced by morphine and other classical opioids. Of particular concern to FDA is the increasing proliferation of products that contain highly concentrated, often semi-synthetically derived 7-OH. These novel products deliver significantly higher levels of 7-OH than occur naturally or are found in traditional kratom leaf products. In its July 29, 2025 media release FDA cites evidence from key studies and assays typically considered in drug scheduling determinations, including rewarding effects in animal studies, physical dependence and withdrawal symptoms, respiratory depression (at least when administered intravenously), and effects in animals generalized to morphine.

Additionally, FDA cites clinical presentations (often referred to as anecdotal reports) and receptor binding profiles. These data support FDA's characterization of 7-OH as a substance with a pharmacological profile that is qualitatively similar to classical opioids with effects such as “euphoria, sedation, respiratory depression, and opioid-like withdrawal syndromes, with users acknowledging its significant addiction potential (Reissig et al., 2025, p. 4). FDA concluded “The pharmacological profile, abuse liability, and emerging patterns of nonmedical use establish 7-OH as a dangerous substance” (Reissig et al., 2025, p. 4). As discussed in Factor 8, such data suggest that 7-OH meets the statutory definition of an opioid as described in the 1970 Controlled Substances Act (CSA).

Although some kratom products have likely been boosted in their 7-OH concentrations in the past, the widespread marketing and consumption of concentrated 7-OH products has emerged nationwide in just the past few years. FDA itself noted a clear “distinction” between kratom and kratom products that “have been used for centuries in both

medicinal and recreational settings” containing naturally low occurring levels of 7-OH compared to what the agency described as the recent widespread appearance of “7-OH opioid products” (e.g., FDA (2025a). FDA emphasized that “7-OH is found in trace amounts in the kratom plant leaf. But this is not our focus. Our primary concern is the concentrated form of 7-OH. This is an important distinction. These concentrated 7-OH opioid products are far more dangerous than traditional kratom leaf products” (Makary, 2025)

Currently, many kratom and related products, including concentrated 7-OH products are marketed as dietary ingredients and/or supplements, though to date no New Dietary Ingredient Notification (NDIN) has been accepted by FDA and the lack of adequately documented history of use prior to 1994 has precluded its acceptance as an ‘old dietary ingredient’ that is exempt from the NDIN requirements as described in the 1994 Dietary Supplement Health and Education Act (DSHEA).

During the FDA’s July 29, 2025, press conference, the DHHS leadership indicated that the Department would recommend the Drug Enforcement Administration (DEA) place 7-OH in the CSA. If DEA concurs, then 7-OH would be placed in Schedule I, along with heroin, LSD, and marijuana as that is the only CSA schedule for substances with high abuse potential and which are not “Commonly Accepted for Medical Use” (CAMU). CAMU is typically determined by FDA’s approval as a drug for medical use, or in a rare recent case with respect to marijuana, a substantial body of medical use, state-level authorization, and clinical evidence was considered adequate to support the designation of marijuana as CAMU despite the absence of FDA formal therapeutic/medical approval (DHHS, 2023a; DEA, 2024).

Permanent placement in Schedule I requires an 8-factor analysis (8-FA), which is the structured evaluation described in the CSA that is determinative of CSA control and scheduling. Factors 1, 2, 3, and 7 are based on chemical, pharmacological, and clinical studies, while Factors 4, 5, and 6 determine public health impact and whether the substance poses an imminent hazard to public health. Factor 8 examines whether the substance is a chemical precursor of a substance that is already controlled in the CSA, or has the same chemical structure, or in the case of opioids is derived from the opium poppy by extraction, or chemical synthesis based on opium or an opium poppy constituent such thebaine or morphine or has a pharmacological profile similar to that of already controlled morphine-like opioids¹.

This recent action represents a shift from a 2018 DHHS decision, which rescinded a prior recommendation to schedule kratom and its alkaloids, including 7-OH. In that

¹ In 21 U.S. Code § 802 – Definitions

(17)The term “[narcotic drug](#)” means any of the following whether produced directly or indirectly by extraction from substances of vegetable origin, or independently by means of chemical synthesis, or by a combination of extraction and chemical synthesis:

(A) Opium, [opiates](#), derivatives of opium and [opiates](#), including their [isomers](#), esters, ethers, salts, and salts of [isomers](#), esters, and ethers, whenever the existence of such [isomers](#), esters, ethers, and salts is possible within the specific chemical designation. Such term does not include the isoquinoline alkaloids of opium.

decision, U.S. Assistant Secretary for Health Admiral Brett P. Giroir noted that the existing science did not support a recommendation to place mitragynine and 7-OH in the CSA because this would have had the effect of banning kratom product and that carried a “significant risk of immediate adverse public health consequences” if users were to switch to more lethal opioids (Giroir, 2018).

Similarly, the United Nations Commission on Narcotic Drugs (UNODC) Commission on Narcotic Drugs (CND) concluded there was insufficient evidence to recommend a critical review of kratom and its alkaloids, including mitragynine and 7-OH, though it advised they be kept under surveillance (UNODC, 2021). Since then, in late August 2025, the UNODC published a warning of emerging products containing 7-OH and 7-OH’s metabolite pseudoindoxyl, recommending further educational awareness campaigns by healthcare professionals, regulators, and law enforcement, as well as enhancing surveillance, testing, detection, and epidemiological surveillance of these products.

The present document provides an 8-FA of 7-OH according to the 1970 Controlled Substances Act. This 8-FA has been developed following the model laid out in FDA’s guidance, Assessment of the Abuse Potential of Drugs (FDA, 2017), while also taking into consideration the experience and evolution in approach to such assessments since the CSA was signed into law in 1970. The present analysis considered and expands upon the pharmacological and epidemiological data that were presented in FDA’s July 29, 2025 scientific assessment (Reissig et al., 2025) and incorporates insights from prior work by Pinney Associates, including the 2018 and 2022 kratom 8-FAs and related analyses (Henningfield, Fant, & Wang, 2018; Henningfield, Wang, & Huestis, 2022).

The Appendices include four documents released by FDA addressing 7-OH science, warnings and educational materials (FDA, 2025a, FDA, 2025b, Makary, 2025; Reissig et al., 2025), as well as the conference transcript in Appendix 5.

The purpose is to provide a structured review of the evidence typically used to inform the FDA and National Institute on Drug Abuse (NIDA) in their CSA scheduling recommendations and the DEA in its potential scheduling action, as well as to provide a resource for public health policymakers, regulators, scientists, and the public in general to learn about the risks associated with 7-OH and the complexities of its potential regulatory and legal control. This 8-FA also discusses policy considerations such as potential scheduling and enforcement approaches; efforts to mitigate unintended consequences such as fueling the formation of illicit (“black”) 7-OH markets and relapse to deadlier classical opioid use; and addressing other potential health problems and medical issues in people who found 7-OH to be more effective, acceptable or assessable than FDA approved medicines, kratom, or other approaches in addressing their health needs including opioid dependence and withdrawal.

Table 1 from FDA (2017) summarizes the 8 factors of the CSA as follows:

Under 21 U.S.C. 811(b) of the CSA, the medical and scientific analysis considers the following eight factors determinative of control of the drug under the CSA (21 U.S.C. 811(c)):

1. Its actual or relative potential for abuse.
2. Scientific evidence of its pharmacological effect, if known.
3. The state of current scientific knowledge regarding the drug or other substance.
4. Its history and current pattern of abuse.
5. The scope, duration, and significance of abuse.
6. What, if any, risk there is to the public health.
7. Its psychic or physiological dependence liability.
8. Whether the substance is an immediate precursor of a substance already controlled.

2 Factor 1: Actual or Relative Potential for Abuse

The actual or relative potential for abuse of a substance is a primary determinant in scheduling considerations under the CSA. This factor is assessed through a combination of preclinical studies in animals and an analysis of human use patterns. For 7-OH, a number of nonclinical studies including self-administration, conditioned place preference, and drug discrimination studies indicate potential for abuse, with effects that are often comparable to, or more potent than, those of morphine. While controlled human abuse potential studies have not yet been conducted, emerging data from user reports and clinical case studies corroborate the findings from animal research, suggesting that concentrated 7-OH products are being used for their rewarding and opioid-like effects.

2.1 Pharmacology

7-OH has been shown to naturally occur at de minimis levels in the kratom plant and is generally formed in vivo from mitragynine, the parent alkaloid, through metabolic oxidation in the liver, mediated by cytochrome (CYP) P450 3A (Kruegel et al., 2019). It appears that low levels of 7-OH may also occur post-harvest in leaves by enzymatic interactions (Karunakaran, Vicknasingam, & Chawarski, 2025; Smith et al., 2024).

7-OH has demonstrated pharmacological properties consistent with potential for recreational use, abuse, and dependence. However, available evidence indicates that 7-OH acts as a partial agonist at opioid receptors, suggesting that by some measures it is weaker in its expression or less efficacious compared to morphine, such as opioid-like effects. Whether the overall abuse potential of 7-OH is most accurately described as lower, higher, or similar to morphine (the most common standard comparator) is not clear at present; however, as discussed by FDA (Reissig et al., 2025), 7-OH has sufficiently similar pharmacology to be characterized as an opioid. Moreover, although its potency (the amount of drug required to produce a given effect) varies widely across measures and studies, it requires smaller amounts of 7-OH by weight (e.g., mg) to produce a variety of abuse-related effects as compared to morphine, therefore

supporting the general description of 7-OH by FDA as a “potent” and even “highly potent” opioid”.

Specifically, 7-OH exhibits high affinity for MORs and acts as a partial agonist, producing G-protein biased signaling with limited beta- (β) arrestin-2 recruitment (Kruegel et al., 2016; Todd et al., 2020). This bias is generally associated with reduced opioid-like effects such as constipation (Gutridge et al., 2020).

The FDA’s 2025 assessment characterizes 7-OH as a potent MOR agonist with high abuse potential and risk of severe dependence stating, “Critically, 7-OH produces respiratory depression, physical dependence, and withdrawal symptoms characteristic of classical opioids, such as morphine, fentanyl, oxycodone, and hydrocodone”. It is important to note that demonstrations of morphine equivalent reinforcing efficacy and respiratory depression in rodent models were by the intravenous (IV) route of administration, whereas virtually all human consumption is by the oral route. Overdose risk by the oral route would seem to be a plausible risk but has not been well-documented in animals and the evidence for apparent 7-OH attributed overdose deaths in humans is not strong. FDA described two cases in which an overdose death occurred and concluded as follows:

“Although FDA’s Adverse Event Reporting System (FAERS) has documented cases reporting adverse events (13 cases, including 2 deaths) suspected to involve 7-OH, ambiguity about the contributory role of 7-OH from uncharacterized products or concomitant medications and underlying disease limits interpretation” (Reissig et al., 2025).

Note that these reports are not limited to a single year but rather all the cases that have been reported to date. Whereas these reports are concerning, and this report agrees with FDA that adverse events related to 7-OH use have been under-reported, the actual numbers of such cases are very low as compared to the thousands reported over time and annually for opioids such as heroin, oxycodone and fentanyl and fentanyl related substances.

Whereas most animal studies indicated that mitragynine is neither potent, strong, nor reliable in producing respiratory depression (e.g., (Henningfield, Rodricks, et al., 2022), 7-OH produced stronger morphine-like respiratory depression by the IV route at lower concentrations than mitragynine (Gonzalez et al., 2025; Harun et al., 2015).

Also, unlike mitragynine, 7-OH reliably substitutes for morphine across antinociception, discrimination, and self-administration paradigms, showing dose-dependent reinforcing and conditioned place preference effects with greater potency than morphine in several animal models (Gutridge et al., 2020; Harun et al., 2015).

7-OH produces strong naloxone-reversible analgesia yet with less respiratory depression and constipation at equianalgesic doses, and exhibits higher oral bioavailability than morphine (Kruegel et al., 2016; Matsumoto et al., 2004). In mice, brain concentrations of 7-OH after mitragynine administration are sufficient to explain

most or all of the opioid-receptor mediated analgesic effects associated with mitragynine use (Kruegel et al., 2019).

2.2 Nonclinical Abuse Potential Models (Rewarding Effects)

2.2.1 Self-Administration

A study by Hemby et al. (2019) evaluated the reinforcing effects of 7-OH in rats and found that 7-OH not only engendered but also maintained self-administration behavior at intravenous doses ranging from 2.5 to 10 µg/infusion, demonstrating reinforcing effects comparable to those of morphine when administered at 50 and 100 µg/infusion, suggesting 7-OH may be 10-20 times more potent than morphine in this test. In contrast, mitragynine did not maintain self-administration, highlighting a critical pharmacological distinction between the two compounds. The reinforcing effects of 7-OH were found to be mediated by both MORs and delta (δ)-opioid receptors (DOR), as intake was reduced by antagonists for both receptor types (NLXZ and NTI, respectively). This contrasts with morphine, whose reinforcing effects in the same study were primarily mediated by MORs.

To contextualize these findings for human risk, an allometric scaling factor can be used to estimate a human equivalent dose. Based on the rat data, the reinforcing intravenous dose of 7-OH for a 70 kg person is estimated to be between 0.161 and 0.322 mg, compared to 1.61 mg for morphine. This calculation suggests that 7-OH might be between 5-10x more potent than morphine in producing reinforcing effects, a key indicator of abuse potential though this should be considered a possibility to be tested and not an established fact. It is crucial to note, however, that the clinical meaningfulness of such estimates is not clear because the animal data are based on intravenous administration, whereas human consumption of 7-OH products is typically oral. The abuse potential of 7-OH in humans has not been directly evaluated in human abuse potential studies by any route of administration using protocols recommended by FDA in its 2017 Guidance (FDA, 2017) nor have other potential effects of 7-OH administration been well characterized in controlled clinical studies.

2.2.2 Intracranial Self-Stimulation

In an intracranial self-stimulation (ICSS) study, neither mitragynine nor 7-OH-MG showed evidence of brain rewarding effects, whereas morphine robustly and dose dependently decreased the stimulation threshold (Behnood-Rod et al., 2020). Thus, the ICSS results suggest lower brain rewarding effects of mitragynine as compared to morphine. Note that ICSS is not recommended in FDAs guidance for abuse potential assessment but is considered a potentially informative model (Henningfield, Comer, Banks, Coe, Collins, Cooper, Fantegrossi, Durgin, Heal, Huskinson, Lanier, Lynch, Miesch, Rowlett, Strickland, & Gannon, 2025).

2.2.3 Drug Discrimination

Drug discrimination studies assess the interoceptive (subjective) effects of a substance by training animals to recognize and distinguish the effects of a test drug from a placebo (saline) or another drug. An animal's ability to generalize the subjective cue of a novel

compound to that of a known drug of abuse, such as morphine, is considered predictive of similar subjective effects and abuse potential in humans.

Several studies have shown that 7-OH fully substitutes for the discriminative stimulus effects of morphine. Harun et al. (2015) trained male Sprague Dawley rats to discriminate morphine (5.0 mg/kg, intraperitoneal [i.p.]) from saline. In subsequent substitution tests, the highest dose of 7-OH (3.0 mg/kg) produced complete substitution for the morphine cue, and this effect was reversed by the opioid antagonist naloxone. Notably, this study found 7-OH to be more potent than morphine in producing these subjective effects.

Further research has reinforced these findings. Obeng et al. (2021) reported that 7-OH fully generalized to morphine in rats, whereas mitragynine only partially generalized. Similarly, Hemby et al. (2019) found that 7-OH substituted for morphine in a dose-dependent manner, while mitragynine did not substitute at any dose tested. The consistent and complete generalization of 7-OH to the morphine cue across multiple studies provides strong evidence that it may produce subjective effects that are qualitatively similar to those of classical opioids.

2.2.4 Conditioned Place Preference

Matsumoto et al. (2008) found that 7-OH administered at 2 mg/kg produced conditioned place preference (CPP) with greater potency than morphine. Similarly, Gutridge et al. (2020) demonstrated that 7-OH at a dose of 3 mg/kg induced CPP in C57BL/6 mice, although it required four conditioning sessions compared to 2 sessions for morphine (6 mg/kg) to establish the preference. This suggests that while 7-OH is rewarding, the onset or strength of the conditioned association may differ from that of morphine under certain experimental conditions. Another study by Chakraborty, Uprety, et al. (2021) also confirmed that 7-OH produces significant CPP, whereas its metabolite, mitragynine pseudoindoxyl, did not, indicating distinct rewarding profiles among related alkaloids. Collectively, these findings consistently show that 7-OH has rewarding effects sufficient to establish a conditioned preference, common in drugs with abuse potential.

2.3 Clinical Studies and Evidence of Abuse Potential in Humans

While there have been no controlled human laboratory studies conducted to date specifically designed to assess the abuse potential of 7-OH, a growing body of epidemiological data, clinical case reports, and user self-reports provide evidence of its nonmedical use and abuse. The FDA's 2025 scientific assessment noted clinical presentations that include reports of "euphoria, sedation, respiratory depression, and opioid-like withdrawal syndromes, with users acknowledging its significant addiction potential". These reports align with the effects predicted by preclinical models and are characteristic of substances with abuse potential, discussed further in Factors 4-6.

2.4 Implications for Abuse Potential

Taken together, the evidence summarized in Factor 1 suggests that 7-OH has meaningful abuse potential despite limitations in the breadth of available studies, the range of study types, and inconsistencies across findings. Preclinical studies suggest robust reinforcing, rewarding, and subjective effects characteristic of a μ -opioid agonist,

with potentially a potency greater than morphine, although not necessarily stronger. This distinction is often misunderstood; potency refers to the amount of drug required to produce a given effect and not the maximal possible effect that can be produced. Thus, for example, in a classic study, Matsumoto et al. (2004) found that the potency of 7-OH varied widely across outcome measures (include guinea-pig ileum contractions, tail flick and hot plate tests) as compared to morphine and mitragynine, however, whereas 7-OH and morphine produced similar maximum effects on several measures, mitragynine's effects were consistently weaker (producing smaller maximum possible effects) and far less potent (taking more mg to produce any effect) than 7-OH and morphine.

From an abuse potential perspective, the most important finding is that both 7-OH and morphine produce a range of qualitatively similar effects, supporting the characterization of 7-OH as an 'opioid' and as a drug with a potential for opioid-like abuse potential. These findings are also consistent with similarities in receptor binding and mechanism of action, suggesting that its abuse related pharmacology is sufficiently similar to that of opioids to warrant considering characterizing of 7-OH as an opioid.

At present, the available evidence does not provide a basis for determining the overall abuse potential of 7-OH relative to morphine. However, that level of pharmacological characterization is not critical to determine whether a substance lacking FDA approval or commonly accepted for medical use meets the requirements for placement into Schedule I of the Substances Act. That 7-OH as a substance exhibits meaningful abuse potential and overall morphine-like opioid pharmacology satisfies the statutory criteria for scheduling.

If 7-OH were to be submitted to FDA as part of a New Drug Application and subsequently approved for therapeutic use, a quantitative determination of its relative abuse potential would be important to guide scheduling – for example if it should be placed alongside morphine in Schedule II, or in a less restrictive schedule (III, IV, or V) based on the totality of evidence.

3 Factor 2: Scientific Evidence of its Pharmacological Effects

Current scientific evidence shows that 7-OH is pharmacologically active with a distinct profile of central nervous system (CNS) mediated effects. It acts primarily as a potent partial agonist at the MOR, but its effects extend to other neurotransmitter systems, indicating that while its effects appear to warrant the designation as an opioid, it has additional effects that appear to differentiate 7-OH from morphine-type opioids in its overall pharmacology.

3.1 Mechanism of Action and Opioid Binding

7-OH's interactions with opioid receptors appear to be the predominate cause of at least its abuse related effects. For example, 7-OH consistently demonstrates high affinity for the MOR, with reported inhibitor constant (K_i) values ranging from approximately 7 nM to 78 nM, significantly higher than that of mitragynine, its parent alkaloid (1700 nM). Studies have shown that both 7-OH and mitragynine demonstrate a preference for activating the G-protein signaling pathway with little to no recruitment of the β -arrestin-2 pathway. This is a significant finding, as β -arrestin-2 recruitment is strongly associated

with the adverse effects of classical opioids, such as respiratory depression and constipation. This G-protein bias suggests a potential for a lower risk profile compared to conventional opioids like morphine, which robustly recruit β -arrestin-2 (Ellis et al., 2020; Kruegel et al., 2016). Nonetheless, other findings with 7-OH indicate meaningful opioid-like abuse potential, as discussed in Factor 2.

For example, in addition to its primary action at the MOR, 7-OH also binds with moderate to high affinity at the kappa (κ -) opioid receptor (KOR) and DOR, where it appears to function as a competitive antagonist (Obeng et al., 2021). This profile as a partial MOR agonist and a KOR/DOR antagonist distinguishes it from classical opioids like morphine, which are full MOR agonists, and may contribute to its unique pharmacological effects. For instance, KOR antagonism is associated with antidepressant and anxiolytic effects, which could align with some of the reported motivations for kratom and 7-OH use (Carlezon, & Krystal, 2016).

3.2 Effects on Other Neurotransmitter Systems

While 7-OH appears to primarily target opioid receptors, there is evidence that it, along with mitragynine, also interacts with other CNS receptors, including adrenergic, serotonergic, and dopaminergic systems. This multimodal activity likely contributes to the complex profile of effects reported by users, which can include both stimulant-like and sedative properties.

A study by James P. Manus et al. (2025) investigated the effects of 7-OH on dopamine release in the nucleus accumbens, a key brain region in the reward pathway. The study found a bidirectional effect: a low dose of 7-OH (0.5 mg/kg) increased dopamine release, while a high dose (2 mg/kg) decreased it. The authors noted that these alterations in dopamine function are not necessarily consistent with those of classic drugs of abuse, suggesting a more complex mechanism of action on the brain's reward systems. Ellis et al. (2020) found that the oxidation of mitragynine to 7-OH significantly strengthens its binding affinity at the MOR but weakens its affinity at adrenergic and serotonin receptors, indicating that the pharmacological profile shifts substantially upon metabolism.

3.3 Antinociception

Numerous studies have demonstrated that 7-OH produces robust, dose-dependent antinociceptive effects in animal models such as the hot plate and tail flick tests (Behnood-Rod et al., 2020; Matsumoto et al., 2004). Its potency in producing analgesia is consistently reported to be significantly greater than that of morphine. For example, Kruegel et al. (2016) reported that 7-OH was approximately 10 times more potent than morphine in producing antinociception. This potent analgesic effect, combined with its high oral bioavailability compared to morphine, and its lack of measurable β -arrestin-2 recruitment makes 7-OH an interesting subject for potential therapeutic development.

3.4 Respiratory Depression

While studies referenced above determined mitragynine and 7-OH lacked measurable β -arrestin-2 recruitment, a study by Gonzalez et al. (2025) found that 7-OH caused dose-dependent reductions in respiratory frequency and minute volume in rats, effects

fully reversed by naloxone. This is in contrast to mitragynine, which unexpectedly increased respiratory frequency with no significant depression of tidal/minute volume. This lack of respiratory depressive effects by mitragynine was confirmed by Henningfield, Rodricks, et al. (2022)'s study showing no respiratory depression in rats administered up to 400 mg/kg oral mitragynine. Mitragynine's stimulant effect was not blocked by naloxone, suggesting a non-opioid mechanism.

3.5 Comparison to Morphine

Comparing the relative potency of kratom, mitragynine, and 7-OH to morphine is important in pharmacological evaluations but is often misinterpreted as indicative of abuse, addiction and/or harm potential. What is more important in abuse potential assessments is the maximum possible effect of a drug as a reward or euphoriant which is generally considered a stronger determinant of the overall abuse potential of a drug and its likelihood of recreational use. Potency should not be considered the same as maximum possible effect.

Numerous studies have shown that 7-OH is more potent than morphine on several measures but most of these do not suggest that 7-OH has stronger maximum possible effects. For example, an in vitro study using electrically stimulated guinea pig ileum, a classic assay for opioid activity, found that 7-OH was approximately 17 times more potent than morphine and 30 times more potent than mitragynine (Horie et al., 2005). A similar study by Takayama et al. (2002) found that 7-OH had 13 times higher potency than morphine and 46 times more than mitragynine. Studies of 7-OH's antinociception potential have reported it at 10 times that of morphine (Kruegel et al., 2016).

However, it is critical to interpret these findings with caution. While informative, results from in-vitro assays and subsequent in-vivo animal models do not always directly translate to the complex human experience. Also, while 7-OH's affinity to opioid receptors relative to morphine can be quantified in a controlled laboratory setting, their respective pharmacological profiles merit further study. Factors such as route of administration, formulation, metabolism rate, bioavailability, blood-brain barrier penetration, and the activation and interactions of multiple neurotransmitter systems create a more complex web of effects than can be observed in a controlled laboratory setting. Therefore, while the existing research provides a valuable pharmacological baseline establishing 7-OH as a potent opioid agonist in some assays, its overall pharmacological effects in humans have not been well characterized and remains an area requiring further clinical research.

3.6 Implications for Abuse Potential

Taken together the data reviewed in this factor are consistent with the characterization of 7-OH as a CNS-acting drug with effects likely to contribute to use and abuse potential. Data from numerous studies indicate that 7-OH is pharmacologically active with dose-related effects and mechanisms of action being similar though not identical to those of morphine-like opioids. The relative potency compared to morphine appears to vary widely across measures, which is not surprising nor atypical of opioids. However, its distinct activity and variability (especially its lack of measurable β -arrestin-2 recruitment and activity at KOR and DOR receptors) suggest that direct comparison and

characterizing 7-OH as an opioid that is up to 13 times more potent than morphine is misleading as a stand-alone indicator of its abuse potential as these estimates are based on animal models that may not necessarily relate to human effects.

Moreover, as mentioned earlier, relative potency is not necessarily indicative of abuse potential. The mixed mechanisms of action of 7-OH may contribute to the diversity of reasons people report for its use (as discussed in Factors 4, 5, and 6); however, this pharmacological complexity does not inherently determine its level of abuse potential. For example, when seeking rewarding and euphoriant effects, many recreational users prefer opioids with a pharmacological profile characterized predominantly by MOR agonism, such as morphine, oxycodone, heroin and fentanyl. Overall, the risk profile of 7-OH remains incompletely understood and warrants further study.

