Pinney Associates

The Abuse Potential of Kratom and 7-Hydroxymitragynine According to the 8 Factors of the Controlled Substances Act

Developed for the Ohio Board of Pharmacy

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Contents

Tables

Figures

Disclosure

This report was funded without restrictions by the Center for Plant Science and Health (CPSH), a 501(c)3 nonprofit entity established by the American Kratom Association to promote science and policy research on plants and their potential health benefits. CPSH had no input into the writing of this report, its methods, or its conclusions. Pinney Associates consults to CPSH on kratom science and regulatory issues and studies. Through Pinney Associates, in support of the American Kratom Association, JH has commented on kratom pharmacology, public health, and regulatory needs for state hearings and the World Health Organization and for a judicial hearing to address questions raised by the court on these same matters, and has conducted research and published numerous peer reviewed studies on kratom pharmacology and abuse potential, and has developed reports and given depositions addressing kratom addictiveness, risks and benefits to kratom users, along with regulatory needs on behalf of several defendants in kratom litigation.

Pinney Associates also consults to developers and marketers of kratom leaf products on kratom science and regulatory issues and studies.

JH, through Pinney Associates, is a paid expert witness in legal cases related to kratom.

List of Abbreviations

Abbreviation	Definition
7-OH (7-OH-MG, 7OHMG, 7-OH-MIT)	7-hydroxymitragynine
8FA	Eight Factor Analysis
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-arrestin-2	Beta (β)-arrestin-2
CFR	Code of Federal Regulations
CNS	Central nervous system
CPP	Conditioned place preference
CSA	Controlled Substances Act
CYP	Cytochrome P450 (i.e., 3A, 2D6, 3A4)
CND	Commission on Narcotic Drugs
DAWN	Drug Abuse Warning Network
DEA	Drug Enforcement Administration
DOR	Delta (δ)-opioid receptor
DSHEA	Dietary Supplement Health and Education Act
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EMA	ecological momentary assessment
FAERS	Food and Drug Administration Adverse Event Reporting System
FDA	Food and Drug Administration
FDCA	Food, Drug, and Cosmetic Act
GMP	Good manufacturing practices
HHS	Department of Health and Human Services
ICSS	Intracranial self-stimulation
IV	Intravenous
Ki	Inhibitor constant
KUD	Kratom use disorder
IND	Investigational New Drug Application
KOR	Kappa (κ)-opioid receptor
MGP	Mitragynine pseudoindoxyl
MOR	Mu (μ)-opioid receptor
NDI	New Dietary Ingredient

Abbreviation	Definition
NDIN	New Dietary Ingredient Notification
NFLIS	National Forensic Laboratory Information System
NIDA	National Institute on Drug Abuse
NIDA IRP	NIDA Intramural Research Program
NIH	National Institutes of Health
NPDS	National Poison Data System
NSDUH	National Survey on Drug Use and Health
SOWS	Subjective Opiate Withdrawal Scale
TEDS	Treatment Episodes Data Set
UNODC	United Nations Office on Drugs and Crime
U.S. (US)	United States
WHO	World Health Organization
WHO ECDD	WHO Expert Committee on Drug Dependence

1 Background and Introduction

This report has been prepared for submission to the Ohio Board of Pharmacy (Board) to assist in its deliberations related to the controlled substance scheduling of “kratom, mitragynine, 7-hydroxymitragynine (7-OH), and other mitragynine-related compounds”. At a Jan. 6, 2026, meeting Board members discussed the emergency rule 4729:0-01.1 – Mitragynine-Related Compounds (NEW) which “proposes the placement of mitragynine-related compounds, which are some of the main active constituents of the plant kratom and substances synthesized from those compounds, into Schedule I” of the Ohio Revised Code.

We understand that the emergency rule, issued Dec. 12, 2025, effective Dec. 12, 2025, and updated Dec 29, 2025 classifies all “mitragynine-related compounds” as Schedule I controlled substances under the Ohio Revised Code, including but not limited to: 7-hydroxymitragynine (7-OH), mitragynine pseudoindoxyl (MGP), dihydro-7-hydroxymitragynine, and 7-acetoxymitragynine. (Table 1) This order specifically exempts “isolated mitragynine, including products that are comprised of natural kratom in its vegetation form”. However, Governor Mike DeWine has also requested that the Ohio Board of Pharmacy pursue the scheduling of mitragynine through the regular rulemaking process.

Table 1: Ohio Board of Pharmacy Section 5: Emergency Rule 4729:9-1-01.1 – Mitragynine-Related Compounds (NEW), issued Dec. 12, 2025, effective Dec. 12, 2025, Updated Dec 29, 2025

The following are classified as schedule I controlled substances:

(A) Mitragynine-related compounds, whether synthetic or naturally occurring substances contained in the plant, or in the resinous extractives of mitragyna speciosa (also known as kratom) and/or synthetic substances, derivatives, prodrugs, isomers, esters, ethers, salts and salts of isomers, esters and ethers with similar chemical structure.

Mitragynine-related compounds include, but are not limited to, the following: 7-hydroxymitragynine; mitragynine pseudoindoxyl; dihydro-7-hydroxy mitragynine; and 7-acetoxymitragynine. Mitragynine-related compounds do not include any of the following:

(1) Any dangerous drug that is the subject of an application approved by the United States food and drug administration under subsections 505(c) or (j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(c) or (j)) (December 12, 2025) for marketing as a dangerous drug;

(2) Any compound used in food consistent with either:
(a) A food additive regulation published in the United States code of federal regulations; or
(b) A "no questions response" issued by the United States food and drug administration in response to a generally recognized as safe notice.

(3) Any drug approved by the United States food and drug administration to [sic] that may be lawfully sold over the counter without a prescription in accordance with section 505G of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355h) (December 12, 2025).

(4) Mitragynine.

In this report we distinguish kratom, mitragynine, and 7-hydroxymitragynine as shown in Table 2:

Table 2: Nomenclature of Substances Discussed in this Report

Kratom	Refers to the leaves of the mitragyna speciosa plant, commonly known as the kratom tree, and extracts of kratom leaves. Natural kratom leaves (that is, “natural kratom in its vegetation form”) can contain more than 50 alkaloids of which many are of little pharmacological activity at any level of exposure or dose and others have potential pharmacological activity but are at such low levels in kratom leaves and extracts as to contribute little to the overall effects observed in animals and reported by humans.
Mitragynine	The most abundant naturally occurring alkaloid in kratom leaves and most kratom extracts. Most marketed kratom products are comprised of natural

	kratom in its vegetation form, or kratom extracts with natural levels of mitragynine and very low levels of other naturally occurring kratom alkaloids. The fact that many kratom consumers find that the benefits they seek and experience are provided by mitragynine isolate products is consistent with other data indicating that mitragynine is a major determinant of the effects of kratom. This is analogous to that of caffeine in coffee which can also contain many alkaloids, and for which caffeine isolate products including many manufactured products with added caffeine, provide satisfying alternatives to coffee despite the fact that other alkaloids can contribute to the effects (Stefanello et al., 2019). As discussed in this report, other naturally occurring kratom constituents and metabolites may also contribute to the effects reported by kratom consumers.
7-hydroxymitragynine (7-OH)	Not present in freshly harvested kratom leaves, but may emerge at low levels, over time, possibly due to enzymatic activity in leaves. 7-OH also emerges in systemic circulation in humans and other species as a metabolite of mitragynine by hepatic metabolism following oral consumption. As has been well documented in many studies, 7-OH has potent and potentially strong mu (μ)-opioid receptor (MOR) mediated activity that can contribute to the effects produced by mitragynine and other kratom alkaloids. Although we and other researchers have used a variety of abbreviations for 7-OH (e.g., 7OHMG and 7HMG), in this report we use the abbreviation 7-OH, as used by the US Food and Drug Administration (FDA) since its July 29, 2025, public briefing in which it raised the increasingly well documented addiction and potential respiratory risks that are MOR mediated.

Recent evaluation of the abuse potential of 7-OH issued on July 29, 2025 by the Secretary of Health Robert F. Kennedy Jr., FDA Commissioner Martin A. Makary, and on Sept. 29, 2025 by Henningfield et al. support a policy of clearly distinguishing between 7-OH and kratom and to treat them as distinctly separate substances to be regulated and controlled differently as warranted by their pharmacology and safety as well as public health effects and consideration. Specifically, this report agrees with the U.S. Department of Health and Human Services (HHS), including FDA, that 7-OH meets criteria for Controlled Substance Act (CSA) scheduling based on its pharmacological opioid-like profile and potential threat to public safety and health (DHHS, 2025; FDA, 2025; Henningfield, Wang, et al., 2025; Makary, 2025; Reissig et al., 2025).

Our report agrees with the plain language statement of the commissioner of food and drugs and secretary of health that the distinction between kratom and 7-OH is “night and day in terms of the public health risk” (DHHS, 2025). Federal public health officials also described a “risk stratification of the synthetic concentrated from the trace amounts

of 7-OH that naturally appear in the kratom leaf and have for centuries have been used in teas and other things" (DHHS, 2025). Consistent with this position, current public health interventions, CSA scheduling considerations, and warnings to healthcare professionals are directed towards 7-OH and not kratom, as clearly articulated by FDA Commissioner Makary's Dear Colleagues Letter (Makary, 2025).

While some kratom products have likely been modified to boost 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 occurring low levels of 7-OH compared to what the agency described as the recent widespread appearance of "7-OH opioid products", as discussed in the July 29 briefing and supported by the FDA report, titled "7-Hydroxymitragynine (7-OH): An Assessment of the Scientific Data and Toxicological Concerns Around an Emerging Opioid Threat" which was developed by FDA and first authored by FDA's Controlled Substance Staff pharmacologist, Dr. Chad A. Reissig, and Director, Dr. Dominic Chiapperino (FDA, 2025; Reissig et al., 2025).

Commissioner Makary's Letter to Colleagues noted 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).

We note that FDA's July 29 action represents a shift from the August 2018 HHS decision by Assistant Secretary of Health Admiral Brett P. Giroir, MD, which included 7-OH in an order to rescind a 2017 FDA recommendation to schedule mitragynine and 7-OH (Giroir, 2018). In his scheduling rescission order, Dr. Giroir noted that the existing science did not support a recommendation to place either mitragynine or 7-OH in the CSA. Dr. Giroir also raised the concern that banning all kratom products carried a "significant risk of immediate adverse public health consequences for potentially millions of users if kratom or its components are included in Schedule I", including (Giroir, 2018):

- Suffering with intractable pain [by people who were self-managing their pain with kratom];
- Kratom users switching to highly lethal opioids, including potent and deadly prescription opioids, heroin, and/or fentanyl, risking thousands of deaths from overdoses and infectious diseases associated with intravenous (IV) drug use;
- Inhibition of patients discussing kratom use with their primary care physicians leading to more harm and enhancement of stigma thereby decreasing desire for treatment, because of individual users now being guilty of a crime by virtue of their possession or use of kratom [an issue noted in this report as of particular concern with respect to pregnant women];

- The stifling effect of classification in Schedule I on critical research needed on the complex and potentially useful chemistry of components of kratom.

Similarly, the United Nations Office of Drugs and Crime (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). As UNODC reported, this was based on the evaluation of the World Health Organization Expert Committee on Drug Dependence.

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 for healthcare professionals, regulators, and law enforcement, as well as enhancing surveillance, testing, detection, and epidemiological surveillance of these products. Extensive research (largely National Institute on Drug Abuse (NIDA) supported) since 2018 continue to support the conclusions of the 2018 and 2022 eight factor analyses (8FAs) of kratom (Henningfield et al., 2018; Henningfield, Wang, et al., 2022a). The exception announced by FDA on July 29, 2025 and by others in 2025 (Alsbrook et al., 2025) it could be concluded with reasonable scientific certainty that 7-OH could be considered a substance with substantial opioid effects warranting CSA scheduling.

The present document provides an update to earlier kratom and 7-OH 8FAs by HHS (Giroir, 2018); two peer reviewed publications by Henningfield et al. (2018, 2022), and a September 2025 7-OH focused 8FA by Henningfield et al. which substantially agreed with and expanded upon the July 29, 2025 HHS release of a report titled "7-Hydroxymitragynine (7-OH): An Assessment of the Scientific Data and Toxicological Concerns Around an Emerging Opioid Threat" (Reissig et al., 2025).

Those reports were developed consistent with the requirements of the US CSA for formal "permanent" scheduling of substances following assessment of the 8 Factors of the CSA (Table 3) as summarized 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 (effective 1971). 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 including the 2018 and 2022 kratom 8FAs and related analyses (Henningfield et al., 2018; Henningfield, Wang, et al., 2022b).

Table 3. Eight Factors Determinative of Control of a Drug Under the Controlled Substances Act, 21 U.S.C. 811(b)

Under 21 U.S.C. 811(b) of the CSA, the medical and scientific analysis of abuse-related data 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

1.1 Discussion of Other Mitragynine-Related Compounds

It is important to note that the Consumer and Retailer Notice: Kratom-Related Products Now Illegal in Ohio (Dec 12, 2025) refers to substances such as 7-OH, MGP, dihydro-7-hydroxymitragynine, and 7- acetoxymitragynine as “kratom-related” products, or “kratom-related” compounds; while the emergency rule 4729:9-1-01..1 referred to these substances as “mitragynine-related” compounds.

Figure 1 below shows a graphic of products that have raised similar concerns by the UNODC, along with its summary caption, released by the UNODC Laboratory and Scientific Portals Service in August 2025 (UNODC, 2025). The UNODC refers to these types of products as “novel kratom-related products” and lists 7-OH, MGP, and paynantheine as substances in this category.

These should not be considered natural kratom or natural kratom extracts but rather synthesized derivatives. Whereas kratom effects and safety are informed by centuries of use in Southeast Asia and decades of use in the US, along with several decades of research in Southeast Asia and the US, the pharmacology and safety of new synthetic derivatives is not informed by such science and experience. A clear regulatory distinction should be made to differentiate such products from natural kratom, kratom extracts, and the primary kratom alkaloid, mitragynine.

Figure 1. Examples of “7-hydroxymitragynine” marketed products and their lab results (Taken from the UNODC Laboratory and Scientific Service Portals, 2025)

Examples of "7-hydroxymitragynine" marketed products and their lab results
Note: Parts designation is described by Krotulski and others as follows: "p" = parts. 0.5p = half as abundant as 1p. 2p = 2x more abundant than 1p.
Source: (Krotulski et al., 2025)

There has been little to no pharmacological evaluation of these and other potential synthetic derivatives. Moreover, unlike natural kratom and mitragynine, they lack decades of real-world human use that could provide a scientifically informed evidentiary basis for evaluating their safety and abuse potential. There is also no historical record of safe or beneficial use for these substances comparable to the established history associated with naturally occurring kratom constituents.

Accordingly, this report neither supports nor opposes the emergency scheduling of such synthetic substances. However, the emergence of these compounds, including recent

experience with 7-hydroxymitragynine, underscores the value of a flexible, science-based regulatory framework in Ohio and other states, comparable to frameworks already adopted in 19 states. Such an approach would allow regulatory policy to evolve in response to emerging scientific evidence and public health considerations, including mechanisms for monitoring and evaluation, the use of product standards, and, where warranted, the application of emergency scheduling tools.

States that have adopted a regulatory framework include Arizona, Colorado, Florida, Georgia, Kentucky, Maryland, Mississippi, Nebraska, Nevada, New York, Oklahoma, Oregon, Rhode Island, South Carolina, South Dakota, Texas, Utah, Virginia, and West Virginia.

2 Recommendations for Regulatory Action

1) Natural kratom leaf products and extracts, including natural mitragynine products, do not warrant CSA scheduling

2) Schedule I placement of kratom and mitragynine would foreseeably have potential unintended consequences including many kratom uses seeking illicit kratom that would not be labeled or otherwise regulated as recommended in this report. Such scheduling would also discourage kratom consumers (including pregnant women) from discussing their kratom use with health professional due to concerns about admitting to a felony narcotic crime. In addition, this may foreseeably result in some people who used kratom to self-manage opioid and other substance use disorders and withdrawal to relapse to those substances with increased risks including overdose death.

3) 7-OH, whether naturally occurring or synthesized, does warrant CSA scheduling based on its abuse potential and overall safety profile and meets the statutory criteria as an opioid, based on it substantial morphine-like opioid pharmacology

4) It is possible that research will identify other substances and the level of their effect that may be unacceptably addictive and harmful and should be prohibited

5) Synthetic products, including those derived from kratom or mitragynine, which are not supported by adequate scientific study and historical use to confirm their safety, merit consideration for CSA scheduling

6) Appropriate content, manufacturing, labeling, and advertising regulations should be implemented for all marketed kratom products as has been initiated in 19 states at this writing. Such regulatory frameworks provide processes to prevent marketing of products that contain highly concentrated or added synthetic/semi-synthetic mitragynine-like compounds for which there are not sufficient safety data. These would also create regulatory safeguards to prevent marketing and formulations that would be attractive to youth.

The foregoing is not to imply that kratom does not merit policy and regulatory oversight to address and mitigate concerns such as were also raised in the Jan. 6, 2026 Ohio

hearing. We appreciate that the Board and the Governor have in their regulatory actions recognized that available evidence to date suggesting a difference in the risk profiles of natural kratom products as compared to concentrated, adulterated, or synthetic/semi-synthetic products for which there is little to no evidence of their effects. However, whereas it is in the interest of public health and consistent with pharmacological evaluations to schedule 7-OH, it is also in the interest of public health and consistent with overall pharmacological evaluations to ensure continued access to natural kratom and derivatives including mitragynine extract, but ideally with regulatory oversight to prevent the problems identified by the Board such as products that are inappropriately marketed, labeled and advertised and to prevent the sale of contaminated and adulterated products. This approach would also allow an avenue for continued development and introduction of additional products that might provide benefit to consumers as the body of evidence grows.

Thus this analysis also recommends that Ohio address concerns that were raised in the Jan. 6, 2026 hearing, including the marketing of kratom products with inappropriate health benefit and medicinal claims and marketing, marketing of formulations that are attractive to minors, and kratom products that are adulterated with other pharmacologically active substances (including added 7-OH), and prohibiting the sale of product that are not manufactured to the standards expected for dietary supplements with respect to contaminants including heavy metal residue.

