Mitragynine-Related Compounds – CSI Comments

77 S. High Street, 17th Floor
Columbus, OH 43215 U.S.A.

Phone: 614 | 466 4143
Fax: 614 | 752 4836

Individual Comments - Mitragynine-Related Compounds

Commenter State	Comment Code	Comment
OH	0 - Blank	
New York	0 - Blank	
OH	1 - Support	I am a registered nurse and also a professional chaplain and have witnessed the worst outcome of kratom use: Death. More than 200 people have died from Kratom use in the State of Ohio. Clinical evidence proves the dangers of synthetic kratom use and the public needs to be protected. It should indeed be classified as a Schedule I Drug and removed before more people suffer and die.
OH	1 - Support	As a registered nurse who has seen the effects of this drug, I firmly agree that it should be labeled as a Schedule 1 controlled substance to make it less accessible. I personally know someone who died of an overdose of this drug and do not want to see this happen to another family if it can be avoided.
Ohio	1 - Support	I'm not sure where to begin on the financial and emotional toll this drug and all drugs in the same class (Kratom, MIT, 7-OH.....) have had on my family. The fact that it is so easy to get and being sold as a "natural supplement" blows my mind. A natural supplement that caused night sweats that stained the sheets yellow, weight gain, irritability, loss of focus and energy, FALLING ASLEEP WHILE SITTING UP AND/OR EATING, loss of testosterone and periods of extreme anger or no feelings at all. I can say that I have been told by the rehab facility that my husband had to end up going to, that the withdrawal from these substances is just as bad IF NOT WORSE than heroin. It took $25,000 to get my husband off of this drug just for him to relapse and easily go into our local gas station and grab liquid MIT only a month after returning home from a 38 day stay at OARC. I thought when Kratom was made illegal to sell that I wouldn't have to worry anymore. I was wrong. Very wrong. Now my husband's freedom and life the way he knew it is no more. He is a 41 year established man who now has no access to his bank accounts (I took it), is being tracked 24/7, has to show receipts and is not allowed to carry cash on him. He has never been addicted to anything in his life, but these compounds destroyed him. Changed him. Changed us and his family. We will never be the same again. I'm not sure why it is such a hard decision to make. Why not just make these prescriptions only? Why weren't these already a schedule 1? My guess? It has to do with money and making money. My husband's life was gambled with, for money. I understand that there will always be addicts, but you can't just walk into a gas station and ask for heroin or cocaine. The kids that I have watched grow up on my street are getting to age where they can go get this substance easily. It has to stop. We have to do better. Be better.

Tennessee	1 - Support	I write in strong support of the Ohio Board of Pharmacy's proposed rule classifying mitragynine-related compounds as Schedule I controlled substances. After reviewing the Board's Business Impact Analysis and accompanying 8-Factor Analysis, it is clear that this rule is not only justified, but necessary. The evidence presented demonstrates that mitragynine-related compounds—including 7-hydroxymitragynine, mitragynine pseudoindoxyl, and semi-synthetic derivatives—possess a high potential for abuse, act as potent μ-opioid receptor agonists, and lack any accepted medical use or accepted safety under medical supervision. I strongly agree with the Board's decision to regulate this entire class of compounds, rather than attempting to control individual molecules in isolation. As the analysis correctly notes, regulating single substances creates predictable loopholes that manufacturers exploit through minor chemical modifications—mirroring the failed, reactive approach previously seen with synthetic cathinones ("bath salts"). A class-based framework is the only scientifically and legally sound way to prevent continued evasion of Ohio's controlled substance laws. These compounds are being manufactured, concentrated, and marketed in ways that bear no resemblance to traditional botanical use. Products containing mitragynine-related compounds are being sold as tablets, gummies, vapes, and flavored confections—often with drug-like claims, opioid-analog branding, and packaging that mimics FDA-approved medications. These products are widely available in gas stations, vape shops, and online marketplaces, creating an unreasonable and preventable risk to public health. The Board's reliance on statutory authority under R.C. 3719.41 and 3719.44 is appropriate and well supported. The 8-Factor Analysis documents escalating poison center reports, emergency department presentations, cases of respiratory depression reversible by naloxone, treatment for mitragynine-related substance use disorder using opioid-use-disorder medications, and a growing number of overdose deaths in Ohio in which kratom alkaloids were listed as a cause of death. These findings meet—and exceed—the legal threshold required for Schedule I classification. While I recognize that this rule will have an adverse impact on certain businesses, the Board has correctly determined that these impacts are outweighed by the demonstrated risks to public safety. Ohio has a responsibility to prevent the unchecked sale of opioid-like substances that are being misrepresented as supplements and sold outside of any meaningful safety or manufacturing oversight. For these reasons, I fully support adoption of the Mitragynine-Related Compounds Rule as proposed and urge the Board to finalize it without dilution or delay. Thank you for your careful, evidence-based approach and for prioritizing the health and safety of Ohio residents.

Ohio	1 - Support	As a specialist in addiction medicine, I believe the proposed rule represents a necessary and timely response to an emerging public health concern. Mitragynine-related compounds—particularly highly concentrated and semi-synthetic derivatives such as 7-hydroxymitragynine and mitragynine pseudoindoxyl—exhibit opioid-like pharmacologic effects, carry significant risk for abuse and dependence, and lack accepted medical use or established safety under medical supervision. The scientific evidence and surveillance data summarized in the Board's 8-factor analysis clearly demonstrate that these substances pose significant health risks. Due to the opioid-like properties of mitragynine-related compounds, I treat withdrawal from mitragynine like withdrawal from fentanyl and other opioids. We have evidence-based treatments for opioid use disorder, including FDA-approved medication treatment with buprenorphine, methadone, or naltrexone. Mitragynine and mitragynine-related compounds have not undergone the rigorous FDA approval process that we expect for a medication to be used to treat a disorder, and do not have an accepted medical use. Of particular concern is the manner in which these products have been marketed and distributed. The sale of potent mitragynine-related compounds in retail and online settings—often labeled or presented in ways that obscure their true pharmacologic effects—creates a substantial risk of unintentional exposure, especially among adolescents and young people.
OHIO	1 - Support	Measures are desperately needed that bans the sale and possession of mitragynine-related compounds. Mitragynine-related compounds include, but are not limited to, the following: 7hydroxymitragynine (7-OH); mitragynine pseudoindoxyl (MP); dihydro-7-hydroxy mitragynine (MGM-15); and 7-acetoxymitragynine.
Ohio	1 - Support	Hello, My name is Avery Pope, I'm 25 and in nursing school in Columbus (Capital University). I am hoping my story helps you understand the dangers of kratom. Friday December 3rd, 2021, my mom called to tell me my older brother Ethan had passed away (Rome GA). Ethan was SO smart, successful and such a great brother. His cause of death was cardiac arrest due to mitragynine intoxication, he had nothing else in his system except his prescription anti depressant. We didn't even know he was taking kratom….my parents discovered through his credit card statements that he had only been taking kratom for less than 1 month. My family is devastated, we miss him terribly. Please consider making Kratom a schedule I controlled substance, nobody should lose a loved one from a purchase they made at a local gas station. Warmest Regards- Avery Pope

New Jersey	1 - Support	Kratom extracts ruined my 30 year old, college-educated son's life. Beginning in 2019, we saw his appearance and behavior deteriorate. He became sullen, withdrawn, and aggressive. He has experienced violent, kratom-induced seizures, withdrawals, depression, pruritus, and gastrointenstinal issues. He has stolen money from us and kratom from convenience stores. He was admitted to the ER in 2023 because of a kratom overdose. He has been to 5 rehabs in the past year and a half because of kratom. Meetings, Vivitrol, and sober living have so far been unsuccessful. During his last rehab stint, he confessed to testing positive for fentanyl. He stated that although he has a history of abusing opioids, he had not taken them recently - instead, he started taking 7-oh, rather than the kratom extracts. He stated that a 7-oh product might have been laced with fentanyl. He has no reason to lie about this. He is currently in another sober living facility. He has no car, license, job, or money. He is now taking suboxone to manage his kratom use disorder. He has stated that the only reason in took it was because it was so easy to get. Further, he said that proper labeling would not have deterred him from taking kratom. Last, he mentioned than he hoped many times over the years that kratom would become illegal because it had ruined his life.
Ohio	1 - Support	I recommend that the proposed rule to categorize synthetic components of kratom as Controlled Schedule 1. The FDA and the Board of Pharmacy have considered this status for it due to the following reasons: The actual or relative potential for abuse. The scientific evidence of the pharmacological effect of the substance.The state of current scientific knowledge regarding the substance.The history and current pattern of abuse. The scope, duration, and significance of abuse. The risk to the public health. The potential of the substance to produce psychic or physiological dependence liability. Whether the substance is an immediate precursor. Thank you.
Ny	1 - Support	I lost my son 6 months ago to kratom powder. This needs to be banned in its entirety.
OH	1 - Support	I want to comment on the effect Kratom has had on me personally. My best friends son, a young man I watched grow up became a victim and statistic because of the accessibility to Kratom. He was everything a person that you would think could escape the addiction to Kratom. He was raised in a Christian home and attended church weekly. He went to a Christian college to follow his dream of being in law enforcement. While in college in Tennessee, he tried Kratom. He purchased it at a gas station. He was able to function and complete his bachelor's degree. He married a girl he met in college and thought his life was on track, but the addictive nature of Kratom kept its grip on him. As his usage increased his marriage crumbled. He ended up in the hospital and then recovery. He went to through three recovery attempts. Eventually was in a sober living facility and was working at a corrections facility. I had lunch with Phillip on a Thursday, we discussed his future, his plans to get his own apartment and excel in his work. The next morning, I received a call that he had overdosed. He had attended a recovery meeting and on His way back to his sober living house had stopped at a gas station and purchased Kratom. That would be the last time he every purchased anything. Phillip spent three hours in a meeting with other people fighting the same fight, and working at a new job that he was so proud and happy to have. And yet, he threw all that away because he could not beat the addiction of something he purchased at a gas station. I think that speaks to the addictive power of this drug. I am asking this drug be removed before someone else loses a loved one.

OH	1 - Support	Keeping 7-oh illegal is the best thing to ever happen. i've watched my husband struggle with a kratom & 7-oh addiction that lead us to a bad spot. It gave him chest pains, he lost weight, was very cool pale & diaphoretic. It is a threat to everyone's well being & life. I also know several stories of people dying & having a heart attack secondary to using this substance. I have watched my husband withdrawal and relapse several times trying to better his life & it's been very heart breaking to watch it all unfold. It was so readily available which he admitted made the addiction harder to stop. I've watched and read so many stories of others losing people due to the mental strain of withdrawal that they committed suicide. I am also a nurse and pretty well rounded to experiencing drug withdrawal and you would have thought you were watching somebody withdrawal from heroin but really it was 7-oh. it's disguised to be "natural, safe & ok" because it's from a leaf. it's all a scam to get you hooked into it & people that sell this crap are more focused on the money lost than people out here dying & battling addiction from it.
OH	1 - Support	I am writing in strong support of Ohio Administrative Code Rule 4729:9-1-01.1, which classifies mitragynine-related compounds as Schedule I controlled substances. Through my work in harm reduction and recovery support, I regularly encounter individuals who are physically dependent on mitragynine-related compounds and require medical withdrawal management, often presenting with no other substances in their system. Despite clear opioid-like withdrawal symptoms, many of these individuals are unable to access appropriate treatment because the substance driving their dependence is not consistently recognized within current treatment, detoxification, and reimbursement frameworks. This gap leaves people suffering without care, delayed from treatment, or forced to self-manage withdrawal — which increases the risk of relapse, overdose, and disengagement from recovery services. This issue is especially harmful for individuals in early recovery. Mitragynine-related products are widely perceived as a "legal" or "natural" alternative to opioids and are often used as a way to seek mood-altering or opioid-like effects without the perceived consequences associated with controlled substances. I have seen many people in early recovery return to substance use through kratom-derived compounds, believing they are making a safer choice, only to find themselves dependent, withdrawing, and at risk of returning to more dangerous substances. The way these products are marketed and sold — in gas stations, vape shops, and online, often in forms resembling candy or supplements — reinforces the misconception that they are safe or benign. In reality, mitragynine-related compounds act on μ-opioid receptors, produce physical dependence, and can lead to significant withdrawal and medical complications. When people realize the severity of their dependence, they are often shocked — and by then, the harm has already occurred. I support the Board's decision to classify mitragynine-related compounds as a class, rather than attempting to regulate individual substances one at a time. This approach reflects lessons learned from past emerging drug trends and is necessary to prevent chemical modification loopholes that place public health perpetually behind the market. Importantly, Rule 4729:9-1-01.1 does not block legitimate scientific research. Instead, it ensures that any future consideration of therapeutic use occurs through FDA-approved research and clinical trials, where safety, dosing, and efficacy can be properly evaluated. This distinction is critical. From a public health and recovery standpoint, permanent scheduling is not about punishment — it is about access to care, clarity in treatment, and preventing avoidable harm, particularly among people working hard to maintain recovery. For