4 Factor 3: Current State of Scientific Knowledge

Research on kratom, including research on 7-OH specifically, has increased enormously in the past decade. For example, the introduction to *Kratom: History, Science, and Therapeutic Potential*, a recently published book featuring contributions from many of the world's leading kratom researchers, notes the rate of annual kratom science publications increased from about 20 per year in 2016 to more than 130 per year by 2024, with the increased fueled heavily by research funding by the National Institutes of Health (NIH), NIDA (Henningfield, Beyer, & Raffa, 2025). This rapidly expanding body of research undoubtedly played a significant role in shaping two important themes in the July 29, 2025 FDA and DHHS documents addressing 7-OH: the characterization of its abuse potential and safety, and the decision to treat 7-OH as a public health concern distinct from kratom itself.

One of the most significant advances to emerge from the hundreds of new studies conducted over the past decade has been the understanding that 7-OH is more appropriately considered a mitragynine metabolite in humans and animals that are given or who self-administer kratom. Additionally, while it has been established that it is either absent from or appears in de minimis levels in freshly harvested kratom leaves, 7-OH may emerge at low levels in the leaves over time, likely as a result of enzymatic processes (Karunakaran, Vicknasingam, & Chawarski, 2025; Smith et al., 2024). Indeed, it was observed several decades ago that 7-OH is less than 2% of the total content of all of the alkaloids in kratom leaves (Takayama, 2004). In many marketed kratom products including leaf powder, encapsulated kratom powder and extracts in the U.S. 7-OH content is lower still ranging from undetectable to about 0.01% to 0.04% by weight (Kikura-Hanajiri et al., 2009).

4.1 Pharmacokinetics

When kratom or pure, single isolate mitragynine extracts are self-administered or administered in clinical studies, mitragynine is metabolized in the liver, a conversion mediated primarily by the CYP3A enzyme, forming 7-OH. A human clinical study by Mongar et al. (2024) found that co-administration of itraconazole, a potent CYP3A4 inhibitor, decreased the formation of 7-OH from mitragynine, reducing its peak plasma concentration (i.e., C_{max}) by 56% and its total exposure (i.e., area under the curve) by 43%.

A large scale clinical trial found that after administration of encapsulated kratom leaf powder, the time to reach maximum plasma concentration (i.e., T_{max}) for 7-OH was between 1.2 and 2.0 hours (Huestis et al., 2024). The elimination half-life (i.e., $T_{1/2}$) was found to be 4.7 hours after a single dose and extended to 24.7 hours after multiple daily doses, indicating potential for accumulation with long term and/or daily use.

A study in beagles found a conversion rate of 23.1% of mitragynine to 7-OH, though this may not be representative of human conversion rates. For instance, Hiranita et al. (2020) reported “the conversion rate of 7-hydroxymitragynine from per oral (PO) mitragynine is low. In a study of pharmacokinetic interaction of kratom and cannabidiol in male rats, the metabolite to parent (mitragynine) exposure ratio percentage of 7-OH-MG remained similar (3.5 and 3.1 with and without cannabidiol, respectively). As there was an increase in mitragynine exposure during this study, it was expected that this would be due to a decrease in metabolism, but this was not the case for 7-OH-MG despite it being primarily metabolized by CYP3A and cannabidiol being a competitive inhibitor of CYP3A (Berthold et al., 2024).

Further rat studies support this finding, showing that 7-OH and mitragynine are quantifiable 8 hours after consumption, and accumulation of mitragynine and 7-OH after multiple oral doses (Chiang et al., 2024; Kamble et al., 2021). Another study by Tanna et al. (2022) reported a similar half-life of 5.67 hours after a single oral 2 g dose of kratom tea. This tea was tested and found to have contained only trace amounts of 7-OH (i.e., less than the limit of quantitation [$< LOQ$]) in the starting product; therefore, the assumption was made that 7-OH was generated from the metabolism of mitragynine in vivo. Concerningly, there appear to be some 7-OH formulations that have been designed to bypass first pass metabolism, artificially increasing bioavailability (Smith et al., 2025).

Kruegel et al. (2019) found that brain concentrations of 7-OH formed from mitragynine in mice are sufficient to explain most or all of the opioid-receptor-mediated analgesic activity of mitragynine. At the same time, mitragynine is found in the brains of mice at very high concentrations relative to its opioid receptor binding affinity, suggesting that it does not directly activate opioid receptors (Kruegel et al., 2019).

Uchaipichat (2025) found that 7-OH-MG exhibited inhibitory potency on UGT1A9, with a half-maximal inhibitory concentration (IC_{50}) value of 51 μM , while moderate potency was observed for UGT1A1 and UGT1A3, with IC_{50} values of 196 and 141 μM , suggesting the potential for herb-drug interactions in individuals consuming high doses of 7-OH-MG. However, the experimental K_i values found in this study were relatively high compared to the maximum plasma concentrations of mitragynine and 7-OH reported in humans.

In a study relevant to breast cancer treatment medications are potential effects of 7-OH (and mitragynine) on as HER2 inhibitors. This in silico study (involving computer simulations to predict pharmacological effects) suggested that the molecular docking included binding energies of -7.56 kcal/mol and -8.77 kcal/mol, respectively, with key interactions involving residues such as Leu726, Val734, Ala751, Lys753, Thr798, and

Asp863. Akbar et al. (2025) found both mitragynine and 7-OH were inhibitors of CYP2D6 and CYP3A4, though neither were found to be P-glycoprotein substrates, which minimizes the risk of efflux-related bioavailability issues. Both studies confirm the potential for significant drug-drug interactions with other substances that are substrates, inhibitors, or inducers of these systems. These should be considered preliminary findings and not necessarily related to abuse potential or safety but provide an example of other research that involves 7-OH and other mitragynine related substances.

While Akbar et al. (2025)'s Absorption, Distribution, Metabolism, Excretion, and Toxicity analysis found that both mitragynine and 7-OH demonstrated high gastrointestinal (GI) absorption, suggesting high oral bioavailability (also a conclusion by Chakraborty, Uprety, et al. (2021), a study in rats reported a low oral bioavailability of only 2.7%, possibly due to poor water solubility, indicating that formulation and species differences may significantly impact absorption (Chiang et al., 2025).

A recent case report that has been accepted for publication at the time of this writing described a patient admitted to a hospital emergency department following "cardio-pulmonary arrest". He was found unresponsive and received approximately 10 min of cardiopulmonary resuscitation; he was successfully revived with two doses of naloxone 4mg intravenously." The patient reported ongoing use of other substances that may have contributed to this event, as well having ingested several times the recommended serving size labeled on the 7-OH product. Thus, whereas causality cannot be definitively determined beyond a likely poly-pharmaceutical contribution is not clear, the responsiveness to naloxone suggests that 7-OH's opioid receptor-mediated activity may have played a role, particularly since no other conventionally screened 'opiates' were detected in the blood (Pullman, Kanumuri, Leon et al. 2025).

4.2 Mitragynine Pseudoindoxyl

Kamble et al. (2020) further discovered that 7-OH is itself converted to mitragynine pseudoindoxyl in human plasma, and to a greater extent than is produced in mice, rats, dogs, and cynomolgus monkeys, possibly explaining potential human effects that may not be predicted in animal studies alone. Mitragynine pseudoindoxyl's effects, however, are still mostly unclear; for instance while 7-OH-MG and mitragynine have shown significant conditioned place preference (Section 2.2.4), mitragynine pseudoindoxyl did not (Chakraborty, DiBerto, et al., 2021).

4.3 Conclusions

The available evidence shows that 7-OH is a potent, orally bioavailable, μ -opioid partial agonist with a G-protein bias that can accumulate in the body upon daily and/or chronic use. Its metabolism is heavily dependent on the CYP3A4 enzyme processes. Its complex pharmacology, involving interactions with multiple opioid receptor subtypes and other neurotransmitter systems, underlies its opioid-like effects, including analgesia, euphoria, and sedation, as well as its potential for abuse and dependence.

5 Factors 4, 5, and 6: History and Current Patterns of Abuse; The Scope, Significance and Duration of Abuse; What, if any, Risk is there to the Public Health

5.1 Factor 4: History and Current Patterns of Abuse

The marketing and apparent sales and consumption of 7-OH have increased rapidly since about 2022, and 7-OH has progressed over the past several years from a minor, little known alkaloid with little to no independent history of use to a commercially available, highly concentrated product at the center of what FDA deems an “emerging public health threat”. This has been driven in part by growing awareness of its potentially potent opioid pharmacology though current use patterns (as gleaned from national surveys, surveillance systems, and online user communities) reveal a user base with diverse motivations. However, these data sources also highlight an escalating pattern of high-dose use of concentrated products that is associated with dependence, withdrawal, and other adverse outcomes.

Traditional use of kratom in Southeast Asia, which involves chewing fresh leaves or brewing them into tea, results in ingestion of only trace amounts of 7-OH. The primary psychoactive effects from traditional kratom preparations are attributed primarily to its most abundant alkaloid mitragynine and the complex interactions of the many other alkaloids in the plant leaves. The market for kratom began to rapidly evolve with the rise of its popularity in the U.S. in the mid-2000s, though use likely dates back as early as the 1980s, brought back by American veterans returning from Southeast Asia and immigrants from those areas. Consumer demand for alternative kratom products, combined with scientific and manufacturing resources and innovation from American entrepreneurs led to explosive growth in the number of kratom extracts and other products artificially enhanced with non-natural amounts of kratom alkaloids and/or other substances.

A pivotal shift occurred with the proliferation of products specifically marketed as “7-OH” products. These products often contain artificially elevated levels of 7-OH, often created through synthetic or semi-synthetic means, such as chemical oxidation of mitragynine, which is much more readily abundant naturally and economically viable than isolating from kratom leaves.

Analysis of these commercial products revealed concentrations of 7-OH that are hundreds of times higher than would be expected in natural kratom leaf. For example, one analysis reported that 7 of 8 products tested contained 109-509% more 7-OH than would be expected in a natural product (Ogozalek, 2023), and news reports identified pill products containing 15 mg of 7-OH per pill, a dose far exceeding natural levels and one that is likely pharmacologically significant. This is in contrast to an analysis of 13 commercial kratom products, which found 7-OH at 0.01-0.04% by weight, aligning with reports that 7-OH represents less than 0.05% of the alkaloid content, substantially lower than mitragynine. This indicates that naturally occurring levels of 7-OH in kratom are minimal compared to the primary alkaloid (Kikura-Hanajiri et al., 2009; Kruegel et al., 2019). These 7-OH products are now readily available online and in retail locations such as gas stations, vape shops, convenience stores, and corner shops, often in a vast

array of formulations like gummies, tablets, and liquid shots (Hill, Henderson, et al., 2025).

5.1.1 Reasons for Use

While national surveys like the National Survey on Drug Use and Health (NSDUH) track kratom use, they do not yet specifically distinguish users of traditional kratom from users of concentrated 7-OH products. General kratom user demographics from the 2019 NSDUH and other surveys indicate that users are generally somewhat more male than female users, with most identifying as “White” or Caucasian, and between the ages of 18 and 49, though results vary widely. The most recent largescale kratom survey at this writing reported the majority of kratom users were males between 30-49 years old who identify as Caucasian (Grundmann et al., 2025). There is evidence that kratom users are generally older, often reporting reasons for use related to potential therapeutic effects (relief of common pain symptoms, elevating energy); there is little evidence of youth use.

However, none of these surveys addressed people who are primarily 7-OH consumers, a critical area in need of research. Thus, extrapolations from kratom-focused surveys are not necessarily representative. This caveat applies to reasons for use as well, although some anecdotal data described below suggest that at least some 7-OH users are people who found it to be more effective or satisfying than kratom for pain and self-management of their opioid use disorder and/or opioid withdrawal.

Those who use kratom and 7-OH report a diverse range of motivations, including for therapeutic or self-medication purposes, such as for pain relief, anxiety, and depression. A significant portion of users, particularly those with a history of opioid use, report using kratom to address opioid withdrawal symptoms or as a substitute for more dangerous illicit opioids. Additionally, current opioid users were more likely to report use kratom for opioid withdrawal, while former opioid users were more likely to report mood elevation as their reason for use (Singh et al., 2020).

The emergence of concentrated 7-OH products appears to be attracting both existing kratom users and new consumers. Analysis of Reddit discussions reveals two primary user groups for 7-OH: individuals seeking potent relief for chronic pain, and individuals seeking strong, opioid-like recreational effects. For example, one Reddit user in a chronic pain forum reported using 7-OH for pain management, often at lower daily doses (e.g., 11 mg/day) without reporting significant adverse effects. In contrast, discussions in subreddits focused on substance use and quitting kratom describe patterns of high-dose, frequent use for euphoric effects, leading to rapid development of dependence and severe withdrawal. This bifurcation suggests that the availability of a more potent, isolated compound is creating distinct patterns of use and risk profiles compared to traditional kratom.

5.1.2 Dosing, Routes of Administration, and Trajectory of Use

Information from online user reports provides detailed, albeit anecdotal, data on current use patterns for 7-OH products. An analysis of 6 Erowid experience reports found a median oral dose of 13.5 mg (range 6.9 mg - 16.9 mg), with a maximum reported dose

of 120 mg. Most reports described oral administration of pills, capsules, or tablets, though sublingual and insufflation (snorting) routes were also mentioned.

A concerning pattern emerging from these reports is the trajectory of use. While some reports describe single-dose experiences, a significant portion describe daily use, escalating over periods from a few days to several months. Reddit users in the “Quitting Kratom” subreddit describe daily use, sometimes up to 5× per day, with doses associated with withdrawal symptoms ranging from 30 mg/day to as high as 500 mg/day. This pattern of escalating, high-frequency dosing is a classic hallmark of substance use disorders and is consistent with the development of tolerance to 7-OH's effects. The availability of 7-OH in discrete, high-dose units like pills and liquid shots facilitates this pattern of use in a way that traditional kratom use (i.e., consuming dried kratom leaf powder) does not.

5.2 Factor 5: Scope, Duration, and Significance of Abuse

National surveillance systems in the U.S. have in recent years begun tracking use of kratom; however, the majority of these systems have yet to track data as it relates to 7-OH use, and attempts at analysis with current data are complicated by these systems combining 7-OH and kratom cases as one category. However, recent efforts to monitor 7-OH specifically, combined with analyses of existing data, reveal concerning signals of increasing human exposure and associated risk as discussed by FDA (Reissig et al. 2025) and in this Factor. The scope of use appears to be significant and growing, marked by a sharp increase in incidents beginning in late 2023 and continuing through 2025.

Adding to the domestic data, the UNODC has noted that since 2024, the U.S. and other jurisdictions worldwide have reported toxicology cases involving high-concentration 7-OH products to its Early Warning Advisory on New Psychoactive Substances (UNODC, 2025).

See further discussion relevant to scope and significance in Factors 4 and 6.

5.2.1 National Surveillance Systems

5.2.1.1 FAERS

FAERS reports involving 7-OH were identified through searches of the FAERS Public Dashboard and open FDA using the term “7-Hydroxymitragynine,” limited to cases in which 7-OH was designated as the primary suspect drug. No date restrictions or deduplication procedures were applied. The two sources largely overlapped, though 2 cases appeared exclusively in the Public Dashboard. In total, 14 unique cases were identified. Corresponding data were extracted from open FDA and qualitatively reviewed. A summary of findings is presented below.

The 14 FAERS case reports involving 7-OH primarily describe patterns of dependence, withdrawal, and psychiatric disturbances. Across patients ranging from their early 20s to mid-60s, reactions commonly included drug dependence, withdrawal syndrome, depression, anxiety, insomnia, somnolence, and impaired quality of life. Several cases noted GI complaints (e.g., nausea, vomiting, diarrhea, constipation), neurological issues

(e.g., dyskinesia, memory problems, dizziness), or musculoskeletal symptoms (e.g., myalgia, restless legs). Some patients reported product quality concerns or suspected tampering, suggesting variability in supply or formulation. Many cases involved concomitant use of prescription medications (e.g., clonidine, gabapentin, antidepressants, Suboxone, benzodiazepines) or other herbal mitragynine products, complicating causality assessments.

Importantly, 2 fatal cases associated with 7-OH consumption were recorded: one involving toxicity from multiple agents including opioids and mitragynine in a 38-year-old male, and another describing accidental poisoning and respiratory depression in association with polypharmacy (including citalopram, lamotrigine, and zopiclone) in a male from Norway. These highlight potential risks of combining 7-OH with other CNS-active substances. Overall, the data remain sparse but suggest that 7-OH is more frequently linked to dependence, withdrawal, psychiatric symptoms, and – in rare but severe cases – fatal outcomes, warranting continued monitoring and further investigation.

5.2.1.2 National Poison Data System

Between February 1, 2025 and April 30, 2025, the National Poison Data System (NPDS) recorded 53 closed human exposure cases involving 7-OH (Table 1). Of these, 24 were classified as abuse cases, and 37 involved single-substance exposures, including 16 single-substance abuse cases. The most common reasons for exposure were intentional abuse (24 cases, 16 single-substance), withdrawal-related use (8 cases, 6 single-substance), and unintentional general exposure (4 cases, all single-substance). Smaller numbers were attributed to suspected suicide (2 cases), adverse drug reactions (4 cases), misuse (3 total cases), therapeutic error (4 cases), and unknown reasons (2 cases).

Most reported clinical effects were moderate (13 cases, 6 single-substance) or minor (6 cases, 3 single-substance), with 3 major outcomes (including 1 single-substance). Five cases were judged as having minimal effects, and one was considered a potentially toxic exposure but could not be followed.

Age distribution showed that the majority of cases occurred in adults (≥ 18 years; 46 cases, including 23 abuse cases and 32 single-substance exposures), while 6 cases involved individuals under 18, and 1 case had unknown age.

Table 1. National Poison Data System Closed Human Exposure Cases^a (01Feb2025-30Apr2025)

	Number of Exposure Cases ^b	Number of Abuse Cases ^c	Single Substance Exposure Cases	Single Substance Abuse Cases
Total cases involving 7-OH	53	24	37	16
Reason				

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	Number of Exposure Cases ^b	Number of Abuse Cases ^c	Single Substance Exposure Cases	Single Substance Abuse Cases
Adverse drug reaction	4		2	
Intentional- abuse	24		16	
Intentional- misuse	4		3	
Intentional- suspected suicide	2		0	
Other- withdrawal	8		6	
Unintentional- general	4		4	
Unintentional- misuse	1		1	
Unintentional therapeutic error	4		3	
Unknown reason	2		2	
Related Clinical Outcomes				
Minor			6	3
Moderate			13	6
Major			3	1
Note followed, minimal clinical effects possible			5	3
Unable to follow, judged as potentially toxic exposure			1	0
Age				
< 18 years	6	1	5	0
≤ 18 years	46	23	32	16
Unknown age	1	0	0	0

Abbreviations: 7-OH = 7-hydroxymisragynine; NPDS = National Poison Data System.

Note: Related clinical outcomes includes cases with clinical effects deemed “related” to exposure based on timing, severity, and assessment of clinical effects by Poison Center Specialists. Definitions available from America’s Poison Centers: NPDS Full Report 2023 (Gummin et al., 2024, p. 235).

a Excludes cases classified as ‘confirmed non-exposure’.

b Cases may involve other substances, besides 7-OH.

Source: Adapted from NPDS dataset.

5.2.1.3 National Forensic Laboratory Information System (NFLIS)

The National Forensic Laboratory Information System (NFLIS) collects drug identification results obtained during law enforcement investigations involving potential

criminal possession and distribution of illicit drugs and substance seizures collected during those operations. Historically, mitragynine has never reached the threshold to be listed among the top 25 most frequently identified drugs, though it has appeared in lower-level reports. Mitragynine has not been reported in annual NFLIS reports because its levels have been relatively stable and low since about 2015. However, data can be obtained from the NFLIS Public Data Query System. As of August 2025, data from the NFLIS Public Data Query System showed 253 mitragynine drug reports in 2024, but specific data for 7-OH seizures are not yet separately reported in publicly available annual summaries. The lack of 7-OH specific data in law enforcement seizure reports represents an important current gap in surveillance.

5.2.1.4 DEA Toxicology Testing Program (DEA TOX)

The DEA TOX program analyzes toxicological evidence from death investigations. Between 2019 and 2025, 103 cases were identified where mitragynine, 7-OH, or mitragynine pseudoindoxyl were detected. A significant limitation of this data is the difficulty in discerning whether deaths are related to one specific alkaloid, as 7-OH is a metabolite of mitragynine. However, the report notes a trend: the number of fatal overdose cases in which one or more of these substances were detected was approximately 3-fold higher for the years 2023 to 2025 compared to the period from 2019 through 2022. This increase coincides directly with the recent market entry of concentrated 7-OH products, suggesting a strong temporal association between the availability of these new products and fatal outcomes.

It is important to note that many reported kratom-associated deaths involve toxic levels of other substances, and many lack the comprehensive toxicological testing needed to confirm a causal role for either mitragynine or 7-OH. Kratom products may also be present at opioid-related fatalities because they are often used to manage opioid use disorder or withdrawal. Additionally, routine toxicology screens may miss novel psychoactive substances, such as designer opioids or benzodiazepines, requiring more specialized and costly testing (Henningfield, Grundmann, Huestis, and Smith, 2024)

5.2.1.5 Other National Surveillance Data

Two important national surveillance systems that monitor substance use trends, NSDUH and the proprietary Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) (which also receives federal funding), have included “kratom” as a tracked substance” but have not differentiated traditional kratom products from concentrated 7-OH products. NSDUH provides prevalence estimates for kratom use (0.6% past-year use in 2024) but does not yet differentiate 7-OH use. As a result, their reported “kratom” data likely represent a combined population of kratom users and those using 7-OH products, a segment that appears to have emerged and grown rapidly in recent years. A further challenge in these surveillance efforts is that some individuals who use 7-OH may continue to report their past or current use simply as “kratom”, even when the product in question would more accurately be classified as a 7-OH product. These two surveillance systems also likely underestimate kratom use overall, possibly due to their survey designs and sampling approaches that primarily target major illicit and prescription drug use (see discussion in Henningfield, Grundmann, et al. (2022). These Kratom focused reports suggested estimates of approximately 1.7 to 2.0 million

past-year kratom consumers from 2019–2021 (Palamar, 2021; SAMHSA, 2023, 2024), with an estimated lifetime prevalence at 3.4 million based on 2018–2019 data (Schimmel, & Dart, 2020).

Other major surveillance systems, such as the Drug Abuse Warning Network (DAWN), which tracks drug-related emergency department visits, and the Treatment Episodes Data Set (TEDS), have not yet reported specific data for 7-OH, though the “New DAWN” system recently identified “7-OH” as a new slang term to monitor.

A more recent nationally representative survey suggests past 30 day (‘current use’) prevalence suggests potentially more than 20 million kratom users ages 18 and older (Grundmann et al., 2025). The recency of this survey conducted in 2024 makes it likely that some respondents were actually primary 7-OH users, possibly contributing to the larger estimated population of kratom consumption in earlier surveys.

Similarly, it is possible if not plausible that some fraction of adverse events reported to FDA’s Adverse Event Reporting System, to the poison control centers, and possibly deaths associated with kratom consumption involved consumption of 7-OH products in addition to or in place of kratom products that do not contain artificially boosted or high concentrations of 7-OH. This conclusion is consistent with the following observations by FDA in its Reissig-led scientific evaluation (Reissig et al., 2025):

“Available surveillance data indicate that abuse of 7-OH is occurring and is associated with serious harms; however, as noted previously, it is difficult to quantify the public health burden because surveillance systems do not provide estimates for the prevalence of 7-OH use and are only beginning to track the specific involvement of 7-OH enhanced products in exposure cases and overdoses. The current epidemiologic data on 7-OH exposures often lack sufficient detail to distinguish with confidence involvement of botanical kratom products from 7-OH enhanced products.” (Reissig et al., 2025, p. 14)

And in its Conclusions section:

“Due to the fact that 7-OH is both a metabolite of mitragynine and naturally present in low amounts in botanical kratom, using toxicology results to identify 7-OH as a primary or sole contributor in human exposures is challenging. There is also a need for improved clinical awareness and population surveillance to better characterize patterns of 7-OH use, the products that people are obtaining, and individual treatment needs following 7-OH exposure. Additionally, questions on 7-OH are not generally included in national surveys, and other data sources that rely on self-reported use of 7-OH likely underestimate the number of 7-OH exposure cases, as individuals may be unaware of the distinction from kratom products. Nonetheless, since specific codes were added earlier this year to document 7-OH exposure cases, U.S. poison centers have identified multiple single-substance cases of 7-OH exposure resulting in serious adverse clinical outcomes.” (Reissig et al., 2025, p. 18)

The foregoing observations of this report and those of Reissig et al. above are consistent with recent conclusions and evaluations by other experts which suggest that some fraction of the adverse events and possibly deaths that have been reported and interpreted as involving or even caused by kratom, were actually more likely attributable to the consumption of 7-OH products in addition to or in place of kratom (Grundmann et al., 2024; Hill, Boyer, et al., 2025; Papsun et al., 2023; Smith et al., 2025; Vadieli, Evoy, & Grundmann, 2025).

Taken together, the foregoing observations support the conclusion that it is urgent to add 7-OH to relevant substance surveillance systems including NSDUH, RADARS, FAERS, and poison control. Similarly, assessment of 7-OH in blood plasma in forensic toxicology examinations as well as kratom research in general is a critical need.

It is beyond the scope of this report to specify how surveillance systems should be designed to distinguish between kratom products and those containing 7-OH, including the precise wording of survey questions or the analytical methods to detect 7-OH. These should be developed with input from appropriate experts and stakeholders, ideally with a fast-track approach with a proposal from FDA and request for comments. A public meeting for comment convened by FDA, ideally with NIDA and DEA involvement may also help to ensure that the approaches to surveillance and biological assessment will be scientifically reliable, valid, and relevant to the emerging marketplace, regardless of whether or not 7-OH is ultimately scheduled.

5.2.2 Published Case Reports

Published case reports provide clinical evidence recorded and reported by trained healthcare professionals; however, these accounts are considered anecdotal and may not be representative of common experiences.

A case report by Wightman and Hu (2025) detailed the experience of a 38-year-old man with a history of opioid use disorder who escalated his use from kratom to concentrated 7-OH products, consuming up to eight 30 mg tablets daily. Upon stopping, he experienced a clear opioid withdrawal syndrome, with a peak Clinical Opiate Withdrawal Scale (i.e., COWS) score of 14. His symptoms, which included anxiety, insomnia, and restlessness, were successfully managed with buprenorphine during an inpatient stay.