Furthermore, as was raised by the Board as a potential concern, such product standards could include warnings about use by pregnant and lactating women. Such product standards and requirements could be established by adoption of all, or many elements of the model Kratom Consumer Protection Act variations that have now been adopted and made law in at least 19 states at the time of this submission. Such standards may be required and enforced as a condition of lawful marketing in Ohio, consistent with approaches used in other states, and may be accompanied by product registration, labeling, and traceability requirements.

2.1 Rationale for Regulatory Recommendation

Two scheduling pathways included in the CSA are discussed in this report: Temporary scheduling and permanent scheduling by rule making.

Under the 1971 US CSA, which Ohio appears to generally follow, there are two scheduling pathways which rely on public health and pharmacological considerations: temporary scheduling (generally referred to as emergency scheduling) and permanent scheduling. These approaches are described in the CSA but are perhaps more lucidly described in a Congressional Research Service Report (Lampe, 2021), and in two peer reviewed publications by leading experts in abuse potential assessment and drug scheduling (Henningfield, Coe, et al., 2022; Henningfield, Comer, et al., 2025). Recent examples from the Drug Enforcement Administration (DEA) published in the Federal Register in 2025, summarized below, addressed substances other than kratom.

2.1.1 Temporary Scheduling by Determination of Imminent Public Health Threat.

The following Federal Register notice summarizes the approach relied upon by the DEA in a recent temporary scheduling action (DEA, 2023, 2025a).

> "To find that temporarily placing a substance in schedule I of the CSA is necessary to avoid an imminent hazard to the public safety, the Administrator must consider three of the eight factors set forth in 21 U.S.C. 811(c): The substance's history and current pattern of abuse; the scope, duration and significance of abuse; and what, if any, risk there is to the public health. Consideration of these factors includes any information indicating actual abuse, diversion from legitimate channels, and clandestine importation, manufacture, or distribution of these substances.[8]
>
> Substances meeting the statutory requirements for temporary scheduling may only be placed in schedule I.[9]
>
> Substances in schedule I have high potential for abuse, no currently accepted medical use in treatment in the United States, and no accepted safety for use under medical supervision.[10]"

It is the conclusion of the present 8FA update that only one kratom-related alkaloid, 7-OH, has a sufficient scientific and public health evidentiary basis for emergency scheduling. It is the only kratom related alkaloid that is the subject of a scheduling request by the FDA, based on the Agency's determination that 7-OH meets criteria of the higher standard for permanent scheduling which includes its determination that the three public health factors standard for temporary scheduling are also met (FDA a, b, c; Henningfield et al. 2025)

2.1.2 Permanent Scheduling Guided by the CSA 8FA

Permanent scheduling is authorized by a scientific analysis of evidence based on the eight factors of the CSA. A recent illustration of this evidence-based approach leading to a determination was provided by the DEA's evaluation of three fentanyl related substances as published in the Federal Register (DEA, 2025b). In these cases, the DEA determined, based on scientific data addressing the pharmacology, toxicology, and epidemiology of these substances, that these substances posed a known and imminent public health threat, as reflected by the evidence collected in Factors 4, 5, and 6 of the 8FA. Because these substances have not been approved for therapeutic use by the FDA and are not the subject of any Investigational New Drug (IND) applications, the DEA proposed placement in Schedule I.

Note that none of the kratom constituents, metabolites, or synthesized derivatives mentioned in this report meet the Factor 8 standard as "immediate precursor of a substance already controlled". That standard is not necessary when the evidence in Factors 1-7 support scheduling.

As concluded in the present 8FA update, and consistent with concerns previously raised by the Board regarding the increased potency of 7-OH, and its metabolite pseudoindoxyl, only one kratom related alkaloid, 7-OH, has been sufficiently characterized through pharmacological study to support consideration of permanent scheduling. 7-OH is the sole kratom related alkaloid for which the FDA has submitted a scheduling request, based on the Agency's determination that it meets the statutory criteria for permanent scheduling.

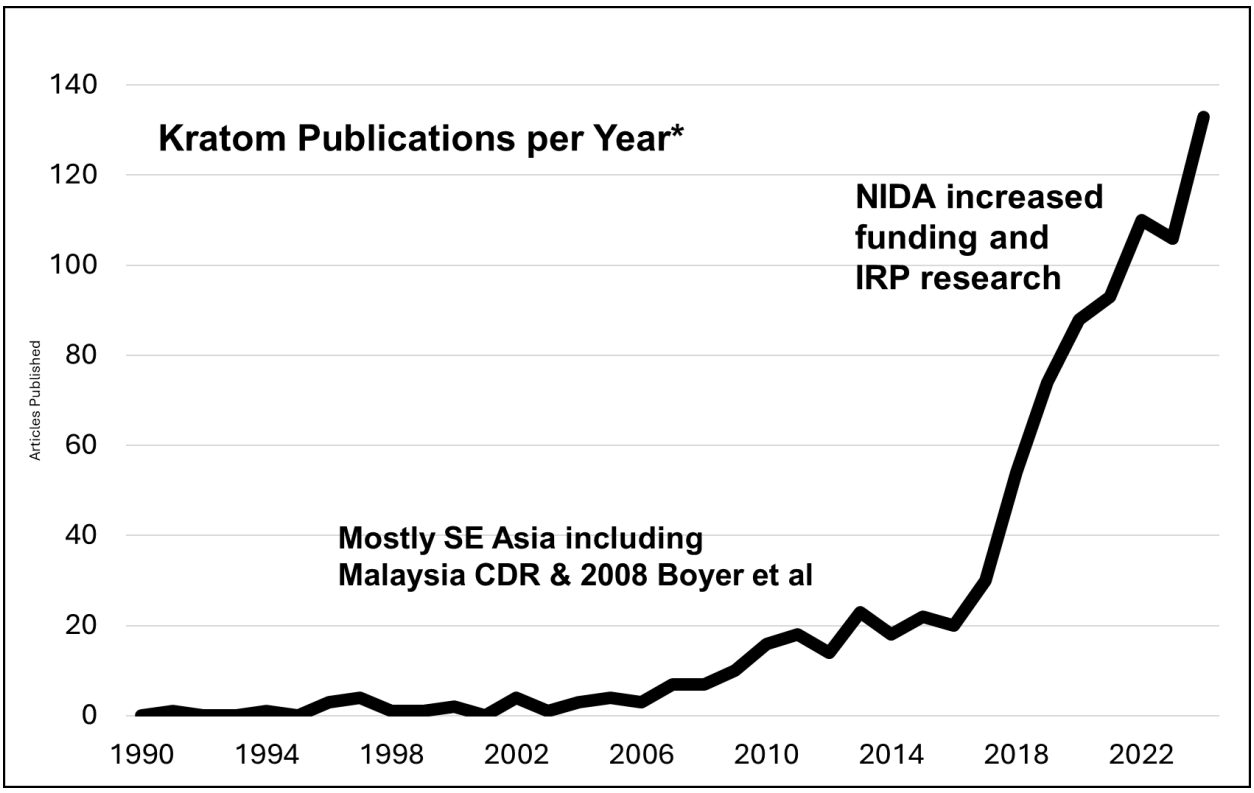
3 Evaluating Kratom and its Alkaloids Under the Eight Factors

In this report, we provide an update focusing on new research published since the Dec. 31, 2021 kratom 8FA published in 2022, titled, Kratom Abuse Potential 2021: An Updated Eight Factor Analysis (Henningfield, Wang, et al., 2022a) . That report was an update of the 2016 submission to the US DEA, FDA, and NIDA, and the 2018 published review (Henningfield et al., 2018). Each of these updates reflects the rapid pace of kratom research, largely by university-based researchers in the US with support by NIDA, as well as research at NIDA's own Intramural Research Program (NIDA IRP).

Thus, the 2021 update (published by Henningfield and Heustis) considered several hundred articles and studies that had been published in the preceding approximately five years. The present update draws from more than 300 publications that have come out since Jan. 1, 2022, though these are not all listed in this report. This reflects the remarkable progress in the scientific evaluation of kratom with the vast majority of the publications supported by NIDA grants primarily to university-based researchers, as well as research conducted by NIDA's IRP.

The rapid pace of research is illustrated in Figure 2 from a recently published book edited by Henningfield, Beyer and Raffa (2025), which summarizes the enormous growth of kratom research over the past decade.

Figure 2: Number of Kratom-Related Publications Available through the PubMed Database



Source: (Henningfield, Beyer, et al., 2025)

The breadth and speed of progress over the past several years provides a strong scientific and public health foundation for our conclusion that natural kratom derived extracts, including many in which mitragynine is the primary alkaloid, do not meet criteria for CSA scheduling, as also concluded by the Assistant Secretary of Health in 2018 and World Health Organization Expert Committee on Drug Dependence (WHO ECDD) in 2021 (Giroir, 2018; UNODC, 2021; WHO, 2021).

Recent data also support the recent determination by the FDA and Secretary of Health, as well as issues raised by the Board, that 7-OH, a kratom metabolite and semi-synthetic derivative, meets statutory criteria for scheduling and characterization as an opioid based on its overall pharmacological profile of opioid-type abuse potential in animal models, potential opioid-like respiratory depressant effects (at least by IV administration), and primarily MOR mediated mechanism of action as presented by the FDA Commissioner and Secretary of HHS on July 29, 2005 (DHHS, 2025; FDA, 2025; Makary, 2025; Reissig et al., 2025)

This updated 8FA agrees with FDA and HHS and is based partially on the 7-OH 8FA submitted to DEA, FDA, and NIDA on Sept. 29, 2025 in Appendix 2. That 7-OH focused 8FA included some of the kratom and mitragynine data that help support FDA and HHS's conclusion in their July presentations and released documents, including a "Dear Colleagues" letter to healthcare providers (Makary, 2025), that 7-OH posed a serious

public health threat that warranted CSA control and prohibition. Additionally, that HHS and FDA's focus as Dr. Makary stated was "on synthetic concentrated kratom", that FDA and HHS "think it's night and day in terms of the public health risk" and that there was a "risk stratification of the synthetic concentrated from the trace amounts of 7-OH that naturally appear in the kratom leaf and have for centuries have been used in teas and other things" (DHHS, 2025).

3.1 Factor 1: Its 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 nonclinical studies including animal abuse-related studies and an analysis of human use patterns. For 7-OH, there have been nonclinical studies including self-administration[1], conditioned place preference[2], and drug discrimination studies[3] that indicate a potential for abuse. Similar studies of mitragynine indicate low abuse potential. In 2021, the Pinney Kratom 8 Factor concluded:

> "Diverse scientific approaches were employed to profile MG [mitragynine]'s abuse potential, finding no evidence of rewarding effects in the IV self-administration and [intracranial self-stimulation] ICSS models, and weak evidence of potential reward in the [conditioned place preference] CPP procedure. MG [mitragynine] only partially generalizes to morphine and more fully generalizes to the nonscheduled alpha-adrenergic agonists, phenylephrine and lofexidine. The new data suggest relatively low abuse potential as compared to morphine-like opioids, stimulants, and other drugs of abuse that demonstrate robust rewarding effects across all such abuse potential models. Similarly, MG [mitragynine]'s potential to produce physical dependence and withdrawal appears relatively low, but not absent, as compared to opioids in animal models. These findings are generally consistent with human reports that MG [mitragynine] has a relatively low abuse and withdrawal potential as compared to recreationally used opioids but can reduce opioid self-administration and withdrawal. Surveys indicate that reducing opioid self-administration and withdrawal are among the most common reasons for kratom use in the US (also discussed in Factors 4, 5, and 6)."

As summarized in the 2025 Pinney Associates 7-OH 8 Factor Analysis (attached), recent evidence supports the conclusion that 7-OH has meaningful abuse potential

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[1] Self administration studies evaluate whether animals will voluntarily administer a substance, typically by pressing a lever, which is used as an indicator of a drug's reinforcing effects and potential for abuse.
[2] Conditioned place preference studies assess whether an animal develops a preference for an environment previously paired with drug exposure, reflecting the substance's rewarding or aversive properties.
[3] Drug discrimination studies examine whether animals trained to recognize the subjective effects of a known drug respond similarly when given a test substance, providing insight into whether the test compound produces comparable central nervous system effects

though the evidence is limited in its range of study types, breadth of available studies, and inconsistencies across findings. This is consistent with FDA's conclusion that 7-OH effects are substantially equivalent to opioids in addictive and, potentially, respiratory depressant effects. However, as we discussed in our 7-OH 8FA, the opioid mediated effects appear to be limited in maximum strength or efficacy consistent with its characterization as a partial opioid agonist. Nonetheless as discussed in Factors 1, 2, and 3 of this report, those effects include morphine like reinforcing effects in animal IV self-administration models and morphine like respiratory depression when administered intravenously to rodents.

3.1.1 Mechanism of Action

Nonclinical studies suggest that both mitragynine and 7-OH act as agonists on a diverse array of receptors (as described in Factor 2). However, while mitragynine shows limited rewarding effects, 7-OH has robust reinforcing, rewarding, and subjective effects characteristic of a μ-opioid agonist, with a potency potentially greater than morphine, although not necessarily stronger due to its MOR agonist effects. 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. In contrast, 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 and has other effects, including alpha adrenergic-mediated effects.

The foregoing is an important distinction to make in particular regarding the Board's assertion that kratom alkaloids in general are structurally and perhaps also functionally similar to controlled opioid analgesics such as morphine derivatives, when in fact it is specifically 7-OH that shares this potency and maximal effect by some measures with morphine.

3.1.2 Abuse-Related Studies in Animals

In animal models, 7-OH consistently produces opioid-like rewarding effects whereas mitragynine does not. For example, in rodent intravenous self-administration studies, 7-OH is readily self-administered and maintains drug-seeking behavior at doses far lower than morphine, suggesting it may be 5 to10 times more potent than morphine in producing reinforcing effects.

Notably, a study by Hemby et al. (2019) showed that rats would self-administer 7-OH at 2.5 to10 μg per infusion, whereas morphine required 50 to 100 μg to achieve similar reinforcement; in contrast, mitragynine did not maintain self-administration. Likewise, in drug discrimination and conditioned place preference tests, 7-OH reliably substitutes for

morphine and produces dose-dependent preference for environments paired with the drug, again often at greater potency than morphine.

These findings demonstrate that 7-OH engenders the key behavioral hallmarks of abuse liability (euphoria/reward/reinforcement and drug-seeking) in controlled experiments, whereas mitragynine (the primary kratom alkaloid) generally does not produce such strong opioid-like signals in the same models. The FDA's scientific assessment accordingly characterizes 7-OH as a "potent" opioid with high abuse potential, noting that it induces "reinforcing efficacy" similar to morphine in animals (Henningfield, Wang, et al., 2025; Reissig et al., 2025).

From an abuse potential perspective, an important finding is that both 7-OH and morphine produce a range of qualitatively similar effects, supporting the characterization of 7-OH as a substance with a potential for opioid-like abuse potential and public health risks. 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.

While the evidence supports the scheduling of 7-OH, as discussed in the 2022 Kratom 8FA and in subsequent animal studies, mitragynine, unlike 7-OH, typically does not sustain self-administration or induce strong conditioned place preference at comparable doses.

Mitragynine has been found to often act as a partial opioid agonist with lower efficacy (ceiling effects), while also resulting in stimulant effects at low doses, and α-adrenergic receptor effects, which are inconsistent with classic opioid profiles. The potential for abuse of kratom is therefore substantially lower in practical terms than that of 7-OH, a conclusion that is consistent with prior HHS reviews that found the existing science does not support scheduling kratom or mitragynine under the CSA.

3.1.3 Abuse-Related Studies in Humans

Human patterns of kratom use, discussed further under Factors 4 and 5 of the 2021 Kratom 8 Factor Analysis, indicate that the majority of kratom consumers use it orally in raw or tea-like decoctions (extracts) for mild stimulant or therapeutic effects (such as pain relief or alleviating alcohol, opioid, or stimulant withdrawal symptoms), rather than to achieve intense euphoria (Govarthnapany et al., 2025; Henningfield et al., 2024; Singh, Azuan, et al., 2025; Singh, Mathandaver, et al., 2025; WHO, 2021).

In clinical studies in which natural kratom powders and teas are administered, participants report only mild adverse gastrointestinal related adverse events that resolve without further medical intervention after discontinuation, though these undesirable effects also appear to provide a self-limiting effect on kratom use (Huestis et al., 2024; Mongar et al., 2024; Tanna et al., 2022).

A classic human abuse potential study following FDA's 2017 guidance (see also Henningfield, Comer et al. 2025 for discussion of such studies when used for novel substances) has not been conducted for kratom or any kratom alkaloid or derivative. However, FDA has contracted for such a study, and has already presented the results of an initial safety study that confirmed that high doses of kratom powder and mitragynine were safe to administer (Reissig, 2024). Participants in the FDA study reported no serious adverse events and no significant changes in vital signs, ECG, or laboratory evaluations. Nausea and vomiting were observed, but no more than 2 events/dose were recorded.

Large-scale surveys and community studies show little evidence of widespread recreational use of kratom among youth – the typical profile of an abused substance. Instead, kratom use skews toward adults (often 30-50 years old) and frequently by those with prior opioid experience seeking a less harmful substitute to a prior drug of abuse. Although dependence can develop with heavy kratom use, most users do not escalate doses to the extreme levels seen with potent opioids, and severe opioid-like intoxication from kratom alone is rare (Grundmann, 2017; Grundmann et al., 2025).

The potential for abuse of kratom therefore can be concluded to be substantially lower than that of concentrated 7-OH. This conclusion is consistent with the 2025 HHS determination that while immediate regulatory action was needed to control the availability of 7-OH (DHHS, 2025; FDA, 2025; Makary, 2025; Reissig et al., 2025), natural kratom products were deemed to be not an area of focus, and the 2021 WHO ECDD recommendation that kratom and its alkaloids undergo continued monitoring but that no additional regulatory control was necessary at the time (in Aug 2025, UNODC released a consumer notice regarding novel kratom-related products including those containing high concentrations of 7-OH and MGP) (UNODC, 2021, 2025).