		these reasons, I strongly support the permanent adoption of Rule 4729:9-1-01.1 and thank the Ohio Board of Pharmacy for taking decisive, evidence-based action to protect Ohioans.
Missouri	1 - Support	I, would like to say I Lost my 38 yr old son to Mitragynine intoxication! This is commonly called Kratom. BRECK was a good Christian , he graduated from Dallas Baptist University with a four yr degree in Business Administration. He was a non drinker Non smoker, non drug user. He was a health and fitness advocate. He was Trained by Cooper Clinic in Dallas,Texas. He ate healthy , intermittent fasted. Exercised every morning, 4:30-5:30. And worked Ten hour days as Warehouse Supervisor, walking 15,000 steps a day. He started Kratom as an all natural supplement , kin to the coffee plant, so he stopped drinking coffee and drank Kratom tea. It was ancient Chinese herb used for hundreds of years. For mild muscle aches, focus, when started this I as an RN looked it up: not much back 6-8 years ago. So no resistance from anyone, as he took it. One morning he did not get up. I thought he was tired. When I went to check him, he was dead in his own bed. The nightmare started! I had no idea how he died. He was also so safety conscious. I had a choice of an autopsy. That amazed me. The young man of 38, for only four months, was dead for no known reason. I requested an autopsy, nothing made sense. Did Ivwant to have my only Son sliced up? No !! But I had to do what my nursing sense and heart told me …. I had to know! Well, he was a perfect physical specimen, nothing wrong! Toxicology Report nothing found in his toxicology EXCEPT, Mitragynine 3400 nanograms. Extremely high. Fatally high! It is complete poison, it is not FDA Regulated nor do we know the strength or contaminants of this botanical? No recommended doseage. No unbiased studies. This product is causing deaths. My son is already dead! I am trying to save someone else's child. Advocates for Kratom are on a payroll, or addicted trading one drug for another. Ban Kratom supporters have already paid the ultimate price a shift and destruction as a family. Missing a piece of your soul. This will be and is fast becoming the next epidemic Drug. If this is available, I assure you , you will know someone affected. Please vote against Kratom enhanced with other chemicals or additives And natural leaf Kratom which converts to mitragynine. Thank you for your time and consideration Deborah Brossett
Ohio	1 - Support	Cuyahoga County has seen an increase in overdose deaths associated with Kratom. Kratom should be classified as a schedule 1 drug in Ohio. This would allow its continued use where appropriate, prescribed by a medical professional, and not be available in gas stations, etc. for anyone to access which can lead to relapse or a gateway for illicit street drugs.
OH	1 - Support	I am writing to express my full and unequivocal support for eliminating synthetic kratom. This substance is causing real harm and is actively destroying lives within our communities. In the State of Ohio alone, statistics indicate that more than 200 people have died from unintentional overdoses involving synthetic kratom. These are preventable deaths. Allowing continued manufacturing and easy access to a substance with such devastating consequences is both dangerous and irresponsible. Synthetic kratom is a harmful substance—it is a synthetic drug that poses serious risks, especially when sold without adequate regulation or oversight. Making it readily available only increases the likelihood of misuse, addiction, and fatal outcomes. This should be a no-brainer. The manufacturing, distribution, and easy

		access to synthetic kratom must be stopped. Protecting public health and safety must take precedence over profit. I urge you to take immediate action to remove this dangerous substance from our communities and prevent further loss of life.
Ohio	1 - Support	I am a nurse that works in a local hospital, who has seen the negative impact of which harmful substances does on an individual and their families. Kratom is one of those substances. I am in favor of removing kratom from the shelves and making it a schedule one
Ohio	1 - Support	Kratom is an addictive drug! Caused the death of a good friend.
OHIO	1 - Support	I am an educator in the state of Ohio and have seen first hand the devastation Kratom causes families. I support any rule that prohibits the selling and use of Kratom in Ohio. It destroys families, is a danger to healthy lives and should not be sold.
Ohio	1 - Support	I am the Clinical Director for a local drug and alcohol rehabilitation facility. In April of 2025, we had our first client come into our program reporting Kratom as their drug of choice and needing help managing the withdrawal symptoms in order to stop taking this substance. At that time we had to Google what Kratom even was. Today, we have 3-4 clients on average in our inpatient program (i.e. average daily census of 40-50 clients) who report their drug of choice to be Kratom. The progression has been lightning fast. They report similar symptoms while in withdrawal management as opiates. And the availability of the substance at this time is a major contributor. Additionally, it is marketed as an alternative to opiates or pain management, and as non-addictive - these clients through their lived experience, spending $80-100/day on their substance, loss of employment, and derailed relationships would like to tell you differently
Ohio	1 - Support	My son died from an accidental overdose to Kratom, on November 8, 2024. He was 27. He became addicted to Kratom, believing it would resolve his anxieties. Due to Kratom's addictive powers, and its ability to hijack one's brain, and the easy accessibility to purchase it from gas stations, vape shops and convenient stores only made it more difficult for him to heal from the disease of addiction. Banning the Kratom from every aspect, may not stop those who want to part-take, but it may cause someone to think twice or seek help before breaking the law.
OH	1 - Support	A very close friend of ours died at the age of 27 from Kratom. He was a wonderful young man, raised correctly with parental support. He had a college degree in law enforcement. He started using Kratom and could not stop. He tried many times. He lost his marriage because of it. He lost his job because of it. He was trying to get help from sober living. He had friend support, parental support and he finally took a dose that caused his death.
OH	1 - Support	Withdrawl symptoms from extended use in excess 150-300mg/day similar to other opiates with exception of signifigantly reduced halflife of other traditional opiates. This increases severe discomfort that can be medically concerning. This should not be sold to the public in the quantities it is allowed to be or the forms it is. Low dose acceptance may be permissable, but without strict regulation this will be an issue as current products are packaged in quantities that permit and encourage users to well exceed the amounts that even the distributors/manufactures notate. This is a public risk in its current form without regulation/intervention. It does have the capacity for theraputic/medical use but at this time current practices in the industry are of legitmate concern.

Ohio	1 - Support	PUBLIC COMMENT – RECORD STATEMENT Re: Proposed Rules – Mitragynine & Mitragynine-Related Compounds Comments Due: January 28, 2026 Submitted to: Ohio Board of Pharmacy ——— THIS RULEMAKING IS NECESSARY — AND THE COST OF INACTION IS MEASURABLE IN LIVES I submit this comment in strong support of both proposed rules scheduling mitragynine and mitragynine-related compounds as Schedule I controlled substances. I do so as a parent who lost a child. On December 6, 2023, my son Austin died. Austin died alone in his bedroom after consuming a natural kratom product he believed was safe. He was not a reckless drug user. Austin was repeatedly told—by vendors, online communities, and industry advocates—that kratom was safe, natural, non-opioid, and incapable of causing fatal harm. I was told the same. Those assurances shaped decisions. Those decisions had consequences. Austin did not survive them. Austin's official autopsy and toxicology report, conducted by the Montgomery County, Ohio Coroner, concluded: Cause of Death: Intoxication by mitragynine Toxicology: Mitragynine only — no fentanyl, no illicit drugs, no prescription opioids, and no 7-hydroxymitragynine (7-OH) Findings: Pulmonary edema and frothy airway fluid consistent with opioid-type respiratory depression There were no other substances to blame. There were no extracts, no synthetics, and no 7-OH consumed. The sole cause of death was mitragynine intoxication, the primary active alkaloid in kratom. This rulemaking is not theoretical. It addresses a documented failure that allows opioid-active substances to be sold without medical oversight while families learn the truth only after it is irreversible. ——— MITRAGYNINE ITSELF IS THE RISK — EVEN IN "NATURAL LEAF" FORM Opponents attempt to shift focus to synthetics or isolated 7-hydroxymitragynine (7-OH). That framing collapses because the opposition's own stories are not about synthetics. They are about natural leaf kratom. Advocates repeatedly claim that natural kratom relieves opioid withdrawal, replaces morphine or fentanyl, and sustains daily opioid-like use. Those effects are attributed—by the advocates themselves—to mitragynine, the defining psychoactive constituent of the kratom leaf. Mitragynine is not pharmacologically static. After ingestion, mitragynine is metabolized in the human body into 7-hydroxymitragynine (7-OH), a compound significantly more potent at the mu-opioid receptor. This conversion occurs in vivo. A person does not need to ingest 7-OH directly for it to exert opioid effects. My son did not ingest 7-OH. His body generated opioid potency on its own. Claims that only synthetics or adulterants are dangerous ignore basic biology. Mitragynine alone is sufficient to cause fatal opioid-type respiratory depression. ——— "IT GOT ME OFF MORPHINE" IS A REGULATORY ALARM, NOT A DEFENSE Opponents frequently present statements such as: "Kratom got me off morphine." "Kratom replaced fentanyl." "Kratom helped me quit prescription opioids." These claims are made explicitly about natural kratom leaf, not synthetic analogs. Any substance capable of suppressing opioid withdrawal, replacing morphine or fentanyl, and maintaining opioid tolerance is functioning as an opioid, regardless of plant origin. There is no legitimate public-health framework in which a morphine-substitute—by the advocates' own description—should be sold in gas stations or vape shops without standardized dosing, medical supervision, or prescription controls. If these claims are true, scheduling is mandatory. If they are false, the public has been deliberately misled. Either way, unregulated access is indefensible. ——— ADVOCATES ARE UNINTENTIONALLY MAKING THE CASE FOR SCHEDULING It is notable that many kratom advocates opposing these rules are, without realizing it, providing the strongest evidence for why regulation has failed and why scheduling is necessary. By asserting that natural kratom leaf replaces morphine and fentanyl, suppresses opioid withdrawal, and sustains dependence, they are describing a substance that meets the functional definition of an opioid

		substitute. These claims should alarm policymakers. Every policymaker should be terrified by claims that a retail product can replace morphine, because that is precisely the scenario controlled-substance laws exist to prevent. These admissions do not weaken the case for scheduling. They complete it. ——— REGULATION HAS FAILED ELSEWHERE — INCLUDING IN KCPA STATES Recent developments in other states further confirm that regulation has failed structurally, not procedurally. For example, Utah, which previously adopted a Kratom Consumer Protection Act framework promoted by the American Kratom Association, is now actively reconsidering that approach, including proposals to ban kratom entirely. That reversal reflects a growing recognition that retail regulation cannot keep pace with potency escalation, biological risk, or opioid-like dependence. Ohio should not wait for the same regulatory collapse to occur here before acting. ——— HOW THE AKA MISREPRESENTS FEDERAL SCIENCE: THE 41486478 STUDY A central talking point advanced by Mac Haddow, on behalf of the American Kratom Association (AKA), is the claim that an "FDA study" found pure or natural kratom leaf to be safe or tolerable. That claim is false. The study cited—PMID 41486478, published in Therapeutic Drug Monitoring—was a controlled clinical trial evaluating short-term tolerability of specific doses of dried kratom leaf powder in healthy adults under medical supervision. It was not an FDA study. It was not an FDA safety determination. It was not an approval. It was not an evaluation of long-term dependence or real-world risk. The FDA has never approved kratom and has repeatedly warned of addiction, toxicity, and death. The AKA's use of this study as evidence of safety is a false attribution of federal approval. ——— CONCLUSION: PREVENTION REQUIRES DECISIVE ACTION Had these rules existed earlier, my son might still be alive. I cannot know that with certainty—but I know this: Failing to act guarantees more families will learn the truth the same way I did. These two rules must be adopted together and without weakening amendments. Scheduling derivatives alone invites circumvention. Leaving mitragynine unscheduled ensures continued harm. The opposition's own words—especially their defense of natural leaf kratom—confirm the risk. Please act so fewer parents are left submitting comments like this one. Lives depend on it. I respectfully request that this comment be entered into the official rulemaking record in its entirety. Submitted by: Dan Gibbs Parent; Ohio resident END SUBMISSION
New York	1 - Support	January 10,2026 To Whom it May Concern, On January 14, 2024 our lives were changed forever. We were notified that our son had died. He was 37 years old. He was using an over the counter supplement called Kratom for his anxiety and depression. It supposedly was all natural and safe. The autopsy report states that he died from Mitregynine intoxication and that there were NO other substances in his system. Despite what some advocacy groups might claim that no one has died from Kratom alone is a lie and this substance is extremely additive and toxic. The ease of availability and false labeling make it more deceiving and dangerous. Please help to ban this toxic substance so that no other family has to endure such a life altering tragedy. It is a pain that never goes away! Respectfully, Barbara and John McGrellis West Babylon, NY
OH	1 - Support	Ban the sale and possession of mitragynine-related compounds. It is killing people.
Ohio	1 - Support	As an ICU RN I feel strongly that anything this hazardous and potentially deadly that ANYONE can obtain should be banned from sales. The regulations of age restrictions also do not help much because under age sales still occur. Also mixing this with other illicit street drugs or