Another case report described a 31-year-old who suffered severe substance-induced psychosis involving both kratom and cannabis, which resulted in self-amputation of his ears and penis (Broul et al., 2025).

5.2.3 Social Media Discussion

To investigate online sources of discussion around 7-OH, the search terms “7-OH”, “7-OH-MG”, “7-OH-MIT”, and “7-Hydroxymitragynine” were included in a boolean search of Erowid (erowid.org) using the Google search term “7-OH OR 7-OH-MG OR 7-OH-MIT OR 7-Hydroxymitragynine site:erowid.org”, and of Reddit (reddit.com) using the Google search term “7-OH OR 7-OH-MG OR 7-OH-MIT OR 7-Hydroxymitragynine site:reddit.com”. The searches were completed in August 2025.

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Six experience reports in the Erowid vault were found. Where provided, information on sex, age, body mass index, dose, route of administration, formulation, duration, and effects were recorded. Most (3/5 experience reports with dates) were recent (i.e., since 2024). The remaining 2 experience reports with dates described experiences from more than a decade ago (2007-2010). One experience report did not report its date.

In terms of demographics, all 6 reports came from males aged 22 years to 39 years (i.e., younger adults). Across these 6 experiences, the median dose was 13.5 mg (interquartile range [IQR]: 6.9 mg – 16.9 mg) or 0.15 mg/kg body mass (IQR: 0.09 mg/kg – 0.19 mg). The maximum dose was 120 mg or 1.5 mg/kg. Two reports (33%) described single-dose experiences, 2 reports (33%) described daily use for 2 days, and 2 reports (33%) described longer-term, daily use from 2 weeks to 6 months. The majority (67% of reports) described oral administration of 7-OH, while the remaining reports described sublingual administration (n=1; 17%) and insufflation (n=1; 17%). The majority (67% of reports) described pill/capsule/tablet formulations, while the remaining 2 (33%) described tincture/liquid formulations. Experiences lasted from 3-6 hours.

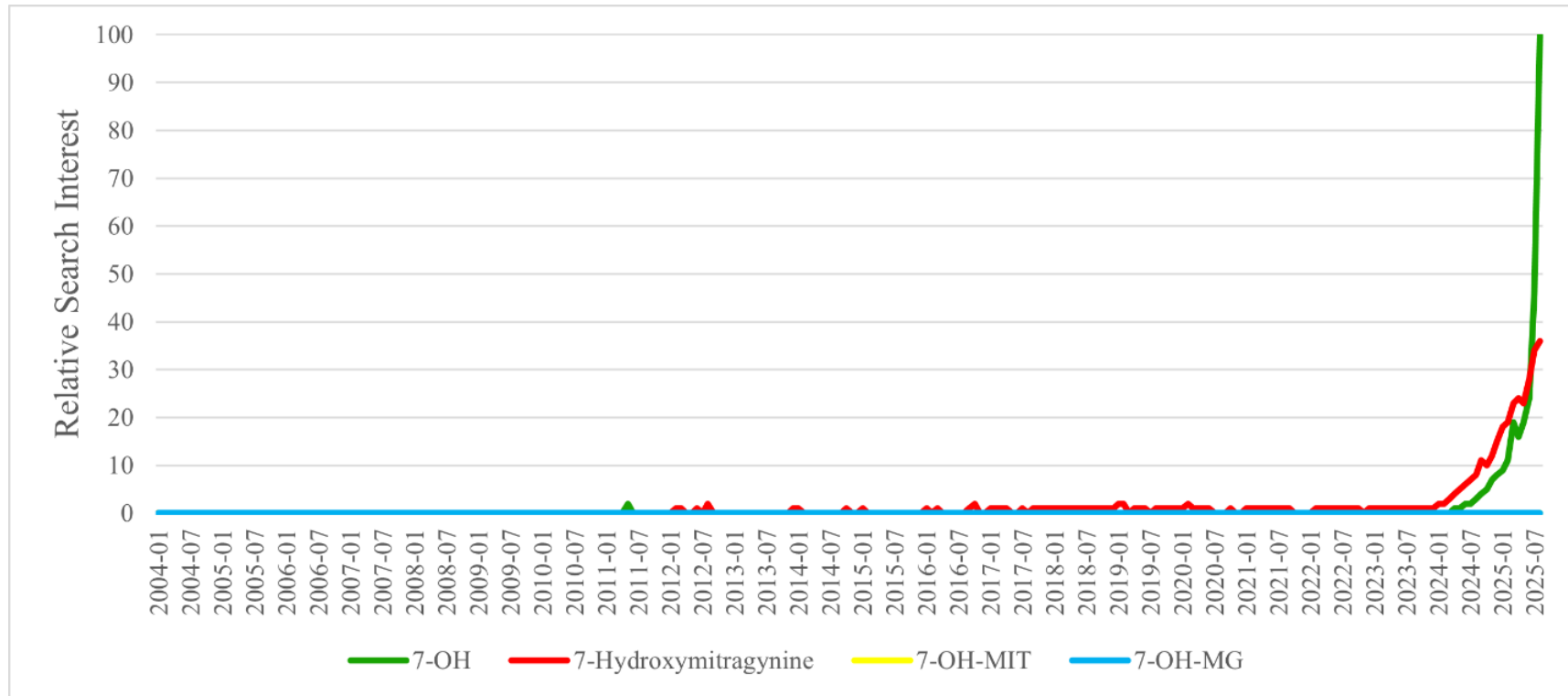
Only one report described concomitant substances, namely cannabis (smoked), though this does not necessarily mean that no other substances were taken. Effects included euphoria (83% of reports), cravings (50%), increased heart rate (33%), itch (33%), tiredness, lethargy, or sedation (33%), constipation (17%), self-reported “withdrawal” (17%), body shakes (17%), numbness (17%), weightlessness (17%), sick feeling (17%), feeling of relaxation (17%), aphrodisia (17%), analgesia (17%), loss of balance (17%), visual distortion (17%), and most significantly, hospitalization (17%) and self-reported “respiratory depression” (17%).

The following review of Reddit posts and comments on 7-OH is non-exhaustive. On Reddit, 7-OH was discussed in the Quitting Kratom subreddit (www.reddit.com/r/quittingkratom). Reddit posts and comments were much less descriptive than Erowid experience reports making inferences difficult. Nevertheless, a number of Reddit users reported using or formerly using kratom and being offered 7-OH, sometimes for free, from stores where they would typically purchase kratom. Most users who reported 7-OH use reported pill/capsule/tablet forms; tinctures/liquid formulations were relatively rare. Most posts reported daily use, up to 5 × daily, with use duration from 5 days to 8 months. Some users attempted to dissuade others from 7-OH use. Effects were consistent with Erowid experience reports, including euphoria, withdrawal, anxiety, insomnia, restlessness, involuntary arm and leg movement, abdominal pain, vomiting, body shakes, tightness in chest, tachycardia, diarrhoea, fatigue, sedation, dizziness, paranoia, anhedonia, kidney pain, and 1 case of hospitalization. Some Reddit users compared the severity of withdrawal from 7-OH to other substances; these included “worse than how I was with the oxy withdrawal” and “50% as bad as Fentanyl withdrawal”. Some Reddit users described stopping 7-OH use “cold turkey”, or using kratom or other substances including suboxone to “taper off” of 7-OH. Many posts and comments were missing data on dose. Among comments reporting withdrawal symptoms and dose, these ranged from 30 mg/day to 500 mg/day. Many posts and comments were missing data on dose. Among comments reporting withdrawal symptoms and dose, these ranged from 30 mg/day to 500 mg/day. Many

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7-OH was also discussed by a number of Reddit users in the Chronic Pain subreddit (<https://www.reddit.com/r/ChronicPain>) who reported using 7-OH for chronic pain management. Only one Reddit user discussing 7-OH for chronic pain reported dose; they reported taking 5.5 mg tablets twice daily (11 mg/day) and did not report adverse effects or withdrawal or withdrawal. This is lower than the doses reported by Reddit users experiencing withdrawal.

To quantify interest in 7-OH over time, Google Trends was used. Google search interest (i.e., the relative volume of Google searches) for “7-OH”, “7-OH-MG”, “7-OH-MIT”, and “7-Hydroxymitragynine” was extracted (Figure 1). Search interest in these search terms was zero from 2004 through 2010. Beginning in 2011, minimal search interest in “7-OH” and “7-Hydroxymitragynine” began, staying low through the end of 2023. Beginning in 2024 however, search interest in “7-OH” and “7-Hydroxymitragynine” grew rapidly, peaking in August 2025 shortly after FDA announced action on 7-OH products, which are the latest available data; search interest may continue to rise in the months following August 2025. Search interest in “7-OH-MIT” and “7-OH-MG” remained negligibly low throughout.

Figure 1. Google Search Interest in 7-OH-Related Search Terms

Note: 7-OH-mitragynine may be referred to by the short-hand versions “7-OH”, “7-OH-MIT”, or “7-OH-MG”.

There are many websites that focus specifically on drug misuse and abuse, some intended to discourage such use as well as those that appear dedicated to providing information in support of, if not to encourage, misuse and abuse of drugs. Many of the kratom-related postings involve what appear to be extremely high dosages of kratom substances and extracts, and self-made extracts from a variety of kratom sources. For example, users may combine several grams of kratom powder, several ounces of kratom leaves, and indeterminate forms of this or other substances. Some people have reported experiencing intoxication, euphoria, and other effects at these very high dosages, though typically their comparisons to other drugs provide a basis for understanding why kratom and kratom products apparently are rarely the substance of choice among people who seek abused drugs and are in search of better ways to get better highs and euphoria. There are self-reports of dependence and withdrawal, but these tended to involve extremely high intakes of kratom, apparently along with other substances.

5.3 Factor 6: What, if any, Risk is there to the Public Health

Factor 6 requires an integrated assessment of the overall risk a substance poses to public health. This involves synthesizing the pharmacological data on its intrinsic pharmacological risks (Factor 2), its potential for abuse and dependence (Factors 1 and 7), and the real-world evidence of its harm (Factors 4 and 5). For 7-OH, the available data indicate a potential risk to public health, which has led the FDA to conclude that it is a “dangerous substance” that poses an “emerging public health threat” and an “imminent hazard”. This risk is fundamentally driven by the substance's potent opioid pharmacology, exacerbated by its increasing availability in highly concentrated, unregulated products.

Evaluation of Factor 6 can include individual and public health benefits evidence as well because real and perceived benefits can contribute to evaluating FDA approved pharmaceuticals as well as substances that have not been approved for therapeutic use (Henningfield, Coe, et al., 2022; Henningfield et al., 2025).

FDA's July 29, 2025 summary of the science (Reissig et al., 2025) and other FDA documents release on July 29 made clear the concerns of FDA and the DHHS have about the risks of 7-OH. In FDA's July 29, 2025 educational slide set “Preventing the Next Wave of the Opioid Epidemic: What You Need to Know about 7-OH (FDA, 2025b), the second slide depicted four waves of the opioid crisis of approximately equal size and shape. These were labeled “prescription pills”, “heroin”, “fentanyl”, and “7-OH”, respectively. While the conclusion that 7-OH presents a potential and imminent public health risk necessitating regulatory attention is supported, caution is warranted against overstating the overdose risk, particularly given the likelihood of misinterpretation by the public and media when hearing references to 7-OH as “more potent than morphine”, even though the term “overdose” is not used in the figure.

Despite evidence suggesting thousands of individuals are currently using 7-OH – including some who appear to be consuming highly concentrated preparations and substantial total doses – the documented incidence of fatalities directly attributable to 7-OH remains very low. Even if, as FDA has suggested, 7-OH-related deaths are

underreported, it is notable that such cases appear to be rare. This low apparent lethality may be explained by two key factors: first, the predominant route of administration among users is oral rather than intravenous; and second, 7-OH exhibits the pharmacological profile of a partial MOR agonist by several measures, as discussed in Factor 2.

The available evidence indicates that 7-OH may indeed pose a “risk to public health” or a “national drug threat”, thereby warranting regulatory attention and interventions as discussed in Factors 4 and 5 and below. However, it remains uncertain whether 7-OH poses a population-level overdose risk comparable to that of other opioids. This uncertainty does not diminish the case for control measures; this report concurs that such measures – including potential scheduling under the CSA – are justified. However, it is important to recognize that some individuals report using 7-OH as their preferred and/or most effective alternative to opioids known to carry high risks of fatal overdose, or as a means of self-managing other serious disorders. Considering this population should inform any policy approaches, particularly those involving criminal penalties for possession if 7-OH is placed in Schedule I, as discussed in the policy section of this report.

5.3.1 Pharmacological Risks

The primary risk inherent to 7-OH is its potent activity at the MOR, which mediates not only its abuse-related effects but also its most dangerous potential adverse effect: respiratory depression. As reported by Gonzalez et al. (2025), 7-OH produces dose-dependent respiratory depression that is reversible with naloxone, a classic feature of opioid toxicity. While some research suggests its G-protein bias and lack of measurable β -arrestin-2 recruitment may confer a degree of safety relative to classical opioids at equianalgesic doses, this risk may preclude 7-OH to be marketed as a dietary ingredient to be used in supplements regardless of whether it is placed in Schedule I.

5.3.2 Abuse, Dependence, and Withdrawal Risk

While the abuse-related risk of 7-OH is primarily attributed to its effects at the MOR receptors, its pharmacology is not identical to that of classical opioids that are primarily active at the MOR (Factor 2). The FDA's 2025 assessment states that 7-OH produces “physical dependence, and withdrawal symptoms characteristic of classical opioids” and notes that clinical presentations include “opioid-like withdrawal syndromes” (Reissig et al., 2025). This is supported by published case reports in the medical literature, with reports of symptoms associated with opioid withdrawal including anxiety, insomnia, rhinorrhea, abdominal discomfort, restlessness, diaphoresis, and chills that were successfully managed with buprenorphine, a standard treatment for opioid withdrawal and dependence (Wightman, & Hu, 2025). However, these preliminary findings merit further study.

As evidenced by user reports, the availability of potent products with concentrations of 7-OH that is far higher than is found naturally may be facilitating patterns of chronic, escalating dose use that can lead to dependence, withdrawal, and other symptoms associated with drugs of abuse. The consequences of this include not only the direct

risk of harm from the substance itself but also the broader medical, psychological, and social harms associated with addiction.

The opioid-like withdrawal syndromes associated with 7-OH dependence presents another risk. Individuals attempting cessation may experience physical and psychological symptoms, which can be detrimental to their work and personal lives, a major barrier to recovery, and a cause to relapse. In some cases, individuals may require medically supervised withdrawal and medication-assisted treatment (e.g., with buprenorphine), placing additional burden on the healthcare system.

5.3.3 Potential Benefits to Consumers and Public Health

Anecdotal reports in public media and other sources indicate that some 7-OH users perceive it to be more effective, acceptable, or accessible than FDA approved medicines, kratom, or other approaches for their conditions. Similar conclusions for kratom were reached in 2016 (Henningfield and Fant, 2016), and in subsequent analyses (Giroir, 2018; UNODC, 2021). Consequently, removal of 7-OH from the licit marketplace without simultaneously ensuring the availability of viable accessible alternatives carries the risks of unintended consequences. These include the risk that current 7-OH consumers may relapse to potentially deadlier opioid use, as well as the likely emergence of an illicit market in which 7-OH products would proliferate without the quality standards that some 7-OH makers and marketers appear to voluntarily adhere. An illicit 7-OH market also raises the potential, if not likelihood, of 7-OH products being replaced or adulterated with fentanyl related substances. While 7-OH's potential benefits do not necessarily affect whether substances or products should be scheduled, these issues should be considered in how scheduling actions are implemented to minimize unintended individual and public health consequences.

5.4 Implications

The widespread use of highly concentrated 7-OH products is a relatively new phenomenon in the U.S., but it appears to be growing rapidly. Since about 2022, data from surveillance systems and user reports from social media, surveys, and case studies provide valuable insights into the patterns of 7-OH use, with users reporting that they are using it for pain management, to self-treat opioid withdrawal, and for recreational purposes. Data from America's Poison Centers also indicate a growing public health problem, with a rising number of exposure cases involving 7-OH and serious health effects. The FDA has also issued warnings about the public health risks associated with 7-OH, citing the high concentrations of the substance in some products and the lack of regulation and quality control.

It is important to note that 7-OH associated outcomes, both at the individual and population levels, have likely been underreported and instead attributed broadly to "kratom". This underestimation arises because current surveillance methodology does not distinguish 7-OH products from traditional kratom preparations, instead aggregating them into a single "kratom" category. This problem is exacerbated by marketing and labeling of many 7-OH products as "kratom" or "kratom derived" with implied safety statements based on studies of kratom and its far more widely studied naturally occurring constituent, mitragynine.

Despite limitations, it is clear that 7-OH is becoming more of a concern and priority for regulatory, law enforcement, and surveillance authorities. Available evidence suggests that there are signals of meaningful real-world nonmedical use and abuse with potentially significant medical outcomes, such as dependence, withdrawal, and development of substance use disorder. However, it is still not clear the severity of the risk posed to the public health by 7-OH. While surveillance systems are capturing an increasing number of cases regarding kratom, this coincides with a rapidly growing kratom market with some estimates suggesting the total market size to be 1-1.5 billion USD. Presumably, a proportion of these cases are due to consumption of concentrated 7-OH products, as many of these cases have been included as “kratom” cases, though this figure is unclear based on current surveillance capabilities.

For example, the 44th WHO Expert Committee on Drug Dependence (ECDD) reviewed the available evidence on kratom and its alkaloids in 2020 (UNODC, 2021). It concluded that there was insufficient evidence to recommend a critical review of these substances. However, the committee also noted the increasing availability of concentrated kratom products and the potential for these products to pose a public health risk. The UNODC has also issued an announcement about new kratom-related products, expressing concern about their potential health effects. However, this report was focused on kratom plant products and extracts and mitragynine studies and not the subcategory of high-concentration 7-OH products, which had not yet emerged as a significant or substantial category of product in the U.S. or globally.

It is critical to characterize the relative risk of 7-OH to that of kratom products that are consistent with the natural constitution of the kratom plant, and to classical drugs of abuse. Despite a growing kratom market, there have been few signals of risk to the public health from natural kratom products, and a number of reports and surveys showing consumers using them for therapeutic purposes (Grundmann et al., 2022; Smith, & Lawson, 2017). FDA in its 2018 determination to rescind the recommendation for CSA control of mitragynine and 7-OH cited a “potentially substantial risk to public health if these chemicals were scheduled at this time” due to potential adverse consequences if kratom is no longer available for people using for symptoms such as intractable pain, psychological distress, risk for suicide, transition from opioids or other potential or harmful drugs (Giroir, 2018). Similarly, reported use of 7-OH includes consumers and patients using for therapeutic purposes, and who may suffer unintended adverse consequences from its sudden removal from the market. Given its distinct risk profile, especially in the context of highly concentrated 7-OH products, careful surveillance and research are necessary and warranted including but not limited to studying 7-OH using accepted FDA toxicological standards (e.g., through NIH funded research or through development as an FDA approved drug).

6 Factor 7: The Psychic or Physiological Dependence Liability

As discussed in Factor 1 and elsewhere, this report agrees with FDA regarding the evidence that some 7-OH consumers can become psychologically and physically dependent and develop substance use and withdrawal disorders, respectively. However, the level of risk and an evidence-based characterization of 7-OH dependency, use disorder, or withdrawal has received little study and more research is warranted,

regardless of the scheduling action and approach. The existing data are likely to be considered insufficient to conclude at present that the 7-OH withdrawal syndrome is sufficiently similar to classical opioids to warrant inclusion in a diagnostic manual.

7 Factor 8: Whether the Substance is an Immediate Precursor of a Substance Already Controlled

It is important to note that 7-OH does not meet the prototypical criteria of Factor 8 as an immediate precursor of a substance already controlled as it is neither an immediate precursor of a substance already controlled, nor is it an opioid based on its botanical origin or chemical structure. It is not an immediate chemical precursor used in the synthesis of any currently controlled substance. Furthermore, 7-OH is a metabolite of mitragynine, a naturally occurring alkaloid from the *Mitragyna speciosa* plant, which is botanically unrelated to the opium poppy (*Papaver somniferum*). Therefore, it is not an opiate derived by extraction or chemical synthesis from opium or its constituents, such as morphine or thebaine.

However, the CSA includes a provision (21 U.S.C. § 802(18)) that guides determination of whether a substance can be determined to be sufficiently pharmacologically equivalent to morphine with respect to key effects related to “addiction liability” to be designated and regulated as an opioid. Specifically, no. 18 states:

“The term ‘opiate’ or ‘opioid’ means any drug or other substance having an addiction-forming or addiction-sustaining liability similar to morphine or being capable of conversion into a drug having such addiction-forming or addiction-sustaining liability.”

This pharmacological definition is critical to the regulatory consideration of 7-OH. It allows the DEA, upon recommendation from DHHS, to classify a substance as an opioid based on its effects, even if it does not meet the structural or precursor criteria of Factor 8. The determination of whether a substance has an “addiction-forming or addiction-sustaining liability similar to morphine” is based on the scientific and medical evidence evaluated under the other factors of the 8-FA, particularly Factors 1, 2, 3, and 7.

An example of this in pharmaceutical development was tapentadol. During its evaluation and development as an analgesic, it was not designated as an opioid based on its chemical structure; however, based on its overall pharmacological profile and similarity to morphine and related opioids, tapentadol was placed in Schedule II of the CSA, along with morphine and oxycodone, following its approval for therapeutic use and is now widely classified as an “opioid”.

8 Scheduling Recommendation

This 8-FA supports FDA’s preliminary July 29, 2025 recommendation that placement of 7-OH in the CSA is warranted. Moreover, because 7-OH has not been approved by FDA for therapeutic use and has not been determined by FDA and DHHS to be commonly accepted for medical use (i.e., CAMU), the only CSA scheduling option is Schedule I.

Specifically, the present analysis supports FDA's "Assessment of the Scientific Data and Toxicological Concerns" which included the following conclusions:

"Based on demonstrated pharmacology, repeated or prolonged use of 7-OH would lead to tolerance, physical dependence, and potentially to opioid addiction — typical of mu opioid agonist drugs of abuse."

The analysis of Factors 1, 2, 3 and 7 in the present report and the FDA analysis both support the conclusion that 7-OH meets the statutory criteria of the Controlled Substances Act's specific provision (at 21 U.S.C. § 802(18)) that guides determination of whether a substance can be determined to be sufficiently pharmacologically equivalent to morphine with respect to key effects related to "addiction liability". Thus, 7-OH can be designated and regulated as an opioid as discussed above in Factor 8.

Moreover, with respect to the determination of whether 7-OH poses a known or imminent public health threat, which is among the criteria for both temporary (i.e., "emergency") scheduling and permanent scheduling, FDA's July 29th analysis concluded as follows:

"The pharmacological profile, abuse liability, and emerging patterns of non-medical use establish 7-OH as a dangerous substance. Current regulatory gaps have enabled widespread availability of these products despite their opioid-like properties and necessitate immediate policy intervention to address this emerging threat to American public health."

Factors 4, 5, and 6 in the present report supports FDA's conclusion that 7-OH poses a likely imminent public health threat, thus supporting the known or imminent public health threat criteria for temporary and permanent scheduling.

8.1 Policy Implementation Considerations to Minimize Unintended Consequences

Evidence suggests that there is likely a proportion of individuals who may benefit from their use of 7-OH, with some considering it a life-saving path away from more deadly illicit opioids. While such reports may not, on their own, be sufficient justification to avoid scheduling 7-OH, they should be considered in how such a regulatory policy is implemented and enforced. As discussed in greater detail in the Research Priorities and Policy Considerations section below, some 7-OH consumers may need time, support, and assistance to identify effective alternatives, and to reduce the likelihood that a significant illicit market for 7-OH will emerge if 7-OH is scheduled.

The FDA appeared careful in its July 29th documents and press conference to distinguish between concentrated 7-OH products and natural kratom products, which it acknowledges often contains detectable levels of 7-OH. For controlled substances the CSA does not set a level of for controlled substances that can be marketed without control. However, there are examples of substances and products that contain low levels of substances. For example, FDA has not banned, and DEA has not scheduled, poppy seeds used in cooking even though their consumption can produce detectable levels of morphine following consumption of poppy seed pastries, curries and other

foods. Other examples include a Parkinson's Disease diagnostic scanning assay that includes small amounts of cocaine related substances that DEA determined did not require scheduling. Implementation may include a performance standard for kratom products such as the maximum allowable amount per serving size.

As discussed in Factor 4, 5 and 6 and in the policy implications of this report, a subset of 7-OH users consider it to be their path away from illicit or pharmaceutical opioids that likely carry greater risks of overdose death than 7-OH. Individuals also report benefits such as relief of pain, sometimes describing 7-OH as more effective or preferred to FDA approved medicines or kratom. Although there are significant gaps in the current body of evidence that do not allow credible estimates of the incidence of such cases or the prevalence among 7-OH users, these reports underscore the importance of carefully planning and implementing any scheduling action. Enforcement priorities should aim to minimize the risks of 7-OH users relapsing to more deadly opioid use, and prevent the emergence of an illicit market in which trafficking organizations such as cartels manufacture and distribute unregulated 7-OH products. Such illicit products may lack the quality controls observed by at least some current manufacturers. Such illicit marketers may also add fentanyl related substances to 7-OH for boosted effects or even replace 7-OH with fentanyl related substances.

To be clear, this discussion of potential unintended public health consequences does not mean that scheduling is not warranted; rather, it underscores the need for thoughtful implementation giving consideration to the potentially thousands of current 7-OH consumers. The timing, scope, and enforcement approach to scheduling and policy implementation should be carefully considered by the DEA/Department of Justice (DOJ) ideally in coordination with CDC, FDA, and NIH, with diverse stakeholder input (including 7-OH consumers). Such coordination would provide the umbrella of supporting surveillance, assistance, and research to detect and minimize unintended consequences, and provide time and assistance to current 7-OH users to find alternatives to 7-OH.