Although human abuse-potential studies for 7-OH have not yet been conducted, emerging real-world data corroborates its apparent high abuse potential. As discussed by FDA (Reissig et al. 2025), clinical case reports and surveys of users document that some individuals seek out concentrated 7-OH products specifically for their opioid-like psychoactive effects, such as euphoria and analgesia, rather than using traditional kratom preparations.

As discussed under Factors 4 and 5 in the 7-OH 8FA, motivations for 7-OH use among some consumers include harm reduction by helping them abstain from their more harmful prior drug of abuse (such as heroin or methamphetamine); however, use also includes patterns of escalating use for recreational purposes. FDA's Adverse Event Reporting System (FAERS) has recorded cases of 7-OH misuse, including instances of hospitalization for withdrawal (discussed under Factor 6).

Which respect to deaths, FDA stated "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; p. 11).

Given the apparently many 7-OH consumers in the US, this suggests that the mortality risk of 7-OH, at least when consumed by the oral route as appears to be most common at present, does not carry the same high risk of death as fentanyl and oxycodone like opioids, however, at least by the intravenous route, it can produce morphine-like respiratory depression (Gonzalez et al. 2025).

3.1.4 Conclusions and Recommendations

Overall, research published since January 1, 2022 supports the conclusions of Henningfield et al. 2022 and the earlier reviews (Giroir, 2018; WHO, 2021), with one important exception. Namely that by 2025, FDA had concluded that 7-OH could warrant CSA scheduling based on its high abuse potential as demonstrated by several models, characterization as an opioid by its overall pharmacology, real world patterns of addiction and withdrawal, and potential morphine-like opioid induced respiratory depressant effects, at least by the intravenous route of administration as summarized in Factor 2 (Henningfield, Comer, et al., 2025; Reissig et al., 2025; Zuarth Gonzalez et al., 2025).

3.2 Factor 2: Scientific Evidence of its Pharmacological Effect, if Known

In 2021, the Pinney Associates Kratom 8 Factor concluded:

> "Kratom's main effects are due to the consumption of MG [mitragynine], but other minor alkaloids and metabolites, including 7-OH-MG [7-OH-mitragynine], may also contribute to effects reported by consumers. Since 2018, many scientific advances improved our understanding of how these alkaloids and metabolites interact. Some alkaloids that contribute little to the effects of kratom may ultimately contribute to safer and more effective new medicines for a variety of disorders, as well as for general health and well-being. Development and approval of such products may be a decade or more in the future, but this rapidly advancing science is explaining how kratom works, and why its pain relieving, and other benefits occur with relatively low levels of abuse, dependence, and harmful decreases in respiration compared to opioids."

There have been several advances in our understanding of kratom pharmacology in recent years, including greater characterization of mitragynine and 7-OH. In animal studies, 7-OH produces analgesic and abuse related effects similar to those of classic opioids. A number of rodent pain assays (tail-flick, hot plate) confirm dose-dependent antinociception, often showing 7-OH to be more potent than morphine in pain suppression. For instance, one study found 7-OH to be about 10 times more potent than morphine for analgesia. It also has high oral bioavailability relative to morphine, meaning a greater fraction of an oral dose reaches systemic circulation, contributing to its strong effect via oral administration. 7-OH consistently demonstrates high affinity for

the MOR, with reported inhibitor constant (Ki) 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 beta (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).

3.2.1 7-OH Respiratory Depression Risk

A key 2025 study (Zuarth Gonzalez et al., 2025) showed that in rats, intravenously administered 7-OH caused significant respiratory depression (decreased breathing rate and volume) at higher doses, comparable to intravenous morphine. 7-OH, and these effects were fully reversed by naloxone. 7-OH was approximately 4.5 fold higher than morphine in decreasing minute volume by 50%. In contrast to 7-OH and morphine, the same study found mitragynine did not cause respiratory depression – in fact, mitragynine slightly increased respiratory rate and had no significant depressive effect on respiratory volume, even at high doses.

The mitragynine findings were generally consistent with those involving oral mitragynine administration and other studies discussed in the article in a study by Henningfield, Rodricks, et al. (2022). This study followed an FDA recommended model including FDA recommended comparator doses of oxycodone and a variety of blood gas measures. They found no respiratory depression in rats given very high oral doses of mitragynine (up to 400 mg/kg administered by gastric delivery through a tube).

Thus, 7-OH appears to carry the potential dangerous respiratory depressant effect characteristic of opioids, at least by the intravenous route of administrations, whereas mitragynine alone shows a much safer profile in this regard. This is a crucial pharmacological distinction for public health and should be considered when regulating these products.

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

7-OH appears to also produce diverse effects in addition to those mediated by MOR receptors. 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 [delta (δ)-

opioid receptor] DOR, where it appears to function as a competitive antagonist (Obeng et al., 2021).

This profile, as a partial MOR agonist and a KOR and DOR antagonist, suggests a pharmacological profile that differs from classical opioids such as morphine, which are full MOR agonists, and may contribute to its overall pharmacological effects. KOR antagonism has been associated with antidepressant and anxiolytic effects, which may align with some of the reported motivations for kratom and 7-OH use. (Carlezon & Krystal, 2016).

Taken together, the data consistently characterize 7-OH as a CNS-acting drug with dose-related effects and mechanisms of action that are similar, though not identical, to those of classical morphine-like opioids. While its pharmacological effects strongly parallel those of opioids, it is more accurately described as a potent MOR agonist with high efficacy in producing analgesia and reward and with the potential for respiratory depression. However, its distinct activity suggests that a direct comparison and characterizing 7-OH as an opioid that is up to 13 times more potent than morphine is misleading without providing the additional context of its nuanced action at opioid and non-opioid receptors, as well as the specific assay that was employed because relative potency can vary across assays.

3.2.2 Scientific Body of Evidence for Other Mitragynine-Derived and Related Compounds

There has been a growing body of evidence regarding some of the other major alkaloids, including speciociliatine, speciogynine, paynantheine, corantheidine (McCurdy et al., 2024). These four alkaloids are chemically related to each other and are either structural isomers or diastereomers of mitragynine.

As described in McCurdy et al., 2024:

> Speciociliatine interacts primarily with opioid receptors and has analgesic actions in some animal models but not in others, indicating possible pharmacological differences among species. Speciogynine and paynantheine (which only differ by the location of a single carbon–carbon double bond) interact strongly with serotonin receptors, while also interacting moderately with opioid receptors, and to a lesser extent adrenergic receptors. Paynantheine is among the more abundant alkaloids, presenting with mild conditioned place aversion and blocking morphine antinociception at low doses, which may indicate partial antagonist effects at the μ-opioid and partial agonist effects at the δ-opioid receptors. Corynantheidine (which only differs from mitragynine by lacking an -OCH3 group) binds strongly to alpha-adrenergic receptors and has weaker interactions at opioid (Ki = 57 nM at μopioid receptor) and serotonin receptors.

The minor alkaloids mitraciliatine and isopaynantheine induce antinociception in animal models that is primarily mediated through κ-opioid receptor activation and do not appear to cause respiratory depression even at very high doses.

3.2.3 Conclusions and Recommendations.

In summary, the pharmacological effects of 7-OH closely parallel those of controlled opioids. It is a potent MOR agonist with high efficacy for producing analgesia and reward, and it carries the characteristic risk of respiratory depression, notwithstanding evidence of receptor bias that may reduce certain adverse effects under specific conditions. In contrast, mitragynine and kratom exhibit a more complex and comparatively milder pharmacology, characterized by partial MOR agonism with substantial involvement of non-opioid receptors, resulting in stimulant and analgesic effects with relatively weaker reinforcing properties and without evidence of respiratory depression. Taken together, the scientific evidence supports the FDA's conclusion that 7-OH functions as a potent opioid for scheduling purposes, while the broader pharmacological profile of kratom helps explain its comparatively benign effect profile and why it has not been considered imminently hazardous in prior expert evaluations.

Available evidence indicates that, outside of mitragynine and 7-hydroxymitragynine, there is limited pharmacological characterization beyond preliminary animal data for many other kratom alkaloids, including speciociliatine, speciogynine, paynantheine, corynantheidine, mitraciliatine, and isopaynantheine. The absence of robust data, however, does not by itself establish harm, and the proactive imposition of a blanket scheduling ban on these substances may be premature and could unnecessarily restrict their evaluation in legitimate research settings. An evidence based regulatory approach, focused on labeling accuracy, content standards, and marketing controls, would better protect public health while preserving the ability to study these compounds and establish clear standards for products permitted on the market.

3.3 Factor 3: The State of Current Scientific Knowledge Regarding the Drug or Other Substance

The 2022 Henningfield, Wang and Huestis Kratom 8 Factor Analysis concluded:

> "Pharmacokinetics and safety data from multiple species, kratom preparations, alkaloids, and metabolites; advances in bioanalytical assays providing more accurate and reliable findings; and data from multiple studies with MG [mitragynine] doses many times higher than those human kratom users take are now available. These studies add to those described in Factors 1 and 2 confirming little evidence of serious adverse or life- threatening effects over a broad range of doses, dosage forms, and in four species (mouse, rat, dog, and monkey).
>
> Other major advances in kratom science come from six clinical studies of long term kratom use effects and safety, as well as the study of anti-nociceptive

effects of kratom and physiological dependence described in Factors 2 and 7. These important advances in kratom science evaluated the effects of long-term kratom use on a variety of physiological parameters including kidney and liver function, hematological parameters, cognition, and on brain function by brain magnetic resonance imaging. Although relatively small studies, none suggest serious adverse consequences of use. It is important to note that these are not definitive safety studies and cannot be used to claim that kratom has no adverse effects on any of the studied physiological domains and limitations of each study were noted in the publications. Nonetheless, the findings are encouraging and should facilitate the conduct of more comprehensive follow-up studies."

Our current scientific knowledge of kratom has grown exponentially in recent years. Kratom has been the subject of intensive study across pharmacology, toxicology, epidemiology, and clinical science. As of 2024, the annual number of peer reviewed publications addressing kratom exceeds 130 per year, compared with only a few dozen annually in the mid-2010s. This rapidly growing body of evidence includes detailed characterization of mitragynine's chemistry, mechanisms of action, metabolism, human use patterns, and associated risks and benefits. Much of this growing knowledge base has been heavily fueled by research funding by the National Institutes of Health's (NIH) NIDA (Henningfield, Beyer, et al., 2025). This rapidly expanding body of research undoubtedly played a significant role in shaping two important themes in the July 29, 2025 FDA and HHS 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.

The pharmacological effects of kratom in its natural form are attributed primarily to its most abundant alkaloid, mitragynine, which typically comprises up to 66% of total alkaloid content (Khairul Azreena Bakar et al., 2024). As discussed in the previous section, mitragynine has a unique pharmacological profile (partial MOR agonist with additional non-opioid receptor actions) that distinguish it from classical opioids.

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, it is now accepted that mitragynine's metabolite, 7-OH, is not naturally present in any appreciable amount in fresh kratom leaves (analyses have found 7-OH content in freshly harvested leaves to be less than 2% of total alkaloids). In commercial traditional kratom products (dried leaf powders, capsules, etc.), 7-OH remains very low. Instead, 7-OH is primarily formed in the body after ingestion of mitragynine, via hepatic metabolism (largely through the CYP3A enzyme pathway). Due to this first pass metabolism, consumption of these kratom products generally results in slow exposure to 7-OH. Pharmacokinetic studies in humans show that after oral kratom administration, 7-OH appears in plasma with a peak between 1.2 and 2.0 hours and has an elimination half-life of ~5 hours (though repeated

dosing can extend the effective half-life up to 24 hours due to accumulation) (Huestis 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 (K. E. Smith et al., 2025).

7-OH is itself further metabolized; one notable metabolite is MGP. Kamble et al. (2020) found that 7-OH converts to MGP in humans to a greater extent than rodents or other tested animals. Note that although 7-OH has been variously reported to be many times more potent than mitragynine and morphine, the estimates involve a wide variety of assays that are not necessarily reflective of potency in either addictive or respiratory effects. For example, studies in the guinea pig ileum model are useful in pharmacology, but do not reliably provide relative potency estimates that correspond to reward or toxicity (see discussion in Henningfield et al. 2024 – toxicology paper).

McCurdy's Symphony metaphor. An additional important advance in the past five years or so is the increasing understanding of both the overall safety of kratom, as well as the diversity of the leading reasons for use in the US and globally, which has been described by the leader of the world's largest kratom research program (funded primarily by NIDA), Dr. Christopher McCurdy. As Dr. McCurdy has discussed in numerous lectures in recent years and in some detail in his 2025 review, "Kratom (*Mitragyna Speciosa*): Recent Advances I Understanding the Chemistry, Pharmacology and Human Use (McCurdy, 2025), his explanatory metaphor is to view natural kratom, and decoctions ("extracts" of natural leaf) as the result of "a symphony of alkaloids and metabolites", and that kratom is not simply a vehicle for mitragynine.

This metaphor has also been discussed in earlier in national meetings, such as those convened by the University of Florida in which there seems to be widespread agreement by many kratom experts that "nature got it right" with respect to kratom's naturally-occurring constituents and the range of their relative levels found in nature. This is despite variations in kratom strains, growing conditions, and other factors.

Thus, whereas many people achieve the benefits they report (e.g., caffeine-like increased focus and energy, and mild pain relief) from mitragynine, it is likely that for other people and other purported benefits, including self-management of withdrawal and cravings for opioids, alcohol, and stimulants, relaxation and relief of stress, that other alkaloids and metabolites may also contribute to the overall experience, with levels of

exposure that appear generally low in risk, as discussed further in Factors 4, 5 and 6. This was also discussed by an international virtual think tank of kratom research leaders, who agreed that whereas kratom can provide relief of opioid withdrawal in animal models and humans, those benefits may be mediated in part by alpha adrenergic agonist effects which is the mechanism of action of the FDA-approved non-opioid medicine (lofexidine) for treating opioid withdrawal (Henningfield et al., 2023).

This is also consistent with what McCurdy and others have reported in the Southeast Asian kratom market, in which kratom leaf and natural kratom decoctions and extracts vary in appearance of the leaves, and with regional variation, as is common with most other plants, including coffee and tea. A caveat is that products should not be marketed with health claims or differential benefits based only on the color of the leaves, but rather should considered in conjunction with its other characteristics, effects, and benefits. Regulatory oversight as described further in this report and as has been passed into law in 19 states at the time of this writing can, and should, prohibit such claims that focus solely on the color of the leaves.

The foregoing appears consistent with FDA's July 2025 statements that the Agency's focus is on 7-OH and not kratom, as well as Ohio's exemption of "natural kratom in its vegetation form" and mitragynine in its December 2025 emergency scheduling action.

However, this report does not support the scheduling of mitragynine, which appears to the be the most important naturally-occurring kratom alkaloid contributing to the benefits sought by millions of kratom consumers in the US. Scheduling mitragynine would be a de facto ban on kratom.

The implications of this science-driven understanding contributes to the conclusion that a healthy and health-serving kratom marketplace should continue to include kratom products, in their naturally occurring variations, including naturally derived extracts, and including products, in which the primary, if not sole, alkaloid is mitragynine. The exception is products with boosted (artificially elevated) levels of 7-OH and highly concentrated 7-OH, whether or not the 7-OH is a semi-synthetic derivative of kratom or fully synthetic.

3.3.1 Conclusions and Recommendations

The current evidence, as a whole, suggests that natural kratom products pose a relatively low risk to the public health, especially when compared to conventional opioids or other substances of abuse. This consensus has been acknowledged by authoritative bodies: for instance, after extensive review, the WHO ECDD in 2021 declined to recommend international control of kratom, finding insufficient evidence of substantial abuse or harm. Likewise, the U.S. Department of Health and Human Services in 2018 concluded that kratom's main constituents did not warrant Schedule I placement at that time (Giroir, 2018). These conclusions were based on the scientific knowledge available and have only been bolstered by subsequent research.

3.4 Factor 4: History and Current Patterns of Abuse

Kratom has a long history of human use, particularly in Southeast Asia (SEA). For centuries, laborers and rural communities in countries including Thailand, Malaysia, and Indonesia have used kratom leaves as a traditional stimulant and remedy for mild pain related to manual labor. Typically, fresh or dried leaves were chewed or brewed into tea to increase endurance, relieve musculoskeletal pain, treat ailments like diarrhea or cough, and substitute for opium in times of shortage.

This traditional context is marked by moderate, routine consumption (often a few leaves at a time) rather than binge use, although actual amount per day can vary widely to satisfy individual needs and desires. For example, in the US, it appears that kratom intake per day and/or per consumption by people using to self-manage pain and withdrawal is higher than for many other commonly reported reasons for use such as energy (Grundmann et al., 2025).

Grundmann conducted the first major national survey of kratom use, patterns of use, reasons for use, demographics of kratom users, and risks and benefits attributed to kratom including addiction and use to treat addictions (Grundmann, 2017). His 2025 survey is another landmark survey as provides a nationally representative approach described in the article as follows:

"A cross-sectional survey utilized a non-probabilistic nationally representative sampling with a total of 11,545 respondents of which 1,049 reported current kratom use, indicating a 9.1% prevalence. The most common kratom products used in the past 30 days were pills, gummies and powder formulations. Pain relief (n = 603, 57.5%) was the most common condition for using kratom, followed by relaxation/stress relief (n = 562, 53.6%) and boost energy (n = 520, 49.6%). The reported benefits were increased energy from tea bags and improved sleep with leaf or extract powders. A significant positive correlation was found between the increased frequency of consuming kratom shots/extract powder and pain relief (p = .009 and 0.015, respectively. A higher incidence of adverse effects was reported as the amount of kratom per dose increased with gummies/capsules/tablets/pills. The lack of standardization and consistency in kratom products results in unpredictable effects, emphasizing the need for increased research to establish reliable safety guidelines for dosage recommendations." Grundmann et al. 2025, p. 1)

Although the survey was not designed to ascertain information about whether some of these "kratom" products had potentially boosted levels of 7-OH and other synthetic mitragynine derivatives, that possibility seems plausible and may have contributed to the increased reports of adverse events with some products that appear that have been associated with increased amount of kratom per dose.