		opiates only increases potential for OD and abuse. Please Keep this out of the State of Ohio, we have enough legal and illegal substance issues. Thank you.
OH	1 - Support	These items can be harmful and deadly and there is no purpose or logic in them being sold in our state.
Ohio	1 - Support	Dear Pharmacy Board, Thank you so much for your consideration of making Kratom a C1 substance in Ohio. It is absolutely essential for this to happen! Kratom and it's analogues are a public health disaster. I have been admitting ALMOST AS MANY patients per week withdrawing from Kratom and it's analogues as I am from Fentanyl for at least the past year. The withdrawal from Kratom is identical to moderate - severe opioid withdrawal, and many of these patients need to go on to Vivitrol or buprenorphine maintenance in MOUD clinic to try to maintian sobreity and avoid relapsing back to the Kratom addiction. These patients addicted to Kratom range from prior herion or fentanyl addicts to newly addicted individuals. I JUST admitted a nurse for Kratom detox this past weekend and a pharmacy tech last week ... both with severe Kratom withdrawal symptoms. Both Kratom and it's analogues have absolutely no demonstrated legitimate medical purpose and no societal purpose (other than to provide an unregualted opioid to any Ohioan who goes into a gas station or vape store). The "advocates" for Kratom and the producers and ditributors are duplicitous in their words and actions, and if not banned the substance will clearly be the next primary opioid in our State's opiid epidemic. I provide these comments as the Past-President of the Ohio Society on Addiction Medicine, and as an addiction medicine physician who has consulted to the State Medical Board of Ohio, the State Pharmacy Board of Ohio, the Supreme Court of Ohio, and the Governor's office periodically over the past 30 years. If you have questions or if further detail would be useful, please do not hesitate to contact me at any time. Sincerely yours, Ted Parran MD FACP FASAM Isable and Carter Wang Professor and Chair in Medical Education CWRU School of Medicine
Texas	1 - Support	Dear Members of the Joint Committee on Agency Rule Review, I am writing regarding the Ohio Board of Pharmacy's January 6, 2026 vote, in which the Board unanimously (8–0) determined that kratom has no accepted medical use. This determination carries significant weight. Under Ohio law, findings regarding medical use fall squarely within the expertise and authority of the Board of Pharmacy. The unanimous nature of this vote reflects a careful review of scientific evidence, public-health risk, and investigative findings. I also write from a personal place. I lost my brother, Matthew, to mitragynine toxicity. Like many families, we were misled by claims that kratom was safe or therapeutic. The Board's decision represents an important acknowledgment of the real-world harm families have experienced. Ohio has historically played a leadership role in evidence-based controlled-substance policy, and this determination establishes a clear administrative record that JCARR can appropriately rely upon in its review. I respectfully urge the Committee to give due deference to the Board's expertise and to the public-safety record developed through this process. Treating kratom as a consumer product or supplement is no longer consistent with Ohio's medical findings. Thank you for your time and for your role in protecting the health and safety of Ohio residents. Thank you from a grieving brother who is concerned about the safety of all Americans.
Ohio	1 - Support	A friend of mine has a son who was hooked on Kratom- he overdosed and died!

Md	1 - Support	I am asking you to please reconsider this ban. First let me clarify that synthetic 7Oh and natural kratom plant material are NOT the same thing. These dangerous 7Oh products are ruining the responsible adult users of natural kratom plant material to treat a variety of mental and or physical issues. The kratom plant and its crushed leaf are a potential life changing alternative to pharmaceuticals. Myself and several people I know personally have used kratom plant material to be able to address chronic pain issues without the obvious serious side effects and addictive opiate medication. The people deserve a right to access and continue to heal themselves with plant based medicine. In addition the amount of individuals who are able to use Kratom instead of traditional MAT (methadone/suboxone) medications. I have personally been consuming Kratom for 8 years, and even as a passionate advocate for Kratom, i completely agree that 7Oh products need to be banned, they are synthetic and dangerous. The natural kratom plant Leaf material is valuable natural alternative and this ban will harm the thousands of responsible consumers. Protect the American consumers right to have safe natural alternatives to pharmaceuticals.
Ohio	1 - Support	I agree with this wholeheartedly as a mother who almost lost a child to this substance. It should be regulated. This is a situation where law is truly protecting citizens.
Ohio	1 - Support	To Whom It May Concern, I am writing to express strong support for the proposed rule classifying kratom and all synthetic kratom compounds as Schedule I controlled substances. I agree with the concerns of the Ohio Deflection Association (ODA) and understand ODA has carefully reviewed the available information and firmly supports this classification as an important step in protecting public health and safety. Kratom and its synthetic derivatives have increasingly appeared in unregulated markets, often without adequate scientific evidence regarding their safety, efficacy, or long-term health impacts. The absence of consistent quality control, combined with the potential for misuse, creates significant risks for individuals and communities. Classifying these substances as Schedule I will help limit their availability while ensuring that appropriate regulatory oversight is in place. Thank you for your consideration. Sincerely, Peggy A. Schneider
Ohio	1 - Support	Kratom (mitragynine related compounds)should not be readily available for anyone to be able to purchase. Our son's best friend died as a result of getting hold of this drug. No one should have to bury a son as a result of a drug that should be regulated! Do the right thing!
Ohio	1 - Support	As a licensed social worker and grief counselor, I have seen first-hand the devastating effects of mitragynine, or kratom. Ohioans are dying as a result of the greed driving the makers of this drug. That this substance is available to the public at large, and marketed toward children, is unconscionable. I strongly urge the board to vote to make all versions of this drug a schedule 1 controlled substance.

NC	1 - Support	Testimony on Kratom and 7-Hydroxymitragynine (7-OH) My name is Cathy, and I am here to speak from lived experience about kratom and its derivative, 7-hydroxymitragynine, commonly known as 7-OH. Kratom and 7-OH are sold legally, yet they act on the brain in ways similar to opioids. They are marketed as natural and safe, but there are no consistent standards for potency, labeling, dosage, or disclosure of chemical content. This lack of regulation creates a dangerous gap between perception and reality. In my case, legality signaled safety. Without clear warnings or medical oversight, use escalated gradually and led to dependence, impaired judgment, and real harm. This did not happen because of recklessness or misuse. It happened because powerful psychoactive substances were made easily accessible without consumer protections. Many products now contain concentrated or enhanced levels of 7-OH, a compound significantly more potent than traditional kratom leaf. Consumers are rarely informed of this distinction or the risk of withdrawal and dependency that can follow. This is a public health issue, not a moral one. Regulation is necessary to ensure transparency, establish potency limits, require accurate labeling, and protect consumers. Treating kratom and 7-OH as harmless supplements ignores their pharmacological reality and leaves individuals and families exposed to preventable harm. Thank you for the opportunity to be heard.

Ohio	1 - Support	Hello, I would like to share my own experience with the drug kratom. And what it's like living with someone addicted to kratom. First off I'd like to state that I AM a recovering addict (just hit 7 years clean) who was addicted to everything from pills (oxy, Vicodin, Percocet, morphine) to cocaine, meth, and later ending up on heroin. I've been though a lot! I've seen a lot! So I like to think I know what I'm talking about. Although I've never personally tried kratom, I have a family member who's addicted to it now! This family member that's now addicted to kratom, NEVER TOUCHED AN ILLEGAL DRUG IN THEIR LIFE! Wont even smoke marijuana! But came across the kratom pills at our local vape shop in Greenville, Ohio. Not truly knowing what "kratom" was, she thought it was a harmless vitamin that could help with mood and energy. Once she took it, she became very talkative, started cleaning every nook and cranny of the house. (Typical opiate/stimulant effects) she now has to take kratom everyday because she's now addicted and will go through withdrawals if she don't take a kratom pill at least once a day!!! That's an opiate if I've ever seen one! Now shes spending all her money on the fruit flavored tablets!!! Now think, if this is being sold out of vape shops, gas stations and so on how many kids/teens are going to become addicted to kratom, not knowing it's an opiate in disguise ! Then possibly moving to harder drugs to combat sickness! My family member would have NEVER touched kratom, if they knew it was an opiate in disguise and they would end up sick after not having kratom! This is awful! This is NOT a miracle drug! THIS IS A LEGIT OPIATE! Oh also, my family member use to be over weight! She has tried for over 20 years to lose some weight even trying the new weight loss shots but nothing would help her lose weight! Until kratom! Shes lost almost 100 lbs since doing kratom! She started doing kratom last year. Summer of 2025. She looks sick now!!! All thanks to kratom!!!! Being sold as some kind of miracle drug!!!! It's been so hard on me. How can I tell someone they have a drug problem, when the pills they are doing are legal?! This is going to ruin so many more families!!! This stuff needs regulation or just banned. Sorry if this is so hard to follow, I just have so much to say about this stuff! Oh also my doctor gave me narcan for this family member because she said PEOPLE CAN EVEN OVERDOSE ON KRATOM!!!! So this is just crazy! This is going to hurt so many innocent kids! We must act NOW!!! To ban all kratom products!!!! They even come in fruit flavored tablets!!!! It's so easy for a teen to get a hold of kratom, it's scary! This is going to fuel new addictions all around the USA!!!!! But ok I just seen this website on the pharmaceutical. gov page so I thought I would submit my experience also for context to lawmaking. Kratom is a drug and should be labeled as a drug! I'm not aware of any warnings for addiction on the packaging of the pills. My family member had no idea The Pandora's box that they opened. Please save our future families and children from kratom! Please I'm begging for this drug to be reviewed and correctly labeled as a dangerous substance!!! My family member reminds me of how I acted when I was addicted to opiates! Very up and down moods. Talk talk and talks some more. Losing weight because the opiate is suppressing her appetite! I mean this is a mirror of an opiate! And from the research I've done there is so many different strains of kratom, depending on what color the plant is gives different highs. I mean come on!!! Let's move to ban this crap!!!
Ohio	1 - Support	Please ban Kratom from Ohio! It Kills and I have had family members and friends affected by this Evil substance.
OH	1 - Support	Please ban this drug..As soon as possible.
Ohio	2 - Oppose	I oppose placing mitragynine-related compounds into Schedule I and request a public hearing to determine whether this rule should be denied or withdrawn. This proposal would eliminate lawful access without meeting the requirements for Schedule I placement.

OH	2 - Oppose	For some of us, 7-OH is the best form of medication assisted treatment. Suboxone (Buprenorphine/Naloxone) didn't work for me. I was violently ill for weeks, puking my guts out all night, into the next day. Methadone gave me nearly identical results. This is very common, as many people have issues tolerating current OUD maintenance drugs currently on the market. I have been using 7-OH as OUD maintenance instead for almost a year now. I have had no such side effects. It has also scratched that itch for a buzz, which neither the Suboxone nor Methadone provided. My life is finally stable and under control. I'm no longer distancing from my family, because I'm constantly cycling in and out of withdrawals. I no longer wake up every morning in severe panic attacks, and having sweat through the sheets, due to the constant nightmares. If I do end up getting withdrawals from running low, they're very mild. It doesn't even come remotely close to the hell I went through when I stopped using Fent. To me, 7-OH is the best possible form of opioid maintenance, and the solution to a stable life, being a functioning addict. My monthly cost is the same as what a week of Suboxone costs, and I dont have to sit in line at the clinic and have dealers trying to sell me laced pills on the way out. I'll be devastated if this stuff ends up banned, as will millions of others in the same situation. The truth is, many people around the world are addicted to substances that are perfectly legal and socially accepted, however are far more problematic than 7-OH or leaf Kratom. If you look at data charts comparing harm to the public caused by drugs, you'll see Alcohol is number 1 in EVERY chart. This means Alcohol is responsible for more harm and deaths to the public than heroin, crack, or meth. Tobacco isn't far behind at number 6, causing more deaths and public harm than the majority of illicit drugs. If the focus of banning Kratom and its alkaloids is public safety, why are we not banning two of the most harmful substances Every single death linked to 7-OH or leaf Kratom contained at least 1 other CNS depressant substance were not caused from kratom alone. If you review the toxicology reports of these cases, you'll come to find ALL of them contain another CNS depressant substance. If you understand the pharmacokinetics of how the alkaloid interacts with your brain, you'd understand that, unlike street drugs (ex. heroin, fentanyl, and their analogues) which are full agonists at the μ-opioid receptor, 7-OH is only a PARTIAL agonist. That makes the alkaloid completely safe in terms of overdose risk because, partial agonists have a ceiling effect. Meaning each dose afterward will NOT increase respiratory depression nor add to the desired effect. Take Buprenorphine/Naloxone (Suboxone) for example, a highly researched μ-opioid receptor partial agonist used in the treatment of OUD (opioid use disorder) for decades with a great safety profile. I feel like 7-OH could be treated in the same way, with monitored programs and guidelines, and end up giving similar results in efficacy and safety as Suboxone.
Washington	2 - Oppose	I oppose placing mitragynine-related compounds into Schedule I and request a public hearing to determine whether this rule should be denied or withdrawn. This proposal would eliminate lawful access without meeting the requirements for Schedule I placement. By proceeding forward with this bill means thousands will be placed at risk for overdosing on illicit substances. Mitragynine and other alkaloids have been proven to be safer than any pharmaceutical alternatives.
Ohio	2 - Oppose	Please do not take this away from the people. I have been using Kratom and its compounds safely for years. It has helped every thing every day on a day-to-day basis. It is no more dangerous than alcohol or tobacco or marijuana. And yet that is all legal. It's senseless.
Texas	2 - Oppose	I oppose placing mitragynine-related compounds into Schedule I and request a public hearing to determine whether this rule should be denied or withdrawn. This proposal would eliminate lawful access without meeting the requirements for Schedule I placement.