9 Research Priorities and Policy Considerations

The recommendation by the FDA to the DEA of a scheduling action to control 7-OH under the CSA represents a significant federal response to what the agency has deemed an "emerging public health threat". This action is a continuation of a complex history of regulatory considerations for kratom and its alkaloids and has continued to highlight gaps in the regulatory and legal framework for regulating novel botanical psychoactive substances. Some experts may feel that potentially lower real-world risks of addiction, abuse, and overdose exist for 7-OH and therefore warrant less restrictive scheduling than those drugs that are placed in Schedule II (i.e., fentanyl and oxycodone) and Schedule I (i.e., heroin).

However, under current law, Schedule I is the only option for 7-OH. The CSA makes clear that if a drug has sufficient abuse potential to warrant scheduling and it is not approved by FDA or designated as CAMU, then placement in Schedule I is required. Further, while the evidence of overdose risk is primarily by the intravenous route and real world-use is primarily by the potentially lower risk oral route, the pharmacological

and toxicological profile of the ‘substance’ or ‘chemical entity’ is the basis for scheduling – regardless of route. If 7-OH is placed in Schedule I, and then in the future, a New Drug Application for a 7-OH containing product is developed and approved by FDA, that product will be removed from Schedule I and rescheduled or removed from CSA control as informed by an 8-FA for that product and other considerations.

Specifically, as per the CSA, approved drugs are scheduled according to their abuse-related risks as guided by the 8-FA in which Schedule V is least restrictive (e.g., cough preparations with less than 200 milligrams of codeine or per 100 milliliters, and pregabalin) and Schedule II is most restrictive (e.g., morphine, oxycodone, amphetamine, cocaine and fentanyl).

Thus, FDA’s report, “7-Hydroxymitragynine (7-OH): An Assessment of the Scientific Data and Toxicological Concerns Around an Emerging Opioid Threat”, summarizes the chemical, pharmacological and epidemiological evidence related to 7-OH safety and abuse potential. Although not structured as a formal 8-FA, it includes key data which formed the basis for its determination that:

- (a) 7-OH demonstrates sufficient pharmacological equivalence on key abuse and safety related variables to be considered an “opioid”, thus triggering CSA’s statutory implications that include placement in Schedule I if not approved as a drug, and placement in Schedule II if under development with an Investigational New Drug (IND) application that has been accepted; and,
- (b) 7-OH is “dangerous” and poses an imminent hazard to public health which satisfies a key criterion for temporary (aka “emergency”) drug scheduling.

A critical implication of these two determinations is that to warrant scheduling, the substance does not need to carry the same or equivalent abuse potential or overdose risk as classical opioids (e.g., frequent reference standards morphine and oxycodone, or epidemiological comparators such as heroin and fentanyl). However, in practice, the greater the risk to public health, the greater the urgency and justification for rapid action.

It is important to note that the definition of CAMU has been recently evolving, as evidenced by the 2024 DEA recommendation to place marijuana into Schedule III of the CSA (DEA, 2024), which states:

“In its most recent evaluation, HHS informed DEA of its view that DEA’s previous approach to determining whether a drug has a CAMU does not adequately account for certain indicia of medical use that, where present, are relevant to determining whether a substance has a CAMU for purposes of scheduling under the CSA. Specifically, HHS observed that DEA’s tests left no room for an evaluation of (1) whether there is widespread medical use of a drug under the supervision of licensed health care practitioners under State-authorized programs and, (2) if so, whether there is credible scientific evidence supporting such medical use.”

DHHS therefore developed an alternative test wherein:

“Under Part 1 of the HHS CAMU test, the Office of the Assistant Secretary for Health (“OASH”) considered whether there is widespread current experience with medical use of marijuana in the United States by licensed [healthcare providers] HCPs operating in accordance with implemented State-authorized programs, where such medical use is recognized by entities that regulate the practice of medicine under these State jurisdictions. Part 2 of the CAMU test evaluated whether there exists some credible scientific support for at least one of the medical conditions for which the Part 1 test is satisfied. The evaluation in Part 2, undertaken by FDA, was not meant to be, nor is it, a determination of safety and efficacy under the Federal Food, Drug, and Cosmetic Act’s drug approval standard for new human or animal drugs. Rather, HHS’s two-part test is designed to evaluate whether a substance, in this case marijuana, has a CAMU for purposes of drug scheduling recommendations and placement in a drug schedule consistent with criteria set forth in 21 U.S.C. 812(b).”

While there are reports of consumers using 7-OH for therapeutic purposes, the available body of evidence falls far short of the level that supported DHHS/FDA designation of “marijuana” as CAMU in its 2023 analysis, led by the Office of the Assistant Secretary of Health (OASH). The analysis included extensive data which confirmed “that more than 30,000 HCPs [health care providers] across 43 U.S. jurisdictions are authorized to recommend the medical use of marijuana for more than six million registered patients for at least 15 medical conditions. OASH’s Part 1 analysis, therefore, supports the finding that marijuana has at least one CAMU in the United States.” Note this evaluation does not mean marijuana has been approved as a drug for any given condition. Rather, the widespread and well-documented medical use was deemed sufficient to satisfy the CAMU requirement and provide the basis for removal of marijuana from Schedule I – a recommendation that is presently under consideration by the DEA. Currently, no comparable body of evidence exists to support a similar CAMU designation for 7-OH

Likewise, neither kratom nor any of its alkaloids (including mitragynine, the predominant active constituent in most kratom products and extracts) have been designated as CAMU. Further, kratom and its alkaloids have not been designated as ‘opioids’ based on botanical origin, chemical structure, or sufficient pharmacological equivalence to morphine. Moreover, several prior 8-FAs have determined that they do not warrant scheduling under the Controlled Substances Act. This includes the 2018 analysis by Assistant Secretary Brett Giroir (Giroir, 2018), which rescinded an earlier recommendation to schedule kratom’s main alkaloids, mitragynine and 7-OH. That rescission was based on the determination that the scientific evidence at the time was underdeveloped and insufficient, and that scheduling carried a “significant risk of immediate adverse public health consequences,” such as driving users to more lethal opioids.

Similarly, the in 2020, the World Health Organization’s Expert Committee on Drug Dependence (ECDD), found insufficient evidence to recommend a critical review of kratom, mitragynine, and 7-OH for international scheduling, though it recommended continued surveillance (UNODC, 2021). Three other 8-FA (one submitted as a comment

to DEA in 2016 [Henningfield and Fant, 2016], and two as peer reviewed publications (Henningfield, Fant, and Wang, 2017; Henningfield, Wang, and Huestis, 2021) also concluded that kratom did not warrant CSA scheduling.

Although these prior evaluations included consideration of 7-OH, they did not find sufficient basis for scheduling at the time. However, the science has advanced significantly in recent years as discussed in Factor 3. Specifically, the introduction to *Kratom: History, Science, and Therapeutic Potential*, a recently published book featuring contributions from many of the world's leading kratom researchers, notes the rate of annual kratom science publications increased from about 20 per year in 2016 to more than 130 per year by 2024, with the increased fueled heavily by research funding by the National Institutes of Health (NIH), NIDA (Henningfield, Beyer, & Raffa, 2025).

The rapid growth in 7-OH marketing and consumption since 2022, coupled with an expanding body of research addressing its abuse potential and safety (Reissig et al. 2025), in addition to the increased body of evidence regarding kratom in general, has altered the public health context. Accordingly, this report concurs with the July 2025 FDA's evaluation that potential and increasing public health risks – exacerbated by extensive 7-OH product marketing and consumer consumption, rising consumer exposure, and new scientific evidence – support the recommendations for scheduling.

As discussed earlier, the foregoing observations of this report and those of Reissig et al. above are consistent with recent conclusions and evaluations by other experts which suggest that some fraction of the adverse events and possibly deaths that have been reported and or interpreted as involving or even caused by kratom, were actually more likely attributable to the consumption of 7-OH products in addition to or in place of kratom (Grundmann et al., 2024; Hill, Boyer, et al., 2025; Papsun et al., 2023; Smith et al., 2025; Vadiiei, Evoy, & Grundmann, 2025).

Taken together, the foregoing observations support the conclusion that it is urgent to add 7-OH to relevant substance surveillance systems including NSDUH, RADARS, FAERS, and poison control. Similarly, assessment of 7-OH in blood plasma in forensic toxicology examinations as well as kratom research in general is a critical need. As discussed in Factor 5, it is beyond the scope of this report to specify how surveillance systems should be designed to distinguish between kratom products and those containing 7-OH, including the precise wording of survey questions or the analytical methods to detect 7-OH, which should be developed with input from appropriate experts and stakeholders.

9.1 Comparison of 7-OH to Kratom and other Substances

Currently, many kratom and related products, including concentrated 7-OH products are marketed as dietary ingredients and/or supplements, though to date no NDIN has been accepted by FDA and the lack of documented history of use prior to 1994 has precluded its acceptance as an ingredient exempt from the NDIN requirements as described in the Dietary Supplement Health and Education Act (DSHEA) of 1994. A crucial aspect to determine 7-OH's risk to the public health is the distinction between traditional kratom and concentrated 7-OH products. The FDA has explicitly stated that its primary concern

is not with natural kratom leaf, where 7-OH is present in only trace amounts, but with the “concentrated 7-OH opioid products” that are “far more dangerous”. While traditional kratom is not without risks and has been associated with dependence and adverse events, its risk profile appears to be substantially lower than that of concentrated 7-OH. The limiting nature of consuming bulky plant powder and the complex interplay of dozens of alkaloids in traditional kratom may moderate its effects and abuse potential compared to isolated 7-OH.

However, neither these statements from FDA nor kratom’s apparent lack of signal of risk to public health should be misinterpreted that the Agency accepts kratom as safe. It has not accepted any submitted NDINs in which the standard for acceptance is that the products specified in the NDIN’s were found to be “acceptably safe”, though this has not been a standard that FDA has formally defined. In December 2023, FDA stated in a federal court hearing in the Southern District of California that the Agency had not yet determined if kratom was hazardous (United States v. Nine2Five, LLC, No. 3:23-CR-00179-TWR [S.D. Cal.], ECF No. 110-8). FDA also reminds the public on its kratom website page that kratom has not been approved for therapeutic use. While this is not directly relevant to the legality or safety of kratom as approval for therapeutic use is not a standard for accepting a substance as a dietary substance, it means that products cannot legally be marketed with disease treatment and prevention claims.

When compared to illicit opioids, FDA describes the risk of 7-OH as a potential “new wave of the opioid epidemic”, and implies the potential risk of fueling an overdose epidemic rivaling that by three earlier waves of prescription drugs, heroin, and fentanyl (and related substances) - a message reinforced by recent pharmacological and epidemiological data presented by FDA (Reissig et al., 2025) and portrayed in a graphic in its educational materials (FDA, 2025b).

9.2 Potential Unintended Consequences of Schedule I Placement and Policy Implications

9.2.1 Potential Unintended Consequences of Scheduling

While scheduling 7-OH under the CSA is intended to mitigate public health risks, such an action has the potential to create unintended negative outcomes. A comprehensive policy analysis must consider potential unintended consequences, which could, in some cases, undermine the primary goal of protecting public health.

9.2.1.1 Relapse by Patients and Consumers to Harmful Opioids

A key consideration in the 2018 DHHS decision not to schedule kratom or its alkaloids was the concern that a ban would cause individuals using kratom to manage opioid withdrawal symptoms or chronic pain to switch to more dangerous and harmful substances such as heroin and fentanyl (Giroir, 2018). These risks and others described by Giroir (see also Henningfield, Fant and Wang (2018); Henningfield, Grundmann, et al. (2019); Henningfield and Fant (2016)) appear plausible if 7-OH is scheduled.

As discussed in Factor 6 of this report, a similar conclusion as pertains to 7-OH is based on admittedly limited anecdotal evidence suggesting that some 7-OH users report that 7-OH to be more effective, acceptable, or assessable than FDA approved medicines, kratom, or other approaches, as was similarly concluded for kratom in 2016 (Henningfield and Fant, 2016), and in subsequent analyses (Giroir, 2018; UNODC, 2021). Nonetheless, it is foreseeable that removal of 7-OH from the licit marketplace carries the risks of unintended consequences of 7-OH consumers relapsing to potentially deadlier opioid use, and resulting in an illicit market in which 7-OH products would proliferate without the quality standards that some 7-OH makers and marketers appear to voluntarily adhere.

An illicit 7-OH market also raises the potential if not likelihood of 7-OH products being replaced or adulterated with fentanyl related substances. This risk is not theoretical and decades of experience with opioids have elucidated what is sometimes referred to as the “whack A mole” effect, whereby reduction in access to one opioid has little effect on overall opioid use as people simply migrate to other opioids. Thus, for example, when the abuse deterrent formulation of OxyContin was marketed in August 2010 and the original OxyContin removed from the market, OxyContin abuse actually decreased. However, surveillance studies over the next two years revealed there was no reduction in opioid use but rather use of other opioids (including fentanyl and hydromorphone selection) rose markedly from 20% to 32% and heroin use nearly doubled (Cicero, Ellis, & Surratt, 2012). Even more sobering is that although high dose and Schedule II opioid prescribing rates have declined in the U.S. since about 2012, annual opioid overdose deaths have continued to increase primarily due to heroin and fentanyl related substances (Henningfield, Ashworth, et al., 2019; Strickler et al., 2020).

9.2.1.2 Restrictions and Impediments to Scientific Research

Placing 7-OH in Schedule I would impose significant regulatory barriers on scientific research. Investigators wishing to study the substance – whether for its risks or its potential therapeutic benefits – would face stringent registration, security, and record-keeping requirements from the DEA, as well as funding limitations in procuring, storing, or administering these substances in research settings (Andreae et al., 2016). This could stifle much-needed research into 7-OH's pharmacology, safety profile, and potential as a lead compound for developing safer analgesics. The G-protein biased agonism of 7-OH is of significant scientific interest for the development of novel pain medications with fewer side effects, and a Schedule I designation could severely hamper progress in this area.

9.2.1.3 Criminalization and Enforcement

Placement in Schedule I could have profound consequences including potentially severe restrictions and criminal penalties for possession and distribution. As the benefits and risks of 7-OH and the extent to which consumers are using 7-OH for therapeutic purposes have yet to be determined, it's important for policy decisions to consider the actions and effects that may have potential unintended consequences and how to minimize the risks.

While there are no reliable estimates of how many people use 7-OH for therapeutic purposes, the potentially thousands of people using 7-OH to refrain from harmful opioid use may benefit from additional federal resources, funding treatment and harm reduction for substance use issues, as well as the DOJ deprioritizing individual possession while prioritizing inappropriate marketing and sales. The specific options and approaches for policy to minimize unintended consequences are beyond the scope of this report; however, this report recommends consideration should be given to risk mitigation before 7-OH is scheduled. A request for comment and possibly a public hearing to give consumers and various important stakeholders consideration is recommended, because preliminary anecdotal reports suggest that for some people 7-OH is their lifeline away from potentially more deadly opioid such as fentanyl. They may need time and assistance to find alternative, acceptable, and effective therapeutic strategies and support.

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11 Appendices

11.1 Appendix 1: Published Findings Related to Abuse, Physical Dependence, Withdrawal, and Safety Signals of 7-OH

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Table 2. Published Findings Related to Abuse, Physical Dependence, Withdrawal, and Safety Signals of 7-OH

Publication or Source	Short Title or Description	Comparators Studied or Mentioned	Abuse-related Variables	Physical Dependence & Withdrawal	Safety Individual Population	Comments
Factor 1: Actual or Relative Potential for Abuse						
Gonzalez et al. (2025)	Mitragynine and 7-Hydroxymitragynine: Bidirectional Effects on Breathing in Rats.	MG: 5.6, 10, 17.8 mg/kg, IV 7-HMG: 1, 3.2, 10 mg/kg, IV Positive control opioid: morphine (10, 32 mg/kg IV). Antagonist: naloxone (1 mg/kg IV).	NA	Did not assess withdrawal	Morphine caused dose-dependent respiratory depression while mitragynine unexpectedly increased respiratory frequency at 10 mg/kg, with no significant depression of tidal/minute volume. High dose (17.8 mg/kg) caused seizures in some rats without respiratory depression. MG's stimulant effect was not blocked by naloxone, suggesting a non-opioid mechanism. 7-OH-MG caused dose-dependent respiratory depression: reduced frequency and minute volume at 3.2 and 10 mg/kg, tidal volume trends toward depression. Naloxone fully reversed 7-HMG-induced respiratory depression (tidal and minute volume restored).	NA
Sudmoon et al. (2025) Discovery of rhynchophylline and mitraphylline in two Thai	Toxicity testing of two Thai Mitragyna species and the investigation of their biological activity via opioid	MG, 7-OH-MG, mitraphylline, and rhynchophylline	NA	NA	Mild motor impairment seen at ≥ 50 mg/kg IP, no lethal effects	MG exhibited moderate affinity for the MOR and KOR, whereas 7-OH-MG had 14x greater binding affinity than MG. Rhynchophylline, MG, and 7-OH-MG were found in other Mitragyna species.

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Publication or Source	Short Title or Description	Comparators Studied or Mentioned	Abuse-related Variables	Physical Dependence & Withdrawal	Safety Individual Population	Comments
Mitragyna species and the investigation of their biological activity via opioid gene expression analysis.	gene expression analysis					
Henningfield, Rodricks, et al. (2022)	Rat respiratory effects & plasma MG & 7-OH-MG	Oxy & MG	General behavior (e.g., sedation)	NA	Oxy: respiratory depression & deaths; MG: no respiratory effect	Plasma MG & 7-OH-MG confirmed high-dose exposure.
Chakraborty, Uprety, et al. (2021)	Oxidative metabolism as a modulator of kratom's biological actions	MG, 7-OH-MG, MGP	7-OH-MG & MG showed significant CPP, though MGP did not	NA	7-OH-MG inhibited GI transit.	7-OH-MG produced from MG via CYP3A mediated oxidation. Acts as a MOR agonist and produced dose-dependent antinociception in tail flick and hot plate. Higher potency by the oral route vs morphine which was higher via SC admin.
Obeng et al. (2021)	Pharmacological comparison of Mitragynine and 7-OH-MG	DAMGO, morphine, fentanyl, buprenorphine, nalbuphine, naltrexone, U69,593; SNC-80 MG, 7-OH-MG	7-OH-MG produced a maximum of 100% drug lever responding in morphine trained rats In MG-trained rats, 7-OH-MG produced a maximum of	NA	100 mg/kg MG lethal (IP), even with 10 mg/kg naltrexone.	7-OH-MG produced significant naltrexone- and naloxone-reversible antinociception in rats in hot plate test.

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Publication or Source	Short Title or Description	Comparators Studied or Mentioned	Abuse-related Variables	Physical Dependence & Withdrawal	Safety Individual Population	Comments
			98% drug lever responding			
Gutridge et al. (2020)	G protein-biased kratom-alkaloids and synthetic carfentanilamide opioids as potential treatments for alcohol use disorder	Kratom extract, mitragynine, paynantheine, speciogynine, 7-OH-MG (3 mg/kg, IP) MP102, MP103, MP105, TRV130 morphine, DAMGO, Leu-enkephalin, U50,488	CPP findings show reward potential for kratom extract and 7-OH-MG	NA	NA	MG, paynantheine, and speciogynine reduced ethanol intake at 10-30 mg/kg in mice. 7-OH-MG reduced intake at 1-3 mg/kg (male) and 3 mg/kg (female). Speciogynine (30 mg/kg) decreased activity. 7-OH-MG (3 mg/kg) increased locomotor activity. Kratom extract #1 (30 mg/kg) and 7-OH-MG (3–10 mg/kg) induced CPP. Morphine induced CPP as expected.
Obeng et al. (2020)	Adrenergic and opioid binding affinities, metabolic stability, plasma protein binding properties, and functional effects of selected indole-based kratom alkaloids	MG, 7-OH-MG, speciociliatine, corynantheidine, 9-hydroxycorynantheidine	NA	NA	NA	7-OH-MG had the highest affinity among tested alkaloids at the MOR, and showed high affinity at the KOR and moderate affinity at the DOR. In rat hot plate tests, 7-OH-MG produced greater potency than morphine and speciociliatine but lower than fentanyl. Analgesic effect blocked by naltrexone. Did not produce hypothermia.
Todd et al. (2020)	Receptor binding of 7-OH-MG,	7-OH-MG, mitragynine, speciofoline	Binding affinity to opioid receptors	NA	Not population-specific	MG and 7-OH function as partial agonists of the human MOR, while speciociliatine does not exhibit measurable binding affinity at the

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Publication or Source	Short Title or Description	Comparators Studied or Mentioned	Abuse-related Variables	Physical Dependence & Withdrawal	Safety Individual Population	Comments
	mitragynine, and speciofoline					MOR, DOR, or KORs. MG and 7-OH demonstrate functional selectivity for G-protein signaling, with no measurable recruitment of β -arrestin.
Hemby et al. (2019)	Abuse liability and therapeutic potential of the <i>Mitragyna speciosa</i> (kratom) alkaloids mitragynine and 7-hydroxymitragynine.	MG: 25-150 μ g/infusion, 7-OH-MG: 2.5-20 μ g/infusion Morphine: 50-100 μ g/infusion	<u>Experiment 1:</u> MG did not substitute for morphine at any dose. 7-OH-MG substituted for morphine in a dose-dependent manner (2.5–20 μ g/infusion), with an inverted U-shaped curve and maximal response at 5–10 μ g/infusion <u>Experiment 2:</u> Morphine and 7-OH-MG both engendered and maintained self admin. MG did not	NA	No lethality reported	NA

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Publication or Source	Short Title or Description	Comparators Studied or Mentioned	Abuse-related Variables	Physical Dependence & Withdrawal	Safety Individual Population	Comments
			7-HMG maintained intake at 2.5-10 µg/infusion, comparable to morphine <u>Experiment 3:</u> Morphine intake reduced by NLXZ (µ1 antagonist) but not NTI. 7-HMG intake reduced by both NLXZ and NTI, suggesting reinforcement mediated by MOR and DOR.			
Kruegel et al. (2019)	Hydroxymitragynine is an active metabolite of mitragynine and a key mediator of its analgesic effects.	MG, 7-OH-MG, MGP	NA	NA	NA	MG is converted in vitro in both mouse and human liver preparations to 7-OH-MG, mediated by CYP P450 3A 7-OH is formed from MG in mice and that brain concentrations of this metabolite are sufficient to explain most or all of the opioid-receptor-mediated analgesic activity of MG. At the same time, MG is found in the brains of mice at very high concentrations relative to its opioid

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Publication or Source	Short Title or Description	Comparators Studied or Mentioned	Abuse-related Variables	Physical Dependence & Withdrawal	Safety Individual Population	Comments
						receptor binding affinity, suggesting that it does not directly activate opioid receptors.
Kruegel et al. (2016)	Synthetic and Receptor Signaling Explorations of the Mitragyna Alkaloids: Mitragynine as an Atypical Molecular Framework for Opioid Receptor Modulators	MG, paynantheine, speciogynine, speciociliatine, 7-OH, morphine, DAMGO, fentanyl, HEK293	Characterization of 7-OH's activity at MOR, KOR, DOR. 7-OH-MG bound MOR with high affinity (K _i ~ 30 nM). Showed G-protein biased signaling	NA	Both 7-OH and MG were found to elicit no measurable β -arrestin recruitment	7-OH-MG produced potent antinociception, 10x more potent than morphine, blocked by naloxone. At equianalgesic doses, 7-OH-MG caused less respiratory depression and constipation than morphine.
Harun et al. (2015)	Discriminative stimulus properties of mitragynine (kratom) in rats.	MG: 3-56 mg/kg IP), 7-HMG: 0.3–3 mg/kg IP, Morphine, codeine, cocaine, diazepam, U50,488H	MG did not substitute for morphine. 7-OH-MG fully substituted for morphine. Effects were dose dependent and naloxone reversible	NA	No lethal toxicity. MG at high doses produced sedation and reduced response. 7-OH-MG elicited responses at much lower doses (0.3-3 mg/kg).	NA
Matsumoto et al. (2004)	Antinociceptive effect of 7-OH-MG in mice	7-OH-MG, MG, morphine	NA	NA	No safety-related signals or adverse effects reported	7-OH-MG showed dose-dependent antinociceptive properties when subcutaneously and orally administered to mice. Also suggests

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Publication or Source	Short Title or Description	Comparators Studied or Mentioned	Abuse-related Variables	Physical Dependence & Withdrawal	Safety Individual Population	Comments
						7-OH-MG may be more orally bioavailable than morphine.
Factor 2 Scientific Evidence of its Pharmacological Effects						
J. P. Manus et al. (2025)	Effects of kratom alkaloids on mesolimbic dopamine release.	MG, 7-OH-MG, (cocaine, amphetamine, opioids mentioned but not directly compared)	NA	NA	NA	Fixed potential amperometry was used to quantify stimulation-evoked phasic dopamine release in the nucleus accumbens (NAc) of anesthetized male and female mice before and after MG (1, 15, or 30 mg/kg, IP), 7-OH-MG (0.5, 1, or 2 mg/kg, IP), or vehicle. MG reduced dopamine release over the recording period (90 min) in a dose-dependent manner, and the low dose of MG significantly increased dopamine autoreceptor functioning in males. Both sexes responded similarly to 7-OH-MG with the low dose of 7-OH-MG increasing dopamine release while the high dose decreased dopamine release. 7-OH-MG did not alter dopamine autoreceptor functioning for either sex. Neither MG nor 7-OH-MG altered the clearance rate of stimulation-evoked dopamine. Findings suggest that these kratom alkaloids do alter dopamine functioning, although potentially not in a way consistent with classic drugs of abuse.