A letter to the international journal, Addiction, by Grundmann and other researchers discussed these concerns. Titled " Not all kratom is equal: The important distinction between native leaf and extract products", the researchers discussed benefits of kratom

use along with potential risks and did not recommend scheduling or banning kratom, but rather the need for regulatory oversight as is emerging in increasing numbers of states across the nation discussed earlier in this report. They and many other leading kratom researchers have recommended that consumers “should consult with their health-care provider before using any kratom product, including and especially kratom extracts.” (Grundmann et al. 2024). The authors of this report agree and note that dietary product regulation, like regulation of conventional foods, drugs, cosmetics, and most recently, tobacco by the FDA generally begins with foundation of data to guide initial regulatory requirements as is beginning in 19 states. However, this is always an evolutionary process guided by science to address emerging issues, risks, and benefits in the effort to minimize risks without losing sight of the benefits and other factors that consumers and, often health professionals take into consideration in decisions to use various products.

In Southeast Asia where kratom use is more widespread in many regions, its use appears more accepted as an asset in daily life and health and not generally associated with impairment, social disruption, crime or deaths (Raffa, 2014). Overall, there are many parallels with the US experience. Including the fact that in SEA, there was and remains heavy use by some fraction of consumers and self-reports of “addiction”

Nonetheless in some countries public health concerns and/or economic factors such as government interest in collecting taxes on pharmaceutical products led to mid 20th century laws making kratom illegal have more recently been replaced with the emergence of kratom as important agricultural crops with accepted use (Charoenratana et al., 2021; Karunakaran, Marimuthu, et al., 2025).

The market for kratom began to rapidly evolve with the rise of its popularity in the U.S. in the early 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 rapid growth in the number of kratom extracts and as well as products artificially enhanced with higher than typically occurring natural amounts of kratom alkaloids and/or other substances? .

A pivotal shift occurred in recent years with the proliferation of products specifically marketed as “7-OH” products (Henningfield, Beyer, et al., 2025; K. E. Smith et al., 2025). 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.

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”. Although reliable estimates of 7-OH prevalence are not available, it is plausible that the number of 7-OH consumers exceeds one million, and that growth in 7-OH use has contributed to the 9.1 percent kratom use prevalence estimate reported in 2025. Surveys measuring “kratom” use may have included respondents who understood or reported 7-OH products as kratom. Notwithstanding these uncertainties, the authors of this report concur with the FDA’s determination that both consumption and marketing of 7-OH have increased substantially in recent years.

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).

3.4.1 Patterns of Use

Traditional use of kratom involves using fresh or dried leaves, sometimes powdered and encapsulated, or crushed for brewing. Many users do not view their use as abuse but as self-treatment and there is some evidence that consumers will self-titrate their intake based on product strength, dose-related GI and nausea effects, or the unpleasant taste. More recently, companies have introduced concentrated extracts and enhanced products (e.g. products enhanced with isolated mitragynine, 7-OH, or other alkaloids) to the market. These products may be used by those with higher tolerance or seeking more pronounced therapeutic effects.

Available data, such as epidemiological surveys, indicate that only a minority of kratom users escalate to very high doses or meet the diagnostic criteria for kratom use disorder (Rogers, Weiss, et al., 2024; Smith, Epstein, et al., 2024; Xu et al., 2021). This includes a cross-sectional survey of over 2,700 kratom consumers that found only 12.3% meeting criteria for past year kratom use disorder (KUD) and over 80% of these consumers had mild cases (meaning only reporting 2-3 out of 11 possible symptoms) (Garcia-Romeu et al., 2020).

A more recent survey in 2023 found a somewhat higher rate (about 25.5% of respondents met the criteria for past year KUD), with over 60% of respondents reporting their symptoms as mild (20% reported moderate, and 14% reported severe symptoms). (Hill et al., 2024), though this survey was conducted after the introduction of isolated and enhanced products to the market, which may have affected these results (this survey did not differentiate between such products and natural kratom products).

There are reports of some kratom users consuming large daily quantities or escalating quantities; however, these individuals often have prior histories of substance abuse (Hill et al., 2024; Palamar, 2021). Further, much of this use can also be categorized as self-treatment for SUD related to other substances (Garcia-Romeu et al., 2020; Henningfield et al., 2024; Stanciu et al., 2024).

With the appearance of 7-OH products, anecdotal evidence (Henningfield, Wang, et al., 2025) suggests a bifurcation in the user base with a group of existing kratom users who use natural kratom products because they find them more effective or more accessible than traditional therapeutics. This group uses these products to treat symptoms associated with ailments that are sometimes treated with other natural products, such as issues with mood, sleep, or mild pain. There is also a subset of this first group who uses kratom as a way to transition or abstain from other drugs of abuse, often with more apparent potential for harm to individual or public health. These users may not view themselves as “abusing” a drug, rather they find it a pragmatic choice for harm reduction or self-treatment.

The second group is a new group who escalate doses quickly and may have transitioned to 7-OH either to avoid consuming large quantities of natural kratom plant matter, or are seeking intense recreational effects. It is unknown what proportion of these 7-OH consumers are using for therapeutic or recreational purposes, but it is possible that a complete ban on 7-OH products may lead to harm from 7-OH consumers reverting back to another drug of abuse.

3.4.2 Conclusions and Recommendations

The history and current patterns of use demonstrate a divergence between traditional kratom use and the recent introduction of high-potency 7-OH products. Kratom has a long history of human use with relatively low-level patterns of abuse (more akin to caffeine or tobacco in some contexts), whereas 7-OH has essentially no historical use until recent years. Companies in this space have effectively created a new class of products that market themselves under the guise of “kratom” products.

This context is vital for appropriate regulatory treatment of natural kratom products and to distinguish them from synthetic or semi-synthetic products, or products with enhanced levels of kratom alkaloids or metabolites. These products should be addressed without penalizing the much larger population of kratom consumers who are

not engaging in high risk behavior but rather are using as a means of harm reduction or necessary self-treatment.

As discussed previously in Factor 4, balanced regulatory oversight of kratom products, consistent with approaches emerging in 19 other states, is warranted. Such oversight should be accompanied by continued, and where appropriate expanded, surveillance and research to better characterize both risks and benefits and to inform the evolution of labeling and regulatory standards over time. The emergence of novel products, including 7 hydroxymitragynine and other mitragynine related derivatives, increases the urgency of establishing a clear research and regulatory framework.

Placement of a substance in Schedule I can have a research deterring effect, although such action may be appropriate for certain high risk compounds, such as 7 hydroxymitragynine. For other substances, including kratom and mitragynine, which are not currently scheduled, research is not subject to these barriers. Accordingly, Ohio is encouraged to expand its own research efforts, including by supporting or incentivizing universities and biomedical researchers to pursue both federal and state funding to advance scientific understanding in this area.

Laws that make possession of products felony crimes, such as Schedule I placement in state and federal CSAs are impediments to the willingness of people, especially pregnant women, to discuss their possession and use with health professionals and we urge the Ohio Board of Pharmacy to consider such negative unintended consequences of scheduling kratom and mitragynine rather than providing balanced regulation.

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

Modern surveys and studies reveal that kratom is used by a diverse range of consumers for a variety of purposes, though primarily for reasons similar to use of other products relied on as natural and botanical therapeutics. These reasons range from providing the consumer with improved mood, help with sleep, or help with mild or moderate pain; it is rare that use is purely recreational.

Several large online and academic surveys in the U.S. (2016–2025) have consistently found the top self-reported reasons for kratom use to be: managing pain (acute and chronic), alleviating anxiety or depression, increasing energy or focus (as a caffeine alternative), and self-treating opioid withdrawal or dependence (Grundmann et al., 2025; Grundmann, Veltri, Morcos, Knightes, et al., 2022; Hill et al., 2024; Smith, Dunn, Grundmann, et al., 2022b; Smith, Panlilio, Feldman, et al., 2024b). Notably, using kratom to reduce or quit other drugs (especially opioids, stimulants, or alcohol) is a recurring theme – a significant subset of users are former opioid-dependent individuals who report kratom as a harm-reduction substitute that helps them avoid relapse into more dangerous opioids. These reasons broadly mirror those documented in Southeast Asian contexts (e.g., users also report using kratom for pain, stamina, and as a

substitute for other drugs of abuse (Govarthnapany et al., 2025; Singh et al., 2023; Singh, Mathandaver, et al., 2025; WHO, 2021).

3.5.1 Prevalence of Kratom Use

Kratom use prevalence is difficult to precisely quantify due to lack of inclusion in past national drug surveys and issues in methodology that make direct comparisons difficult, as discussed elsewhere (Henningfield, Grundmann, et al., 2022). Previous attempts at estimating total kratom use prevalence in the United States (U.S.) found results ranging from 1.8 million to over 16 million users in the U.S (Henningfield, Wang, et al., 2022a).

The National Survey on Drug Use and Health (NSDUH) first included questions on kratom in 2019. Results suggested an estimated 0.7% of the U.S. population (roughly 2.1 million people) used kratom in the past year as of 2019. Lifetime use was about 1.4% of the population. These estimates were substantially lower than earlier estimates of 3-5 million consumers (Henningfield et al. 2018). In 2024, NSDUH data suggested lifetime kratom use was increasing (to ~1.9%, with past-year use around 0.4%) but still far lower than estimates by other nationally representative surveys and kratom marketers that suggested that there were more than 10 million kratom consumers, and Grundmann et al.'s 2025 survey suggesting potentially 20 million or more kratom consumers nationwide (Henningfield, Grundmann, et al., 2022). For comparison, past year cannabis use has been appears to be approximately 15%, and opioid pain reliever misuse, 3.3% (SAMHSA, 2025). Importantly, NSDUH does not distinguish 7-OH, and other synthetic kratom derivatives. Hopefully this survey will soon be modifies to collect such vital data.

Table 4: Kratom and 7-OH Prevalence and AE Data from Federal Data Sources

Survey/Data Source	2022 Findings (Kratom)	2026 Findings (Kratom)	2025 Findings (7-OH)
Drug Abuse Warning Network (DAWN)	No reports in DAWN from 1970 to 2011 "New DAWN" began in 2019 and has not listed kratom	Kratom was not mentioned in "New DAWN" annual reports from 2022-2024 "New DAWN" ceased data collection on June 13, 2025	"7-OH" added to DAWN slang terms database in 1Q25
Monitoring the Future (MTF)	Kratom use is not assessed	Kratom use is not assessed	
National Forensic Laboratory Information Service (NFLIS)	Since 2016 NFLIS did not include mitragynine/kratom reports because the rates are below the threshold for inclusion	Not included in NFLIS reports because levels have been relatively stable and low since about 2015 Mitragynine-related information is available through the NFLIS DQS-P (Data Query System - Public) As of January 13, 2026, 278 mitragynine reports for 2024; 209 mitragynine reports for 2025 (partial year)	24 reports of 7-OH and 1 report for mitragynine pseudoindoxyl in 2025
National Survey on Drug Use and Health (NSDUH)	Paid responders on national panel (n = 67,625). 2019 Prevalence Lifetime Use: 1.4%; Past Year Use: 0.7%	Paid responders on national panel (n = 70,241). 2024 Prevalence Lifetime Use: 1.9%; Past Year Use: 0.4% Note that about 2% of lifetime NSDUH kratom use reports were from 12–17 year-olds, and about 4% of past-year kratom use reports were from 12-17 year-olds.	

Survey/Data Source	2022 Findings (Kratom)	2026 Findings (Kratom)	2025 Findings (7-OH)
Treatment Episodes Data Set (TEDS)	No reports. This does not mean there were no reports but suggests subthreshold signal	No reports. This does not mean there were no reports but suggests subthreshold signal	
FDA Adverse Event Reporting System (FAERS)	Not included	1,468 FAERS reports involving "mitragynine" as a suspect or interacting product were identified. Of these, 1,370 reports (93.3%) were classified as serious. Among all reports, 721 cases reported death as an outcome. The earliest FAERS report was submitted in 2008. In 2024, there were 205 "mitragynine" reports. Of these, 190 (92.7%) were serious cases. Among these the following outcomes were reported: Other serious outcome: 125 cases, Death: 62 cases, Hospitalization (initial or prolonged): 57 cases, Disability: 23 cases, Life-threatening event: 17 cases, Congenital anomaly: 1 case There were also 15 non-serious cases reported. Source: FAERS Public Dashboard	14 unique cases involving 7-OH, including two fatalities
National Poison Data System (NPDS)	Not included	In 2024, 1,645 cases involving kratom, including 1,027 single substance exposure cases. Of single substance kratom cases, over half were 20+ years of age (820), intentional	53 cases, including 37 single substance exposure cases.

Survey/Data Source	2022 Findings (Kratom)	2026 Findings (Kratom)	2025 Findings (7-OH)
		exposures (608), and treated in a health care facility (803). 7 deaths were reported among single-substance kratom cases.	There were 24 abuse cases, including 16 single substance abuse cases
DEA Toxicology Testing Program (DEA TOX)		Between 2019 and 2025, 103 cases were identified where mitragynine, 7-OH, or mitragynine pseudoindoxyl were detected	

Note that that some surveys that provide information about the use and effects of kratom do not provide a basis for estimating prevalence. This includes the Substance Abuse and Mental Health Services Administration's Treatment Episode Data Set (TEDS), which records reasons for drug treatment admissions or the Drug Abuse Warning Network (DAWN); neither of these data sources have ever flagged kratom as an emerging pharmacological threat. This is similarly the case with respect to DEA's NFLIS which does not provide an estimate of prevalence of use, and National Drug Threat assessments which have never listed kratom as a National Drug Threat.

Thus, while these data are helpful in elucidating the landscape of kratom use, it is vital to remain cognizant of the limitations of each of these sources of data, especially as kratom has only recently been added to these surveys, and 7-OH even more recently added, if at all. For instance, the Board's report noted that in the first seven months of 2025, U.S. poison control centers received 1,690 reports involving kratom – surpassing the total number of kratom-related calls in all of 2024. However, it is important to note that until recently (February 2025), all kratom-related calls to U.S. poison control centers were logged under a general kratom code.

Thus, while 7-OH has been tracked separately since then, the full distribution of calls for natural kratom vs. other kratom-related compounds is unknown. Additionally, calls to U.S. poison control centers are, in most cases, self-reports or second-hand reports without full knowledge of number of substances ingested. Therefore, there is no way to be absolutely certain that reports of single-substance kratom cases truly included only kratom (and not other substances concomitantly).

Similar limitations apply to adverse event data derived from the FDA Adverse Event Reporting System (FAERS). FAERS is a passive surveillance system that relies on voluntary reporting and is therefore subject to substantial underreporting, reporting biases, and the absence of independent verification of causality. In the context of kratom, submissions may disproportionately reflect more severe or atypical outcomes, particularly in light of heightened regulatory scrutiny and media attention. Limitations in FAERS were also discussed in FDA's July 29 released data (Reissig et al. 2025).

Misclassification is also common for botanical products: mitragynine may be recorded under multiple product names, general "herbal supplement" categories, or nonspecific descriptors, and 7-OH is frequently not captured at all. Additionally, FAERS cannot establish causal relationships, and many kratom-related reports may involve polydrug exposure, co-ingestion of other substances, or incomplete toxicological data, further complicating efforts to attribute reported outcomes solely to kratom.

This recent inclusion of mitragynine and 7-OH to FAERS and National Poison Data System (NPDS) is notable, but those data must also be interpreted in context. With kratom being consumed monthly by millions in the U.S., a few thousand annual calls (many of which are likely minor or precautionary cases) is a relatively low incident rate. For comparison, substances like caffeine, dietary supplements, or common medications also generate

thousands of poison center calls annually, often without indicating a major public health menace.

The severity of kratom-related calls is generally low in most cases: prior analyses (Eggleston et al., 2019; Post et al., 2019) found that while minor symptoms (nausea, tachycardia, drowsiness) are frequently reported, serious outcomes (such as life-threatening conditions) are uncommon and usually involve polydrug use.

3.5.1.1 Internet Monitoring

Internet based monitoring of user reports can provide qualitative information that may be useful in informing policy and regulatory considerations, but such data must be interpreted cautiously and within the limitations discussed in this section. These reports generally do not allow for assessment of their reliability, nor do they establish whether the reported effects attributed to a specific substance were in fact caused by that substance or by other contributing factors. In addition, such data rarely provide an appropriate basis for comparison with control conditions, as would be expected in scientific studies designed to evaluate the risks and benefits of substances.

Erowid is an online forum where individuals can post anonymous reports describing their experiences after taking licit and illicit substances. There were N=613 experiences in the Erowid Experience Vaults for 'Kratom (also Mitragyna speciosa)' available as of 12 January 2026.

This qualitative summary focused on all experience reports under the Erowid topics 'Bad Trips' (n=3), 'Train Wrecks & Trip Disasters' (n=2), and 'Health Problems' (n=31; n's not mutually exclusive, since a report could appear under multiple topics), which represent experience reports biased toward negative outcomes.

Reports are provided by individuals and not medical practitioners and are subject to the usual limitations of self-report data including but not limited to recall bias. Adverse effects where kratom was reportedly used concomitantly with other drugs or foods are separated under subheadings because it is not possible to parse out the cause of the reported adverse effects when other substances are involved. Reports should be interpreted with caution. Note also that no concomitant substances being reported does not mean that no concomitant substances were taken. Erowid Experience IDs (ExpIDs) are provided.

3.5.1.1.1 Adverse Effects

General Adverse Effects, Including Gastrointestinal Effects

With Concomitant Substances Reported

Among the n=3 'Bad Trips' experience reports, kratom use was secondary to psychedelics in n=2 reports, namely smoked salvia extract and insufflated ketamine, respectively (ExpID: 116546; ExpID: 114588); in these reports where kratom was secondary, the reporters were experienced with substance use in general and kratom in particular ("I take 7.5g Kratom 2 times daily" and "daily user of kratom") and reported experiencing visual hallucinations,

dissociation, apathy, nausea, sensory overload, anxiety, and depression. Doses of kratom were relatively lower in these two reports (7-7.5 g or 0.06-1 g/kg body mass, oral).