IL	2 - Oppose	This rule is very flawed in that it fails to differentiate between natural kratom and synthetically created compounds like those in 7OH products. Numerous existing eight-factor analyzes of natural kratom have shown that it has low potential for abuse and is relatively safe, and is therefore ineligible for scheduling based on your criteria. Many comments in this rule's reasoning attempt to lump in natural kratom with concerning substances that are currently being considered for scheduling by federal agencies like the FDA, but, the FDA explicitly excluded natural kratom from their statements regarding scheduling 7OH, and their 2024 ascending dose study concluded that natural kratom is well tolerated at all levels. To lump natural kratom in with the conclusions generated by synthetically created compounds is bad science, and the two require separate consideration.
PA	2 - Oppose	My name is David Anderson, and I am writing to oppose placing mitragynine-related compounds into Schedule I and I request a public hearing to determine whether this rule should be denied or withdrawn. This proposal would eliminate lawful access without meeting the requirements for Schedule I placement. Eliminating lawful access to mitragynine-related compounds will be a public health detriment. Scores of people rely on mitragynine to help treat chronic pain, as getting prescription pain relievers has become increasingly difficult, nearly-impossible for most people, regardless of their level of pain, and furthermore some people find mitragynine-related compounds a more effective and sustainable alternative to traditional pain medications. Just as many, if not more, rely on mitragynine-related compounds as a way to detox manageably from dangerous street opioids, drugs that can and do kill every single day. Many people including myself use kratom's chief alkaloid mitragynine, along with other mitragynine-related compounds, as a cessation aid, and furthermore a deterrent to relapse. Safe, lawful access to mitragynine-related compounds is saving lives, has already saved countless lives. Making mitragynine-related compounds illegal will result in many deaths, it is an undeniable truth. People taking these compounds for pain will see their quality of life reduced. This is the case for my wife, who is diagnosed with psoriatic arthritis, an extremely painful disease causing erosion and degeneration of a person's joints. Despite this very serious, chronic, permanent diagnosis with no cure, her doctors refuse to prescribe narcotic pain medication for her. If ever there was a person who deserved powerful painkillers, it is my wife, who often struggles to walk due to her debilitating pain; yet her doctors will not prescribe her pain medication that would be effective. She relies on kratom's alkaloids and mitragynine-related compounds to have a tolerable existence, and fill the often wide gaps left by her prescriptions, and there are so many people in her situation. People like me who rely on kratom's alkaloids and mitragynine-related compounds to get off, and stay off of dangerous, deadly drugs or alcohol may return to using those drugs or alcohol as they see no alternative, and may not be able to maintain their abstinence without it. This is already occurring in states that have wrongly banned kratom and its alkaloids/related compounds. Please, please consider the public's safety and regulate, do not prohibit. I am asking you on behalf of myself, my family, and my community: we rely on access to kratom and mitragynine-related compounds. We rely on it to live our lives. We are not druggies, we are contributing members of society, we are Americans, and we have a right to put in our bodies what we see fit as responsible adults. Thank you for your time and consideration. -David Anderson.

OHIO	2 - Oppose	I oppose placing mitragynine-related compounds into Schedule I and request a public hearing to determine whether this rule should be denied or withdrawn. This proposal would eliminate lawful access without meeting the requirements for Schedule I placement. Responsible adults 21 and over adults should be able to have access to all forms mytragynine. Thank you very much.
OH	2 - Oppose	I oppose placing mitragynine-related compounds into Schedule I and request a public hearing to determine whether this rule should be denied or withdrawn. This proposal would eliminate lawful access without meeting the requirements for Schedule I
Oh	2 - Oppose	Kratom has been a godsend for me and countless others who used it to get off hard drugs. If you follow through with this, you will see a large increase in overdoses and fentayl. Why not ask your voters what they want, and use due process rather than just banning something without any scientific basis?
Ohio	2 - Oppose	I don't feel that it's right to bam Kratom. It has saved a lot of lives and saved a lot of people from addiction as well as chronic pain. It is a natural plant and there are 0 risks of overdose. If marijuana is legal, kratom should be as well as kratom isn't even mind altering like marijuana. This will hurt more people than it will help. We need to have access to this plant. I agree there should be regulations, bit banning kratom is 100% wrong to do.
Pennsylvania	2 - Oppose	I vehemently oppose a total kratom ban, as a responsible consumer whose life has been positively impacted by this plant. I support reasonable regulation INSTEAD of prohibition. PLEASE, do NOT schedule kratom as a controlled substance, and keep it legal for adults in the state of Ohio. Kratom saves lives, and I am proof of that.
Connecticut	2 - Oppose	Dear Ohio state officials- I vehemently oppose a total kratom ban, as a responsible consumer whose life has been positively impacted by this plant. I support reasonable regulation INSTEAD of prohibition. PLEASE, do NOT schedule kratom as a controlled substance, and keep it legal for adults in the state of Ohio. Kratom saves lives, and I am proof of that.
OH	2 - Oppose	I oppose placing mitragynine-related compounds into Schedule I and request a public hearing to determine whether this rule should be denied or withdrawn. This proposal would eliminate lawful access without meeting the requirements for Schedule I placement. Additionally, these attacks on our freedoms are concerning. What has happened to this country where so many blatant lies and misinformation are used to prohibit citizens from chosing how we manage our day to day. Tylenol is far more dangerous than Kratom and Kratom compounds. Alcohol is a killer and no one is trying to ban it. Please just leave this alone. Please submit today. This rule is broad and easy to miss.
Ohio	2 - Oppose	I respectfully urge policymakers to pursue reasonable regulation of natural kratom rather than an outright ban. Kratom has helped millions of adults manage pain, reduce reliance on far more dangerous substances, and improve quality of life—often when conventional options failed or caused harm. Banning kratom would not eliminate demand; it would push people toward unsafe alternatives or an unregulated black market, increasing risk rather than reducing it. Sensible regulation—such as age restrictions, product testing, labeling standards, and purity requirements—protects consumers while preserving access for those who depend on it responsibly. Please listen to patients, veterans, and working families whose lived experiences show that kratom, when regulated and used responsibly, can be a harm-reduction tool. Regulation saves lives; prohibition puts them at risk.

Ohio	2 - Oppose	I oppose the scheduling of mytraginine and related compounds I to schedule 1 I call for hearings to determine whether this rule should be denied or withdrawn this action would eliminate lawful access without meeting the requirements for scheduling
Michigan	2 - Oppose	I am a 70 year old woman and have used Kratom for my chronic pain for eleven years. I haven't had any problems with it at all. I believe it is a miracle from God. I only take it as needed. Compared with the Opioids I was taking and the Fentanyl patch I wore daily Kratom is much safer and not addictive. You could solve the problem by enacting the KCPA in your state. This guards against the dangerous products out there. Thank you for your time Betty L Ostrander
Ohio	2 - Oppose	My name is Madelyn Wallingford and I am submitting this public comment to express my serious concern regarding the proposed scheduling of kratom as a schedule I substance. My Story: I am a former opioid addict who spent five years struggling with severe dependence that began with legally prescribed pain medication (Tramadol) for a documented spinal deformity. This escalated into heroin and fentanyl use. I have twelve opioid overdoses recorded in my medical history and a mild brain injury as a result. I'm one of the lucky ones — I nearly died. Traditional treatment pathways, including inpatient rehabilitation and medication-assisted treatment, were not effective for me. My pain was never mitigated (physically or mentally). And I personally don't blame our recovery infrastructure; mental illness and chronic pain are challenging to treat. Kratom was the intervention that allowed me to stop using opioids quickly and permanently, thanks to a friend who introduced me with a cup of tea. I have now been clean for over 5 years. I can't stress enough how much my life has turned around. This calls me here today as an advocate to stand up for the life I'm able to have now. Since beginning kratom use, I have remained abstinent from drugs and alcohol, regained stable employment (an amazing job too), restored my relationships with my family, and, most importantly, became a healthy, present mother. With kratom, I'm able to deadlift a 35 lb toddler off the floor without serious pain, but I'm also not out of it and nodding off. It's the perfect balance for me. My quality of life has improved in ways that no other intervention achieved. My entire family can attest to this transformation. In addition, my doctors have no concerns about my health. I just completed treatment for hepatitis C (which I contracted during my addiction). My gastroenterologist noted that, after having liver tests and scans done, that my liver looks healthy and normal for an adult of my age. If there had to be negatives I could point out, I would say I still worry sometimes about my liver health due to some reports of kratom causing acute liver injury. My response is to buy from small-batch vendors, stay hydrated, and eat a wholesome diet. I genuinely want to be responsible with my health because I'm no longer suicidal — my body matters to me now that I'm clean and no longer suffering. My Message: I am deeply concerned that a blanket ban fails to distinguish between high-risk synthetic derivatives and the traditional botanical product that many individuals like myself rely on for harm reduction and relief. Prohibiting kratom does not eliminate demand for pain relief or relief from withdrawal—it simply removes a lower-risk alternative and drives vulnerable people back toward far more dangerous substances. This is a significant point: there are bigger fish in the sea right now that we should be concerned about. Kratom is so benign compared to other substances, even the ones that I've been addicted to and have experience with. Unlike hard opiates, I never lost a job or stole from my family to further a kratom habit. Kratom is such a mild and extraordinarily useful plant for people who are slipping through the cracks of pain relief, mental health care, and addiction treatment. At a time when Ohio continues to suffer devastating losses from opioid overdoses, it is difficult to

		understand how removing a harm-reduction option with a documented record of helping people transition away from opioids serves the public interest. I'm just not hearing of enough harm within the Kratom community, of which I am active, that warrants this kind of reaction. I have friends who are dropping like flies still from addictions to street drugs. If I could get them all on kratom instead, why not? How could kratom possibly do more harm than hard drugs? It can't. I know it can't. I respectfully urge the Board to reconsider a total ban and instead pursue evidence-based regulation that prioritizes consumer safety, quality control, age restrictions, and accurate labeling, rather than prohibition. In this case, regulation protects lives. Prohibition endangers them. Thank you for your time and for considering the real-world consequences of this decision on people like me and our families.
OH	2 - Oppose	I oppose placing mitragynine-related compounds into Schedule I and request a public hearing to determine whether this rule should be denied or withdrawn. This proposal would eliminate lawful access without meeting the requirements for Schedule I placement.
Ohio	2 - Oppose	Like many Ohioans, I use Kratom to safely and effectively relieve chronic pain from back issues. I have used it responsibly for many years without any negative effects while it has definitely provided pain relief. Without Kratom, I will be forced to increase my use of opioids and therefore increase my risk of overdose, unsafe driving, etc. I am asking that you allow the ELECTED legislature of this state take reasonable steps to ensure the safe and well-regulated use of this product, as proposed in SB299 and HB587 without imposing a total ban, which is radical and entirely undemocratic. Give our elected officials the opportunity to resolve this issue before you put so many of us in danger of increased opioid dependence. We, the people, deserve this. Thank you.
Minnesota	2 - Oppose	I oppose placing mitragynine-related compounds into Schedule I and request a public hearing to determine whether this rule should be denied or withdrawn. This proposal would eliminate lawful access without meeting the requirements for Schedule 1 placement.
Ohio	3 - Against Natural Ban	Please don't ban natural plain leaf kratom in Ohio . It's a safer alternative to traditional opiates that's alkoloids are partial agonist meaning it causes a lot lower potential for respiratory depression and less addiction potential. Than traditional opiates !Kratom is in the same botanical family as coffee. Please consider passing a kratom consumer protection act here instead of a full ban .
OH	3 - Against Natural Ban	Kratom is a natural substance that helps people deal with pain etc. The powder is safe. Synthetic drugs are not. Keep the powder legal.
Ohio	3 - Against Natural Ban	My Kratom Story I am one of the many everyday Americans whose life was stabilized—not destroyed—by natural kratom leaf. Before kratom, my options were limited and dangerous. Like so many others, I lived in a system where the only "approved" answers to pain, anxiety, or dependence were pharmaceuticals that came with serious risks: addiction, withdrawal, loss of function, and loss of dignity. When those failed—or caused harm—there was nowhere else to turn. Kratom changed that. I did not use extracts. I did not use synthetic products. I used natural, whole kratom leaf, the same way millions of people have for generations. For me, kratom was not about getting high. It was about functioning. It allowed me to get through the day, take care of my responsibilities, and live a stable, productive life without turning back to substances that were far more dangerous and far more addictive. What frustrates me most about the current conversation around kratom is how disconnected it is from reality. Natural kratom leaf is not comparable to concentrated extracts or isolated compounds. You cannot equate a plant leaf to highly processed products designed to spike potency. That distinction matters. Even state leaders have acknowledged this difference—saying extracts were the concern, not the leaf—yet now the leaf itself is being