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Publication or Source	Short Title or Description	Comparators Studied or Mentioned	Abuse-related Variables	Physical Dependence & Withdrawal	Safety Individual Population	Comments
Obeng et al. (2022)	Interactive Effects of m-Opioid and Adrenergic $\alpha 2$ Receptor Agonists in Rats Pharmacological investigation of the primary kratom alkaloid mitragynine and its metabolite 7-hydroxymitragynine	MG, 7-OH-MG, morphine, methadone, clonidine, lofexidine, U69,593, naltrexone, yohimbine	MG showed low affinity at $\alpha 2A$ and $\alpha 2C$ receptors MG bound MOR with $K_i \sim 1700$ nM. 7-OH-MG showed stronger MOR affinity ($K_i \sim 78$ nM) but no $\alpha 2$ binding at ≤ 10 μM .	NA	No toxicity or lethality reported.	MG has weak affinity for MOR but meaningful interactions with $\alpha 2$ -adrenergic systems. Combined activity may account for kratom's mixed reported stimulant/analgesic profile. In hot plate tests, MG did not produce significant antinociception across routes (IP, SC, oral). In contrast, 7-OH-MG produced robust, naloxone-sensitive antinociception. MG and 7-OH-MG enhanced potency of $\alpha 2$ agonists (clonidine/lofexidine)
Maxwell et al. (2021)	Oral pharmacokinetics in beagle dogs of the mitragynine metabolite, 7-hydroxymitragynine.	MG, 7-OH-MG	NA	NA	NA	Following a single oral dose (1 mg/kg) of 7-HMG, plasma samples were obtained from healthy female beagle dogs. Absorption of 7-HMG was rapid, with a peak plasma concentration (C_{max} , 56.4 ± 1.6 ng/mL) observed within 15 min post-dose. In contrast, 7-HMG elimination was slow, exhibiting a mono-exponential distribution and mean $t_{1/2}$ of 3.6 ± 0.5 h. Oral dosing of 1 mg/kg 7-HMG was well-tolerated with no observed AEs or significant changes to clinical laboratory tests. The exposure of 7-HMG after MG dosing due to metabolism corresponds to a 0.24 mg/kg dose of 7-HMG indicating a 23.1%

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Publication or Source	Short Title or Description	Comparators Studied or Mentioned	Abuse-related Variables	Physical Dependence & Withdrawal	Safety Individual Population	Comments
						conversion of MG to 7-HMG in beagle dogs.
Ellis et al. (2020)	Receptor binding and signaling of kratom	MG, 7-OH-MG, other alkaloids	Binding affinity to opioid receptors	NA	Not population-specific	Identified MOR partial agonism for 7-OH-MG and MG, biased signaling.
Takayama et al. (2002)	Synthesis and Opioid Agonistic Activities of Mitragynine-Related Indole Alkaloids	MG, 7-OH-MG, pseudoindoxyl Morphine	NA	NA	NA	In vitro tissue assays and in vivo mouse hot plate and tail-flick tests showed potent naloxone reversible antinociception
Factor 3 Current State of Scientific Knowledge						
Akbar et al. (2025)	Screening, docking, and molecular dynamics analysis of Mitragyna speciosa (Korth.) compounds for targeting HER2 in breast cancer.	MG, 7-OH-MG, paynantheine, speciociliatine, speciogynine	NA	NA	NA	MG was found to be BBB permeant, whereas 7-OH-MG was not BBB permeant, which could reduce the likelihood of CNS-related side effects. Neither were found to be P-gp substrates, which minimizes the risk of efflux-related bioavailability issues. However, both were inhibitors of CYP2D6 and CYP3A4 enzymes. 7-OH-MG demonstrated MOR binding and partial agonist activity. 7-OH-MG showed potent G-protein biased MOR agonism.

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Publication or Source	Short Title or Description	Comparators Studied or Mentioned	Abuse-related Variables	Physical Dependence & Withdrawal	Safety Individual Population	Comments
						7-OH-MG and MG both demonstrated high GI absorption, suggesting high oral bioavailability. Docked to HER2 binding pocket with lower binding energies, and 7-OH-MG demonstrated stable hydrogen-bond interactions with residues critical for HER2 inhibition.
Chiang et al. (2025)	In Vitro and In Vivo Pharmacokinetic Characterization of 7-Hydroxymitragynine, an Active Metabolite of Mitragynine, in Sprague-Dawley Rats.	MG MGP, 7-OH-MG	NA	NA	NA	7-OH-MG exhibited high permeability in Caco-2 cells 7-OH-MG exhibited lower plasma protein binding in rats compared to MTG. Lower plasma protein binding of 7-OH-MG may lead to a larger volume of distribution and a shorter $t_{1/2}$ than MTG. 7-HMG showed a rapid elimination with short metabolic half-lives in rat liver microsomes (0.4 ± 0.0 h) and hepatocytes (0.3 ± 0.0 h). After oral dosing, the C_{max} was 28.5 ± 5.0 ng/ml, and T_{max} was 0.3 ± 0.1 h, which indicated rapid absorption of 7-HMG. The $t_{1/2}$ of 7-HMG was 0.5 ± 0.0 and 1.7 ± 0.5 h after IV and oral dosing, respectively, which indicated 7-HMG eliminates rapidly from the systemic circulation. In contrast to other studies, this study found poor oral bioavailability

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Publication or Source	Short Title or Description	Comparators Studied or Mentioned	Abuse-related Variables	Physical Dependence & Withdrawal	Safety Individual Population	Comments
						of 7-OH-MG, though this may be due to poor water solubility. The concentration of 7-HMG fell below the LLOQ after 8 h following IV administration and 4 h following oral administration.
Uchaipichat (2025)	Inhibitory effects of Kratom constituents, mitragynine and 7-hydroxymitragynine, on 4-methylumbelliferone glucuronidation by human UDP-glucuronosyltransferases.	MG, 7-OH-MG	NA	NA	NA	7-OH exhibited the highest inhibitory potency on UGT1A9, with IC₅₀ value of 51 µM, while moderate potency was observed for UGT1A1 and UGT1A3, with IC₅₀ value of 196 and 141 µM, respectively. The inhibitory potency of 7-OH on UGT2B15 was low (IC₅₀ > 200 µM), while negligible effects were observed for UGT1A6 and UGT2B7. 7-OH competitively inhibited UGT1A3 (K_i = 33 µM) and noncompetitively inhibited UGT1A9 (K_i = 29 µM). Values are relatively high compared to the maximum plasma concentrations reported in humans, suggesting an unlikely potential for herb-drug interactions via UGT inhibition.
Berthold et al. (2024)	Pharmacokinetic Interaction of Kratom and Cannabidiol in Male Rats	MG, 7-OH-MG, speciociliaine, paynantheine, speciogynine, corynantheidine measured	NA	NA	NA	The metabolite to parent (i.e., mitragynine) exposure ratio percentage of 7-OH-MG remained similar (3.5 and 3.1 with and without cannabidiol, respectively). As there was an increase in MG exposure during this study, it was expected that this would be due to a decrease

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Publication or Source	Short Title or Description	Comparators Studied or Mentioned	Abuse-related Variables	Physical Dependence & Withdrawal	Safety Individual Population	Comments
		OPMSS Gold kratom extract (11.8 mg/mL MG, 2.8 mg/mL speciociliatine, 2.2 mg/mL paynantheine, 1.5 mg/mL speciogynine). CBD (33.3 mg/mL cannabidiol)				in metabolism, but this was not the case for 7-OH-MG despite it being primarily metabolized by CYP3A and cannabidiol being a competitive inhibitor of CYP3A
Chiang et al. (2024)	Multiple-Dose Pharmacokinetics and Safety of Mitragynine, the Major Alkaloid of Kratom, in Rats.	MG, 7-OH-MG (Morphine, oxycodone, methadone mentioned but not directly compared)	NA	NA	NA	Female rats showed significantly higher exposure to 7-OH-MG compared to male rats after multiple doses of MTG; similar results in mice (may not be applicable to humans, as women have higher expression of CYP3A activity than men); whereas male rats have higher expression than female rats.
Huestis et al. (2024)	Human Mitragynine and 7-Hydroxymitragynine Pharmacokinetics after Single and Multiple Daily Doses of Oral Encapsulated Dried Kratom Leaf Powder.	Kratom leaf powder Measured MG and 7-OH-MG	NA	COWS and SOWS No opioid-like withdrawal observed after cessation of either single or 15 day dosing.	Mild AEs including GI upset (vomiting, nausea), dizziness, fatigue. No serious AEs reported. Hematology, liver/kidney panels normal.	Controlled clinical PK study of kratom leaf capsules — first large double-blind, placebo-controlled trial with single and repeated dosing Mean metabolite ratio of 7-OH-MG ranged from 21-31% after a single oral dose of kratom capsules (MTG content 6.7-53.2mg) and 15-18% after multiple doses of kratom.

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Publication or Source	Short Title or Description	Comparators Studied or Mentioned	Abuse-related Variables	Physical Dependence & Withdrawal	Safety Individual Population	Comments
Mongar et al. (2024)	Effects of Itraconazole on Pharmacokinetics of Mitragynine and 7-Hydroxymitragynine in Healthy Volunteers.	Kratom tea, MG, 7-OH-MG	NA	NA Only single dose study, no tapering or withdrawal monitoring	Total of 15 AEs were recorded during period 1: drowsiness (56.2%), vomiting (31.2%), dizziness (31.2%), headache (18.7%), fatigue (18.7%), and nausea (12.5%), while other typical AEs such as diarrhea, fever, skin itchy, irritation, constipation, anorexia, and heartburn were not observed. In period 2, the only AE observed was vomiting (6.3%). All events were resolved on the same day without any treatment and did not lead to any drop outs	After oral administration of kratom tea (MTG content 23.6 mg), the mean metabolite ratio of 7-OH-MG was 11.5-16.2%. The median C _{max} for MTG of 159.12 ± 8.68 ng/mL was attained in 0.84 h. While median C _{max} for 7-OH of 12.81 ± 3.39 ng/mL was observed at 1.77 h.
Tanna et al. (2022)	Clinical Pharmacokinetic Assessment of Kratom (Mitragyna speciosa), a Botanical Product with Opioid-like Effects, in Healthy Adult Participants	Kratom tea from purified Mitragyna speciosa (2 g)	NA	NA	Kratom tea was well-tolerated in 5 of 7 enrolled participants. 2 participants experienced nausea and vomiting; 1 withdrew due to these AEs, and 1 was withdrawn due to abnormal appearing urine deemed likely unrelated to kratom consumption. 2 participants experienced lightheadedness and headache, deemed unrelated to kratom and related to placement of IV catheter.	PK results of 3S and 3R alkaloids included the following: Plasma concentrations for 3S/3R alkaloids were quantifiable 15 min after consumption, suggesting rapid absorption. Multiple peaks during absorption reflected delayed GI emptying common with opioids. Minimal 3S/3R alkaloids were excreted unchanged in urine. 3S alkaloids (MG, speciogynine, and paynantheine) followed biphasic concentration-time profile; displayed higher peripheral volumes of

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Publication or Source	Short Title or Description	Comparators Studied or Mentioned	Abuse-related Variables	Physical Dependence & Withdrawal	Safety Individual Population	Comments
					No patients experienced severe AEs.	distribution and clearance than 3R alkaloids; exhibited longer terminal $t_{1/2}$, higher CL/F and Vz/F, lower dose-normalized AUC _{inf} and C _{max} , shorter T _{max} than 3R alkaloids. 3R alkaloids (mitraciliatine, speciociliatine, isopaynantheine) followed monophasic concentration-time profile.
Kamble et al. (2021)	Pharmacokinetics of Eleven Kratom Alkaloids Following an Oral Dose of Either Traditional or Commercial Kratom Products in Rats	Traditional Kratom (lyophilized kratom tea) Commercial Kratom (OPMS liquid shot)	NA	NA	NA	Among the 11 alkaloids, only MG, 7-OH-MG, speciociliatine, and corynantheidine showed systemic exposure 8 h postdose, and the dose-normalized systemic exposure of these four alkaloids was higher (1.6–2.4-fold) following the administration of the commercial OPMS liquid. Paynantheine and speciogynine levels were quantifiable up to 1 h postdose, whereas none of the other alkaloids were detected.
Hiranita et al. (2020)	Potential Contribution of 7-Hydroxymitragynine, a Metabolite of the Primary Kratom (Mitragyna Speciosa) Alkaloid Mitragynine, to the μ -Opioid Activity of	MG and 7-OH binding activity and efficacy at the MOR were compared Plasma levels following PO MG administration were measured Antinociception in	In rats discriminating morphine (3.2 mg/kg, IP) from vehicle, the discriminative stimulus effects of MG were assessed 90 min after PO administration.	NA	32 mg/kg MG was lethal.	Binding activity of 7-OH at MOR (K_i = 78 nM) was 22-fold lower than morphine and 9-fold higher than MG. Following PO administration of MG (HCl salt, 55 mg/kg), C _{max} of 7-OH (85 ng/mL) was 14-fold less than MG. T _{max} of 7-OH and MG were 30 and 84 min, respectively. 7-OH is a more potent and efficacious MOR agonist than MG,

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	Mitragynine in Rats	hotplate assay was assessed	MG (up to 178 mg/kg) produced 76% morphine-lever responding (ED ₅₀ =51 mg/kg).			suggesting that conversion to this metabolite may contribute to the in vivo MOR of MG.
Kamble et al. (2020)	Metabolism of a Kratom Alkaloid Metabolite in Human Plasma Increases Its Opioid Potency and Efficacy	7-HMG in pooled mouse, dog, monkey, and human plasma was evaluated	NA	NA	NA	Stability varied across species with high stability in mouse, rat, and monkey plasma (>80% 7-HMG remained after 120 min), intermediate stability in dog plasma (>61% remaining after 120 min), and low stability in human plasma (~40% 7-HMG remaining after 120 min). Incubation of human plasma produced an unknown converted metabolite with NMR data matching MGP. Study findings suggest potential for human plasma to form MGP.
Factor 4 History and Current Patterns of Abuse						
Factor 5 The Scope, Significance and Duration of Abuse						
Factor 6 What, if any, Risk is there to the Public Health						
Broul et al. (2025)	Case Report: Cannabis and kratom-induced self-amputation of ears and penis.	NA	NA	NA	NA	31 year old suffered severe substance-induced psychosis involving kratom and cannabis that resulted in self-amputation.

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Publication or Source	Short Title or Description	Comparators Studied or Mentioned	Abuse-related Variables	Physical Dependence & Withdrawal	Safety Individual Population	Comments
Grundmann et al. (2025)	Prevalence and Use Patterns of Kratom (<i>Mitragyna speciosa</i> Korth.) in a US Nationally Representative Sample.	NA	NA	NA	Adverse events more frequently reported with gummies/capsules/tablets/pills at higher doses	No 7-OH-MG specific data Survey of 11,545 respondents, 1,049 current kratom users (9.1% prevalence) Motivations for use (among users): Pain relief: 57.5% (n=603). Relaxation/stress relief: 53.6% (n=562). Energy boost: 49.6% (n=520). Higher reported frequency of kratom shots/extract powder consumed was correlated with use for pain relief
Hill, Boyer, et al. (2025)	De facto opioids: Characterization of novel 7-hydroxymitragynine and mitragynine pseudoindoxyl product marketing.	7-OH-MG, MGP	NA	NA	Did not assess withdrawal directly, but authors noted widespread online reports of 7-OH-MG dependence and withdrawal	Identified 304 marketed 7-OH and/or MGP products. 82.2% = 7-OH alone. 14.5% = 7-OH + MGP combos. 3.3% = MGP alone. Formulations: chewable/sublingual tablets (60.2%), liquid shots (20.7%), gummies (4.3%), drink mixes (4.0%), vapes (3.0%), syrups (2.3%), capsules (2.0%), strips (2.0%), food (1.3%), powder (0.3%). Claims: 73.4% made “general wellbeing” claims (focus ↑ 58%, relaxation 47%, energy boost 39%).

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						37.8% made “functional” claims (pain relief 26%, anxiety/stress reduction 21%). 12.5% made explicit “drug” claims (opioid receptor activity, analgesia, sedation). Dosing/costs: Recommended dose range = 1-700 mg; mean = 20 mg/dose (7-OH higher than MP). MP mean recommended dose = 10.1 mg. Mean cost per recommended dose = \$3.97 (7-OH); ~\$5 for MP. Marketing: 93.1% falsely marketed as “kratom” despite being semi-synthetic opioids. Many brands mimic prescription medications (names like “Curevana,” “Pain Crusher Rx,” packaging like blister packs or syrups).
Osawa and Johnson (2025)	Postmortem distribution of mitragynine and 7-hydroxymitragynine in 51 cases	Fluid and tissue specimens from 51 postmortem cases to investigate the distribution of MG and its active metabolite 7-OH.	NA	NA	NA	Central and peripheral blood concentrations were compared, with an average heart blood to femoral blood ratio being 1.37 for MG and 1.08 for 7-OH. This ratio >1.0 suggests that MG has some propensity toward postmortem redistribution; however, the difference in concentrations of MG and 7-OH was not statistically significant.

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Publication or Source	Short Title or Description	Comparators Studied or Mentioned	Abuse-related Variables	Physical Dependence & Withdrawal	Safety Individual Population	Comments
						Large average MG to 7-OH ratios of 30.9 in femoral blood and 32.4 in heart blood were observed compared to average ratios of 14.8 in vitreous humor and 16.9 in urine.
Smith et al. (2025)	The rise of novel, semi-synthetic 7-hydroxymitragrine products.	NA	NA	NA	NA	Letter to editor Began marketing novel semi-synthetic products with varying routes of administration (e.g. sublingual tablets, nasal sprays) containing 14-25 mg. 7-OH-MG per labeled dose, often with brand names alluding to narcotics. These newly marketed products may contain up to 98% 7-OH-MG, together with other kratom alkaloids. Concerningly, some product formulations circumvent first-pass metabolism, increasing bioavailability. Chronic 7-OH product use could result in opioid-like physical dependence and possibly addiction. Scale and severity may be distinct from kratom leaf-based and extract products, which have not produced widespread severe addiction, but rather mild-moderate physical dependence. Currently, 7-OH products contain trace amounts of MG and 'new'

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Publication or Source	Short Title or Description	Comparators Studied or Mentioned	Abuse-related Variables	Physical Dependence & Withdrawal	Safety Individual Population	Comments
						chemicals yet to be identified. The safety of these unknown chemicals are unknown
Vadie, Evoy and Grundmann (2025)	The Impact of Diverse Kratom Products on Use Patterns, Dependence, and Toxicity	NA	NA	NA	NA	Although alkaloid content naturally ranges from 2-5% in native leaf material, it can be up to 60% in concentrated extracts. Concentrated kratom products may pose risks not comparable to traditional use, and may require regulatory oversight and clinical evaluation before marketing and therapeutic use.
White (2025)	Kratom's Use and Impact on Pediatric Populations.	MG and 7-OH-MG	NA	NA	Reviewed a case series of 6 neonates exposed prenatally: withdrawal onset ~24 h after birth (jitteriness, irritability, vomiting, poor feeding, crying). Treated successfully with morphine or buprenorphine taper .	Review/Letter Poison control (2011–2017, n=1,807 exposures): 10.2% <20 years old. 48 children <13 (42 used kratom only); 137 adolescents 13–19 (80 kratom only). Admission rates after kratom-only exposure: 14.3% (<13 yr), 21.3% (13–19 yr), 27% (≥20 yr). Symptoms: opioid-like (confusion, drowsiness, nausea, vomiting), stimulant-like (agitation, seizures, tremor, tachycardia, hypertension, chest pain, tachypnea). Respiratory depression rare. Children/adolescents may use as a simulant “smart drug” or by athletes for pain/stamina reasons.

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Publication or Source	Short Title or Description	Comparators Studied or Mentioned	Abuse-related Variables	Physical Dependence & Withdrawal	Safety Individual Population	Comments
Wightman and Hu (2025)	A Case of 7-OH Mitragynine Use Requiring Inpatient Medically Managed Withdrawal.	NA	NA	NA	Patient reported withdrawal symptoms upon cessation of 7-OH use including anxiety, insomnia, rhinorrhea, abdominal discomfort, restlessness, diaphoresis, and chills COWS score peaked at 14 on day 2	38 year old man with history of opioid use disorder reported escalation of use including kratom to 7-OH. Abstinent from opioids then started using kratom at 31 (30 g a day) 3 months before presentation, switched to 7-OH, with escalating use (up to eight 30 mg tablets daily, taking them every 1-2 hours). Patient received buprenorphine and transitioned to residential care.

Abbreviations: 7-OH-MG (7-HMG; 7-OH) = 7-hydroxymitragynine; AE(s) = adverse event(s)/adverse effect(s); BBB = blood brain barrier; C_{max} = maximum concentration; CNS = central nervous system; COWS = Clinical Opiate Withdrawal Scale; CPP = conditioned place preference; CYP = cytochrome; DOR = delta (δ)- opioid receptor; GI = gastrointestinal; IC₅₀ = half maximal inhibitory concentration; IP = intraperitoneal; Ki = inhibitor constant; IV = intravenous; KOR = kappa (κ)- opioid receptor; LLOQ = lower limit of quantitation; MG (MTG) = mitragynine; MGP (MP) = mitragynine pseudoindoxyl; MOR = mu (μ)- opioid receptor; NA = not available; Oxy = oxycodone; P-gp = P-glycoprotein; PK = pharmacokinetic; SC = subcutaneous; SOWS = Subjective Opiate Withdrawal Scale; t_{1/2} = half life; T_{max} = time to maximum concentration.

11.2 Appendix 2: Press Release: FDA Takes Steps to Restrict 7-OH Opioid Products Threatening American Consumers

FDA NEWS RELEASE

FDA Takes Steps to Restrict 7-OH Opioid Products Threatening American Consumers

Agency alerts health care professionals and consumers of 7-hydroxymitragynine risks

[More Press Announcements \(/news-events/newsroom/press-announcements\)](#)

For Immediate Release:

July 29, 2025

The U.S. Food and Drug Administration today is taking a bold step to protect Americans from dangerous, illegal opioids by recommending a scheduling action to control certain 7-hydroxymitragynine (also known as 7-OH) products under the Controlled Substances Act (CSA).

The FDA is specifically targeting 7-OH, a concentrated byproduct of the kratom plant; it is not focused on natural kratom leaf products. 7-OH is increasingly recognized as having potential for abuse because of its ability to bind to opioid receptors. The FDA is releasing a new [report](https://www.fda.gov/media/187899/download?attachment) (<https://www.fda.gov/media/187899/download?attachment>) to educate the public about the health concerns of 7-OH and its distinction from the kratom plant leaf.

"Today, we're taking action on 7-OH as a critical step in the fight against opioid addiction," **said HHS Secretary Robert F. Kennedy, Jr.** "We will protect the health of our nation's youth as we advance our mission to Make America Healthy Again."

This recommendation follows a thorough medical and scientific analysis by the FDA and is one of several efforts to address the agency's concerns around the growing availability and use of 7-OH opioid products. There are no FDA-approved 7-OH drugs, 7-OH is not lawful in dietary supplements and 7-OH cannot be lawfully added to conventional foods.

"Vape stores are popping up in every neighborhood in America, and many are selling addictive products like concentrated 7-OH. After the last wave of the opioid epidemic, we cannot get caught flat-footed again," **said FDA Commissioner Marty Makary, M.D., M.P.H.** "7-OH is an opioid that can be more potent than morphine. We need regulation and public education to prevent another wave of the opioid epidemic."

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The availability of 7-OH products is a major concern to the FDA, as consumers can easily purchase products with concentrated levels of 7-OH online and in gas stations, corner stores and vape shops. The FDA is particularly concerned with the growing market of 7-OH products that may be especially appealing to children and teenagers, such as fruit-flavored gummies and ice cream cones. These products may not be clearly or accurately labeled as to their 7-OH content and are sometimes disguised or marketed as kratom. The FDA has also published educational materials (<https://www.fda.gov/media/187900/download>) for consumers to be more informed about these harmful products.

In June, the FDA issued warning letters to seven companies for illegally distributing products containing 7-OH, including tablets, gummies, drink mixes and shots. Today, the FDA is also issuing a letter to health care professionals (<https://www.fda.gov/media/187898/download?attachment>) and is warning consumers (<https://www.fda.gov/drugs/information-consumers-and-patients-drugs/hiding-plain-sight-7-oh-products>) about the risks associated with 7-OH products.

Under the CSA, drugs, substances and certain chemicals are placed into one of five schedules based upon their medical use, potential for abuse and safety or dependence liability. The Drug Enforcement Administration is reviewing the recommendation and has the final authority on scheduling, which requires a rulemaking process that includes a period for the public to provide comments before any scheduling action is finalized.

Related Information

- Hiding in Plain Sight: 7-OH Products (<https://www.fda.gov/drugs/information-consumers-and-patients-drugs/hiding-plain-sight-7-oh-products>)

Media:

HHS Request for Comment ([https://www.hhs.gov/request-for-comment-form/index.html?](https://www.hhs.gov/request-for-comment-form/index.html?Agency=ASPA)

Agency=ASPA)

202-690-6343

Consumer:

888-INFO-FDA

###

11.3 Appendix 3: FDA Report: 7-Hydroxymitragyine (7-OH): An Assessment of the Scientific Data and Toxicological Concerns Around an Emerging Opioid Threat

7-Hydroxymitragynine (7-OH):

An Assessment of the Scientific Data and
Toxicological Concerns Around
an Emerging Opioid Threat



7-Hydroxymitragynine (7-OH):

**An Assessment of the Scientific Data and
Toxicological Concerns Around
an Emerging Opioid Threat**



FDA Center for Drug Evaluation and Research

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EXECUTIVE SUMMARY

Recent reports indicate increased availability and marketing of 7-hydroxymitragynine (7-OH) in the U.S., raising public health concerns due to its pharmacology. This report provides an overview on the chemical, pharmacological, and epidemiological data on 7-OH. It focuses on the characterization of 7-OH-containing products in the marketplace, the evidence of increasing human exposures, and the extensive body of preclinical studies in the scientific literature that indicate the predominant mu opioid agonist pharmacology of 7-OH. These data sources indicate that 7-OH is a potent opioid that poses an emerging public health threat, especially when considering the increasing availability of enhanced or concentrated 7-OH products in the marketplace.

7-OH is a naturally occurring substance in the kratom plant (*Mitragyna speciosa*), but only a minor constituent that comprises less than 2% of the total alkaloid content in natural kratom leaves. However, 7-OH demonstrates substantially greater mu-opioid receptor potency than kratom's primary alkaloid constituent mitragynine, as well as other classical opioids such as morphine. In vitro studies reveal 7-OH exhibits high binding affinity for mu-opioid receptors ($K_i = 7.2\text{-}70\text{ nM}$), with functional activity as a mu agonist. Animal behavioral studies demonstrate its rewarding effects from self-administration and conditioned place preference methods, consistent with its opioid properties. Critically, 7-OH produces respiratory depression, physical dependence, and withdrawal symptoms characteristic of classical opioids, such as morphine, fentanyl, oxycodone, and hydrocodone.