The reporter who used kratom concomitantly with ketamine stated: "I'm never combining them again and can't recommend anyone else to combine them either". Among the n=31 'Health Problems' experience reports, one reporter (female, age 43 years; ExpID: 116269) with a history of alcohol use disorder who had "taken Kratom almost daily for over 10 years, and I have never had any withdrawal if I went without it" reported experiencing sweating, nausea, involuntary movements, tinnitus, anxiety, restlessness, and body pain after taking prescription naltrexone (50 mg oral) concomitantly with kratom (5 g or 0.08 g/kg oral). They reported visiting the ER, where healthcare practitioners described the reason for the visit as "alcohol withdrawal". A male (age unknown; ExpID: 67650) reported experiencing sedation, nausea, dysphoria, constipation, abdominal pain, and vomiting after taking kratom (12 g or 0.1 g/kg oral) stirred in grape juice.

With No Concomitant Substances Reported

A male (age 25; ExpID: 98883) reported feeling of relaxation, euphoria, constipation, nausea, and severe abdominal pain that lasted for weeks after taking kratom (6 g or 0.08 g/kg) daily for a few days. This individual had a history of pancreatitis. A male (age 24; ExpID: 103310) reported experiencing abdominal pain and had an esophagogastroduodenoscopy which identified intestinal inflammation after taking kratom (4 g or 0.07 g/kg oral) once per week for approximately one year. They reported: "now I take kratom a lot less (once or twice a week) I take it with black cumins seed oil and my intestinal problems have reversed significantly." A male (age unknown; ExpID: 79456) reported experiencing nausea, vomiting, and facial swelling after taking a relatively large dose of kratom (18 g or 0.2 g/kg oral).

<u>Adverse Effects Related to Renal and Urinary Issues</u>

With No Concomitant Substances Reported

In the n=1 'bad trip' where no concomitant substance was reported, a male (age not reported; ExpID: 56786) reported taking kratom at an uncommonly large dose of 41.6 g or 0.6 g/kg over the course of 24 hours; the effects reported include tiredness, loss of concentration, nausea, miosis, urinary retention (which did not require medical intervention), feeling of relaxation, and dissociation. These symptoms lasted approximately one day.

Among the n=31 'Health Problems' experience reports, a male (age unknown; ExpID: 51161) reported experiencing feeling drunk, headache, lethargy, depression, constipation, abdominal pain, urine discoloration, urinary retention, and fever after consuming kratom (orally) approximately once per week for a few months. A male (age unknown; ExpID: 45265) reported experiencing euphoria, urinary retention, and hematuria after repeated kratom use (dose/duration unknown). A male (age 36; ExpID: 113752) reported

experiencing abdominal pain, erectile dysfunction, testicular pain, and dysuria after taking kratom (4 g or 0.03 g/kg oral) infrequently for approximately three months.

Adverse Effects Related to the Cardiovascular System, Including Syncope

With Concomitant Substances Reported

A female (age 20; ExpID: 96240) reported feeling drunk, impaired motor function, thirst, increased energy, aphrodesia, increased mood, nausea, euphoria, vomiting, headache, tachycardia, and hot flashes after taking kratom (15 g or 0.3 g/kg oral) concomitantly with alcohol. They stated: “I think the alcohol is more to blame for my nausea, and the kratom could have been a positive experience if I'd eaten less of it and hadn't drank, too (the label on the bag said not to combine with alcohol).”

A male (age 18; ExpID: 102572) reported experiencing feeling of relaxation, sedation, impairment of motor function, shallow breathing, disorientation, confusion, and nausea after taking kratom (13 g or 0.2 g/kg oral) concomitantly with carisoprodol, alprazolam, and cannabis.

A male (age not reported; ExpID: 60718) reported experiencing euphoria, vision blurred, convulsions, syncope, bradycardia, and impaired motor function after taking kratom (1 tsp oral) concomitantly with psychedelic mushrooms and cannabis. A male (age 62; ExpID: 100175) reported experiencing fatigue and ‘diaphragm cramp’ after taking kratom (5 tablespoons approximately once per week for approximately one year) concomitantly with alcohol and caffeine.

A male (age 22; ExpID: 99430) reported experiencing feeling drunk and syncope after taking kratom (3 g or 0.04 g/kg oral) concomitantly with alcohol. A female (age 47; ExpID: 86136) reported experiencing nausea, headache, vomiting, chest pains (from smoking), laryngitis (from oral), increased thirst, and apathy after taking kratom (dose not reported) orally and smoked concomitantly with (and as a substitute for) methadone.

With No Concomitant Substances Reported

Among the n=2 ‘Train Wrecks & Trip Disasters’ experience reports, one was unrelated to kratom use and instead reported local drug taskforce intervention in a kratom shipment to the individual’s residence (ExpID: 44892).

In the other ‘Train Wrecks & Trip Disasters’ report, a male (age 23; Exp 105426) described kratom as their “stim of choice” (potentially implying past experience with kratom use) and reported sudden heart palpitations, tachychardia, pre-syncope, and syncope after reportedly taking 4.6 g or 0.05 g/kg ground/crushed kratom PO. The individual reportedly recovered after approximately 40 minutes and did not seek medical attention due to their rural location.

Among the n=31 ‘Health Problems’ reports, a male (age 25 years; ExpID: 81443) reported nausea, feeling drunk, increased thirst, impaired motor function, heart palpitations,

tachycardia, dizziness, and anxiety after taking kratom (7 g or 0.09 g/kg oral). This individual had a history of premature ventricular contractions. Another male (age 23 years; ExpID: 115740) reported experiencing dissociation, impaired cognition, tachycardia, convulsions, and panic attacks after taking kratom intermittently for approximately two years. They reported that “I've been to a neurologist and have had a general practitioner take blood samples and all that; everything came back normal and I spent quite a large sum on these tests.” A male (age not reported; ExpID: 73969) reported experiencing tachycardia, anxiety, nausea, dizziness, and tremors after taking kratom (2 g or 0.03 g/kg oral).

Adverse Effects Related to the Liver

With Concomitant Substances Reported

Among the n=31 ‘Health Problems’ experience reports, a male (age 37; ExpID: 93736) reported euphoria, abdominal pain, difficulty breathing, constipation, ALT increased, and AST increased after taking “Kratom Extract that is supposed to be the strongest concentration ever, .25g being equal to 10g regular kratom” (0.25 g or 0.003 g/kg oral) concomitant with raw seafood. A female (age 26; ExpID: 106023) reported experiencing dissociation, headache, nausea, fever, chills, sweating, tiredness, ALT increased, urine discoloration, and jaundice after taking 2-3 tsp kratom orally daily for two weeks concomitantly with alcohol. Similarly, a male (age 26; ExpID: 100091) who self-reported that “

Test results in the past have suggested that I have a somewhat sensitive liver” reported sedation, euphoria, nodding, nausea, vomiting, dehydration, liver enzymes elevated, jaundice, body shakes, and sweating after taking kratom (10 g or 0.1 g/kg orally five times over two weeks) concomitantly with alcohol and cannabis. They reported that they were “discharged from hospital after a week with a diagnosis of a drug-induced hepatic injury.”

The fact that many kratom consumers report use for self-management of pain and addiction, including to alcohol and likely have histories of chronic acetaminophen use and alcohol consumption greatly complicates determination of the potential contribution of kratom to liver diseases.

With No Concomitant Substances Reported

Among the n=31 ‘Health Problems’ experience reports, a female (age 22; ExpID: 88678) reported tiredness, loss of appetite, abdominal pain, jaundice, increased alanine aminotransferase (ALT), increase aspartate aminotransferase (AST), and hepatitis after taking kratom (3 g or 0.04 g/kg oral) daily for two weeks.

A male (age not reported; ExpID: 71949) reported euphoria, abdominal pain, vomiting, chills, urine discoloration, nausea, jaundice, cholestatic hepatitis, elevated ALT, elevated AST, elevated alkaline phosphate, elevated bilirubin, and elevated serum albumin after taking a kratom extract (4 g or 0.06 g/kg). They concluded that “It very well could have been that the extract was tainted with lab chemicals.” A female (age 20; ExpID: 112623)

reported experiencing dissociation, nausea, dizziness, tiredness, vomiting, fever, abdominal pain, hepatitis, elevated ALT, and elevated bilirubin after taking kratom (2 g or 0.04 g/kg oral).

A male (age not reported; ExpID: 102799) reported experiencing headache, fever, chills, pain, and jaundice after taking kratom (7 g or 0.09 g/kg) daily for several months. Medical professionals reportedly told this individual that they had liver toxicity. A male (age unknown; ExpID: 95669) reported experiencing liver enzymes increased and jaundice after taking kratom (4-10 tablespoons oral) daily for one week. They reported that: “I had a liver biopsy and the diagnosed the blockage of the bile duct caused by a unknown substance... After I started on the Ursodiol, I recovered really fast.”

A reporter reported that their girlfriend (female, age 38; ExpID: 96857) had experienced jaundice, chest pain, shortness of breath, and liver enzymes increased after taking a relatively high dose of kratom (12 g or 0.4 g/kg). A male (age 23; ExpID: 105711) reported experiencing abdominal pain, urine discoloration, jaundice, and bilirubin increased after taking kratom (8 g or 0.1 g/kg oral) in extract form. They stated: “I went to one of those 24 hour clinics the next morning, and was informed that I had drug-induced hepatoxicity... I am well aware that my experience was not with 'pure' kratom leaves and that the extracts in those capsules likely have some sort of synthetic filler.”

Adverse Effects Related to Dependence

A female (age unknown; ExpID: 69770) reported experiencing euphoria, analgesia, increased energy, aphrodesia, nausea, depression, tolerance, and withdrawal after “long-term” kratom use (oral). They reported that “It’s probably not as addictive as opiates, but I personally was addicted to it for a while. More psychologically than physically. I wasn’t a super-user so the withdrawal wasn’t physically unpleasant so much as depressing... maybe this is just a coincidence. Maybe kratom isn’t the crook, but I think that it’s something to keep in mind.”

A male (age not reported; ExpID: 107532) reported experiencing withdrawal systems after taking a relatively large dose of kratom (50 g or 0.6 g/kg oral) daily for approximately one year concomitantly with oxycodone and naltrexone. This individual reported ceasing oxycodone and continuing with kratom before taking a single dose of naltrexone, at which point withdrawal symptoms began. They stated: “The reason I am writing this is so no one ever has to feel the way I did by taking naltrexone why [sic] under the influence of kratom. I would not take any naltrexone for at least 2-3 days after quitting kratom.”

A male (age 50; ExpID: 101874) reported experiencing blood pressure increased and withdrawal after escalating kratom use at an unspecified dose and duration. They stated that: “The withdrawal was bad but not overwhelming... I think kratom is fine in moderation like anything else.”

3.5.1.1.1.1 Reasons for Use

Reasons for use in the experience reports above were not commonly reported, but included harm reduction (choosing/substituting kratom over/for alcohol, opioids, and other substances), as an antidepressant, and for a legal high.

3.5.1.1.1.2 Comparisons between Kratom and 7-OH

Among the n=15 experiences in the Erowid Experience Vaults for '7-Hydroxymitragynine (also 7-OH; 7-OH-Mitragynine; 7-HO-Mitragynine; 7-OH-MIT)' as of 12 January 2026, one male (age 29; ExpID: 118316) experienced with kratom use stated that they would "rank the experience of taking 3x14mg of [7-OH alone] higher than most kratom experiences I have had".

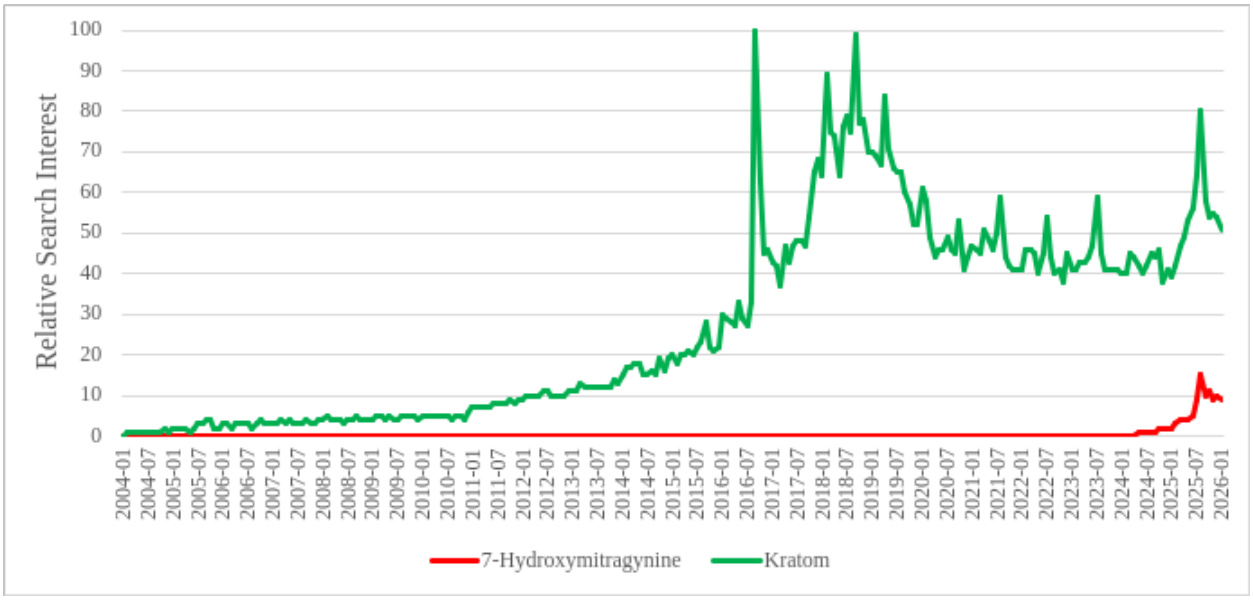
A male (age 31; ExpID: 118938) reported that "Immediately after dosing [7-OH] I noticed this felt nothing like regular kratom... It's significant more addictive than kratom. More clean than kratom and I'd rate it up there with most morphine derivatives."

A male (age 36; ExpID: 118770) reported that "I'm a semi-regular Kratom user... I've never had any withdrawals from Kratom even after taking it multiple days in a row, but have heard those stories. 7-hydroxy is different. This product is a legitimate narcotic."

3.5.1.1.1.3 Online Search Interest

Online search interest in 'Kratom' (Plant topic) and '7-Hydroxymitragynine' (Pill topic) were assessed with Google Trends (U.S. only). Search interest in kratom increased steadily from 2004 to 2010 before increasingly non-linearly through and peaking circa 2018 before decreasing to a constant level from 2022 to 2024. Search interest in kratom spiked again from 2024 to 2025, exactly when search interest in 7-OH increased. It is likely that increased interest in kratom in the last two years was simply a result of increased interest in 7-OH.

Figure 3 Relative Google Trends Search Interest in '7-Hydroxymitragynine' (7-OH) and 'Kratom' from 2004 to 2026



3.5.2 Conclusions and Recommendations

These reports, along with those reported in the 2025 7-OH 8 Factor Analysis (Henningfield, Wang, et al., 2025), though inherently limited by self-reporting, recall, bias, and incomplete disclosure of concomitant substance use, provide qualitative insight into adverse events potentially related to kratom consumption and use patterns associated with kratom and 7-OH products.

From a policy and regulatory perspective, such qualitative data are important to consider but also vital to mind the limitations of the reliability of such reports.

Dependence and withdrawal related to use of natural kratom products were described by a minority of users and were generally characterized as milder than traditional opioids; however, severe precipitated withdrawal was reported when naltrexone was taken shortly after kratom use, consistent with opioid receptor antagonism.

Many of the more severe or atypical adverse events occurred in the context of polydrug use, including alcohol, benzodiazepines, opioids, psychedelics, and prescription medications, with several reporters attributing harms to drug combinations rather than kratom alone. Reasons for kratom use were inconsistently reported but included harm-reduction substitution for alcohol or opioids, mood or energy enhancement, analgesia, and legal psychoactive use.

In contrast, the limited number of Erowid reports involving 7-OH consistently described it as qualitatively distinct from kratom leaf, with users characterizing 7-OH as more potent, more opioid-like, and more addictive, frequently drawing comparisons to morphine or other narcotics and reporting withdrawal effects not experienced with kratom.

Complementary Google Trends data show that U.S. search interest in kratom rose steadily until approximately 2018, stabilized from 2022 to 2024, and then increased again from 2024 to 2025 in parallel with a sharp rise in searches for 7-OH, suggesting that recent increases in kratom-related search activity are likely driven by growing interest in 7-OH rather than renewed demand for traditional kratom leaf products.

Kratom has been sold in the U.S. for at least two decades (and there is some evidence that it has been marketed in this country for longer). Even so, documented growing use of kratom has been a recent occurrence and the incidence rate of patterns of escalating harmful use and negative health outcomes are relatively rare.

Several observational surveys (Grundmann, 2017; Grundmann et al., 2025; Smith et al., 2021) found that the majority of U.S. kratom consumers are adults, often middle-aged, and a large proportion had histories of other substance use disorders or chronic pain conditions. For example, Grundmann et al,. 2025 found that 55% of kratom users were men; the majority of whom were 30-49 years of age. More than half were college attendees or graduates and had incomes ranging from $30-149,000. Most were employed and were using kratom for pain relief and stress relief. Youth or adolescent use has remained low;

national surveys such as Monitoring the Future have not added it to youth surveys and poisoning data show very few cases relative to adults.

Although the Board and Governor Dewine have discussed kratom-related deaths and deaths in which "kratom was listed as a cause", case by case evaluations of deaths in which kratom may have been consumed have largely been found to have involved other substances and/or reasons for the death. For example, on February 6, 2018, FDA made the following statement on its website (FDA, 2018): "we now have 44 reported deaths associated with the use of kratom….Overall, many of the cases received could not be fully addressed because of limited information provided; however, one new report of death was of particular concern. This individual had no known historical or toxicological evidence of opioid use, except for kratom. We are continuing to investigate this report" It was eventually determined that the death was the result of an automobile accident without evidence that kratom use was a factor.

In fact, kratom only deaths appear rare and have not been listed as contributing to the national drug overdose death epidemic. Specifically, the DEA has never listed kratom as a public health threat in any of its annual National Drug Threat Assessment reports and has not listed kratom alkaloids in any of its National Forensic Laboratory Information System (NFLIS) reports since 2016. Furthermore, DEA does not discuss kratom overdose or addiction risks (in contrast to its statements on opioids) but does note that it has listed kratom as a Drug and Chemical of Concern, meaning that it monitors kratom closely.