		targeted. That makes no sense. Scheduling or banning natural kratom leaf does not protect people like me. It harms us. It removes a safer alternative and pushes people back toward substances with far higher overdose and dependency risks. History has shown us this over and over again: prohibition does not eliminate substance use—it only makes it more dangerous. People who struggle will always exist. If it's not kratom, it will be something else—often something far worse. Taking away a harm-reduction tool does not solve addiction. It accelerates it. I am not asking for kratom to be unregulated. I support responsible regulation, quality standards, age limits, labeling, and consumer protections like the Kratom Consumer Protection Act. What I oppose is the reckless decision to treat a natural leaf like a Schedule I drug—on par with substances that have no accepted use and extreme abuse potential. That comparison is not just wrong; it's insulting to the lived experiences of people like me. Kratom gave me stability when the system had nothing else to offer. It helped me stay away from substances that truly destroy lives. For that, I am grateful—and I am terrified of losing access to something that has kept me safe. Please do not erase our voices. Please do not punish responsible adults because of misinformation or fear. Regulate kratom—but do not ban the leaf that has helped so many of us survive.
Ohio	3 - Against Natural Ban	Dear Honorable Members, I am writing to respectfully express my opposition to any effort to prohibit or place natural kratom leaf under Schedule I, and to urge your support for the Kratom Consumer Protection Act (KCPA) as a reasonable and effective regulatory solution. Classifying kratom alongside Schedule I substances is disproportionate and unsupported by the lived experiences of the vast majority of responsible consumers. Such a designation would be comparable to scheduling widely used stimulants like caffeine as illicit drugs. Prohibition does not address the root causes of substance misuse and instead removes safer alternatives from individuals who rely on them for daily functioning. Kratom has provided meaningful relief and stability in my life. As a single, disabled woman, kratom tea has allowed me to manage chronic pain and maintain quality of life without reliance on prescription opioids that the doctors won't prescribe or illicit substances. I am deeply concerned that prohibition would unjustly punish the estimated 98% of consumers who use kratom responsibly in an attempt to address misuse by a small minority. The KCPA offers a balanced and evidence-based approach. It prioritizes consumer safety through age restrictions, product labeling, contamination standards, and third-party laboratory testing. States including New York, New Jersey, Rhode Island, and Pennsylvania have already adopted this framework, demonstrating that regulation—not prohibition—is both feasible and effective. I, along with many other advocates, do not support highly concentrated or synthetic kratom-derived products. My personal use is limited to third-party lab-tested natural kratom leaf, and I believe regulation should focus on preserving access to such products while restricting unsafe formulations. I respectfully urge you to support the Kratom Consumer Protection Act and to reject any proposal that would criminalize responsible kratom consumers. Thoughtful regulation protects public health without removing a vital harm-reduction tool from those who depend on it. Thank you for your time and consideration. Respectfully Dennis

OHIO	3 - Against Natural Ban	My name is Crystal, and thank you for taking the time to read this letter. I recently learned that there is discussion about scheduling natural whole kratom leaf, despite HHS DEA and Governor Mike DeWine clearly stating that the concern was with synthetic extracts, not the natural plant. I am writing to ask you—please do not ban natural kratom leaf. Natural kratom leaf is not the same as so-called "7-OH" tablets or synthetic products. The amount of 7-hydroxymitragynine produced from natural kratom leaf through human metabolism is extremely small—approximately 0.002%. Kratom leaf contains over 60 alkaloids that work together in balance, much like cannabis does and other natural remedy. Banning the whole plant would not only harm patients, but also halt legitimate research, despite more than 20 years of existing study on kratom. What is currently causing harm is a synthetic byproduct, not the plant itself. Unscrupulous chemists have learned how to synthesize 7-hydroxymitragynine into concentrated, dangerous forms that are now being sold over the counter while masquerading as kratom. This is no different than the distinction between willow bark and aspirin—aspirin is a synthesized derivative, not the original plant. No one would confuse the two, and the same distinction must be made here. I am a chronic pain patient and have been disabled since 2020, after my physician abruptly stopped my prescribed pain medication due to the DEA's overreach beginning in 2017. I suffered severe iatrogenic injuries from alternative, non-FDA-approved treatments—including gabapentin, steroids, and invasive procedures—which left me with type 2 diabetes, tachycardia, high blood pressure, metabolic dysfunction, and bone loss. I was 37 years old when I became fully disabled. Despite extensive imaging and testing that clearly show severe pathology, doctors are now too fearful to prescribe appropriate pain treatment. I passed every drug test, followed every rule, and still was labeled "drug-seeking." I was even told I would receive pain medication only if I agreed to an invasive implant procedure—something I refused on ethical grounds. As a result, I was cut off completely. I was abandoned by the medical system. No one helped me taper safely. I suffered multiple strokes during withdrawal and was forced to survive using medications identical to what had previously been prescribed—simply to stay alive. That taper lasted nearly two years. By April 2022, I was in such unbearable pain that I contemplated ending my life. It was at that point that someone I trusted mentioned natural kratom leaf—not extracts, not synthetics, but plain powdered leaf prepared as tea. I was terrified to try it at first because of the stigma around it. I researched extensively, spoke with others, and intentionally avoided extracts and synthetic products. When I finally tried a small amount of natural kratom leaf, something extraordinary happened: for the first time in years, I stood up and walked without agony. I did not feel high. I did not feel impaired. I felt functional—like myself again. Kratom does not eliminate pain the way opioids do, but it restores dignity and quality of life. It quiets the desperation that untreated pain creates. It gave me back the ability to live. I later tried a synthetic "7-OH" tablet out of curiosity and had a terrifying reaction—panic, fear, and distress. The difference between natural kratom leaf and synthetic 7-OH is night and day. They are not the same, and they should never be treated as such. Alcohol, tobacco, and caffeine—substances far more dangerous—are legally sold everywhere. Alcohol alone is neurotoxic and socially devastating, yet accepted with zero medical use. Meanwhile, kratom leaf continues to save lives quietly, especially for people abandoned by the healthcare system. According to leading kratom toxicologist Dr. Marilyn Huestis, nearly all kratom-related deaths involve polysubstance use, including fentanyl, cocaine, or methamphetamine. Kratom is not the cause—it is present alongside far more lethal substances. Kratom does not create intoxication. It does not function like opioids. While it interacts with certain receptors, that does not make it an

		opioid—just as caffeine affecting adenosine receptors does not make it a narcotic. Please do not punish patients by banning a plant that is helping them survive. Regulate Kratom leaf do not ban. Remove dangerous extracts. Protect natural kratom leaf. Without it, I—and many others like me—have nothing left. You will have far more suicide and overdose deaths on your hands if Kratom leaf is banned Respectfully, Crystal

OHIO	3 - Against Natural Ban	To the Honorable Members of the Ohio Legislature, I am writing to share my personal experience and to respectfully urge you to keep pure kratom leaf legal in the State of Ohio. For most of my life, I have lived with severe headaches and chronic migraines that eventually became a daily, overwhelming burden. The pain was relentless. I sought help from countless doctors and specialists, undergoing CT scans, MRIs, chiropractic treatments, acupuncture, and trying numerous prescription medications. Despite spending thousands of dollars and years searching for answers, I was left without relief. The medications prescribed to me often made things worse. I experienced memory loss, confusion, and difficulty functioning at work and in everyday life. I felt trapped—forced to choose between unbearable pain or medications that robbed me of my ability to think clearly and live normally. At my lowest points, the constant pain made me question whether life could ever feel manageable again. Within the past year, I discovered kratom in its natural form. I began brewing the crushed leaf as a tea, cautiously and out of desperation. For the first time in years, I experienced real improvement. My migraine episodes were reduced by nearly half, and the intensity of my pain decreased significantly. I was finally able to function without the debilitating side effects caused by prescription drugs. Kratom is not a miracle cure, but it has given me something I had nearly lost—relief, stability, and hope. It has helped me more than any prescription medication ever did, and it allows me to manage my condition without sacrificing my mental clarity or ability to work. If kratom were to become illegal in Ohio, I truly do not know where I would turn next. I respectfully ask you to consider the many Ohio residents like myself who rely on pure, natural kratom to manage chronic pain and maintain a basic quality of life. Please do not take away a natural option that has helped so many when so few alternatives remain. Thank you for listening to my story and for your consideration. Sincerely, Frank Zell Mayfield, Ohio
Ohio	3 - Against Natural Ban	I am writing as an advocate for reguation of natural kratom rather than the overeach of prohibition. Kratom has saved hundreds of thousands of lives. It is far safer than alcohol or cigarettes, and in its natural form, it is not dangerous. I am against alcohol but would never think od prohibiting it from anyone over 21. The science you used to make your decision was flawed. Rhode Island just overturned their ban in July 2025. Please consider regulation before you make a horrible decision that will harm tens of thousands of responsible adults.
OH	3 - Against Natural Ban	I wanted to speak out against the ban on NATURAL kratom products to state that banning those products would be a disservice to Ohioans. I am 51 years old, a professional in manufacturing and safely using natural Kratom for many years. It helps my restless leg syndrome and prevented me from having to take additional pharmaceuticals. Kratom is effective, safe and a less expensive alternative to pharmaceuticals. I completely agree with the decision to ba synthetic and concentrated forms of kratom. Those products are much stronger and the makeup of the products are in question. Stating that Kratom is schedule 1 is completely inaccurate. The product helps me and should be available. I support stronger oversight of the products and would have no problem if the state wanted to create licenses for sale and quality standards. Please do not create a knee jerk reaction and eliminate a product that so many people find helpful.
Ohio	3 - Against Natural Ban	I think the banning of natural kratom is a huge mistake and will cause the deaths of many and many people by unfairly pushing them people who don’t want to use pain medication to back on pain pills or street drugs. It’s a harm reduction tool

Ohio	3 - Against Natural Ban	Hello, My name is Erin. I am a resident of Fairborn, Ohio. I am writing this today to testify about how 100% mitragynine leaf has helped me in my recovery from alcohol abuse and benzopine addiction. I suffer from ptsd and severe depression. I started going to a counsler and psychologist when I was about 19 over trama from a violent middle school incident. My mother did not have a way to get me help when it initially happened. I was left to deal with my trauma on my own. I was in bad shape my first visit to a counsler. That same visit she chased down the prescribing doctor to get me prescriptions for Paxil and Xanax. I filled them the same night after being urged by the counsler. I took them both as the dosage said. For the first time in a long time I felt relief. I felt relaxed. I felt great like I was not a broken human anymore. I quickly got addicted. I didn't want that good feeling to end. My husband caught on quick. He called the doctor and told them I would take all my medication in a few days. So I had to find a new doctor. I did quickly. When I would run out of benzos I would replace them with alcohol. The cycle repeated for years. In 2011 I was sick of living like that. I looked for help and entered the cadas program. When thay ended I went back to my ways. Did the cadas program a 2nd time. I went back to drugs and alcohol everytime. In 2019 I was sick and tired of feeling sick and tired. I looked online for how other people quit. I saw a forum about 100% mitragynine. I read how other people like me have used 100% mitragynine leaf to stop their addictions. I found some online and ordered. I have been free from benzos and alcohol for 6 years now. I have had a good job for over 5. My relationship with my kids and husband have never been better. I do not want my kids to grow up with trama from my addictions. 100% mitragynine helps me stay clean from my drugs of choice. It is comparable to a cup of coffee. It has helped many ohioans in their early recovery abstain from using. I fear for my sobriety from my drugs of choice if 100% mitragynine leaf gets criminalized. Many ohioans are also at risk if 100% mitragynine leaf gets banned. It is a natural plant in its dried plant form. The human cost will be many relapsing and maybe even many over dose deaths because people will go back to what they know made them feel good. 100% mitragynine has saved my life. I am so grateful for finding this plant and my family supports my use of the plant. Please take in consideration the human fallout and please don't ban 100% mitragynine leaf. Thank you for hearing my story. Erin Fairborn, Ohio
ohio	3 - Against Natural Ban	I have used kratom powder for years without any problems. Please keep it legal.
OH	3 - Against Natural Ban	I am writing to ask that you keep powder Kratom legal. I and other family member have used it for years with no issues. If you want to ban 7-oh and extracts I am all for that. But please do some research and I think you will see the benefits of the powder. Thank you
Ohio	3 - Against Natural Ban	I respectfully urge the Board to keep natural kratom legal. For many adults, natural kratom leaf has helped reduce reliance on far more dangerous pharmaceutical or illicit substances. I fully support banning synthetic or adulterated products, but natural kratom should not be treated the same. Prohibition would push people toward unregulated markets or back to higher-risk medications. Reasonable regulation—such as age limits, product testing, and labeling—protects public health far better than a ban. Please consider the many responsible adults who rely on natural kratom as a safer alternative. Thank you for your consideration.
Ohio	3 - Against Natural Ban	I am against some of the proposed rule. I think you did a great job on distinguishing between 7oh (and their components) and natural/only mitragynine products. 7OH IS NOT KRATOM. I was waiting for 7oh to get banned due to how addictive it is. I have never touched 7oh but I do know several people that have and I watched the change in them. However, I do not agree that natural kratom or only products