Recently, there has been a concerning proliferation of concentrated 7-OH products that are sold over the counter and online. The enhanced amount of 7-OH in these products is likely synthetically derived through oxidate chemical conversion of mitragynine isolates or kratom extracts. Given the trace amounts of 7-OH that are naturally present in kratom, direct extraction of 7-OH from plant material would simply be unfeasible economically.

Surveillance data from multiple sources, including America's Poison Centers National Poison Data System (NPDS), Drug Enforcement Administration toxicology testing programs, and social media monitoring, suggest increasing human exposure to these concentrated 7-OH products. Clinical presentations include euphoria, sedation, respiratory depression, and opioid-like withdrawal syndromes, with users acknowledging its significant addiction potential.

The pharmacological profile, abuse liability, and emerging patterns of non-medical use establish 7-OH as a dangerous substance. Current regulatory gaps have enabled widespread availability of these products despite their opioid-like properties and necessitate immediate policy intervention to address this emerging threat to American public health.



INTRODUCTION

The Context for 7-OH Concerns

7-Hydroxymitragynine (7-OH) is a component of the plant kratom (*Mitragyna speciosa*), a tropical evergreen tree in the Rubiaceae family that grows in the wetlands of Southeast Asia (Brown et al., 2017). Kratom leaves contain over 50 alkaloids, with mitragynine and 7-OH being the primary psychoactive constituents (Warner et al., 2016). Its leaves, consumed as a tea or in dry leaf form, have been used for centuries in both medicinal and recreational settings, largely due to the properties of its alkaloids mitragynine and 7-OH. Typically, 7-OH occurs in botanical kratom in amounts no more than ~.01-.04 percent by dry weight (Heywood et al., 2024). Medicinally, kratom has been used to treat headaches, diarrhea, insomnia, anxiety, opioid use withdrawal, and more, while in recreational use cases, it has been associated with feelings of euphoria (Hill et al., 2025). Currently, there are no FDA-approved drugs containing kratom or kratom-derived drug substances such as 7-OH for any therapeutic indications.

Kratom products have grown in popularity since the mid-2000's; however, kratom, mitragynine, and 7-OH have faced regulatory scrutiny in the United States due to concerns about their safety and potential for abuse. None of these substances are lawful when added to conventional foods, as dietary supplements, or as ingredients in any FDA-approved drug, and yet, these substances are still sold in various markets. At the state level, some jurisdictions have implemented restrictions on their sale and use. Until now, 7-OH has not been the sole target of a regulatory response but has always been addressed alongside the kratom plant and mitragynine.

FDA issued its first import alert for kratom in 2012. At the time, kratom was being marketed in various forms for human consumption despite a lack of approved drug uses or established safety as a dietary ingredient. In the years since, additional import alerts have been issued by the Agency. The Drug Enforcement Administration (DEA) and the Department of Health and Human Services (HHS) had given consideration to kratom, as well as its constituents, mitragynine and 7-OH, to determine whether these substances should be recommended for control under the Controlled Substances Act (CSA). Those actions were ultimately suspended in 2018, with the Assistant Secretary for Health at that time stating that the science was incomplete, and the available data were not adequate to support a recommendation to control these substances under the CSA.

Contemporary Outlook

Given the concerning trends with 7-OH and other kratom-related products, FDA has now determined that a more comprehensive assessment of available scientific and medical data on 7-OH is warranted. Many of the products available today, which are often associated with or advertised as kratom, no longer resemble botanical kratom. Instead, they contain "enhanced" or concentrated amounts of 7-OH and are formulated as powders, capsules, and liquid extracts designed to generate a stronger effect on users. Other products are explicitly advertised as 7-OH-containing products. One analysis of websites selling 7-OH products found that most (82.2 %) were formulated as chewable/sublingual tablets, shots, or gummies and marketed specifically as 7-OH only products (92%). The mean cost per recommended dose/serving was \$3.97 (Hill et al., 2025).



As described below, research has shown that 7-OH is a potent mu-opioid receptor agonist, demonstrating pharmacological characteristics that define classical opioids like morphine and fentanyl. Based on its opioid pharmacology, there is significant potential for abuse of 7-OH. In fact, in various preclinical studies it has demonstrated greater potency than classical opioids. For example, 7-OH produces respiratory depression with more than 3-fold greater potency than morphine. Since the substance's therapeutic and psychoactive effects are mediated through the same mu-opioid receptor pathways as classical opioids, it can be considered to have opioid properties warranting similar regulatory consideration (Hill et al., 2025; Obeng et al., 2021).

In this report, FDA presents its new assessment of the available scientific data and literature on 7-OH, as well as more recent law enforcement data and the rapidly evolving trends in kratom-related products. FDA still has concerns about the safety of kratom products more broadly and the unlawful marketing of them under several regulated product categories in the Federal Food, Drug, and Cosmetic Act. However, there is a recognized need for more immediate action to address 7-OH because it is a substance with potent mu opioid agonist properties and significant abuse liability.



ANALYSIS OF DATA ON 7-HYDROXYMITRAGYNE (7-OH)

7-OH Sources and Products vs. Kratom

The alkaloid 7-hydroxymitragynine (7-OH) is a naturally occurring substance in the kratom plant (*Mitragyna speciosa*), but only a minor constituent, described as early as 1994, when it was reported to comprise about 1.6% of the total alkaloid content of kratom leaves (Ponglux et al., 1994). This early reported value is in agreement with more recent assessments that have consistently demonstrated 7-OH as comprising less than 2% of the total alkaloid content in natural kratom as noted below.

7-OH has the chemical structure shown in Figure 1. Its IUPAC name is methyl (E)-2-[(2S,3S,7aS,12bS)-3-ethyl-7a-hydroxy-8-methoxy-2,3,4,6,7,12b-hexahydro-1H-indolo[2,3-a]quinolizin-2-yl]-3-methoxyprop-2-enoate, and it has the molecular formula $C_{23}H_{30}N_2O_5$, with a molecular weight of 414.40 amu.

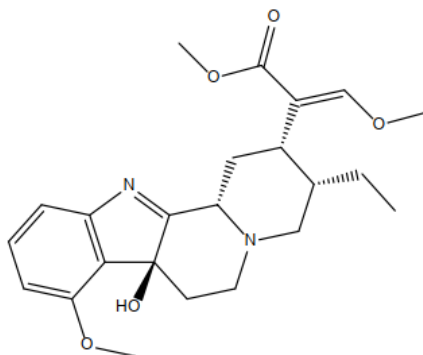


Figure 1. 7-Hydroxymitragynine Chemical Structure

Although details are not well-known, 7-OH is present in some products in amounts far exceeding its natural levels in the kratom plant. The 7-OH in these products is likely derived from the kratom plant. These 7-OH-enhanced products likely involve additional chemical synthetic steps by the producers of these products, converting the more abundant plant alkaloid mitragynine into 7-OH via chemical oxidation.

Data are available regarding 7-OH as a percentage of the total alkaloid content in kratom, and also as a percentage of dried botanical kratom leaf material and other kratom-derived products in the U.S. marketplace. One recent review reports 7-OH as comprising 2% of the total alkaloid content in kratom (Hossain et al., 2023) and this result can be extended to samples of kratom grown in the U.S. (Leon et al., 2009). In another analysis of 13 commercial products purported to contain kratom, the 7-OH content by weight ranged from 0.01-0.04% (Kikura-Hanajiri et al., 2009) a finding in agreement with others that have reported 7-OH to account for less than 0.05% by weight, substantially lower than reported mitragynine amounts (Kruegel et al., 2019). A more



recent study used ecological momentary assessment to evaluate the motivations and patterns of use of adult U.S. kratom consumers (Smith, Panlilio, Feldman, et al., 2024; Smith, Panlilio, Sharma, et al., 2024). As part of the study, subjects provided samples for quantitative testing of their own kratom products that they obtained and were self-administering. Across the 341 samples, the 7-OH content (expressed as a percentage by weight/weight or weight/volume, as indicated) ranged from below the limit of quantitation (< 0.005%) to a maximum of 0.21% with a mean of 0.01% (Sharma et al., 2025). These data suggest 7-OH is present in botanical kratom (i.e., leaf) at relatively low or trace amounts and may be a postharvest oxidative derivative of mitragynine (Karunakaran et al., 2024).

Common forms of kratom sold online include powders, capsules, resin extracts, crushed leaves, and tablets, although loose powder and prepared capsules have been reported to be the most frequently used formulations (Garcia-Romeu et al., 2020; Smith, Panlilio, et al., 2024). While kratom use characteristics are complicated by the diversity of products in the marketplace, survey studies have reported on consumption patterns. Garcia-Romeu collected data from regular kratom users and found that most users reported using 1-3g (49%) or 4-6g (33.4%) of botanical kratom per consumption (Garcia-Romeu et al., 2020). In other survey studies, the self-reported average consumption of kratom powder was 4-5 g per serving with serving sizes ranging between 2.6- 7.5 g (Rogers et al., 2024; Smith et al., 2022). When quantifying the amount of mitragynine consumed through the use of kratom, individuals self-reported consuming an average of 31.3 mg of mitragynine/serving and a range of 78.3 – 134.6 mg of mitragynine per day (Sharma et al., 2025).

Mitragynine, as the most abundant alkaloid in kratom, accounts for about 66% of the *total alkaloid content* of kratom and less than 2% of dried leaf content *by weight*, although there are reports of regional and seasonal variability in the tree's alkaloid composition (Arndt et al., 2011; Leon et al., 2009; Sengnon et al., 2023). For example, Chear and colleagues collected fresh kratom leaves from different locations in Peninsular Malaysia and determined their alkaloid profiles. The mitragynine concentration ranged from 9.38 to 18.85 mg/g or 0.38% to 1.89% of dried leaf weight while the 7-OH concentration ranged from 0.05 to 0.15 mg/g or 0.005% to 0.015% (Chear et al., 2021).

Despite the low amounts of 7-OH in botanical kratom, there are reports of its more-enhanced presence in commercial kratom-related products (Grundmann et al., 2024), although some products have been identified in reports from nearly a decade ago. For example, Lydecker and colleagues tested eight commercially available kratom products for their alkaloid content(s). In seven of the eight products tested, they found levels of 7-OH to be 109-509% higher than expected, based on naturally occurring levels of 7-OH reported in the kratom plant (Lydecker et al., 2016). More recently, the Tampa Bay Times purchased twenty kratom-derived products from local stores. One of those products consisted of pressed pills and contained 15 mg/pill of 7-OH, an amount far greater than observed in any botanical kratom preparation to date (Ogozalek, 2023). In addition to the verified amounts of 7-OH in the products obtained by Lydecker et al. and the Tampa Bay Times, other products *labeled* and/or *purported* to have high levels of 7-OH appear to be readily available for purchase online.

In summary, the low amounts of 7-OH in natural botanical kratom products is well-established as a percentage of alkaloid content, as a percentage of dried kratom leaf material, and in products representing other dosage forms made from natural kratom and consistent with its natural



composition. However, there are also a concerning and increasing number of products being sold that have unexpectedly and unnaturally high levels of 7-OH. This poses a threat to public health that is more clearly understood based on the pharmacological properties and effects of 7-OH, discussed in the preclinical data section below, and also in the limited information available on known patterns of human use and resulting harms discussed below. These sections will present and discuss the evidence in the available data that establishes the mu opioid agonist pharmacology associated with 7-OH in particular.

Patterns of 7-OH Use, Human Exposures, and Law Enforcement Data

There are several sources of information to characterize the current patterns of 7-OH use and the resulting harms to individuals who knowingly or unknowingly are exposed to 7-OH at significant doses from 7-OH-enhanced products, as described in the subsections below.

National Drug Early Warning System (NDEWS)

The National Drug Early Warning System (NDEWS) provides real-time surveillance from sentinel sites across U.S. to detect early signals of potential drug epidemics using novel (e.g., street reporting, web monitoring) and traditional data sources (e.g., OD deaths, treatment admissions).

NDEWS analyzed Reddit posts mentioning 7-OH during January to September 2024 and found that posts increased over this time. These posts are broad and can vary in content but have included warnings from Reddit users about respiratory depression, potency, dependence and long-lasting withdrawal (NDEWS, 2024).

Social Media

A variety of social media outlets were assessed for mentions and/or discussions of 7-OH. Websites included:

- erowid.org - a member-supported organization providing access to information about psychoactive plants, chemicals, and related issues;
- bluelight.org - an international message board that educates the public about responsible drug use by promoting free discussion, advocating harm reduction, and attempting to eliminate misinformation;
- reddit.com - online forum that functions as a vast collection of user-driven communities, known as sub-Reddits, each centered around specific topics.

It is important to note that all considerations of these social media sources are, at best, anecdotal in considering the risks and abuse potential associated with 7-OH products. However, it is clear that there is fairly widespread understanding of the availability of products specifically targeting high levels of the substance 7-OH, distinct from kratom products generally. In analyzing these social media posts, some relevant themes have been identified and include mention of the following: euphoria and an opioid-like "buzz"/high as motivation for consuming 7-OH; availability of "candy-like" formulations which users acknowledge as having a risk of overconsumption to their own detriment; perceptions of therapeutic value of 7-OH in self-treating pain and anxiety; concerns over loss of access to these products if they were to be banned; acknowledgement that use of these products could lead to overdose and serious



outcomes including death; and acknowledgement that use could lead to addiction and has caused users to experience withdrawal symptomology much like that produced by other commonly abused opioids.

Drug Enforcement Administration Toxicology Testing Program (DEA TOX)

The Drug Enforcement Administration Toxicology Testing program (DEA TOX) conducts analyses of voluntarily submitted leftover or previously collected biological samples from drug overdose victims to identify novel psychoactive substances (NPS) and other drugs of abuse in subjects with fatal and nonfatal overdose. The DEA TOX database was queried for reports of mitragynine, 7-OH, or mitragynine pseudoindoxyl from 2019-2025. A total of 103 cases, some fatal and some non-fatal, were identified in this selected sample; this database does not include all overdose cases, and the number of samples voluntarily submitted for analysis may vary year to year based on unknown factors.

It is notable that the utility of the DEA TOX data is limited because it generally cannot be discerned whether deaths are related to mitragynine, 7-OH, or mitragynine pseudoindoxyl, or some combination thereof. In addition, although 7-OH and mitragynine pseudoindoxyl are not typically found in appreciable amounts in fresh kratom leaves (Hill et al., 2025), both are metabolites of mitragynine, complicating forensic assessments of causality (Kamble et al., 2020). These are significant limitations in making inferences from these data; however, the number of fatal overdose cases in which one or more of these substances were detected for 2023 to 2025 are approximately three-fold higher than for the years 2019 through 2022, coinciding with the more recent entry of more-concerning kratom-related products in the marketplace, such as 7-OH.

Human Exposures in Pharmacokinetic Studies

Pharmacokinetic (PK) data for 7-OH are sparse, as to our knowledge, no clinical studies have been performed using isolated or purified 7-OH. Nonetheless, there are 7-OH PK data derived from a small number of studies using botanical kratom. Most available clinical PK data for 7-OH are variable, which may be for several reasons such as genetic differences in kratom plants, different formulations (e.g., teas, capsules, etc.), and methods of analysis. Much of the data is also from non-controlled studies making it difficult to interpret the results. Huestis and colleagues conducted a randomized, between-subject, double-blind, placebo-controlled dose escalation study of 500-4000 mg encapsulated dried kratom leaf powder corresponding to mitragynine doses of 6.65-53.2 mg. Twelve subjects enrolled in the study (n=12). Blood plasma levels of mitragynine and 7-OH were assessed after a single dose, and then again after 15 days of continuous dosing. According to the study authors, peak plasma levels of 7-OH (i.e., C_{max} values) and exposure (i.e., area under the curve, (AUC)) were lower than mitragynine but increased in a dose proportional manner and ranged from 3.6 to 22.7 ng/mL while the time to peak plasma levels (i.e., T_{max} values) ranged from 1.2 – 1.8 h. The half-life of 7-OH increased with increasing dose and ranged from a mean of 1.7 to 4.7 hours. During the multiple dose phase of the study, 7-OH steady state was reached in about 7 days (Huestis et al., 2024).

In another study examining the PK properties of 7-OH, sixteen healthy subjects (n=16) received kratom tea containing 23.6 mg of mitragynine. Subjects were administered tea in two sessions: once with tea alone, and in a second session following pretreatment with itraconazole, a



CYP3A4 inhibitor. The 7-OH C_{max} was 12.81 ± 3.39 ng/mL which occurred 1.7 h after administration (T_{max}). In the second session after pretreatment with itraconazole (200 mg), the C_{max} decreased 56% with a concomitant 43% decrease in AUC. These data describe the PK of 7-OH and demonstrate that the metabolism of mitragynine to 7-OH is heavily dependent on CYP3A4 (Mongar et al., 2024).

Tanna et. al., assessed the PK of a single orally administered dose of kratom (2 g), in the form of a tea, to healthy adult subjects ($n = 5$ completers). According to the authors, there were only trace amounts of 7-OH ($< LOQ$) in the starting product, therefore, the assumption was made that 7-OH was generated from the metabolism of mitragynine *in vivo*. The authors identified a PK difference between enantiomers of kratom alkaloids in either the 3S or 3R configuration. 7-OH has a 3S configuration which, according to the authors, leads to a shorter T_{max} , lower exposure (AUC), longer terminal half-life, and a higher volume of distribution during the terminal phase compared to the 3R alkaloids. Measured 7-OH in plasma samples demonstrated that 7-OH had a $C_{max} = 16.1$ nM, $T_{max} = 1$ h, half-life = 5.67h, and an $AUC_{0-120h} = 103$ nM x h. (Tanna et al., 2022).

Epidemiological Data Sources

Limitations with the Epidemiological Data Sources

Because 7-OH appears to be a novel, emerging public health threat, the ability of public health surveillance systems to monitor 7-OH specific risks may be limited. For example, large national surveys such as the National Survey on Drug Use and Health include questions about use of kratom, but not 7-OH. Additionally, there may be a lack of awareness among consumers of kratom-related products that they are obtaining 7-OH enhanced products, and thus use of 7-OH would likely be underreported in data collected using self-report. Many forensic laboratories test for mitragynine as a marker of kratom use. In these cases, 7-OH overdose cases and fatalities may incorrectly be classified as kratom and/or mitragynine-related (Smith, Boyer, et al., 2024). Furthermore, toxicology reports documenting presence of 7-OH are difficult to interpret, because 7-OH is a known metabolite of mitragynine in humans. All of these issues complicate the real-world assessment of risks associated with use of 7-OH containing products as distinct from risks associated with kratom and other mitragynine-containing products.

FDA's Adverse Event Reporting System

Although FDA's Adverse Event Reporting System (FAERS) has documented cases reporting adverse events (13 cases, including 2 deaths) suspected to involve 7-OH, ambiguity about the contributory role of 7-OH from uncharacterized products or concomitant medications and underlying disease limits interpretation. Therefore, we do not include further analysis of these FAERS cases here.



America's Poison Centers, National Poison Data System

National Poison Data System (NPDS) receives near real-time data from the nation's poison centers (PC), providing information and assistance to callers on exposures to prescription drugs, over-the-counter medications, unapproved products, and other substances. PC healthcare professionals systematically follow up on exposure cases to document medical and clinical effects. Quality control measures are used to ensure data accuracy and completeness. Notably, 7-OH specific NPDS codes were only recently added (Feb-May 2025), and therefore the NPDS reporting period is limited to 2/1/2025-4/30/2025. As shown below, there were a total of 53 exposure cases involving 7-OH during this time period, the majority of which involved abuse-related reasons for use (i.e., "intentional abuse"). Most single-substance 7-OH exposure cases resulted in minor or moderate clinical outcomes, with several documented has having major clinical outcomes.

**Table 1. National Poison Data System Closed Human Exposure Cases*,
2/1/2025-4/30/2025**

	Number of exposure cases**	Number of abuse cases**	Single substance exposure cases	Single substance abuse cases
Total cases involving 7-OH	53	24	37	16
Reason				
Adverse drug reaction	4		2	
Intentional- abuse	24		16	
Intentional- misuse	4		3	
Intentional - Suspected suicide	2		0	
Other - Withdrawal	8		6	
Unintentional - general	4		4	
Unintentional- misuse	1		1	
Unintentional therapeutic error	4		3	
Unknown reason	2		2	
Related clinical outcomes				
Minor			6	3
Moderate			13	6
Major			3	1
Not followed, minimal clinical effects possible			5	3
Unable to follow, judged as potentially toxic exposure			1	0
Age				
<18 years	6	1	5	0
≥ 18 years	46	23	32	16
Unknown age	1	0	0	0
*Excludes cases classified as 'confirmed non-exposure'				
**Cases may involve other substances, besides 7-OH				
Related clinical outcomes include cases with clinical effects deemed "related" to exposure based on timing, severity, and assessment of clinical effects by Poison Center Specialists. Definitions available from America's Poison Centers: NPDS Full Report 2023. Page 235.				



Note: This analysis used the case listing data in NPDS to identify and characterize cases documented as involving 7-OH. As of July 2025, an in-depth review NPDS case narrative data was ongoing; this further review may yield different numbers from those presented here.

Summary of Epidemiological Data and 7-OH Concerns

Available surveillance data indicate that abuse of 7-OH is occurring and is associated with serious harms; however, as noted previously, it is difficult to quantify the public health burden because surveillance systems do not provide estimates for the prevalence of 7-OH use and are only beginning to track the specific involvement of 7-OH enhanced products in exposure cases and overdoses. The current epidemiologic data on 7-OH exposures often lack sufficient detail to distinguish with confidence involvement of botanical kratom products from 7-OH enhanced products.

Preclinical Data Characterizing 7-OH Pharmacology

Although there are limited data from human studies to characterize effects of 7-OH in humans, as noted above, there is a large body of in vitro and animal studies that provide extensive evidence of 7-OH as a potent mu opioid agonist, as described in below subsections.

In Vitro Data

Receptor Binding Studies

7-OH has been shown to have affinity and activity at mu opioid receptors. In a study using human embryonic kidney (HEK) cells with cloned, human opioid receptors, 7-OH demonstrated high affinity for the mu opioid receptor ($K_i = 47 \text{ nM}$) relative to kappa ($K_i = 188 \text{ nM}$) and delta opioid receptors ($K_i = 219 \text{ nM}$) (Kruegel et al., 2016). In a second study using HEK 293 cells expressing human mu and other opioid receptors, 7-OH demonstrated high affinity for mu opioid receptors ($K_i = 16 \pm 1 \text{ nM}$) and its affinity was greater than mitragynine ($K_i = 238 \pm 28 \text{ nM}$) and lower than morphine ($K_i = 1.50 \pm 0.04 \text{ nM}$) (Todd et al., 2020). Using an in vitro radioligand binding assay with CHO cells expressing murine-derived opioid receptors, 7-OH demonstrated relatively high affinity for mu-opioid receptors ($K_i = 37 \pm 4 \text{ nM}$), relative to mitragynine ($K_i = 230 \pm 47 \text{ nM}$), although its affinity was lower than morphine ($K_i = 4.6 \pm 1.8 \text{ nM}$) (Varadi et al., 2016). Other studies conducted using whole brain homogenates of guinea pig brain tissue have also demonstrated that 7-OH has high affinity at mu opioid receptors ($K_i = 8.0 \text{ nM}$) relative to kappa ($K_i = 6.7 \text{ nM}$) and delta opioid receptors ($K_i = 6.8 \text{ nM}$) (Matsumoto et al., 2004). Obeng and colleagues evaluated the binding affinity of 7-OH using human recombinant HEK 293 cells expressing mu opioid receptors. Their results are in agreement with the data presented above where the authors found that 7-OH binds with high affinity ($K_i = 7.2 \text{ nM}$) to mu opioid receptors relative to delta ($K_i = 236 \text{ nM}$) and kappa ($K_i = 74.1 \text{ nM}$) receptor subtypes (Obeng et al., 2020). A number of additional binding studies are in keeping with the data described above, demonstrating the affinity of 7-OH for mu opioid receptors across a variety of binding assays (Chakraborty et al., 2021; Matsumoto et al., 2008; Obeng et al., 2021; Takayama et al., 2002).

The results of the receptor binding studies with 7-OH are in keeping with *in silico* receptor binding models that suggest 7-OH has high affinity for the mu opioid receptor. The *in silico* modeling results were subsequently confirmed with a radioligand binding assay where 7-OH demonstrated high affinity for cloned, human mu opioid receptors ($K_i = 70 \text{ nM}$). (Ellis et al.,



2020). Collectively, the available receptor binding data demonstrate the affinity and binding of 7-OH to mu opioid receptors.

Functional Studies

Many of the studies referenced above performed additional assessments of 7-OH to determine its functional activity after binding (i.e., agonist or antagonist effects). These studies have consistently demonstrated that 7-OH produces mu-opioid agonist effects. For example, Kruegel and colleagues examined the functional activity of 7-OH and mitragynine in HEK cells expressing opioid receptors using a bioluminescence resonance energy transfer (BRET) assay. Both mitragynine and 7-OH functioned as partial agonists, producing E_{max} values of 34% and 47% respectively and EC₅₀ values of 339 ± 178 nM and 34.5 ± 4.5 nM (Kruegel et al., 2016). Activation of the mu opioid receptor pathway was also investigated using forskolin-stimulated cyclic adenosine monophosphate (cAMP) accumulation in Chinese Hamster Ovary (CHO) cells expressing mu opioid receptors. In this assay, 7-OH produced a maximal activation (E_{max}) of 85.9%, a value similar to that produced by the positive control comparators DAMGO (86.2%) and morphine (86.9%). These data suggest 7-OH acts a full mu opioid agonist (Todd et al., 2020). Similarly, Matsumoto and colleagues concluded that 7-OH was “found to have an opioid agonist property on μ - and/or κ -opioid receptors” based on its ability to inhibit contraction of isolated guinea pig ileum. In this assay, 7-OH displayed approximately 13-fold greater potency than morphine and 46-fold greater potency than mitragynine. The inhibition was reversed by naloxone, suggesting the effects are mediated via mu opioid receptors (Matsumoto et al., 2004). Other functional assays produced results that are aligned with Matsumoto and colleagues. For example, using a cAMP mobilization assay as a measure of functional effects, 7-OH acted as a full agonist with an EC₅₀ of 7.6 nM, and was more potent than mitragynine (EC₅₀ 307.5 nM) (Obeng et al., 2020). Likewise, when evaluating the agonist activity of 7-OH in an electrically stimulated guinea pig ileum, 7-OH acted as a full agonist and was more potent than morphine (Takayama et al., 2002). Finally, using a [³⁵S] GTPγS functional assay, 7-OH produced an E_{max} of 77% with an EC₅₀ of 53.4 nM, further demonstrating its agonist effects (Varadi et al., 2016).