Note that NIDA has concluded that deaths involving only kratom have been rare for more than a decade. The Assistant Secretary of Health and FDA both came to similar conclusions in 2018 (Giroir 2018), and 2024, respectively, as discussed below. Taken together, the conclusions of Assistant Secretary Giroir that whereas the role of kratom is drug overdose death is unclear because most deaths involve other substances or conditions, banning kratom could foreseeably lead to thousands of overdose deaths by kratom consumers relapsing to the use of opioids and other drugs (Giroir, 2018 and discussed below by Henningfield et al., 2024).

It is not clear when FDA stopped listing numbers of estimated kratom deaths but in February 2024 it issued the following statement on its "FDA and Kratom" website:

> In rare cases, deaths have been associated with kratom use, as confirmed by a medical examiner or toxicology reports. However, in these cases, kratom was usually used in combination with other drugs, and the contribution of kratom in the deaths is unclear.

As of this writing, FDA has not changed this statement.

Limitations in ascertaining kratom's potential involvement in cases of potential or known kratom exposure have been discussed in detail elsewhere, e.g. (Henningfield et al., 2024; Papsun et al., 2023). This includes the fact that in contrast to many drugs of abuse and substances that carry substantial overdose risk and in which there is an understanding of

the signature apparent mechanisms and pathophysiological basis of death, (e.g., respiratory depression due to opioids) kratom associated deaths show no such pattern with most listed as “kratom intoxication”, or simply attributed base one evidence of exposure or “high” levels of mitragynine even though a lethal oral mitragynine dose has not been established for animals or humans (Henningfield et al., 2024, 2022).

Neither this report nor prior publications by Henningfield and colleagues, or other leading kratom researchers, assert that kratom is without risk. Rather, the prevailing conclusion of NIDA, FDA, and the peer reviewed literature is that kratom associated deaths are relatively rare when compared with substances driving the ongoing U.S. overdose crisis. As summarized in a recent toxicological assessment, available human epidemiology, forensic toxicology, and animal data are consistent with a broader margin of safety and lower overall overdose risk relative to the primary contributors to the overdose epidemic.

Recent studies and evidence have not changed the conclusion of the following peer reviewed assessment of kratom toxicology:

“None of the foregoing should be taken to imply that kratom or MG [mitragynine] is without potential as a primary or contributing cause of death in some cases, but rather that the human epidemiology, forensic toxicology, and animal studies are consistent with the profile of products with a broader margin of safety and lower overall risk of overdose as compared to the main contributors to the US drug overdose epidemic.” (Henningfield et al., 2024)

We agree with Papsun et al. (2023) that ‘Current interpretation of MG [mitragynine] in a forensic case is subject to a number of confounding factors, including limited chemical stability, appropriate chemical analysis that ensures separation and identification of pertinent alkaloids, the lack of regulation of commercial kratom products and risks of contamination and adulteration, underlying medical conditions, and frequent detection with other substances.’ Suggestion of a lethal dose of kratom or MG [mitragynine] in humans should be based on the known toxicology or pathophysiological effects of kratom or its constituents and on animal studies of LD50 with appropriate algorithms.” (Henningfield et al., 2024, p. 9)

More recent data have not changed this assessment, except with respect to highly concentrated 7-OH products which are the focus of FDA and Secretary of Health concerns, which our Sept. 29, 2025, 7-OH 8FA supported (Henningfield, Wang, et al., 2025).

It is also possible, if not plausible that increases in prevalence of kratom use since the 2022 Pinney Kratom 8 Factor (Henningfield, Wang, et al., 2022a), is related to the emergence of synthetic or semi-synthetic mitragynine-related compounds such 7-OH which have also coincided with increases in signals of adverse events or negative health outcomes associated with kratom. It is vital that surveys and those trained to report incidents are familiar with these products and can distinguish natural products from these newer compounds for which there are little data regarding their safety. Additionally, regulation of product labeling and packaging (such as those adopted through Kratom Consumer Protection Acts in 19 states) could reduce the risk of deaths that are associated with

products that may be marketed as kratom but are actually adulterated or contaminated products, and/or products that contain no kratom at all, but rather are synthetic derivatives.

These data highlight the need for a nuanced approach to regulation stratified by relative risk that would provide an avenue for continued access for potentially tens of thousands of daily kratom users who would otherwise shift to black market opioids, or illicit sources of 7-OH, which would inadvertently worsen the public health opioid epidemic.

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

While there have been individual reported cases of problematic kratom use, the totality of the data (as described in Factors 4 and 5) indicate that the overall public health risk posed by kratom in its natural form is relatively low. This is supported by multiple scientific and regulatory reviews (Giroir, 2018; WHO, 2021) that did not find kratom to be an imminent hazard. The majority of adverse effects associated with use of kratom are related to gastrointestinal issues (nausea, vomiting, constipation) that may contribute to users self-titrating their use before they experience the level of rewarding effects associated with traditional drugs of abuse. Regular high-dose use of kratom has the potential to illicit dependence and withdrawal symptoms, though as reported in surveys and in internet monitoring (Factor 5), these symptoms are typically less severe than from classical opioids and many users taper without medical intervention or relying on inpatient care. The public health burden of availability of natural kratom products, therefore, exists but has been relatively modest compared to other drugs of abuse, and may be contributing to users abstaining from those other more harmful substances.

In contrast, available evidence indicates that 7-OH poses a greater risk to the public health, driven by 7-OH's opioid pharmacology combined with its appearance in highly concentrated, unregulated products. An important study informing this conclusion was conducted by Zuarth Gonzalez et al. (2025) and identified a risk of potentially lethal respiratory depression at high doses. It is notable however that documented incidence of 7-OH-attributable fatalities is low, and it appears 7-OH has not caused a wave of overdose deaths despite its growing availability. This may be due to the fact that most use of 7-OH is oral (slower onset, lower risk than injected opioids) and 7-OH's partial opioid agonist nature may moderate its overdose potential to a degree. However, an unregulated market has the potential to cause an "arms race" in providing escalating doses to consumers. Additionally, that products containing concentrated or enhanced levels of mitragynine-like compounds are being sold in forms attractive to children (gummies, candies) is alarming. Even adults who are naive to opioids might overdose if they misjudge these products (thinking "herbal supplement" and not realizing potency). Thus, as identified by the Board report, unregulated availability of these products poses a risk of accidental or uninformed misuse by vulnerable groups.

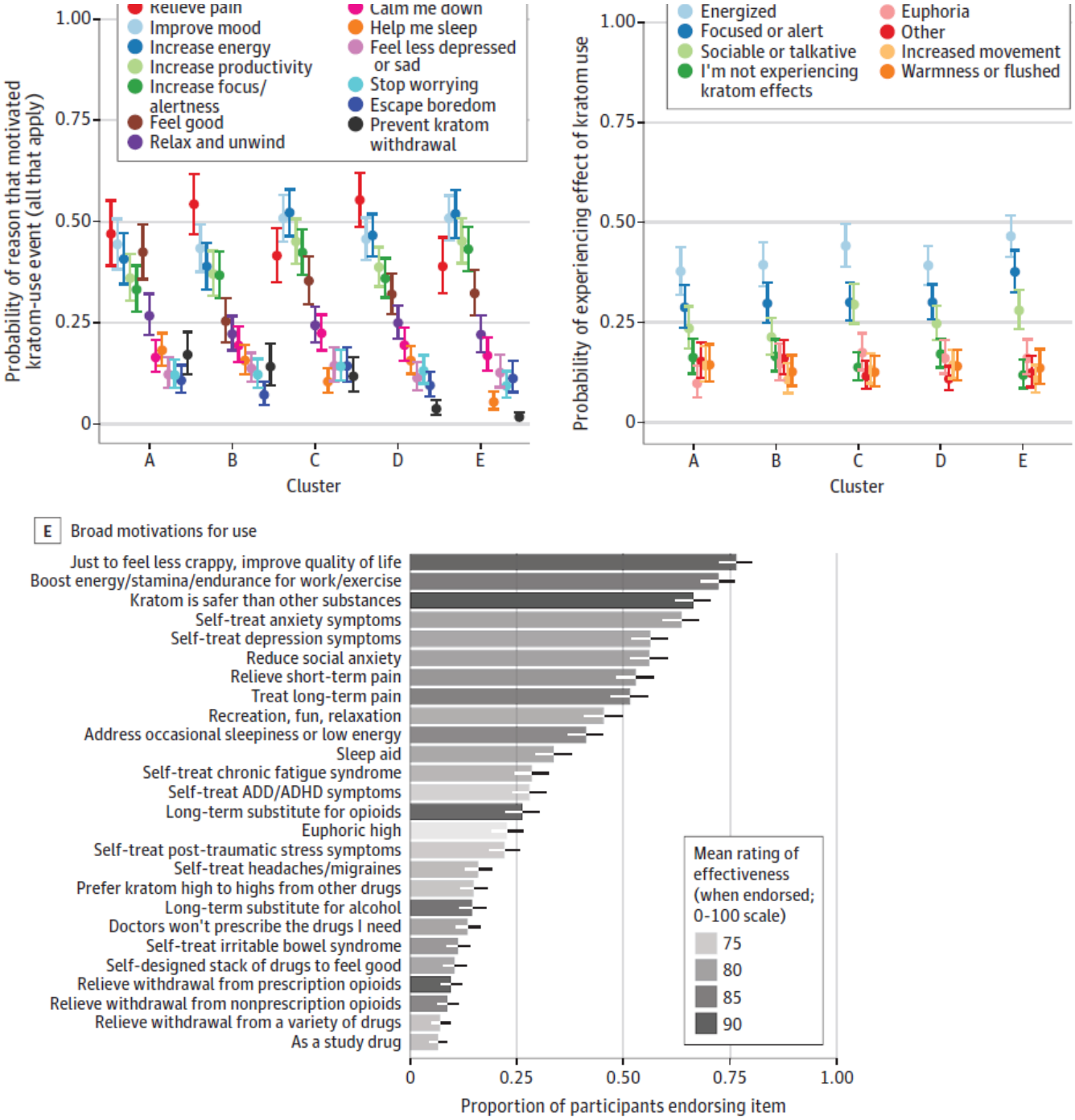
3.6.1 Reasons for Use and Benefits of Use

It's important in regulating kratom and mitragynine-related compounds to consider any public health benefits that may be lost if these substances were scheduled. As mentioned

above in Factor 5, a subset of individuals use kratom as a safer alternative to opioids for pain or as a self-treatment for opioid dependence. As HHS in 2018 and 2021 and WHO in 2021 noted, banning kratom could have the unintended effect of driving people to illicit drugs of abuse, such as classical opioids, increasing the risk of overdose deaths. Similarly, WHO noted potential therapeutic applications of kratom or its components that merit further research, and outright placement in Schedule I may stifle that research. This does not mean kratom is without risks – but those risks (e.g., a few hundred poison calls, some emergency room visits for withdrawal) are generally lower severity than risks from Schedule I opioids and should be weighed against kratom's apparent benefits.

Reasons for using kratom range from providing the consumer with improved mood, help with sleep, or help with mild or moderate pain; it is rare that use is purely recreational. Several large online and academic surveys in the U.S. (2016–2023) have consistently found the top self-reported reasons for kratom use to be: managing pain (acute and chronic), alleviating anxiety or depression, increasing energy or focus (as a caffeine alternative), and self-treating opioid withdrawal or dependence (Grundmann et al., 2025; Grundmann, Veltri, Morcos, Knightes, et al., 2022; Hill et al., 2024; Smith, Dunn, Grundmann, et al., 2022b; Smith, Panlilio, Feldman, et al., 2024b). Notably, using kratom to reduce or quit other drugs (especially opioids, stimulants, or alcohol) is a recurring theme – a significant subset of users are former opioid-dependent individuals who report kratom as a harm-reduction substitute that helps them avoid relapse into more dangerous opioids. For instance, a recent survey by Grundmann et al. (2025) reported that among 11,545 respondents (of which 1,049 were current kratom users), 57.4% (n=603) used kratom products for pain relief; 53.6% used for relaxation/stress relief (n=562); and 49.6% used to boost energy (n=520). Other reasons for use included improving sleep (42%); improved focus/concentration (34%), euphoria (27%), and opioid withdrawal assistance (22%). Higher reported frequency of kratom shots/extract powder consumed was correlated with use for pain relief.

Figure 4: [C] Proximal motivations for use; [D] Acute effects; [E] Broad motivations for use



Source: (Smith, Panlilio, Feldman, et al., 2024b)

These reasons broadly mirror those documented in Southeast Asian contexts (e.g., users also report using kratom for pain, stamina, and as a substitute for other drugs of abuse (Govarthnapany et al., 2025; Singh et al., 2023; Singh, Mathandaver, et al., 2025; WHO,

2021). The DEA's 2016 public call for comments yielded thousands of testimonials describing kratom being used for quality-of-life improvements – such as better sleep, relief from posttraumatic stress disorder symptoms, or managing depression – rather than for intoxication. That said, a minority of users do take kratom in social or recreational settings, sometimes in high doses to achieve sedating opioid-like effects.

Similarly, 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 & 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.

3.6.2 Estimated numbers of Kratom Consumers in Ohio.

Estimates of kratom consumer nationwide have varied widely over the past decade from a little over 2 million by the National Survey on Drug Use and Health, which appears to underestimate novel substances in it panels of respondents to the most recent nationally representative internet survey by Grundmann et al (2025) which estimates an approximately 9% prevalence of past 30 day kratom consuming adults. It is likely that some fraction of these respondents were using novel kratom derivatives and may have overestimated the population that is primarily consuming natural kratom leaf based products and extract. An earlier nationally representative survey estimated approximately 6.1% prevalence for approximately 10.5 million kratom consumers (Covvey et al., 2020). See discussion of the challenge of kratom prevalence estimates by (Henningfield, Grundmann, et al., 2022).

Based on an estimate of Ohio's adult population of 8.2 million the Covvey et al. 2020 and Grundmann et al. 2022 suggest that past 30 day kratom consumers number more than 500,000 and less than 738,000. The opinion of the authors of this report is that 738,000 is a likely overestimate for reason discussed above. Regardless, there are a substantial number of kratom consumers who would become felon criminals if they continued to possess kratom, as suggested by several surveys including the Grundmann et al. 2025 survey, the majority of these kratom consumers are 30 to 50 years of age, work and many with education beyond high school. Most surveys suggest more kratom consumers are men than women with the prevalence of men in Grundmann survey approximately 55%

Although some of these kratom consumers may discontinue their kratom use, many would continue, however, they would be less likely to discuss their use with health professional which these authors and others (e.g., Swogger et al. (2022)) recommend. That includes pregnant women.

These concerns and others were expressed by Assistant Secretary of Health Brett Giroir who requested a departmental review of the FDA's 2017 proposal to schedule kratom. Giroir rescinded that recommendation making clear that the evidence did not support scheduling and that FDA had failed to consider the serious adverse public health consequences of a kratom ban, as stated below (Giroir, 2018):

Furthermore there is a significant risk of immediate adverse public health consequences for potentially millions of users if kratom or its components are included in Schedule I, such as,

- Suffering with intractable pain [by people who were self-managing their pain with kratom];
- Kratom users switching to highly lethal opioids, including potent and deadly prescription opioids, heroin, and/or fentanyl, risking thousands of deaths from overdoses and infectious diseases associated with intravenous (IV) drug use;
- Inhibition of patients discussing kratom use with their primary care physicians leading to more harm and enhancement of stigma thereby decreasing desire for treatment, because of individual users now being guilty of a crime by virtue of their possession or use of kratom [an issue noted in this report as of particular concern with respect to pregnant women];
- The stifling effect of classification in Schedule I on important research needed on the complex and potentially useful chemistry of components of kratom.

3.6.3 Conclusions and Recommendations

Additional research is needed to more fully characterize the risks associated with 7 hydroxymitragynine, both on its own and in comparison with kratom products and with classical drugs of abuse. This need for further research should not be interpreted as an absence of sufficient scientific evidence to support initial regulatory frameworks, but rather as a means of informing the ongoing evolution of policy and regulation as new data emerge.

Multiple surveys suggest that most kratom use is motivated by use to self-manage various health conditions, and/or to contribute to well-being and achievement of goals and responsibilities in daily life (Coe et al., 2019; Grundmann, Veltri, Morcos, Knightes, et al., 2022; Jeffrey M Rogers et al., 2022; Smith, Dunn, Grundmann, et al., 2022a; Smith & Lawson, 2017; Smith, Panlilio, Feldman, et al., 2024a; Smith, Rogers, et al., 2024; Swogger et al., 2015; Zamarripa et al., 2024). 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).

Despite evidence suggesting many 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.

3.7 Factor 7: Its Psychic or Physiological Dependence Liability

Kratom contains more than fifty alkaloids that collectively contribute to its pharmacological effects. Mitragynine is the most abundant alkaloid in kratom leaf and appears to account for many of the reported benefits. It is a partial μ-opioid receptor agonist with additional α-adrenergic and other non-opioid effects that likely contribute to alertness and relief of withdrawal symptoms. Mitragynine is not reinforcing in animal studies and produces little respiratory depression across a wide range of doses (Henningfield et al., 2024; Henningfield, Rodricks, et al., 2022; Henningfield et al., 2021; Smith, Epstein, et al., 2024).

In recent surveys of kratom use disorder, a growing body of survey-based research has examined the prevalence, characteristics, and clinical relevance of KUD among active users. These studies, largely conducted by academic research groups and funded by NIDA, consistently show that while a measurable minority of kratom users meet Diagnostic

and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria for a substance use disorder, the overwhelming majority of cases are mild and driven primarily by physical dependence rather than by compulsive use or significant psychosocial impairment.

For example, Smith, Dunn, Rogers, Garcia-Romeu, et al. (2022) examined prevalence of KUD in a sample of 129 current U.S. kratom users recruited online. 29.5% of respondents met criteria for past-year KUD, though importantly most of these cases were classified as mild (14.0%) or moderate (7.0%), with only 8.5% meeting criteria for severe KUD. More than half of respondents (52.7%) had never met criteria for KUD, and an additional 17.8% had previously met criteria but were in remission at the time of survey. The most frequently endorsed DSM-5 criteria were tolerance, withdrawal, craving, and using more than intended, whereas classic indicators of addiction-related outcomes, such as abandoning obligations or experiencing major social harm, were uncommon.