		containing mitragynine should be included. I have been using natural kratom and only mitragynine products on and off for 11 years. I am a responsible consumer and I don't take a lot at once. I believe that natural kratom and mitragynine products only should be REGULATED, not banned. Kratom has helped give my my life back. I was a heroin addict stuck in the cycle. It finally broke when I started using kratom. There was a period where I did go back out but when I started to consistently use kratom, I stopped using heroin. I will have 7 years off heroin this year. I was able to go back to college and get my degree. I have a wonderful job and I am able to live my life and be a positive person for society. I am urging you to adopt the KCPA (kratom consumer protection act). There needs to be regulation for this plant.
Ohio	3 - Against Natural Ban	Natural, plain leaf kratom has saved me from a debilitating heroin addiction for over 10 years. The issue is not the plant, it is the people modifying it and making synthetic versions. Please keep natural kratom legal because I don't know what I'd do without it. Just regulate it to be in its natural form.
Ohio	3 - Against Natural Ban	I'm begging for you not to take natural Kratom away from us. I have been dealing with chronic pain, addiction, depression, and anxiety for many years. I discovered Kratom going on 7 years ago. I was in and out of mental hospitals and tried suicide twice. I'm now living my best life ever. Kratom has helped me tremendously with my pain, anxiety, alcoholism, and depression. I've been very content and happy with my life. If you take this away everything I suffered with may go back to the way it was and that scares me to death. This is very important for many people. Kratom is a wonderful alternative from taking opioids. Thank you for your time
Florida	3 - Against Natural Ban	I'm a 71 year old great grandmother who has been consuming pure leaf kratom for 9 years to help manage pain from 5 medical conditions. If plain leaf kratom is made illegal in Ohio, I won't be able to visit my friends and family anymore. That's very upsetting because I'm getting old and I so enjoy my trips there. Please support the Kratom Consumer Protection Act instead. It's the wiser thing to do.
Ohio	3 - Against Natural Ban	I am writing to strongly oppose the proposed ban on kratom in the state of Ohio. Kratom has been a life-changing natural tool for me. It helps me manage anxiety and depression, allows me to stay motivated, and gives me the ability to function in daily life without relying on pharmaceuticals that often come with serious side effects, dependency, or long-term health risks. For many of us, kratom is not a recreational substance — it is a form of self-care and stability. Banning natural kratom would not protect the public. It would harm thousands of Ohio residents who responsibly use the plant to avoid opioids, alcohol, and prescription medications. Kratom saves lives. Removing legal access pushes people back toward far more dangerous substances or into unregulated black markets, which creates exactly the kind of risk lawmakers say they want to prevent. There is a critical difference between natural kratom leaf and synthetic or chemically altered products. Many of the safety concerns being cited involve lab-created extracts or adulterated products, not traditional kratom leaf. These should not be lumped together. Punishing responsible consumers for the actions of bad actors or dangerous synthetics is neither fair nor effective policy. Please listen to the voices of the people who actually use kratom responsibly. We deserve access to safe, natural alternatives that help us thrive. Thank you for your time and consideration.

Mississippi	3 - Against Natural Ban	Pure leaf Kratom has been a god send to me and my husband. It helped my husband to continue to work while needing double knee replacement as a plumber for the last 11 years. Without Kratom he wouldn't be able to walk much less work. Kratom helped me overcome an addiction to pain pills. It's helped me now with my depression and my chronic pain. I have Trigeminal Neuralgia which is some of the worst pain known . I don't think I would be able to survive without the help of Kratom with this pain. It helps me work and tend to my family without being intoxicated. There are many testimonies just like mine about this plant . Banning this plant would hurt folks just like me and my husband . I believe Kratom is a tool that helps so many.
Illinois	3 - Against Natural Ban	I am a 40-year-old adult who has consumed whole-leaf kratom responsibly for more than 15 years. It has helped me manage chronic insomnia, joint and muscle discomfort from years of dance and Taekwondo, and focus challenges related to my ADHD. Like many adults, I have turned to natural, lower-risk options to manage ongoing health issues, and kratom has been part of that approach. I urge the Board not to ban whole-leaf kratom. Prohibiting the natural leaf would not meaningfully improve public safety and would instead criminalize responsible adults who have consumed a traditional, minimally processed plant without incident. Whole kratom leaf is not concentrated or semi-synthetic, such as 7-hydroxymitragynine. I respectfully ask the Board to consider the real-world consequences of a leaf ban and the importance of distinguishing between whole-plant products and more potent or altered substances. Thank you for your time and consideration. Respectfully, Michael Fasano
Ohio	3 - Against Natural Ban	I am writing to oppose any permanent scheduling or prohibition of natural kratom leaf in Ohio. I am a responsible adult who has used natural kratom tea for years without incident. Like many Ohioans, I use the natural plant in its traditional form, not synthetic or high potency derivatives. I agree that synthetic kratom products and adulterated extracts pose legitimate concerns, and I support their restriction. However, banning or scheduling natural kratom leaf would be an overreach that ignores real-world use patterns in Ohio. Natural kratom is widely used by working adults, older residents, and individuals seeking alternatives to opioids. Treating the raw plant the same as synthetic concentrates will not reduce harm and it will push consumers toward unregulated markets and eliminate product transparency. Ohio has one of the largest kratom markets in the country, supporting hundreds of small businesses and thousands of jobs. A permanent ban would cause immediate economic harm while failing to address the specific products associated with adverse events. I respectfully urge the board to reject prohibition and instead support a regulatory framework modeled after the Kratom Consumer Protection Act (KCPA), a brilliant piece of legislation which has been adopted successfully by both Republican and Democratic led states. Regulation, (including age limits, labeling requirements, laboratory testing, and bans on synthetic or spiked products) is a more effective and responsible approach than criminalization. Please do not make Ohio the first state in a decade to enact a new statewide ban on natural kratom. Regulation protects consumers. Prohibition does not. Thanks!
Oh	3 - Against Natural Ban	No one has a problem with you formalizing this rule but leave natural kratom alone like you said in the actual emergency scheduling of the kratom related products. Stop trying to ban mitragynine and just formalize this rule allowing for kratom in its vegetative state.

NH	3 - Against Natural Ban	My Kratom journey 🌿 🤍 I have been using Kratom for the last 8yrs after being on pain medication for 30yrs anxiety and depression meds for 10. I have degenerative and cervical disc disease, spinal stenosis, herniated and bulging disc, bone spurs on the spine, which has given me scoliosis as an adult , fibromyalgia, trigeminal neuralgia aka suicide disease, basically I live with 10/20 of the most painful conditions to live with and many more other chronic pain conditions. I lost my mother to the pain clinic and big pharmas drugs in April 2013...She didn't abuse them, she took less than what she was prescribed, but tramadol and morphine took her life. After losing my parents 7 months apart and seen what the struggled with medication wise per Dr's orders and how it destroyed them...I vowed to live a holistic as possible life style. I just recently came off my blood pressure medication as well. In 8 yrs I haven't had to consume over 50,000 pills. I get yearly blood work, as well as yearly ultra sounds on my organs. I have improved so much and all under my Dr's care with tapering off off my medications.... my blood work and organs scans have improved every year as well as my organs reversing the damage that the medication has done for the most part. Without kratom i wouldn't be able to enjoy the simple things in life such as taking a simple walk outside or just the ability to get out of bed daily. I don't believe I would still be alive today if it wasnt for kratom. I have family in Ohio and I frequently visit. Please dont take away my only relief and ability to visit your beautiful state and my family.
NC	3 - Against Natural Ban	My name is Jenni, and I’m sharing my story to shed light on the life-saving power of **unadulterated whole leaf Kratom**. For 15 years, I was dependent on FDA-approved prescription opioids to manage chronic pain from **Multiple Sclerosis and Crohn’s disease**. Eventually, I made the painful decision to take myself off these medications. The withdrawal was brutal, but I succeeded and got clean. A year later, I faced **Post-Acute Withdrawal Syndrome (PAWS)** which causes waves of pain, anxiety, depression, insomnia, and fatigue that made daily life unbearable. Determined not to return to pharmaceuticals, I searched for safe, holistic ways to heal and manage my pain. That search led me to whole leaf Kratom, the pure, natural, and unprocessed. I’ve used Kratom for over a decade, and it truly **saved my life**. It eased the residual pain and emotional distress from withdrawal while helping me manage the ongoing symptoms of MS and Crohn’s. For the first time in years, I could function without the fog or dependency of opioids. I was present with my family again, felt joy, and began to reclaim my life. One of the most surprising benefits was how much Kratom helped my **Crohn’s disease**. While not a cure, it drastically reduced my gastrointestinal distress, cramps, and unpredictable digestion. I regained the ability to eat, nourish myself, and live without constant fear of flare-ups. It also stabilized my mood, easing the anxiety and depression that had long shadowed me. I’m now deeply concerned about **synthetic or adulterated Kratom products**, especially those enhanced with **7-hydroxymitragynine (7-OH)**. Research from Dr. Christopher McCurdy of the University of Florida confirms that 7-OH is only produced in trace amounts naturally and becomes active after the body metabolizes Kratom. Manufacturers isolating or concentrating this compound are creating dangerous, addictive products that misrepresent the plant’s natural form. I urge lawmakers and the public to distinguish **whole leaf Kratom** from these lab-altered versions. In its natural state, Kratom helped me stay off opioids for over a decade and regain my quality of life. Please don’t let deceptive manufacturers destroy the reputation of a plant that has given people like me our lives back.

Ohio	3 - Against Natural Ban	PROHIBITION DOESN'T WORK it just makes the black market bigger and more dangerous for a lot more people. PLEASE don't ban pure unadulterated Kratom leaf and instead regulate. I suffer with excruciating severe chronic pain from Degenerate disc disease & facet joint arthropathy from my neck down through my lumbar, sciatica problems ,slipped L-4 L-5 disc ,Barrett's esophagus, kidney disease ,anxiety ,depression ,hypothyroidism ,osteoporosis and rheumatoid arthritis all through my body. I've had so many surgeries (including C5-7 neck fusion) and procedures that I feel like a living Raggedy Ann -all stitched together. My alarm clock is extreme pain and stiffness - I can barely get out of bed and walk - I drink my Kratom leaf tea & about a half hour later my pain levels drop to manageable - I can get up walk better and simply take care of my husband and myself in everyday life. I love the fact that with Kratom leaf I have clarity of thought and I can concentrate better- I have NO BUZZ only pure pain relief and that is definitely not something I could say when I was taking my Dr prescribed medications. I'm GRATEFUL for Kratom leaf tea every single day. If Kratom leaf gets banned it's going to not only negatively effect me and my family but my community as well. Please regulate Kratom leaf and help us Ohio Kratom consumers stay safe instead of banning. Thank you for your time