Animal Data on Behavioral and Physiological Effects

Conditioned Place Preference

Conditioned place preference (CPP) is a commonly utilized animal model to study the rewarding effects of drugs. In this paradigm, an animal is conditioned to associate a particular environment with a drug treatment, and an alternative environment with a non-drug condition. After repeated sessions, the animal is then observed under non-drug conditions to determine which environment the animal prefers. CPP is established if the animal spends more time in the drug-paired compartment vs. the vehicle-paired compartment (Mombelli, 2022; Prus et al., 2009). Many drugs of abuse produce CPP, though notably, it is not a direct measure of reinforcing effects.

Using the CPP paradigm, several studies have demonstrated the ability of 7-OH to produce rewarding effects and that it does so more potently than morphine. Gutridge and colleagues employed C57BL/6 mice and demonstrated the development of CPP after 3 mg/kg 7-OH. CPP was observed after both doses although 7-OH required more sessions (4 sessions) whereas morphine (6 mg/kg) was able to establish CPP in two sessions (Gutridge et al., 2020). Similarly,



other studies have demonstrated the ability of 7-OH (2 mg/kg) to produce CPP, and that it does so with greater potency than morphine (Matsumoto et al., 2008).

Drug Discrimination

Drug discrimination is an experimental method in which animals identify whether a test drug produces interoceptive effects similar to those produced by a drug to which the animals are trained to differentiate from placebo, and which has known pharmacological properties. If the known drug is one with abuse potential, drug discrimination methods can be used to predict if a test drug will have abuse potential in humans (Balster & Bigelow, 2003; Solinas et al., 2006).

For abuse assessment purposes, an animal is trained to press one bar when it receives a known drug of abuse (the training drug) and another bar when it receives placebo. A challenge session with the test drug determines which of the two bars the animal presses more often as an indicator of whether the test drug is more like the known drug of abuse or more like placebo. A test drug is said to have "full generalization" to the training drug when the test drug produces bar pressing >80% on the bar associated with the training drug (Ator & Griffiths, 2003; Swedberg, 2016; Walker, 2018; Young, 2009). A test drug that generalizes to a known drug of abuse will likely be abused by humans (Balster and Bigelow, 2003).

Male Sprague Dawley rats were trained to discriminate morphine (5.0 mg/kg i.p.) from saline using a 30 min pretreatment time and FR10 schedule of reinforcement. After successful training, substitution tests with 7-OH (0.3, 1.0 and 3.0 mg/kg) were performed. The highest dose of 7-OH (3.0 mg/kg) produced complete substitution for the morphine stimulus cue. Moreover, pretreatment with naloxone significantly reversed the 7-OH substitution and resulted in saline-like responding. Notably, in this study, 7-OH was more potent than morphine (Harun et al., 2015).

In a second study, the discriminative stimulus effects of 7-OH were examined in separate groups of rats trained to discriminate either morphine (3.2 mg/kg i.p., 15 min pretreatment) or mitragynine (32 mg/kg i.p., 30 min pretreatment) from saline. After successful acquisition of discrimination training 7-OH was administered in substitution tests. 7-OH was administered i.p., with a 15 min pretreatment time in a dose range of 0.1-17.8 mg/kg. In the morphine-trained rats, 7-OH produced complete substitution at doses above 0.56 mg/kg, with the 1.0 mg/kg dose producing 100% drug-lever-appropriate responding and a resultant ED₅₀ of 0.28 mg/kg. Notably, the dose-response curve was shifted to the left, demonstrating an increased potency of 7-OH relative to morphine. In addition, pretreatment with 0.032 mg/kg naltrexone shifted the dose-response curve to the right suggesting substitution was mediated via mu-opioid receptors (Obeng et al., 2021). Taken together, the drug discrimination data demonstrate the ability of 7-OH to substitute and mimic the stimulus effects of morphine, and that 7-OH is more potent in doing so. These data are a strong indication that 7-OH produces subjective effects in humans that are similar to opioids, along with an associated abuse potential.

Self-Administration

Self-administration is a method that assesses whether a drug produces reinforcing effects that increase the likelihood of behavioral responses in order to obtain additional drug (i.e., whether an animal will press a lever for a drug injection). Drugs that are self-administered by animals are



likely to produce rewarding effects in humans, which is indicative of abuse potential. Generally, a good correlation exists between those drugs that are self-administered by animals and those that are abused by humans (Balster & Bigelow, 2003; Brady et al., 1987; Johanson & Schuster, 1981; Panlilio & Goldberg, 2007). It is notable that self-administration is a behavior that is produced by drugs that have been placed into every schedule of the CSA. Additionally, rates of self-administration for a particular drug will go up or down if the available drug dose or the work requirement (bar pressing for drug) is altered. Positive results from a self-administration study provide an abuse potential signal, suggesting that a drug has rewarding properties, but not necessarily that it produces more rewarding effects than another drug in humans.

7-OH produces reinforcing effects and is self-administered by rodents. In the study, rodents were trained to self-administer morphine (100 µg/infusion) and faded to 50 µg/infusion once stable responding was achieved. Thereafter, extinction sessions were performed to confirm acquisition of the self-administration training prior to substitution tests. Substitution tests were performed with 7-OH doses of 2.5, 5, 10 and 20 µg/infusion. In the substitution tests, 7-OH produced an inverted U-shaped curve and the number of infusions for 5 and 10 µg/infusion of 7-OH were significantly greater than vehicle, demonstrating the reinforcing effects of 7-OH (Hemby et al., 2019).

The self-administration of 7-OH was blocked by both a mu opioid antagonist (naloxonazine) and a delta opioid antagonist (naltrindole), suggesting its reinforcing effects are mediated via opioid receptors. In addition, peak morphine self-administration occurred at 50 µg/infusion while peak 7-OH infusions occurred at 5 µg/infusion, demonstrating a substantially increased potency of 7-OH relative to morphine.

There are some pharmacokinetic (PK) data available from animal studies involving the administration of isolated, i.e., single entity, 7-OH. Following a single oral dose (1 mg/kg 7-OH) to beagle dogs, absorption was rapid, with a peak plasma concentration (i.e., C_{max}) of 56 ± 1.6 ng/mL 15 minutes post-dose. The elimination half-life was slower, producing a mean of 3.6 ± 0.5 h. No AEs were observed, and no abnormal laboratory findings were reported (Maxwell et al., 2021). In adult male and female mice, the PK parameters of 7-OH were investigated after a single oral dose of 50 mg/kg 7-OH. The tissue distribution of 7-OH was observed in descending order: liver > kidney > spleen > lung > brain. Plasma C_{max} values were 0.6 and 0.9 µg/mL in males and females with a T_{max} value of 0.5 hr. Area under the curve (AUC) values over 48 hours (AUC_{0-48 hr} µg/mL) were 1.4 and 2.9 in male and female mice (Berthold et al., 2022).

Antinociceptive Effects

The antinociceptive effects of 7-OH were investigated in mice using the tail flick and hot plate tests. These tests are commonly used to examine pain and analgesic effects in rodents (D'Amour & Smith, 1941). In these tests, rodents are subject to a heat stimulus and timed for the duration it takes to move their tail (i.e., tail flick) or produce a response such as jumping, licking, or shaking of limbs (i.e., hot plate).

In the tail flick test, subcutaneous administration of 7-OH (2.5 – 10 mg/kg) produced both time and dose-related antinociceptive effects. Notably, the dose-effect curve for 7-OH was shifted to the left, indicating a greater potency than the positive control comparator, morphine. Similar results were observed in the hot plate test, and when morphine and 7-OH were administered



orally. Naloxone (2 mg/kg s.c.) inhibited the effects of 7-OH and morphine in both tests (Matsumoto et al., 2004; Matsumoto et al., 2008). Concurrent results were observed by Obeng and colleagues using the hot plate test. In their study, 7-OH (0.0032 – 3.2 mg/kg, i.v.) produced maximum antinociceptive effects and was more potent morphine but less potent than fentanyl when administered intravenously. Likewise, naltrexone (0.1 mg/kg) reversed the antinociceptive effects of 7-OH suggesting the antinociception was mediated via mu opioid receptors (Obeng et al., 2020).

Respiratory Depression

A major risk of opioid exposure and cause of opioid-induced death is respiratory depression (Baldo & Rose, 2022; Bateman et al., 2023). To examine the respiratory effects of 7-OH in rodents, whole body plethysmography was used in freely moving, awake rats. Both morphine (10 and 32 mg/kg, i.v.) and 7-OH (1, 3.2, and 10 mg/kg, i.v.) induced significant respiratory depression as assessed by minute volume, tidal volume, and breathing frequency. The mu-opioid agonist naloxone (1.0 mg/kg i.v.) reversed these effects, a finding consistent with the mu opioid effects of 7-OH (Zuarth Gonzalez et al., 2025). These data highlight a potential risk factor of 7-OH exposure and suggest 7-OH may expose individuals to similar risks as classic opioids, including respiratory depression.

Physical Dependence and Withdrawal

It is well-established that chronic administration of opioids leads to the development of tolerance and physical dependence that may culminate into a withdrawal syndrome. In parallel with some of the hot plate tests described above, the ability of 7-OH to produce physical dependence and withdrawal was examined. Mice were treated with subcutaneous 7-OH (10 mg/kg b.i.d.) or morphine (10 mg/kg b.i.d.) for five days. Tolerance was assessed as a reduction of analgesia in the hot plate test. After five days of treatment, both morphine and 7-OH showed a decreased analgesic response on the hot plate test, demonstrating the development of tolerance. In addition, cross-tolerance was also observed between morphine and 7-OH suggesting a similar mechanism of action between the drugs. Finally, after five days of escalating doses of 7-OH and morphine (8–45 mg/kg b.i.d.) the development of withdrawal was assessed with a 3 mg/kg s.c., dose of naloxone injected two hours after 7-OH administration. Both morphine and 7-OH treatment produced signs of withdrawal such as jumping, rearing, urination, ptosis, forepaw tremor, and diarrhea (Matsumoto et al., 2005).

Summary of Preclinical Data

From the studies described above, 7-OH has high affinity for mu opioid receptors and functional activity as an agonist at these receptors. Consistent with this pharmacological activity, 7-OH is self-administered by animals, substitutes for morphine in drug discrimination studies, produces antinociception, and physical dependence leading to withdrawal when administered to rodents. Moreover, 7-OH has consistently demonstrated an increased potency relative to morphine in preclinical rodent studies. These observations suggest 7-OH has pharmacological properties representative of a full mu opioid agonist and an associated high potential for abuse.



CONCLUSIONS

The data described in this report indicate that 7-OH has a significant potential for abuse and associated harms. Conclusively, 7-OH has high affinity and agonist activity at mu opioid receptors. Consistent with this pharmacological mechanism of action, 7-OH demonstrates rewarding effects in that it is self-administered by animals and also produces conditioned place preference, two well-established animal behavioral models measuring rewarding effects as a predictor of abuse potential in humans. In animal drug discrimination studies, 7-OH substitutes for morphine with full generalization. 7-OH is also demonstrated to produce antinociception consistent with opioid pharmacology, and to produce physical dependence when administered to rodents, as evidenced by a classic set of withdrawal signs associated with opioid withdrawal upon discontinuation of opioid administration. Moreover, 7-OH in all above models has consistently demonstrated an increased potency relative to morphine.

Due to the fact that 7-OH is both a metabolite of mitragynine and naturally present in low amounts in botanical kratom, using toxicology results to identify 7-OH as a primary or sole contributor in human exposures is challenging. There is also a need for improved clinical awareness and population surveillance to better characterize patterns of 7-OH use, the products that people are obtaining, and individual treatment needs following 7-OH exposure. Additionally, questions on 7-OH are not generally included in national surveys, and other data sources that rely on self-reported use of 7-OH likely underestimate the number of 7-OH exposure cases, as individuals may be unaware of the distinction from kratom products. Nonetheless, since specific codes were added earlier this year to document 7-OH exposure cases, U.S. poison centers have identified multiple single-substance cases of 7-OH exposure resulting in serious adverse clinical outcomes. Also, although anecdotal, social media and online forums indicate growing awareness and use of 7-OH, and many testimonials of the negative opioid-mediated effects users have experienced, including 7-OH dependence, associated withdrawal syndrome, and addiction.

In the current marketplace in the U.S., 7-OH is increasingly being marketed over-the-counter and online, in concentrated forms or sufficient doses to cause harms to those individuals engaging, knowingly or unknowingly, in use of 7-OH. Based on demonstrated pharmacology, repeated or prolonged use of 7-OH would lead to tolerance, physical dependence, and potentially to opioid addiction—typical of mu opioid agonist drugs of abuse. This public health threat is troubling and requires immediate and impactful policies to educate consumers and take regulatory action that limits access to 7-OH containing products.



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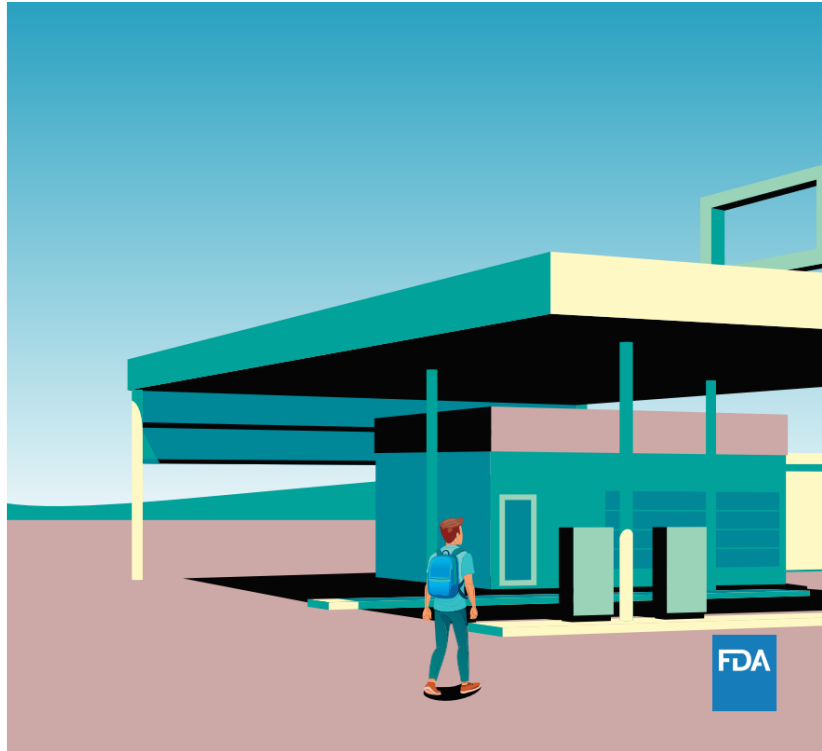


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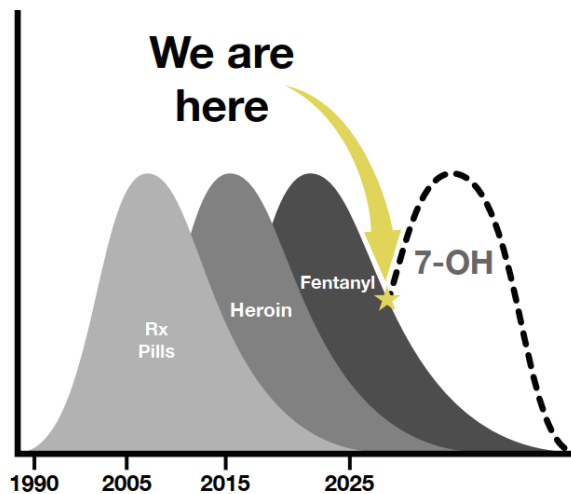
11.4 Appendix 4: FDA Slide Set: Preventing The Next Wave of the Opioid Epidemic: What You Need to Know About 7-OH

Preventing
The Next Wave
of the Opioid
Epidemic:

What You
Need to
Know About
7-OH



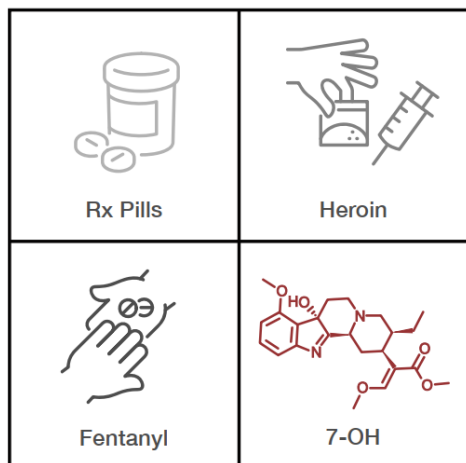
The Opioid Epidemic is Evolving with 7-OH. We Can and Must Act Now to Prevent a New Wave.



Note: The next potential phase of the opioid crisis may be defined by the emergence of novel synthetic opioids like 7-OH, combined with an increasing prevalence of concurrent use of opioids and other controlled substances.



7-OH is Engineered to be Addictive. It is a Potent Opioid by Design.



7-OH (formally known as 7-Hydroxymitragynine) is a powerful psychoactive compound that occurs naturally in very small amounts in the Kratom plant.

7-OH products are concentrated derivatives often falsely marketed as Kratom.

Street names include 7-Hydroxy, 7-OHMG and '7'.



Preventing The Next Wave of the Opioid Epidemic: What You Need to Know About 7-OH

3

This Opioid is not Prescribed or Purchased on the Street - It's Sold like Candy at Retail Stores and Online.



What began as doctor-prescribed painkillers migrated to back-alley dealers when prescriptions dried up. Opioids have disturbingly gone mainstream with 7-OH—no prescription needed, no dealer required. This dangerous opioid is sitting on store shelves, making gas stations and convenience stores risky places where kids can purchase these drugs as easily as buying candy.

4

Preventing The Next Wave of the Opioid Epidemic: What You Need to Know About 7-OH



Hiding in Plain Sight: 7-OH Products are Designed to Look Like Everyday Treats Like Gummies, Candies and Ice Cream.



Note: These images are select illustrative examples and do not represent the full scope of 7-OH products on the market. Consumers should read packaging and labels carefully to determine whether a product contains 7-OH.



Preventing The Next Wave of the Opioid Epidemic: What You Need to Know About 7-OH

5

While Some 7-OH Products are Marketed as Natural Kratom, They are Not the Same. 7-OH Presents Significant Risks.



Crushed/Powdered Leaves
with Natural 7-OH Levels



Kratom 7-OH Significantly
Concentrated Extract

**7-OH is 13x
more potent
than morphine.**



“Enhanced” or “spiked” kratom products may appear to be natural leaf, but actually contain as much as 500% more 7-OH than would be expected naturally.

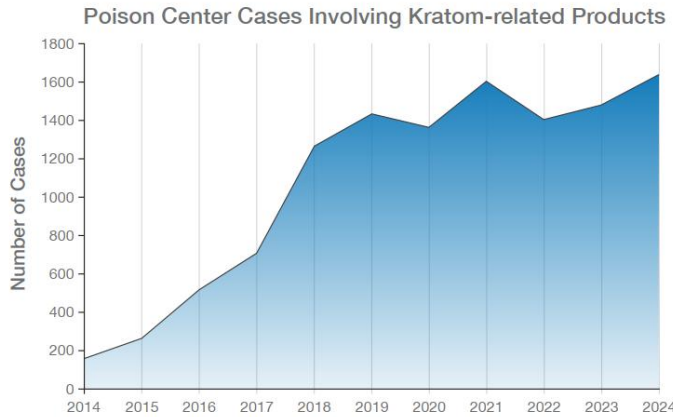
6

Preventing The Next Wave of the Opioid Epidemic: What You Need to Know About 7-OH



Poison Control is Sounding the Alarm on 7-OH.

American families are reporting side effects such as dependency, withdrawals, overdose and even death.



Note: Kratom-related products refers to a broad category of botanical kratom products and other kratom-derived products, including an unknown number of 7-OH involved cases; a classification code for 7-OH products was added to the National Poison Data System only in February, 2025.

*Data reflect partial year.



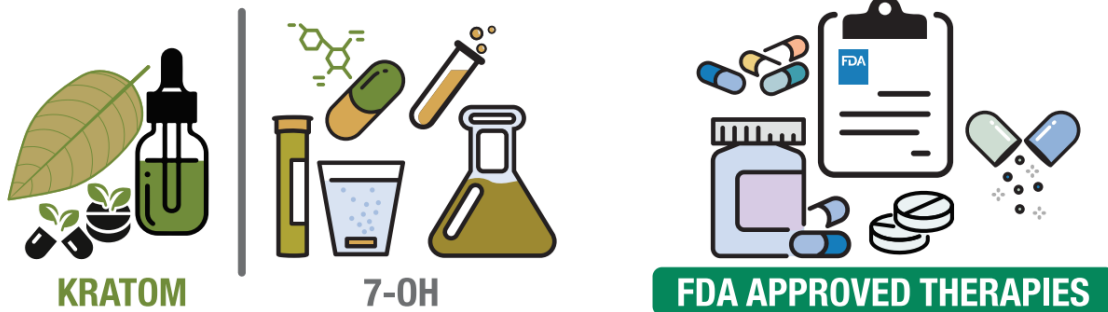
Preventing The Next Wave of the Opioid Epidemic: What You Need to Know About 7-OH

7

In 2025*, approximately 40% of 7-OH reports were among individuals abusing the drug.

There is No Safe Swap. 7-OH is an Opioid, Not an Alternative for Approved Treatments.

Kratom-related products, including 7-OH, are not safe or approved treatments for opioid or SSRI (selective serotonin reuptake inhibitors) withdrawal symptoms, chronic pain, or to treat depression, anxiety and other mood disorders.



8

Preventing The Next Wave of the Opioid Epidemic: What You Need to Know About 7-OH



Protect You and Your Family



If you believe someone is experiencing an adverse event from a 7-OH product, contact the Poison Help Line (1-800-222-1222) or visit www.poisonhelp.org for help.

If someone is unresponsive, dial **911** immediately!

- Avoid buying any products with 7-OH.
- When buying candy or other treats for you or your family, examine the packaging and label so you don't accidentally buy a treat containing 7-OH.
- Talk to your health care professional if you need help with opioid addiction, anxiety, mood disorders, pain, or other ailments.



Preventing The Next Wave of the Opioid Epidemic: What You Need to Know About 7-OH

9

“Even better than rolling back a public health crisis would be never having one in the first place: Let's not allow 7-OH to drive the next wave of the U.S. opioid epidemic.”

– Marty Makary, M.D., M.P.H., FDA Commissioner

10

Preventing The Next Wave of the Opioid Epidemic: What You Need to Know About 7-OH



Scan the QR code or visit fda.gov/7-OH for additional resources and to learn more.



11.5 Appendix 5: Department of Health and Human Services Press Conference Transcript

Measures to Safeguard American Public from Dangerous Opioid 7-OH

Participants:

HHS Secretary Robert F. Kennedy, Jr.

HHS Deputy Secretary Jim O'Neill

FDA Commissioner Dr. Marty Makary

Melody Woolf (chronic pain survivor).

Hubert H. Humphrey Building Auditorium

200 Independence Ave SW Washington, D.C.

Tuesday, July 29 at 10:30 AM Eastern Daylight Time.

Announcement accessed at <https://www.hhs.gov/press-room/hhs-opioid-7oh-press-conference-kennedy.html>

CONFIDENTIAL

1

1 RE: Press Conference on Opioid 7-Oh Public Safety with Deputy
2 Secretary Jim O'Neill, Commissioner of Food and Drugs, Dr. Marty
3 Makary, DEA Assistant Administrator Tom Prevost, Melody Woolf,
4 Senator Markwayne Mullin, Secretary Robert Kennedy
5

6 STEPHANIE: Thank you for being here today. We're looking
7 forward to this press conference. Appreciate all of you being
8 here. I am honored to introduce to the stage Deputy Secretary Jim
9 O'Neill.

10 MR. O'NEILL: Thank you, Stephanie (phonetic). HHS is
11 honored to host today our friends in the Department of Justice. We
12 look forward to collaborating with you over the next four years to
13 make America healthy again. We're also honored to welcome Senator
14 Mullin, who has been a wonderful friend of this department from the
15 Health Committee.

16 I've had the pleasure of working with people -- many people
17 on the frontier of innovation. Innovation in health care,
18 innovation in government, innovation in business, working to make
19 things better. But not all innovation is positive. Dark
20 innovations in chemistry have exacerbated the addiction crisis in
21 this country. Synthetic opioids, like Carfentanil and the
22 substance we're here to take action on today, 7-Hydroxymitragynine.

23 7-OH carries a high risk of addiction on purpose. It is a
24 powerful opioid agonist, many times more potent than morphine.
25 We've seen a disturbing rise in reports of overdoses, poisonings,

1 and emergency room visits linked to products containing 7-OH.
2 These substances are often sold online or in convenience stores
3 with no quality control, no dosage control, and no warnings. This
4 is a recipe for public health disaster.

5 Young people, Veterans, and people who suffer from chronic
6 pain or addiction are being misled into thinking that these are
7 safe alternatives. They're not. Here at HHS, we're committed to
8 gold standard science, safety, and compassion. We know people are
9 looking for relief, but that relief must be grounded in reality.
10 We owe it to the American people to act decisively, and that's what
11 we're doing today, initiating a process to schedule 7-OH as an
12 illicit substance.

13 To share more, I'd like to welcome to the stage my good
14 friend and colleague, the Commissioner of Food and Drugs, Dr. Marty
15 Makary.

16 DR. MAKARY: Thank you, Deputy Secretary O'Neill. It's
17 great to be here. 7-OH is not just like an opioid; it does not
18 just have opioid binding properties. 7-OH binds to the mu-
19 receptor, which means, scientifically, by definition, it is an
20 opioid. And yet, it is sold in vape stores, in smoke shops, in
21 convenience stores, in gas stations that are popping up all over
22 the United States, and nobody knows what it is. It is a synthetic
23 concentrated byproduct of kratom. Our focus is not on kratom; our
24 focus is on 7-OH, which, according to the Journal of Medical
25 Chemistry, is 13 times more potent than morphine.