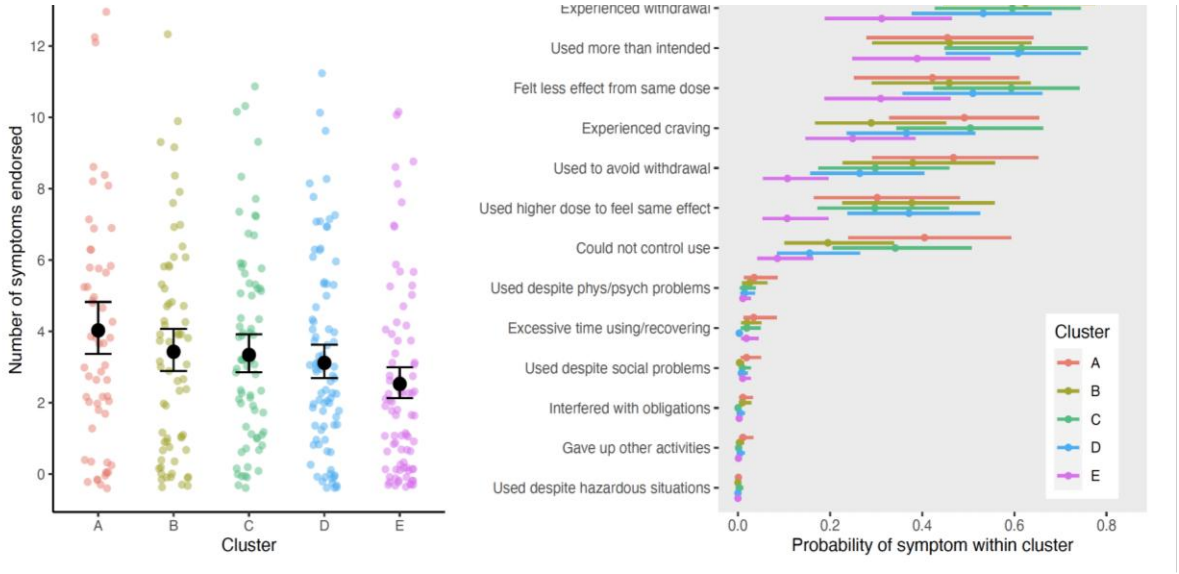
These results were largely confirmed in a much larger survey conducted by Hill et al. (2024), which assessed 2,061 current kratom consumers recruited between February and May 2023. In this sample, 25.5% of participants met DSM-5 criteria for current KUD, with most cases being classified as mild (66%) or moderate (20.0%), with severe KUD (13.9%) representing a small fraction of the total. Tolerance (81.3%) and withdrawal (68.0%) were the most commonly reported symptoms among those with KUD, while symptoms reflecting function impairment, such as failure to meet work or family requirements, were endorsed by a small fraction of the group. The authors also reported that individuals with a history of another substance use disorder were approximately 2.8 times more likely to meet criteria for KUD, suggesting that vulnerability to KUD is likely influenced by many other factors common to use disorders rather than kratom exposure alone.

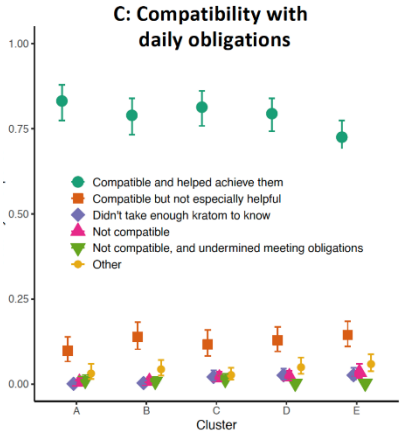
A study by Smith, Panlilio, Feldman, et al. (2024b) found in a 2022–2023 ecological momentary assessment (EMA) and survey study of 357 near-daily kratom users that 66.7% met DSM-5 criteria for KUD. However, this elevated prevalence must be interpreted in context: participants were specifically selected for very frequent use, and most KUD cases were defined by exactly two or three criteria. Notably, only three individuals (approximately 1% of the sample) met KUD criteria based solely on tolerance and withdrawal, indicating that most KUD-positive respondents also endorsed at least one additional symptom such as craving. Even in this heavy-use cohort, reports of social, occupational, or interpersonal impairment attributable to kratom were rare, and many participants reported perceived benefits such as improved mood, pain control, or productivity.

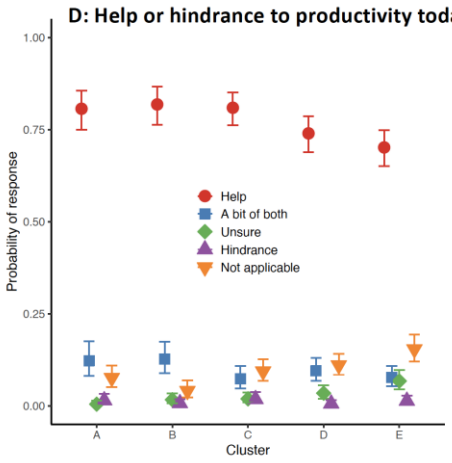
Across all clusters, kratom users reported low to moderate endorsement of DSM substance-use symptoms, with average symptom counts remaining modest and well below levels typically associated with severe substance use disorder (Figure A). The most commonly endorsed symptoms involved tolerance, withdrawal, craving, and using more than intended, while markers of serious dysfunction, such as hazardous use, giving up activities, interference with obligations, or continued use despite social or health problems, were rare across all groups (Figure B). Differences between clusters reflected differences in physical tolerance to kratom, not widespread compulsive or harmful use.

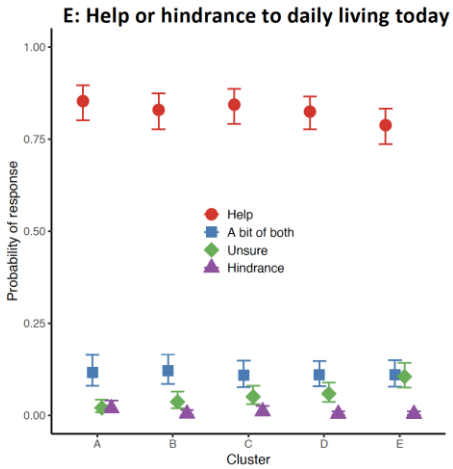
Consistent with this pattern, the large majority of respondents across clusters reported that kratom use was compatible with daily obligations and often helped them meet those obligations (Figure C), as well as improving productivity and daily living (Figures D and E). Reports of hindrance or incompatibility were uncommon, and even clusters with higher symptom endorsement were far more likely to report benefit than harm. Overall, these findings indicate that most kratom users perceive their use as functionally supportive rather than impairing, with limited evidence of severe or disruptive substance-use pathology. Such use is sometimes referred to as “beneficial”, “instrumental” and “therapeutic” despite the fact that no kratom product has been submitted to the FDA for approval as a new drug, nor does FDA recognize kratom as a substance Commonly Accepted for Medical Use (Kirsten E. Smith et al., 2025).

Figure 5: [A] Number of DSM Symptoms endorsed; [B] Prevelance of Specific Symptoms; [C] Compatability with Daily Obligations; [D] Help or Hindrance to Productivity Today; [E] Help or Hindrance to Daily Living Today









Source: (Smith, Panlilio, Feldman, et al., 2024b)

A survey by Rogers, Weiss, et al. (2024) assessed 395 active U.S. adult kratom users and found that the probability of reporting symptoms associated with KUD is consistently higher than completely stopping (cessation) kratom use rather than after missing a single dose. Most (95.9%) reported regularly using whole-leaf kratom products; 16 (4.1%) reported regular extract use. Subjective Opiate Withdrawal Scale (SOWS) scores were mild to moderate on average (13.5, Standard Deviation 11.9). KUD symptom counts were mostly in the mild/moderate range (80.7%). Withdrawal and KUD symptoms were more closely associated with dose frequency than dose amount. Men reported more acute effects, withdrawal symptoms with cessation, and KUD symptoms than women.

Figure 6: Experiences AFTER MISSED DOSE of Kratom vs Experience AFTER STOPPING Kratom Use

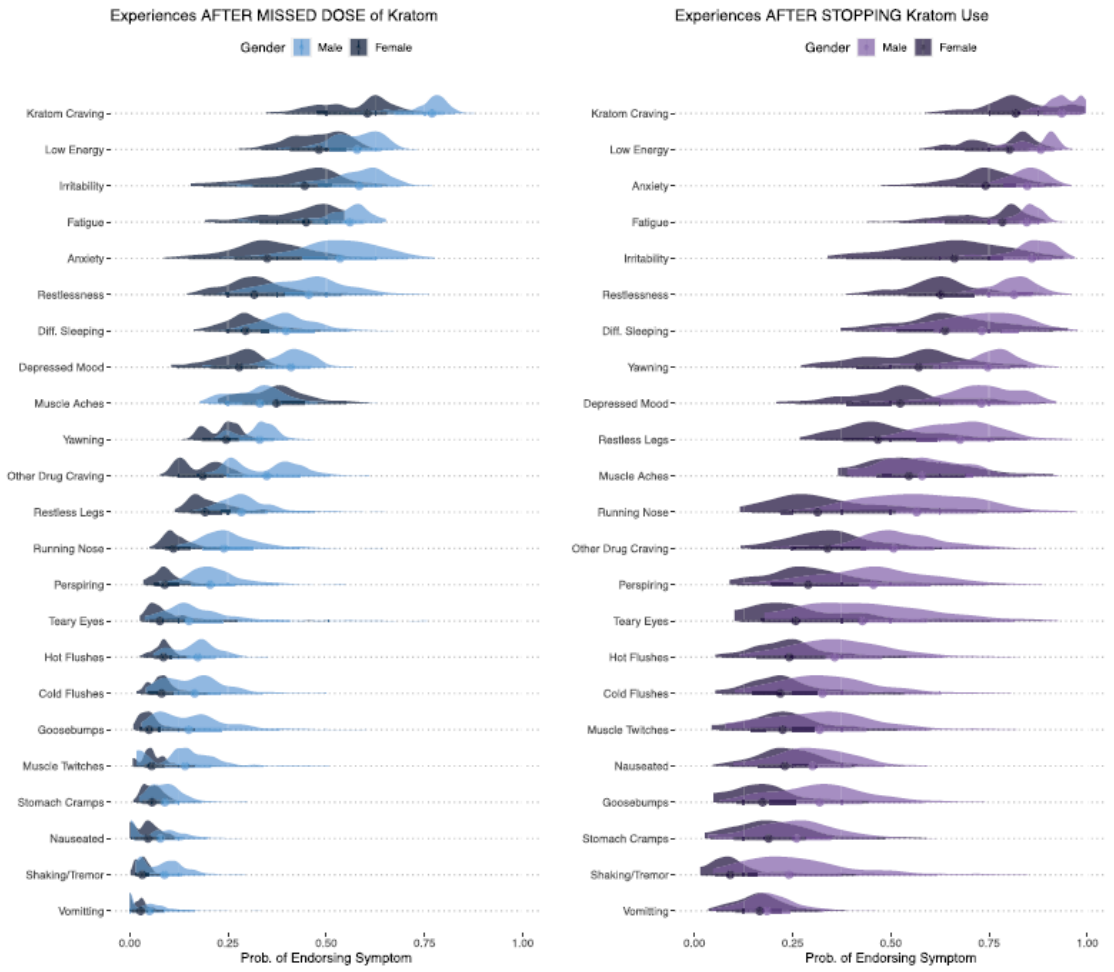


Fig. 3. Model-fitted distributions of the probability of endorsing a given kratom withdrawal symptom under two circumstances: after one missed dose (left panel) and after stopping use for at least one day (right panel). Distributions are displayed from highest to lowest base rate (vertically) and by participant sex/gender (color coding). Estimates were fit from binomial models, controlling for other demographic factors, dose amount, and dose frequency. Inferential statistics and effect sizes for sex differences are shown in Table 3.

Source: (Rogers, Weiss, et al., 2024)

Across these studies, a substantial proportion of individuals who technically meet criteria for KUD do not view their kratom use as problematic and do not experience meaningful impairment in daily life (Hill et al., 2024; Smith, Dunn, Rogers, Garcia-Romeu, et al., 2022). Many respondents reported that kratom improved their ability to work, manage pain, or maintain emotional stability, and a minority reported interference with major life obligations.

To date, there are no similar published, peer-reviewed, survey-based epidemiologic studies (past 2–3 years) that clearly distinguish 7-OH-specific use disorder or withdrawal prevalence using previously validated methods. This is a clear gap in the research that should be addressed in future surveys. This is explicitly highlighted as a measurement problem in FDA's 2025 scientific assessment (Reissig et al., 2025) which notes that consumers may be unaware they are obtaining 7-OH-enhanced products and that 7-OH use would likely be underreported in self-report data. This report also notes that forensic testing often uses mitragynine as a marker, which can lead to misclassification of 7-OH cases as "kratom/mitragynine-related."

3.7.1 Conclusions and Recommendations

Overall, these recent NIDA-funded clinical studies and surveys highlight that while some kratom users develop symptoms indicative of substance use disorder, the severity of these symptoms is generally milder and more manageable than opioid or stimulant use disorders and without adverse social, occupational, or criminal related consequences. The current data suggest that for many, use of kratom is primarily as a daily self-maintenance or self-therapeutic, similar to caffeine dependence, rather than a trajectory of more problematic and risky use.

Kratom consumers who seek assistance in managing their own use disorders and withdrawal should be provided with such assistance. This has been recently discussed elsewhere (e.g. Swogger et al. 2022; Smith Dunn Epstein et al 2022. We include a verbatim recommendation from Smith et al. (p. 3).

> Clinicians should consider the full spectrum of kratom's actions rather than focusing on one system; however, if the opioid system is the focus, then clear and systematic assessment measures should be used before an intervention is chosen.
>
> Finally, we suggest that all authors undertaking kratom research in humans consider what "advantageous" entails within a broader context of KUD or other SUD treatment. Buprenorphine/naloxone may be the best treatment for patients with moderate-severe KUD who are not opioid-naïve (especially if they have a history of OUD) and who wish to begin pharmacotherapy, but this should be carefully determined on a case-by-case basis in light of the patient's history and treatment goals. Given our limited understanding of the mechanisms of action for kratom alkaloids and the lack of standardization of kratom products, pharmacotherapies for KUD should be approached with caution and with patients' full informed consent regarding treatment options.

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

Mitragynine and 7-OH are not immediate precursors of any currently controlled substances in the technical sense of chemical scheduling. A precursor is defined typically as a compound that is primarily used to manufacture a controlled drug and is a direct chemical forerunner of that drug. Neither mitragynine nor 7-OH is used to synthesize any controlled opioid like morphine or fentanyl. They are structurally unrelated to the opiates derived from opium poppy, and they are not known to be converted into any other controlled drug other than other alkaloids such as mitragynine-like compounds.

4 Additional Scientific, Regulatory, and Policy Considerations

4.1 Regulatory/Policy Analysis of Dietary Supplements

As discussed by the Board in its January 6, 2026 meeting, neither kratom, nor mitragynine, nor any other kratom constituent are approved as drugs by FDA for therapeutic use, nor are the recognized as Commonly Accepted for Medical Use (CAMU) – a determination that was made by DHHS with FDA for “marijuana” (Henningfield, Comer, et al., 2025).

The main relevance of such a determination for CSA scheduling is not whether it should be scheduled, but rather which schedule should be considered if the abuse potential and public health risk indicated the scheduling is warranted. If the drug product, or substance with such abuse potential is approved by FDA for therapeutic use or designated as CAMU, then it can only be placed in Schedules II, III, IV or V, commensurate with its abuse potential. If the substance is not approved or recognized as CAMU it can only be placed in Schedule I, and if place in Schedule I can only be removed if it is subsequently approved by FDA.

That does not include dietary substances, whether regulated as conventional foods or the special category of dietary ingredients and supplements, such as kratom. This is codified in the Federal Food, Drug, and Cosmetic Act (FDCA), but may be more lucidly understood in a recent chapter by a former director of FDA’s Office of Dietary Supplements, Robert Durkin and his colleagues (Durkin et al. 2025). Here we present a summary of some key points that may be of interest when considering kratoms risks, benefits, use, and potential restrictions on marketing and labeling if Ohio implements its own approach to kratom regulation.

Products derived from the botanical *Mitragyna speciosa*, broadly referred to as “kratom,” are regulated, marketed, and sold as dietary supplements in the U.S. (Durkin et al., 2025). In the U.S., dietary supplements are regulated by FDA as a unique type of food – separately from drugs, conventional foods, and cosmetics – with a formal regulatory definition provided in the Dietary Supplement Health and Education Act (DSHEA) which was signed into law on October 25, 1994 (ODS, 1994). As such, the Board’s concern that mitragynine-related compounds (including specifically kratom), are not approved for medical use does not apply to dietary supplements derived from kratom.

Prior to DSHEA, dietary ingredients were frequently regulated by FDA as food additives, with the belief that dietary supplements consisted of adulterated foods containing either unapproved or unsafe food additives. This presented a significant challenge, given that the process for introducing new food additives is costly, time-consuming, and requires that new food additives be available widely throughout the entire food supply with significantly broader exposure versus if the ingredient was intended to be used far more narrowly and in a limited number of products, such as dietary supplements. DSHEA, a bipartisan effort that was unanimously passed by Congress, conveyed unique "statutory and regulatory requirements for dietary supplements and their dietary ingredient constituents" such that FDA's regulation of dietary supplements would be less arduous while at the same time more consistent from that point forward (Durkin et al., 2025).

Per section 201 (21 USC 321) (ff)(1) of the Food, Drug, and Cosmetic Act (FDCA), a dietary supplement is "a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:

- (A) a vitamin;
- (B) a mineral;
- (C) an herb or other botanical;
- (D) an amino acid;
- (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
- (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E)" (ODS, 1994)

Additionally, among other characteristics, a dietary supplement must be swallowed into the alimentary canal, not be intended to be a replacement for a conventional food, and not contain a dietary ingredient that has been previously studied or approved as a drug (Durkin et al., 2025). By this definition, kratom, a botanical, and its extracts and constituents including alkaloids, flavonoids, and metabolites meet the criteria for dietary supplements.