Organization Comments - Mitragynine-Related Compounds

Organization or Business	Commenter State	Comment Code	Comment	Letter Submitted?
Ohio Alliance of Recovery Providers	Ohio	1 - Support	On behalf of the Ohio Alliance of Recovery Providers (OARP), a statewide organization of addiction treatment providers, certified by the Ohio Department of Behavioral Health, we write in strong support of the proposed changes to Ohio Administrative Code rule 4729:9-1-01.1 and what would be the newly created 4729:9-1-01.2 rule to classify all forms of kratom as Schedule I drugs. As you are well aware, drugs, substances, and chemicals that fall under the Schedule I category have no currently accepted medical use and a high potential for abuse. We wholeheartedly agree with that assessment, and we believe it will be in the best interest of all Ohioans. We are particularly concerned about the accessibility of kratom to vulnerable populations, including individuals in recovery and young people, who may perceive it as a benign or “natural” product. Scheduling kratom as a Schedule I substance would reduce availability and send an important public health message about the risks it poses.	Yes
Ohio Prosecuting Attorneys Association	Ohio	1 - Support	Kratom products are unregulated, psychoactive products that are often marketed deceptively, even sometimes sold in forms that are attractive to children. Kratom is sold in gas stations, convenience stores, vape shops, and on the internet. While these unregulated products are dangerous for any consumer, they create dangers that are particularly acute for Ohio children. Children may be more susceptible to this style of marketing and at greater risk of eventual harm from use of the product. Children who cannot purchase these products on their own may be more likely to mistake them for candy or some other harmless snack and to become the victim of accidental ingestion. And as with other controlled substances children may be more likely to become addicted or to suffer other lifelong consequences from the use of these products. Banning these products will reduce early exposure to these risks and early exposure to addictive substances that could have lifelong consequences for youth. Finally, the wide availability of these products at places like gas stations, convenience stores, and vape shops combined with the fact that there is no prohibition on having the products open and accessible in vehicles may lead to people to believe that it is safe to consume kratom products and	Yes

			drive. Kratom can cause sedation and impaired coordination. This raises the risks of impaired driving on our highways. It also presents unique problems for law enforcement interdiction efforts since kratom is not now typically tested for in drug screens or as part of a roadside test.	
NAMI Ohio	OH	1 - Support	Nationally it is estimated that 10.9 million users of drugs other than alcohol reported they were using these substances “a little more or much more” than they did before the COVID-19 pandemic began. At a time when Ohio families are grappling with unprecedented addiction compounded by the stress of a global pandemic, we consider the commercialization of an addictive drug with such scientifically proven public health harms to be unacceptable.NAMI Ohio wants to express the negative risks to a person’s mental and physical health that have been documented and include nausea, seizures, hallucinations, and other psychotic symptoms. Some users have reported becoming addicted to Kratom. At this time, there are no specific medical treatments or behavioral therapies for kratom addiction. Scientists need more research to determine effective treatment options.	Yes
Cuyahoga County ADAMHS Board	OH	1 - Support	Synthetic kratom derivatives—including 7-hydroxymitragynine and Mitragynine pseudoindoxyl—pose significant and well-documented risks to public health and safety. These substances are highly potent, pharmacologically similar to opioids, and have been associated with dependency, overdose, psychiatric destabilization, and dangerous interactions with other substances. They are frequently marketed in misleading ways that minimize risk and obscure potency. From a behavioral health system perspective, frontline treatment providers, emergency departments, and crisis services are increasingly managing the consequences of these compounds. The lack of permanent regulatory controls has contributed to consumer confusion and inconsistent enforcement, increasing preventable harm.	Yes

Community Overdose Action Team	Ohio	1 - Support	The addictive potential of mitraginine-related compounds can lead to physiologic dependence, creating a cycle in which individuals substitute one dependence for another while believing they have chosen a safer option. This dynamic contributes to delayed diagnosis, delayed initiation of MOUD, fragmented care, and heightened vulnerability to relapse and overdose. In effect, mitraginine-related compounds undermine our community's efforts to reduce opioid-related harm. According to COAT's data, mitraginine and 7-OH have been identified in our local toxicology findings, including in autopsy reports, both as a single substance and in combination with other substances.3 While polysubstance exposure is common in overdose deaths, the detection of mitraginine and 7-OH underscore that these are not benign OTC products and that their presence can be associated with serious outcomes—as a single agent and particularly when combined with other sedating or psychoactive agents.	Yes
Prevention Action Alliance	OH	1 - Support	Prevention Action Alliance supports the Board's proposed rule addressing mitragynine-related compounds. These substances—designed to be structurally or pharmacologically similar to mitragynine—present serious and emerging public health concerns. Evidence indicates that such compounds are often developed or modified to evade regulation while retaining psychoactive effects, increasing the risk of misuse, dependence, and adverse health outcomes.	Yes
The Ohio Council of Behavioral Health & Family Services Providers	Ohio	1 - Support	In recent years, the public health risks posed by Kratom and Mitragynine-related compounds have become increasingly apparent. Similar to opiate substances, Ohio Council member organizations have reported a growing number of individuals presenting for detoxification or treatment related to dependence on Kratom and Kratom-related products. These clinical observations align with the current research and concerns outlined by the Ohio Board of Pharmacy regarding the substances' potential for misuse and the development of dependence. Beyond the growing anecdotal evidence of treatment providers, the known effects of Kratom and its active compounds raise serious clinical concerns that support reclassification. These substances interact with the same brain systems as opioid drugs, and can produce effects such as pain relief, sedation, and feelings of euphoria. With repeated or high-dose use, individuals may develop tolerance and dependence, followed by withdrawal symptoms when use is reduced or discontinued: reflecting patterns of harm consistent with other opioid-like substances.	Yes

Northeast Ohio Opioid Consortium	Ohio	1 - Support	On behalf of the Northeast Ohio Opioid Consortium, we write to express our support for the classification of kratom and any synthetic kratom compounds, including mitragynine-related substances, as Schedule I controlled substances under Ohio law. We also urge the Board to support and enable rigorous scientific research and clinical trials to determine whether kratom or its derivatives may have safe and effective medical uses under controlled conditions.	Yes
Cleveland Clinic	Ohio	1 - Support	We appreciate the Board's efforts to address the growing concerns associated with mitragynine-related compounds and strongly support proposed Rule 4729:9-1-01.1 which classifies these substances as Schedule I controlled substances. The inclusion of compounds such as 7-hydroxymitragynine (7-OH), mitragynine pseudoindoxyl (MP), dihydro-7-hydroxy mitragynine (MGM-15), and 7-acetoxymitragynine is both prudent and necessary to safeguard public health.	Yes
Pinney Associates / American Kratom Association		1 - Support	Natural kratom leaf products and extracts, including natural mitragynine products, do not warrant CSA scheduling. 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.	Yes
Ohio Psychiatric Physicians Association	Ohio	1 – Support	OPPA supports the Board's determination that these substances meet the statutory criteria for Schedule I classification, including high potential for abuse, lack of accepted medical use, and absence of demonstrated safety under medical supervision. We also recognize and appreciate the Board's careful evaluation of the relevant statutory factors and its consideration of public health and safety impacts in developing these rules.	Yes

Consumer Action for a Strong Economy	VA	2 - Oppose	This proposed classification would ban the use of kratom products in Ohio (exempting kratom in its natural leaf form), criminalizing those adults who use regulated kratom derivatives. When examined thoroughly, taking into consideration the diverse group of individuals who have come to depend on these formularies, this policy is empty window dressing at best, and a cruel denial of freedom from physical and emotional pain at worst. By way of analogy, banning kratom-derived products is akin to banning chewing gum in response to an explosion in the use of chewing tobacco. Kratom-derived products are used by many thousands of Ohio residents to help alleviate chronic pain, stress, and depression. Critically, their use has shown to be enormously beneficial to many seeking to curb their addiction to deadly opioids, which have destroyed the lives of countless Ohioans. A sweeping ban on products that have verifiable benefits for recovering addicts is a mistake that would needlessly increase suffering for more people than can be counted.Many adults report they currently use kratom products to cope with pain or opioid withdrawal. Compare that with the thousands of deaths involving heroin or opioids. If these products are suddenly made illegal, some will turn back to the illicit market where fentanyl is widespread and the odds of overdose very high.	Yes
HAVEN Access Inc.	Tennessee	2 - Oppose	Schedule I placement requires findings that a substance has a high potential for abuse, no accepted medical utility, and a lack of accepted safety even under medical supervision. The proposed rules do not demonstrate these findings using real-world, population-level evidence. Instead, they rely on speculative, indirect, or incomplete reasoning while disregarding the lived experiences of individuals who utilize kratom-derived products and the consequences of abruptly eliminating lawful access. The mitragynine-related compounds proposal functions as a broad catch-all that effectively sweeps naturally occurring alkaloids and future derivatives into Schedule I without individualized analysis. Combined with the separate mitragynine proposal, this approach raises serious concerns regarding overbreadth, duplication, and the absence of a coherent, consolidated review. Eliminating lawful access through permanent Schedule I placement would cause immediate and foreseeable harm, including driving individuals toward illicit markets or less safe alternatives, while failing to meet the statutory standards required for such classification.	Yes

First choice kratom	Ohio	3 - Against Natural Ban	Hello we own first choice kratom we have 3 locations one in Columbus dayton and Cincinnati. We have 8 employees who would lose there jobs and us 3 owners its our career and we all have families. There is no reason why natural kratom should be banned. There is nothing natural kratom can do to you you cant overdose. If you take to much your stomach cant handle it you will throw up. We have so many customers who it changed there life's they can get up and move and work. Then we have people who was on drugs no jobs no house or car. Now they have it all because kratom changed there life. Then you have peo like me who workout i take it before and after the gym it helps my body so much. So the only thing that should he banned is the fake kratom called 70h and all the kratom extracts. Those are made by humans and we dont sale any of that . Natural kratom has saved so many people so please actually look into it or actually try it and you will see it wont do anything to hurt you	No
Global Kratom Coalition		4 - Requested Clarification	To strengthen the rule and ensure it achieves its intended purpose, GKC respectfully requests that the Board: • define synthetic kratom-related compounds as alkaloids that are chemically synthesized or isolated and concentrated beyond levels occurring naturally in kratom leaf • explicitly exclude kratom in its natural vegetation form, i.e., natural kratom leaf products with naturally occurring alkaloid levels including trace amounts of otherwise banned alkaloids. • align the rule text with the FDA Commissioner's statements concerning natural kratom leaf in his July 29, 2025 FDA/HHS press conference and the Governor's stated intent to except kratom in its vegetation form, i.e., kratom leaf. • improve definitional precision to reduce enforcement ambiguity	Yes
Botanic Tonics, LLC ("BT"), manufacturer of a whole kratom leaf (whole kratom leaf infused in water) dietary *supplement, feel free* CLASSIC® ("Feel Free")		4 – Requested Clarification	As explained and corroborated in the GKC comments, the applicable science and law favors the scheduling of concentrated kratom alkaloid isolates ("synthetics"), but not the scheduling of natural kratom leaf ("kratom leaf'). The former (the synthetics) are indistinguishable from opioids in their addictive potential and risk of injury. The latter (kratom leaf) have been proven in clinical trials not to present any significant or unreasonable risk of illness or injury, including the risk of severe addiction. BT has a direct and substantial interest in each of these proceedings. BT currently sells Feel Free in Ohio through distributors. Its annual revenues from the sale of Feel Free exceed $5 million.	Yes

Cleveland Clinic

January 22, 2026

State of Ohio Board of Pharmacy
77 South High Street, 17th Floor
Columbus, OH 43215

Re: Rules 4729:9-1-01.1 and 4729:9-1-01.2

Submitted Via: RuleComments@pharmacy.ohio.gov

Cleveland Clinic is a not-for-profit, integrated healthcare system dedicated to patient-centered care, teaching, and research. Cleveland Clinic Health System operates 23 hospitals with more than 6,700 staffed beds, including a main campus near downtown Cleveland and 15 Northeast Ohio regional hospitals, as well as 280 outpatient locations. Cleveland Clinic employs over 5,700 physicians and researchers, and 16,800 nurses. Last year, our system cared for 3.5 million patients, including 14.1 million outpatient visits and 333,000 hospital admissions and observations. Below are our comments on the above-captioned rule.

Our prior correspondence to the Board has consistently highlighted the significant risks posed by Kratom and its related compounds. As we have noted in earlier letters, these substances have been associated with serious adverse health effects, including addiction, withdrawal symptoms, and, in some cases, life-threatening toxicity. The unpredictable potency and lack of regulation further exacerbate these risks, posing particular dangers to vulnerable populations, including adolescents and individuals with substance use disorders.

We appreciate the Board's efforts to address the growing concerns associated with mitragynine-related compounds and strongly support proposed Rule 4729:9-1-01.1 which classifies these substances as Schedule I controlled substances. The inclusion of compounds such as 7-hydroxymitragynine (7-OH), mitragynine pseudoindoxyl (MP), dihydro-7-hydroxy mitragynine (MGM-15), and 7-acetoxymitragynine is both prudent and necessary to safeguard public health.

Additionally, we fully support the Board's proposed Rule 4729:9-1-01.2, which bans the sale of mitragynine, the primary psychoactive alkaloid found in the Mitragyna speciosa plant, commonly known as kratom. However, we are concerned that criminalizing the personal possession of these products will create hesitancy for people to seek care. Therefore, we urge the Board to develop language that discourages the possession of these products by eliminating the sale and marketing of such products in legitimate businesses rather than turning possessors into criminals.

By enacting this rule, the Board is taking an important step to protect Ohioans from the significant health risks associated with kratom use. The prohibition of mitragynine aligns with our mission to promote patient safety and uphold the highest standards of care in our community. By banning the sale of these substances, the Board is taking proactive steps to prevent their misuse and potential harm within our communities.

We support the Board's comprehensive approach to regulating mitragynine-related compounds, as it aligns with our commitment to patient safety and public health. The Cleveland Clinic has long advocated for evidence-based policies to address emerging threats posed by novel psychoactive substances. The proposed rule reflects a thoughtful and measured response, and we commend the Board for prioritizing the well-being of Ohioans. We urge the Board to move forward with these much-needed controls and reiterate our willingness to provide additional information or support as needed.

Thank you for conducting a thoughtful process that allows us to provide input on such important issues and for your consideration of our feedback. Should you need any further information, please contact me.