1 We have a history in public health of being asleep at the
2 wheel. 30 years after cigarettes were widely used, then we started
3 raising public health concerns. After heroin, crack, cocaine, and
4 other street drugs became popular, about 10 years later, the
5 medical establishment and public health community responded.
6 Eighteen years after the approval of OxyContin by the FDA, we woke
7 up to a terrible crisis that may have killed almost a million
8 Americans. And then again, right afterwards, with fentanyl.

9 We have a history of being asleep at the wheel. For the
10 sake of our nation's children, let's not get caught flat-footed
11 again.

12 Public health is supposed to prevent disasters, not just
13 clean them up after they've killed thousands and thousands of
14 people. Why do we get caught flat-footed time and time again? In
15 my opinion, it's because of a disconnect between the ivory towers
16 and the streets. Have experts been to the vape stores? It affects
17 what we see in the operating room.

18 I learned from living and working in inner-city Baltimore
19 that you have to be proximate to a problem to understand it. We
20 can't just talk about it on panels, at medical conferences, and in
21 the ivory towers of the medical establishment. I saw on the
22 streets of Baltimore how some of my patients that I would bump into
23 switched from the prescription opioid that I would prescribe to
24 heroin because they couldn't afford the co-pay.

25 I've been surprised going to these vape stores at what I'm

1 seeing. First of all, roughly 85 percent of the vape products are
2 illegal vape products. We know that because the FDA publishes a
3 list of legal vape products, and no cutesy, fruity flavor designed
4 to appeal to children or a video game vape product device is legal
5 or approved by the FDA.

6 I've been surprised that the candies and gummies and drinks
7 and ice cream cones -- here's one drink with 7-OH in it. There are
8 other products that get added to drinks. Do we understand what 7-
9 OH is at public health scale? Let's not get caught flat-footed
10 again. We're not targeting the kratom leaf or ground-up kratom.
11 We are targeting the concentrated synthetic byproduct that is an
12 opioid.

13 The Trump Administration is deeply committed to preventing
14 another wave of the opioid epidemic. And this is deeply personal
15 for many people. It's deeply personal for the Secretary of Health
16 and Human Services, who will share how, at a young age, he
17 struggled with addiction.

18 It's personal for a family friend, a good family with a good
19 kid who is addicted, knows they're addicted, wants to stop their
20 addiction, but can't stop. That story is going on all across the
21 United States, and we don't have research or numbers or statistics
22 on the scale of that problem. Let's not allow another wave of the
23 opioid epidemic to get -- catch us blindsided again. I've met some
24 of these families. Let's be honest, there's also a lot we don't
25 know. This may be the calm before the storm. It may be the tip of

1 the iceberg. But let's be aggressive and proactive.

2 Today, the FDA is announcing that we are initiating action
3 to recommend scheduling of 7-OH as a controlled substance by the
4 DEA. We are also releasing a report on 7-OH to educate the public,
5 including the other names it goes by.

6 And finally, we need to educate the public, including the
7 medical community. I've talked to many doctors who don't know what
8 7-OH is. We need to be proactive so we don't get caught blindsided
9 again. Thank you very much.

10 Now, I'd like to introduce DEA Assistant Administrator Tom
11 Prevoznik.

12 Tom, if you could come up here?

13 He leads the Diversion Control Program Office. And he's
14 worked with HHS to uncover billions in health care fraud.

15 Thank you, Tom.

16 MR. PREVOZNIK: Thanks, Marty.

17 DR. MAKARY: Thank you.

18 MR. PREVOZNIK: Good morning, and thank you all for being
19 here. Let me start by saying DEA's mission is to protect the
20 public health and safety, period. That means taking action when
21 dangerous, unregulated substances threaten American lives. DEA
22 just received the Department of Health and Human Services' formal
23 recommendation for 7-Hydroxymitragynine. And now that we have it,
24 we'll review it expeditiously, thoroughly, and in accordance with
25 the law.

1 We don't play politics with science, and we don't cut
2 corners when it comes to public safety. DEA is the agency charged
3 with making the final scheduling decisions under the Controlled
4 Substances Act. But we don't act alone. We rely on HHS and the
5 FDA to conduct rigorous science-based evaluations, including the
6 eight-factor analysis that considers abuse potential, medical use,
7 and public health risks.

8 DEA will now begin the legal rulemaking process, which
9 includes an opportunity for the public to comment before any final
10 scheduling decision is made. That means full transparency, and all
11 voices will be heard. DEA will do what we've always done, follow
12 science, follow the law, and do what's right to keep our
13 communities safe. Thank you.

14 DR. MAKARY: Thank you, Tom. One of the dangerous things
15 about 7-OH is how much confusion it can cause. Many 7-OH products
16 are marketed as kratom extracts or enhanced kratom. But in
17 reality, they are the concentrated synthetic potent form that is an
18 opioid.

19 Our next speaker, Melody Woolf -- Melody, come on up here --
20 has experienced suffering looking for pain relief, and she's going
21 to share a bit about her story and how the dangerous 7-OH product
22 affected her life.

23 Thank you, Melody.

24 MS. WOOLF: So very good to be here today. My name is
25 Melody Woolf, and I'm from Kalamazoo, Michigan. I have three grown

1 children, and I'm going to be celebrating my 39th wedding
2 anniversary on July 31. So, I'm very happy to get to do this and
3 have my family see me doing this today.

4 I'm also a 20-year chronic pain patient. I spent eight of
5 those years in bed. Our home was a pretty dismal place. My kids
6 had fans on in their rooms at night because they needed to sleep,
7 and they could hear me crying in the downstairs. They were able to
8 go to very few activities because I was bedridden. And they had no
9 parent to take them. My husband was working, and so they missed
10 out on a lot of activities that they should have been at.

11 And to be quite truthful, my marriage was headed for a
12 divorce. But remember, I'm celebrating my 39th wedding anniversary
13 soon. I saw many doctors at the Cleveland Clinic, the University
14 of Michigan Rheumatology, and so many specialists.

15 I was taking up to 11 medications at one time from one
16 doctor, and one of them being the highest patch count for fentanyl.
17 It didn't really help my pain. It made it easier to take because
18 it made me sleep a lot. It made me groggy. But you know what? It
19 also made me mean.

20 And like I said, our house was a dismal place, and I'm just
21 so thankful that I found a botanical called kratom. And right
22 away, my life improved; I was out of bed. I was doing activities
23 with my kids, and I lost a lot of weight too. Being in bed for
24 eight years -- it affects your health very negatively. So I got my
25 life back. I've taken tent camping trips to both eclipses. And

1 things just turned around for my family.

2 In 2022, during COVID time, my daughter and son-in-law lost
3 their childcare. I got a call, "Mom, would you like to come move
4 in with us for the year?" I said, "Yes," immediately. "Don't you
5 have to ask Dad?" "No." It was very thrilling for me to get to
6 spend the entire year with my granddaughter. And it was kratom
7 only, the powdered leaf, that saved my life.

8 And now, I'm seeing something very dangerous happen. 7-OH
9 is being sold over the counter, and it is not the plant. It's a
10 concentrated substance that is very dangerous to consumers. 7-OH
11 is not what helped me get out of bed and get a quality of life
12 again that I enjoy.

13 I check out my smoke shops to make sure that they're selling
14 products appropriately, that there's labeling on them, that they
15 have a no-minors, and that kratom is behind the counter locked up.
16 I did that on Sunday. I said, "Where are your kratom products?"
17 He said, "Oh, here they are." He handed me a 7-OH product. And I
18 said, "That's not kratom," and he was very confused. He said,
19 "It's not? I thought it was." And I said, "No, it's not." I
20 briefly explained it to him.

21 And then when I told him that I do not take 7-OH, and I
22 never would, he said, "Well, I'm very glad to hear that, because
23 many of my customers tell them that it takes them back to their
24 heroin days." And there is the big danger.

25 So this is what's happening. 7-OH is pulling people away

1 from the opioid use that they've been trying to get away from. 7-
2 OH needs to be off of the shelves. Thank you.

3 MR. MAKARY: Thank you, Melody.

4 Now, we're going to hear from Senator Markwayne Mullin from
5 Oklahoma. And he has been a champion in Congress on addressing the
6 opioid epidemic.

7 And so, Senator Mullin, great to have you here, and thanks
8 for speaking.

9 MR. MULLIN: Thank you, sir. Appreciate it.

10 We all get involved in issues for purposes of either passion
11 or personal experiences. And with the opioid crisis or the drug
12 epidemic we've had throughout the country, it's affected almost all
13 of us, either directly or indirectly.

14 For us, my wife and I, it's affected us directly.
15 Unfortunately, we have family members that we love and we want to
16 take care of. And if you've ever dealt with a family member that
17 is struggling with drug use, and you're the caregiver of that
18 individual, they go missing for days, and you're worried about your
19 phone ringing. You're afraid to be away from your phone. The
20 phone rings at two o'clock in the morning. You pick it up because
21 you're afraid to hear what you're worried about 24/7, is they found
22 him dead.

23 And typically, it's, hey, I got arrested. I got in a fight.
24 I'm in trouble. Got stabbed. Can you come get me? And the list
25 goes on. And I could give you horror stories of all the phone

1 calls that my wife and I received over the last 20 years.

2 And then when someone goes and they go to rehab and you get
3 out -- and because, my Lord, we've been to every rehab center you
4 can imagine. And I'm sure some of you guys have experienced the
5 same thing. And they're clean, they're doing better, and they find
6 out they can go to a gas station, or a vape shop, or a skate shop,
7 or a bike shop, and they can find something that's legal for them
8 to take that gives them the same high. And they can still pass
9 drug tests, even though they're on probation.

10 But yet, it's a road to the same addiction. And you see the
11 pattern. You see it in their face. You see it in their eyes. You
12 see it in their words. You see it in their behavior. And you're
13 going, "Oh, my gosh, here we go again."

14 And you go get them drug tested, and they pass, and you're
15 going, what is going on? How can they pass this? "What are you
16 doing?" "I'm not doing anything. I'm not doing anything illegal."
17 But you can read it, because you've been with that loved one so
18 long. You see it, and you're helpless. And once again, you know
19 where the road is headed.

20 And then honestly, those of our family members that we've
21 struggled with addiction, when they actually get put in prison,
22 it's probably the first night you actually sleep well, because you
23 know where they're at. You know you're not going to get that phone
24 call. You don't like it, but you can breathe for the first time.
25 And in our case, a person gets out after years in prison, and they

1 find it in a drugstore again. And these individuals that are
2 selling it know what they're doing. They know the individuals
3 they're targeting. They know the loophole and sell it as a dietary
4 substance.

5 Well, they probably do lose weight, but not for the purposes
6 that we would like them to. And now that the industry has grown
7 from nothing to over a \$9 billion industry, more than even opioids
8 that are selling on the street, which is at \$5 billion a day.
9 Because they justify it. It's legal, but it's an addiction that's
10 ruining lives. It's an addiction that's truly killing people,
11 because it leads them down a road that sometimes they'll never
12 recover from, and we've known this.

13 And for the first time, we have a Secretary who not only has
14 a backbone to do something about it, but he does it because he has
15 personal experience. He understands addiction better than probably
16 any of us in this room. And it takes somebody like that who
17 understands the danger that this causes to stand up and push
18 against this. I say, illegal industry because they're using every
19 loophole they possibly can.

20 And once again, selling it as an energy drink or a dietary -
21 - but, yet the packages look like it came off the shelf of a cereal
22 box or a candy bar, or one of their favorite Mountain Dew drinks.
23 The list goes on. They know who they're targeting.

24 And so, Secretary Kennedy, thank you for standing up and
25 actually doing something about this. Because this isn't anything

1 new. This has been around for years. But without your leadership,
2 this would never happen. So from my family and every single family
3 that has dealt with this, God bless you and thank you.

4 MR. KENNEDY: Thank you very much. Thank you for those kind
5 words, Markwayne. Thank you to Jim O'Neill, to Tom Prevoznik, to
6 Marty Makary, and to Wendy as well. Thank you for that, for
7 sharing your story.

8 I spent 14 years as a heroin addict. And so I've been 43
9 years in recovery. And so I spent a lot of time talking about
10 addiction and reading about it. And typically in most societies,
11 you have about 10 percent of the population that suffers from
12 addiction. But when there is availability, that can become a
13 crisis. And you can have, for example, in Yemen, virtually 100
14 percent of the adult population is addicted to Khat because it's
15 available on every corner.

16 And my addiction started because of -- let me say this, it
17 was precipitated by availability. And in April of 1968, three
18 years -- three months before my dad died, the French Connection,
19 the biggest heroin bust in history -- heroin recovery, happened
20 altogether. They got out of one automobile, 200 pounds of heroin -
21 - pure heroin. And they ended up getting, I think, about 1,600
22 pounds over time.

23 That heroin was then stolen from the evidence locker room in
24 the Manhattan DA's office, and it was distributed on the streets of
25 New York. And for several years, there was \$2 heroin, so it was

1 available in deuces. And there were people on every corner in
2 Harlem, every corner in the Lower East Side, who were selling \$2
3 heroin. And 72nd Street in Central Park, there were over 100
4 dealers selling it at that time.

5 And I had iron willpower in other parts of my life. I gave
6 up candy for Lent when I was 13. I never ate candy again until I
7 was in college. I gave up desserts for Lent the following year,
8 and I never had another dessert until I was playing sports in
9 college and trying to bulk up for sports. I felt I could do
10 anything with my willpower. But this compulsion was absolutely
11 impervious to my will. And part of the problem was just the
12 availability. It was too easy to get this drug for me.

13 And if you look at the waves of addiction that Marty talked
14 about throughout history, they're all precipitated by availability.
15 Morphine was invented in 1803. And during the 1880s and 1890s,
16 there was an addiction crisis in this country. One because of the
17 availability of opium that was coming in through immigrant supply
18 chains. And the other was there was a lot of Civil War Veterans
19 who had become addicted, and it was widely available. Cocaine was
20 available in medicinal drinks and in popular drinks like Coca-Cola.

21 And Congress, in response to that crisis, made heroin and
22 cocaine illegal in 1914. And we had a break from it for many, many
23 years. And then the drug culture began in the 1960s, where it was
24 psychedelics, et cetera. But the real addiction crisis began after
25 1969 when that heroin became available. And you got a whole

1 generation that was hooked on that.

2 And then in 1970, Congress again acted to criminalize heroin
3 possession. And we got a little bit of freedom until the 1880s --
4 I mean, 1980s, when there was the drug cartels in Mexico and
5 elsewhere, developed supply lanes through the Bahamas and Mexico
6 that the DEA was not ready for at that time.

7 There were huge surpluses of cocaine in our country. And
8 the drug dealers figured out a way to market it very cheaply
9 through a new form of cocaine called "Crack." And throughout the
10 80s and 90s, we had the crack crisis in our country because of the
11 availability. And then in 2000, we had the oxycodone crisis,
12 because suddenly, opiate pills were available partly because of the
13 agency capture at the FDA that Marty is now dismantling. And with
14 that, FDA's action abetted that crisis.

15 And so when we have that availability, it turns into a
16 national crisis, and we're still losing 80,000 kids a year. Three
17 years ago, we lost 106,000 kids to addiction. That's double the
18 number of children that died, of American kids who died during the
19 20-year Vietnam War. It's two Vietnam Wars' worth of casualties a
20 year from this crisis.

21 And as Markwayne said, "All of us are touched." President
22 Trump is touched. His family also suffered from addiction. My
23 family, I lost a brother to this disease. I lost a niece during
24 COVID, a niece who I raised in my house, who was like a daughter to
25 me. I lost another niece to injuries who's now a quadriplegic

1 because of this disease. All of our families are touched. Every
2 American family.

3 The financial cost to our country is in the trillions. And
4 what we're determined to do is to avert a fourth wave of addiction.
5 I became an addict because it was so available. But I still had to
6 go to Harlem. Or, I had to go to the South Bronx. Or, I had to go
7 to the Lower East Side, and now you can go to any gas station.

8 And the people who are marketing these drugs, we looked --
9 we met with Pam Bondi yesterday talking about this issue and with
10 these people from the DEA. And they showed us maps of the places
11 where the vape shops and the smoke shops where this stuff is being
12 sold. And they're around military reservations in our country.
13 And the DEA has done measurements of urine in our troops, and
14 they're skyrocketing.

15 The more it's directly correlated to the number of vape
16 shops in their area. They're putting them around schools. They're
17 putting them in our poorest neighborhoods. And now they're putting
18 them in every gas station. And they're marketed for children.
19 They're gummy bears. They're bright colors. They're candy-
20 flavored. This is really a sinister, sinister industry.

21 As Marty pointed out, we've been -- our agency's been asleep
22 at the wheel for all of these other crises. And now we're going to
23 wake up, and we're going to stop this before it starts.

24 So I want to thank all of these ladies and gentlemen for
25 their commitment to making sure that this does not happen again in

1 our country and averting the fourth wave of addiction. Thank you
2 very much.

3 STEPHANIE: Thank you, Secretary Kennedy.

4 We're now going to take questions from the press. If you
5 can, please keep your questions to the reason we're here today.
6 And also give your first name, last name, and outlet. We have a
7 microphone for you.

8 MR. LIM: David Lim with Politico. Thanks for taking my
9 question. In 2018, former FDA Commissioner Scott Gottlieb said FDA
10 scientists conducted an analysis suggesting that kratom compounds
11 had opioid-like properties. And he said that there was, "No
12 evidence to indicate kratom is safe or effective for any medical
13 use."

14 I know the FDA's warning letters and actions today are
15 concentrated on concentrated 7-OH products. But does the
16 government today believe kratom itself is safe to consume? And
17 then secondly, the DEA previously attempted to temporarily schedule
18 7-OH in 2016 before backing off after receiving public blowback.
19 Is the Trump Administration prepared to finalize the scheduling
20 process even if it receives similar concerns now?

21 DR. MAKARY: So first of all, we're not prepared to say
22 anything is 100 percent safe, especially when it has psychoactive
23 properties. But what we are saying is that our focus is on
24 synthetic concentrated kratom. And you point out a good point.
25 And that is that, if we talk about all 7-OH, then we're not

1 distinguishing to the public the risk stratification of the
2 synthetic concentrated from the trace amounts of 7-OH that
3 naturally appear in the kratom leaf and have for centuries and have
4 been used in teas and other things.

5 So our scheduling recommendation will delineate trace
6 amounts from synthetic concentrated amounts. Great question.
7 Thank you.

8 MS. LAWRENCE: Hi, Lizzy Lawrence, reporter with STAT. I'm
9 curious how many, if there are any, known cases there are of 7-OH
10 being recorded as the sole cause of a fatal overdose?

11 DR. MAKARY: We have terrible statistics. Because if
12 somebody comes in with a 7-OH overdose, I'm not even sure a doctor
13 would know to ask about 7-OH. Very few doctors I've spoken with
14 know what's in these vape stores or know what 7-OH is. I've had to
15 explain it to the dozen or so doctors I've talked to.

16 So I think we're just starting to understand. It's very,
17 very reminiscent of when we prescribed opioids to patients who
18 didn't need them after minor surgical procedures. Or too many
19 opioids for those who did need an opioid, and we would notice some
20 people were coming back for refills at a very high rate. But we
21 hadn't put the two together because we hadn't recognized the
22 addictive nature.

23 So we need better statistics. There is a commitment from
24 NIH to do some research to try to understand this. But this is not
25 something where, after 50,000 Americans have died from it, we want

1 to start that process.

2 Thank you, Lizzy.

3 MS. OWERMOHLE: Hi, Sarah Ower mohle, CNN. To David's
4 question, what kind of regulation and guidance, or scientific
5 evaluation could we see in the future about natural kratom?

6 DR. MAKARY: Look, I think there have been physicians who
7 have had concerns about some claims around natural kratom. We have
8 to prioritize what we work on. So we are going after the killer
9 first, which is the synthetic concentrated kratom, and then we can
10 look into that other question. But we think it's night and day in
11 terms of the public health risk. Thank you.

12 MR. MCFARLANE: Hey, thank you. I'm Scott with CBS. You
13 mentioned the doctors need to become more familiar with the danger
14 here. And you've issued a letter, I think, today to doctors. But
15 what, in fact, changes today? I'm sorry, are you issuing a new
16 regulation? Are you going to do the scheduling? What actual
17 change is HHS affecting today?

18 DR. MAKARY: Yes, so great question. Thank you for that.
19 So a couple of things. One, we're issuing a report -- an FDA
20 report on 7-OH, explaining it. We are putting that out there, and
21 we'd love for you to let Americans know about that report so they
22 can learn.

23 It has both a deep science component and a section for
24 laypeople so they can understand the issue. We think every school
25 board should be talking about this. We are number 2 issuing a

1 letter today to the DEA to recommend scheduling above a
2 concentration threshold as a controlled substance. Number three,
3 we are sending a Dear Doctor Letter to every physician in the
4 United States, warning them about this. And we're going to
5 continue to try to educate the public. So, a couple of very
6 definitive actions today.

7 And of course, we announced a couple of weeks ago that we
8 have let distributors to the retail stores know that we have
9 serious safety concerns and specified those concerns.

10 MS. MANTO: Hi, Margaret Manto with NOTUS. You said that
11 you're thinking about this in terms of concentration, where it's
12 like trace amounts of 7-OH and kratom versus the much more
13 concentrated product. Is this a framework that you think the FDA
14 could use for other dietary supplements?

15 DR. MAKARY: I think it's a good idea. Thank you for
16 suggesting it. We do something called an Eight-Factor Analysis.
17 So our scientific team and the scientific team at the DEA
18 independently try to evaluate is there a threshold? And they look
19 at animal studies and a whole bunch of other criteria to look at
20 dependence and addictive thresholds.

21 So we have a threshold that is calculated in two different
22 mathematical ways to try to distinguish what we're talking about
23 with concentrated kratom from the trace amounts that appear in the
24 kratom leaf. Thank you.

25 MS. ASSAF: Thank you, Caitrin Assaf, Gray Media. I know

1 you said this process is just beginning. But of course, that takes
2 time. So in the meantime, can you tell us how quickly can we see
3 these products removed from shelves or at least made harder to
4 obtain? And then what message do you want to give to Americans who
5 are seeing this and saying, "Oh, I thought it was totally safe,"
6 and maybe still today can actually go and get it?

7 DR. MAKARY: So, effective immediately, the letters are out
8 to the distributors. And we've actually gotten some positive
9 feedback from some of those distributors. So we're sounding the
10 alarm with the distributors of the synthetic concentrated kratom.

11 We also want to create a national conversation. Where
12 parents talk to their children. Kids are sometimes using these
13 substances, and the parents don't know. And sometimes the kids are
14 using it, and they don't actually know what's in these substances.
15 So this is a time, as with other new addictive substances that
16 enter the United States, for us to have these conversations. And I
17 hope school boards, places of worship, all talk about the illegal
18 substances in these vape and smoke shops. Thank you.

19 MS. WHYTE: Hi, Liz Whyte with the Wall Street Journal.
20 Also very present in smoke shops and vape shops are high-potency
21 cannabis products and synthetic cannabis products, such as Delta 9,
22 Delta 8, THCA, high THC products. And these have been linked in
23 the medical literature already to psychosis. Is there a reason
24 that this kind of well-established smoke shop problem is not
25 something you're going after?

1 DR. MAKARY: So I personally, in my writings as a physician,
2 in my statements, and also the Department of Health and Human
3 Services, have expressed serious concerns about people using these
4 cannabis products. We don't want kids to use them. Cannabis use
5 disorder is a real thing. And as you appropriately mentioned,
6 there are now studies linking it to psychosis and even
7 cardiovascular problems. So that is an entirely separate public
8 health campaign, and it's an important issue. Thank you.

9 STEPHANIE: Okay, last question right here.

10 MS. SEITZ: Thank you. Amanda Seitz with the Associated
11 Press. I was wondering if you could say what class you're
12 recommending that it be scheduled, and how quickly you're expecting
13 the DEA to act.

14 DR. MAKARY: Class 1. It is an opioid by definition. It
15 will be ultimately up to the DEA to decide. Thank you.

16 STEPHANIE: Thank you so much.

17 (End of press conference)

18

19 CERTIFICATE

20 I certify that the foregoing is a correct transcript from the
21 electronic sound recording of the proceedings in the above-entitled
22 matter.

23

24 /s/ Vivian Saxe 9/2/25

25 VIVIAN SAXE, CERT**D 631 DATE

11.6 Appendix 6: Dr. Martin A. Makary 7-OH Letter to Colleagues



July 29, 2025

Dear Colleague,

I am writing to warn you about an opioid that few physicians may be aware of. It's called 7-hydroxymitragynine (7-OH).

7-OH is found in trace amounts in the kratom plant leaf. But this is not our focus. Our primary concern is the concentrated form of 7-OH. This is an important distinction. These concentrated 7-OH opioid products are far more dangerous than traditional kratom leaf products.

Concentrated 7-OH products have exploded in popularity in recent years, with vape shops, gas stations and corner stores selling pills, gummies, candies, and even eye-catching products like ice cream cones containing 7-OH. You may also see 7-OH referred to as 7-OHMG, 7-Hydroxy, 7-HMG, or 7. Additionally, some kratom leaf products marketed as "spiked" or "enhanced" may contain 7-OH at a level 500% higher than would be naturally expected in kratom leaf.

Notably, [one study](#) in the Journal of Medicinal Chemistry found 7-OH to be 13 times more potent than morphine. Aside from addiction, 7-OH side effects include withdrawal symptoms, insomnia and anxiety, seizures, and fatal respiratory depression. The FDA is seeing increases in adverse events and related reports to poison control and is concerned about the growth of 7-OH product sales nationwide. We have already issued warning letters to several firms for illegally distributing 7-OH products and are working alongside our partners at the DEA to move forward with adding certain 7-OH products to the controlled substances schedules.

Like many physicians, I find it painful to recall the many opioid prescriptions I wrote in the early 2000s for routine procedures, unaware of the high potential for abuse. Our recognition of the abuse potential and our delayed response as a medical community resulted in a national health crisis. Let's not get caught flat footed again. In addition to the FDA's ongoing regulatory activities and education efforts, I appreciate your vigilance on this issue.

For more information, please refer to our new report and educational resources, which can be found at www.fda.gov/7-OH.

Sincerely,

A handwritten signature in black ink, which appears to read "Martin Makary".

Martin A. Makary, M.D., M.P.H.
Commissioner of Food and Drugs

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