Dietary supplements must be manufactured according to Title 21 of the Code of Federal Regulations (21 CFR Part 111) "Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements." For any kratom-containing or kratom-derived dietary ingredient/supplement, these good manufacturing practices (GMPs) include identifying and confirming the identity and specifications for every dietary ingredient used to manufacture a dietary supplement.

Dietary ingredients and dietary supplements that were available on the market before DSHEA are differentiated from those that have been introduced after DSHEA was enacted (Durkin et al., 2025). Any dietary ingredient that was not marketed in the U.S. as a dietary ingredient or a dietary supplement prior to October 25, 1994 is considered to be a "New Dietary Ingredient" (NDI). If it cannot be shown that the NDI is present in the food supply in a chemically unaltered form, then a New Dietary Ingredient Notification (NDIN) must be

submitted to FDA at least 75 days before the ingredient enters the market, as the Agency established in 1997 and codified in 21 CFR §190.6.

Kratom, along with many other dietary ingredients and supplements, was used and marketed prior to 1994, as anecdotally reported by people who immigrated from Asia; however, the level of evidence and documentation required by FDA for determination that they meet criteria as old dietary ingredients and "grandfathered" without an NDIN.

Importantly however, the manufacturers and distributors of any food, including kratom products that are marketed as dietary supplements, are not required to either *seek* or *gain* FDA's approval before putting their food or dietary supplement product(s) on the market (Durkin et al., 2025). The NDIN requirement to sell NDIs is merely a requirement to *notify* FDA as to why the dietary supplement is reasonably expected to be safe based on the conditions of use included on the product labeling. After receipt of FDA's response, or alternatively if no Agency response is received within the 75-day period, the company that submitted the NDIN has satisfied the obligation laid out in section 413(a) of the Act and can proceed to place the NDI-containing dietary supplement on the market "regardless of whether the FDA objects with the company's basis for concluding that their product is safe*"* (Durkin et al., 2025). The authors estimate only seven kratom-related NDINs have been submitted to FDA to date (as of 2025). This lack of a requirement for premarket FDA approval for a dietary supplement does require the manufacturer or distributor of the dietary supplement to have an evidentiary basis to conclude that their product is safe – that is, the supplement does not present an unreasonable risk of illness or injury – before going to market.

Regarding scheduling, while the FDA has recommended banning kratom under the CSA twice (in 2014-2016 [Henningfield et al., 2018] and 2018 [Henningfield et al., 2024]), it remains unscheduled. Following the first FDA recommendation in 2014, the DEA requested that HHS conduct a scientific and medical assessment of kratom's major alkaloid, mitragynine, as well as one of its active metabolites, 7-OH, specifically in order to make a determination as to whether kratom and these constituents should be recommended for CSA scheduling (Durkin et al., 2025). Pending the HHS assessment, on August 31, 2016 the DEA announced a plan to temporarily add mitragynine and 7-OH to Schedule I in order "to avoid an imminent hazard to the public safety" (DEA Notice of Intent; 81 FR 59929), although on October 13, 2016, the DEA withdrew its notice of intent due to receiving "numerous comments from members of the public challenging the scheduling action and requesting that the agency consider these comments and accompanying information before taking further action" (DEA Withdrawal of Notice of Intent; 81 FR 70652). The following year, HHS officials again recommended to DEA that mitragynine and 7-OH be permanently placed in Schedule I of the CSA, but in August 2018 then Assistant Secretary of HHS, Dr. Brett Giroir, instructed FDA to withdraw its 2017 scheduling recommendation to the DEA, stating that "this decision is based on many factors, in part on new data, and in part on the relative lack of evidence, combined with an unknown and potentially substantial risk to public health if these chemicals were scheduled at this time" and indicating that further research was needed (Giroir, 2018). And, in fact, contrary to the concerns raised by the

Board, the scientific evidence base to date supports that kratom does not meet requirements for CSA scheduling, either due to the potential for abuse or concerns that kratom poses a clear threat to public health (Henningfield et al., 2018; Henningfield et al., 2024; Henningfield, Wang, et al., 2022a).

4.2 Characterization of 7-OH as a Morphine-like Opioid.

Note that kratom is not an opioid (see discussion by Henningfield et al. 2022, 2024), however, this report agrees with FDA that 7-OH can be considered an opioid based on its substantial opioid pharmacological effects (Reissig et al. 2025).

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 important in the regulatory consideration of 7-OH. It allows the DEA, upon recommendation from HHS, to classify a substance as an opioid based on its effects, even if it does not meet the chemical, 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 8FA, 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" – of the morphine type and not naloxone type based on its overall pharmacology. The fact that naloxone binds to the same receptors as morphine do not make it a morphine type opioid. Although there is not a simple algorithm for such a determination, the authors of this report agree with FDA's apparent determination that 7-OH can be similarly characterized based on its overall pharmacology including rewarding, respiratory depressant and other effects.

Table 5: Summary of References Published since Jan 1, 2022 Reviewed by the authors for this Report by CSA Factor

Factor 1: Actual or relative potential for abuse	
(Henningfield, Rodricks, et al., 2022; Zuarth Gonzalez et al., 2025)	(Henningfield, Rodricks, et al., 2022; Zuarth Gonzalez et al., 2025)
(Bowe & Kerr, 2024)	(Bowe & Kerr, 2024)
(Huestis et al., 2024)	(Huestis et al., 2024)
(Henningfield, Wang, et al., 2022a)	(Henningfield, Wang, et al., 2022a)
(Henningfield et al., 2023)	(Henningfield et al., 2023)
(Japarin et al., 2023)	(Japarin et al., 2023)
(Jarka & Gregoire, 2023)	(Jarka & Gregoire, 2023)
(Prevete et al., 2025)	(Prevete et al., 2025)
(Smith, Epstein, et al., 2024)	(Smith, Epstein, et al., 2024)
(Smith, Panlilio, Feldman, et al., 2024a)	(Smith, Panlilio, Feldman, et al., 2024a)
(Smith, Rogers, et al., 2024)	(Smith, Rogers, et al., 2024)
(Yunusa et al., 2024)	(Yunusa et al., 2024)
(Yue et al., 2022)	(Yue et al., 2022)
(Yusoff et al., 2022)	(Yusoff et al., 2022)
Factor 2: Scientific evidence of pharmacological effect	
(Abduraman et al., 2025)	(Karunakaran, Ganasan, et al., 2025)
(Annuar et al., 2024)	(Limcharoen et al., 2022)
(Berthold et al., 2022)	(Manus et al., 2025)
(Berthold et al., 2024)	(Mat et al., 2023)
(Chiang et al., 2024)	(Mongar et al., 2024)
(Chiang et al., 2025)	(Nukitram et al., 2022)
(Das, 2024)	(Obeng et al., 2022)
(Deebel et al., 2023)	(Obeng et al., 2024)
(Dufour et al., 2024)	(Ortiz et al., 2023)
(Effendy et al., 2023)	(Owaid et al., 2025)

(Farkas et al., 2023)	(Paankhao et al., 2024)
(Farkas et al., 2025)	(Pansai et al., 2024)
(Fauzi et al., 2022)	(Qureshi et al., 2024)
(Zuarth Gonzalez et al., 2025)	(Tanna et al., 2022)
(Hartley et al., 2022)	(Tanna, Nguyen, et al., 2023)
(Hassan et al., 2023)	(Tanna, Cech, et al., 2023)
(Hill et al., 2022)	(You et al., 2022)
(Hiranita et al., 2022)	(Yunusa et al., 2023)
(Hoshina & Liang, 2024)	(Yunusa et al., 2024)
(Hughes et al., 2022)	(Zainudin et al., 2023)
(Indriani et al., 2025)	(Zhang et al., 2023)
(Janthongkaw et al., 2023)	
(Janthongkaw et al., 2024)	
Factor 3: Current state of scientific knowledge	
(Ahmad et al., 2022)	(Hong et al., 2023)
(Akbar et al., 2025)	(Hossain et al., 2023)
(Alford et al., 2025)	(Hughs et al., 2023)
(Allison et al., 2022)	(Huisman et al., 2023)
(Anand & Hosanagar, 2022)	(Kamble et al., 2023)
(Angyal et al., 2023)	(Karunakaran et al., 2022)
(Annuar et al., 2024)	(Kedzierski & Mata, 2023)
(Arenson et al., 2023)	(Kim et al., 2023)
(Arenson et al., 2024)	(Koturbash et al., 2024)
(Bachu et al., 2023)	(Laforest et al., 2023)
(Bachu et al., 2024)	(Larsen et al., 2022)
(Bade et al., 2024)	(Le et al., 2022)
(K. A. Bakar et al., 2024)	(Leksungnoen et al., 2022)

(Bayu et al., 2024)	(Leyrer-Jackson et al., 2022)
(Basheer et al., 2023)	(Li et al., 2023)
(Begum, Arzmi, Helal Uddin, et al., 2024)	(Liang et al., 2024)
(Begum, Arzmi, Khatib, et al., 2024)	(Mahaprom et al., 2025)
(Bonnet et al., 2022)	(McCurdy et al., 2024)
(Chathiran et al., 2025)	(Manwill et al., 2022)
(Chen et al., 2025)	(Nakajima et al., 2024)
(Chichagi et al., 2024)	(Nam et al., 2024)
(Chou et al., 2022)	(Papadi et al., 2022)
(Citti et al., 2023)	(Pont-Fernandez et al., 2023)
(Collar & Barrett, 2024)	(Prevete et al., 2023)
(Dhoble et al., 2025)	(Rayanakorn et al., 2025)
(Doharszky et al., 2024)	(Riley, 2025)
(Dror et al., 2024)	(Rogers, Weiss, et al., 2024)
(Edinoff et al., 2024)	(Rogers, Colvin, et al., 2024)
(Emerick et al., 2024)	(Rossheim et al., 2024)
(Garba et al., 2024)	(Sakamoto et al., 2022)
(Garza-Garcia & Qu, 2024)	(Schotte et al., 2023)
(Garmon & Olson, 2022)	(Striley et al., 2022)
(Gorelick, 2022)	(Sudmoon et al., 2025)
(Green et al., 2024)	(Suhaimi et al., 2023)
(Green et al., 2025)	(Suhaimi et al., 2025)
(Groff et al., 2022)	(Suriaga et al., 2024)
(Grundmann, Garcia-Romeu, et al., 2024)	(Swart et al., 2024a)
(Grundmann, Smith, et al., 2024)	(Swatek & Peterson, 2024)
(Haider et al., 2023)	(Swogger et al., 2022)
(Harun et al., 2022)	(Thongsepee et al., 2025)

(Hatch et al., 2024) (Helander & Rylski, 2023) (Henningfield, Rodricks, et al., 2022) (Henningfield, Grundmann, et al., 2022) (Henningfield et al., 2024) (Heywood et al., 2024)	(Uchaipichat, 2025) (Vicknasingam et al., 2024) (Viwatpinyo et al., 2023) (Wei, 2024) (Yang et al., 2023) (Zul Aznal et al., 2022)
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	
(Abdali et al., 2024) (Adzrago et al., 2022) (Ahmed et al., 2023) (Alameh et al., 2025) (Alghalith et al., 2024) (Ameline et al., 2024) (Anderer, 2025) (Arhin et al., 2023) (Awad et al., 2024) (Axelsson et al., 2022) (Axelsson et al., 2025) (Bakir et al., 2025) (Beckerdite & Wu, 2024) (Behonick et al., 2022) (Bowman et al., 2023) (Brogdon et al., 2022) (Broyan et al., 2022) (Broul et al., 2025) (Cauldron et al., 2024)	(Palamar, 2022) (Parent et al., 2022) (Parent et al., 2024) (Peran et al., 2023) (Penzak et al., 2023) (Perez, 2023) (Piercey et al., 2025) (Prevete et al., 2023) (Prozialeck et al., 2022) (Reich et al., 2022) (Rhee et al., 2024) (Rogers, Weiss, et al., 2024) (Rogers, Colvin, et al., 2024) (Rianprakaisang et al., 2023) (J. M. Rogers et al., 2022) (Roma et al., 2023) (Sablaban & Gautam, 2023) (Saengmolee et al., 2022) (Saingam et al., 2023)

(Chiappini et al., 2022)	(Schmid et al., 2022)
(Chichagi et al., 2024)	(Settle et al., 2023)
(Chinnappan et al., 2023)	(Schwensohn et al., 2022)
(Choo et al., 2022)	(Sekar et al., 2022)
(Dadamyan et al., 2025)	(Settle & Yang, 2022)
(Dasgupta & Ye, 2024)	(Settle et al., 2024)
(DeJonge et al., 2023)	(Sharron et al., 2025)
(Dodulik et al., 2024)	(Shi & Shea, 2024)
(Donroe & Fiellin, 2022)	(Singh et al., 2023)
(Eckhardt & Nickel, 2023)	(Smith, Dunn, Epstein, et al., 2022)
(Ellis et al., 2024)	(Smith, Dunn, Grundmann, et al., 2022b)
(Eudaley et al., 2022)	(Smith, Dunn, Grundmann, et al., 2022a)
(Evoy et al., 2025)	(Smith, Dunn, Rogers, Garcia-Romeu, et al., 2022)
(Falise et al., 2023)	(Smith, Dunn, Rogers, Grundmann, et al., 2022)
(Faucher et al., 2024)	(Smith, Rogers, Dunn, et al., 2022)
(Gandhi et al., 2024)	(Smith, Rogers, & Strickland, 2022)
(Gerona et al., 2025)	(Smith, Feldman, Dunn, McCurdy, Grundmann, et al., 2023)
(Gnanasegaram et al., 2024)	(Smith, Feldman, Dunn, McCurdy, Weiss, et al., 2023)
(Gorelick, 2024)	(Smith, Rogers, et al., 2023)
(Govarthnapany et al., 2025)	(Smith, Sharma, et al., 2023)
(Grundmann, Veltri, Morcos, Knightes, et al., 2022)	(Smith, Epstein, et al., 2024)
(Grundmann, Veltri, Morcos, Knightes Iii, et al., 2022)	(Smith, Feldman, et al., 2024)
(Grundmann, Hendrickson, et al., 2023)	(Smith, Panlilio, Feldman, et al., 2024b)
(Grundmann, Hill, et al., 2023)	(Smith, Panlilio, Sharma, et al., 2024)
(Grundmann, Veltri, et al., 2023)	(Smith, Rogers, et al., 2024)
(Grundmann, Smith, et al., 2024)	

(Grundmann et al., 2025)	(K. E. Smith et al., 2025)
(Rodzlan Hasani et al., 2023)	(Spungen et al., 2024)
(Hill et al., 2023)	(Stanciu et al., 2022)
(Hill et al., 2024)	(Stanciu et al., 2024)
(Hill, Boyer, et al., 2025)	(Swart et al., 2024b)
(Hill, Henderson, et al., 2025)	(Swatek & Peterson, 2024)
(Ismail et al., 2022)	(Sykora, 2025)
(Jain & Lloyd, 2025)	(Tampanna et al., 2025)
(Jaunay et al., 2024)	(Tassavor et al., 2025)
(Johnson et al., 2023)	(Thepthien et al., 2024)
(Khalid et al., 2023)	(Torrico et al., 2023)
(Kiyokawa et al., 2023)	(Thewjitcharoen et al., 2022)
(Krantz et al., 2023)	(Tobacyk et al., 2022)
(LeSaint et al., 2022)	(Tobarran et al., 2022)
(Li et al., 2023)	(Torres-Ortiz et al., 2022)
(LoParco, Yockey, et al., 2024)	(Umbehr & Lukaszewicz, 2022)
(LoParco, Bone, et al., 2024)	(Vadiei et al., 2025)
(Lund et al., 2022)	(Valle et al., 2025)
(Martin et al., 2022)	(Vanani et al., 2023)
(Miller et al., 2025)	(White, 2025)
(Muhamad et al., 2024)	(White et al., 2025)
(Mun, Timmons, et al., 2025)	(Wightman & Hu, 2025)
(Mun, Panlilio, et al., 2025)	(Xu et al., 2021)
(Nadarajan et al., 2024)	(Yang et al., 2023)
(Ng & Ha, 2024)	(B. Yang et al., 2024)
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1 Appendix 1: Kratom Abuse Potential 2021: An Updated Eight Factor Analysis

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REVIEW
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Kratom Abuse Potential 2021: An Updated Eight Factor Analysis

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Drugs are regulated in the United States (US) by the Controlled Substances Act (CSA) if assessment of their abuse potential, including public health risks, show such control is warranted. An evaluation via the 8 factors of the CSA provides the comprehensive assessment required for permanent listing of new chemical entities and previously uncontrolled substances. Such an assessment was published for two kratom alkaloids in 2018 that the Food and Drug Administration (FDA) have identified as candidates for CSA listing: mitragynine (MG) and 7-hydroxymitragynine (7-OH-MG) (Henningfield et al., 2018a). That assessment concluded the abuse potential of MG was within the range of many other uncontrolled substances, that there was not evidence of an imminent risk to public health, and that a Schedule I listing (the only option for substances that are not FDA approved for therapeutic use such as kratom) carried public health risks including drug overdoses by people using kratom to abstain from opioids. The purpose of this review is to provide an updated abuse potential assessment reviewing greater than 100 studies published since January 1, 2018. These include studies of abuse potential and physical dependence/withdrawal in animals; *in-vitro* receptor binding; assessments of potential efficacy treating pain and substance use disorders; pharmacokinetic/pharmacodynamic studies with safety-related findings; clinical studies of long-term users with various physiological endpoints; and surveys of patterns and reasons for use and associated effects including dependence and withdrawal. Findings from these studies suggest that public health is better served by assuring continued access to kratom products by consumers and researchers. Currently, Kratom alkaloids and derivatives are in development as safer and/or more effective medicines for treating pain, substances use disorders, and mood disorders. Placing kratom in the CSA via scheduling would criminalize consumers and possession, seriously impede research, and can be predicted to have serious adverse public health consequences, including potentially thousands of drug overdose deaths. Therefore, CSA listing is not recommended. Regulation to minimize risks of contaminated, adulterated, and inappropriately marketed products is recommended.

Keywords: dietary supplement, safety, abuse potential, epidemiology, substance use disorder treatment, opioid pharmacology, Controlled Substances Act

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