Sincerely,

David Streem, MD
Medical Director
Alcohol and Drug Recovery Center

Public Comment for OAC 4729:9-1-01.1

(Synthetic Kratom Compounds)

Comment:

On behalf of our Cuyahoga County ADAMHS Board, we submit this comment in **support of the Ohio Board of Pharmacy's proposed rule** classifying synthetic Mitragynine-related compounds as Schedule I controlled substances.

Synthetic kratom derivatives—including 7-hydroxymitragynine and Mitragynine pseudoindoxyl—pose significant and well-documented risks to public health and safety. These substances are highly potent, pharmacologically similar to opioids, and have been associated with dependency, overdose, psychiatric destabilization, and dangerous interactions with other substances. They are frequently marketed in misleading ways that minimize risk and obscure potency.

From a behavioral health system perspective, frontline treatment providers, emergency departments, and crisis services are increasingly managing the consequences of these compounds. The lack of permanent regulatory controls has contributed to consumer confusion and inconsistent enforcement, increasing preventable harm.

Classifying synthetic kratom compounds as Schedule I substances provides critical clarity and authority for prevention, enforcement, and public health response efforts. This rule is a necessary and appropriate step to protect Ohioans and align state policy with emerging national guidance and FDA concerns.

We appreciate the Board of Pharmacy's leadership and strongly support adoption of this rule.

Respectfully submitted,

Jason M. Joyce
CEO
ADAMHS Board of Cuyahoga County
2012 West 25th Street Cleveland, OH 44113

NAMI Ohio
National Alliance on Mental Illness The State's Voice on Mental Illness
1225 Dublin Road, Suite 210, Columbus, OH 43215

January 21, 2026

Re: Support to rule changes

OAC 4729:9-1-01.1 – This proposed rule classifies kratom-related compounds as Schedule I controlled substances. This rule covers synthesized kratom-alkaloids that were recently highlighted by the FDA such as 7-hydroxymitragynine (7-OH) and mitragynine pseudoindoxyl (MP). This is the follow-up rule to the emergency rule adopted by the Board on December 12, 2025.

Members of the Board of Pharmacy:

Thank you for the opportunity to provide written remarks in support of the permanent ban of synthetic Kratom.

My name is Luke Russell, Executive Director of NAMI Ohio. We are proud to be part of the largest mental health advocacy organization in the country. We represent over 500,000 Ohio citizens and their families in Ohio whose lives have been invaded by mental illness. NAMI Ohio has thirty-nine affiliates throughout Ohio, serving all 88 counties. These Affiliates offer over 4000 education, support, and advocacy programs every year in Ohio (for free) to over 44,0000 individuals. Every day, somewhere in Ohio, NAMI is offering a support group, education program, or advocating for an individual and family in need. Each of you have constituents with mental illness and their families are desperately seeking your support.

Those living with mental illness and their families rely on Ohio's mental health system to provide the care they so desperately need. NAMI Ohio applauds recent efforts to improve our behavioral care health system. This includes the recent work with children and families, work across our communities on prevention and crisis services, expanding access to mental health telehealth care, and the statewide work on improving substance use disorder access and care. More Ohioans are now getting the mental health services and help they need. Key to true wellness and recovery is access to affordable medications.

While Kratom isn't considered a controlled substance to most states nor the federal government, the use of kratom is not recommended by the FDA and the DEA has it listed as a drug of concern. Researchers who have studied kratom think its side effects and safety problems more than offset any potential benefits. Poison control centers in the United States received 1,800 reports involving the use of kratom from 2011 through 2017, including reports of death. Half of these exposures resulted in serious negative outcomes such as seizures and high blood pressure. Five of the seven infants who were reported to have been exposed to kratom went through withdrawal.

Nationally it is estimated that 10.9 million users of drugs other than alcohol reported they were using these substances "a little more or much more" than they did before the COVID-19 pandemic began. At a time when Ohio families are grappling with unprecedented addiction compounded by the stress of a

global pandemic, we consider the commercialization of an addictive drug with such scientifically proven public health harms to be unacceptable.

NAMI Ohio wants to express the negative risks to a person's mental and physical health that have been documented and include nausea, seizures, hallucinations, and other psychotic symptoms. Some users have reported becoming addicted to Kratom. At this time, there are no specific medical treatments or behavioral therapies for kratom addiction. Scientists need more research to determine effective treatment options.

Thank you again for allowing me to provide written testimony.

OHIO PROSECUTING ATTORNEYS ASSOCIATION

196 EAST STATE STREET • SUITE 200 • COLUMBUS, OHIO 43215 • TELEPHONE 614/221-1266 • FAX 614/221-0753 • WWW.OHIOPA.ORG

January 23, 2026

Ms. Summer Reyburn
Policy and Public Affairs Liaison
Ohio Board of Pharmacy
77 South High Street, 17th Floor
Columbus, OH 43215-6126

RE: Support for Proposed OAC Rules 4729:9-1-01.1 and 4729:9-1-01.2

Ms. Reyburn –

I write on behalf of Ohio's prosecuting attorneys to express our support for the recently proposed rules classifying kratom-related compounds and the primary compound in kratom as Schedule I controlled substances thereby banning the sale and possession of these substances in Ohio.

As you and the Board of Pharmacy are well aware, kratom products have a high potential for abuse. These products can, however, be viewed by consumers as a safe way to self-medicate for things like pain, anxiety or stress, a safe alternative to other drugs of abuse, or a safe way to manage something like opioid use disorder. This is due to the products' legal status, marketing, and wide availability. This causes our Association concern for several reasons.

Dangerous for Ohio Children and Youth

Kratom products are unregulated, psychoactive products that are often marketed deceptively, even sometimes sold in forms that are attractive to children. Kratom is sold in gas stations, convenience stores, vape shops, and on the internet. While these unregulated products are dangerous for any consumer, they create dangers that are particularly acute for Ohio children. Children may be more susceptible to this style of marketing and at greater risk of eventual harm from use of the product. Children who cannot purchase these products on their own may be more likely to mistake them for candy or some other harmless snack and to become the victim of accidental ingestion. And as with other controlled substances children may be more likely to become addicted or to suffer other lifelong consequences from the use of these products.

According to the website HealthyChildren.org, an online resource of the American Academy of Pediatrics, kratom "can cause liver damage, hallucinations and convulsions or seizures." "At higher doses, kratom reduces anxiety and causes sleepiness, the way strong pain drugs like opioids (heroin or fentanyl) do" and in fact "can cause people to stop breathing at high doses."[1]

Banning these products will reduce early exposure to these risks and early exposure to addictive substances that could have lifelong consequences for youth.

Substance Use Disorder

According to FDA Commissioner Dr. Marty Makary, 7-OH, a synthetic byproduct of kratom, binds strongly to the body's opioid receptors and is up to 13 times more potent than morphine and has compared emerging problems to previous waves of the opioid crisis.[2] It produces respiratory depression, physical dependence, and withdrawal symptoms similar to opioids like morphine and fentanyl. Exacerbating this is the fact that kratom is reportedly marketed as a way to mitigate opioid withdrawal symptoms and stop opioid use, placing the very people it claims to help at greater risk of addiction and its consequences.

Beyond the tragic public health problems and problems for individuals who are suffering from addiction or who become addicted are the public safety and criminal justice issues that historically go along with substance abuse – most notably the increase in crimes like theft, burglary, forgery, and fraud. Given the unregulated nature of these products and the likelihood that they are manufactured, marketed, and sold without sufficient testing to protect consumers, the risk for accidental injury and even death is higher for the consumer and consequently, so is the risk of prosecution of the people distributing these products for something like involuntary manslaughter or reckless homicide. Finally, one of the saddest byproducts of the of the opioid crisis was the increased burden on our foster care system and on caretakers due to parental addiction issues.

Given the potency of some of these products and the similarity of them to opioids, we should indeed, as Dr. Makary of the FDA suggests, get out in front of this problem and avoid being caught flat-footed as we were during previous waves of the opioid crisis.[3] Doing so will help prevent the development and exacerbation of substance use disorders and the attendant consequences.

Highway Safety

Finally, the wide availability of these products at places like gas stations, convenience stores, and vape shops combined with the fact that there is no prohibition on having the products open and accessible in vehicles may lead to people to believe that it is safe to consume kratom products and drive. Kratom can cause sedation and impaired coordination. This raises the risks of impaired driving on our highways. It also presents unique problems for law enforcement interdiction efforts since kratom is not now typically tested for in drug screens or as part of a roadside test.

Banning kratom products as proposed will bring clarity to this issue for the public and will enable law enforcement to more consistently enforce our impaired driving laws, improving highway safety.

---

[1] https://www.healthychildren.org/English/ages-stages/teen/substance-abuse/Pages/kratom-what-parents-need-to-know-about-this-risky-substance.aspx

[2] https://nypost.com/2025/07/29/opinion/beware-synthetic-kratom-7-oh-powers-a-new-opioid-crisis/

[3] Id.

For these reasons, we support the adoption of the proposed rules scheduling kratom and kratom-related compounds as Schedule I controlled substances.

Respectfully,

Louis Tobin
Executive Director

OARP

Ohio Alliance Of Recovery Providers

January 26, 2026

Executive Director Steven W. Schierholt, Esq.
Ohio Board of Pharmacy
77 S. High Street, 17th Floor
Columbus, Ohio 43215-6126

RE: OAC 4729:9-1-01.1 Mitragynine-related compounds
OAC 4729:9-1-01.2 Mitragynine (NEW)

Dear Executive Director Schierholt and members of the Ohio Board of Pharmacy,

On behalf of the Ohio Alliance of Recovery Providers (OARP), a statewide organization of addiction treatment providers, certified by the Ohio Department of Behavioral Health, we write in strong support of the proposed changes to Ohio Administrative Code rule 4729:9-1-01.1 and what would be the newly created 4729:9-1-01.2 rule to classify all forms of kratom as Schedule I drugs. As you are well aware, drugs, substances, and chemicals that fall under the Schedule I category have no currently accepted medical use and a high potential for abuse. We wholeheartedly agree with that assessment, and we believe it will be in the best interest of all Ohioans.

OARP members are dedicated to the prevention and treatment of substance use disorders, and we work daily with individuals and families affected by addiction. In recent years, we have observed increasing use of kratom among patients with substance use disorders, often under the mistaken belief that it is a safe or therapeutic alternative to opioids. In our experience, kratom use has been associated with dependence, withdrawal symptoms, relapse risk, and delayed engagement in evidence-based treatment.

Kratom's active compounds exert opioid-like effects, yet the substance remains unregulated, unstandardized, and not approved by the U.S. Food and Drug Administration for any medical use or even as a dietary supplement. Variability in potency, contamination concerns, and the lack of reliable dosing information present serious risks to public health. From a treatment perspective, these factors complicate recovery and undermine our harm-reduction and prevention efforts.

We are particularly concerned about the accessibility of kratom to vulnerable populations, including individuals in recovery and young people, who may perceive it as a benign or "natural" product. Scheduling kratom as a Schedule I substance would reduce availability and send an important public health message about the risks it poses.

We commend Governor DeWine and the Board of Pharmacy for your careful review of the scientific, clinical, and public safety considerations related to kratom. We believe the proposed rules are a necessary and responsible step to protect patients, support recovery, and prevent further harm in our communities.

Sincerely,

Brian Bailys
President, Ohio Alliance of Recovery Providers
CEO, Thrive Peer Recovery Services

CONSUMER ACTION for a STRONG ECONOMY

JANUARY 25, 2026

Dear Ohio Board of Pharmacy --

On behalf of tens of thousands of Ohioans suffering from a wide range of ailments, mental and physical debilitations, chronic pain, severe emotional distress, and chemical dependence, as well their loved ones, family, friends, and caregivers, Consumer Action for a Strong Economy (CASE), writes today to express our strong opposition to the proposed classification of mitragynine (commonly known as kratom) derived products as a Schedule I Controlled Substance.

This proposed classification would ban the use of kratom products in Ohio (exempting kratom in its natural leaf form), criminalizing those adults who use regulated kratom derivatives. When examined thoroughly, taking into consideration the diverse group of individuals who have come to depend on these formularies, this policy is empty window dressing at best, and a cruel denial of freedom from physical and emotional pain at worst. By way of analogy, banning kratom-derived products is akin to banning chewing gum in response to an explosion in the use of chewing tobacco.

Kratom-derived products are used by many thousands of Ohio residents to help alleviate chronic pain, stress, and depression. Critically, their use has shown to be enormously beneficial to many seeking to curb their addiction to deadly opioids, which have destroyed the lives of countless Ohioans. A sweeping ban on products that have verifiable benefits for recovering addicts is a mistake that would needlessly increase suffering for more people than can be counted.

There are alternative approaches that would address concerns related to the use of kratom and kratom-derived products absent an outright ban. Regulations could be enacted that would limit kratom-derived products to adults 21 and over, place clear warning labels on the kratom products, require independent lab testing for potency and contaminants, or crack down on misleading or youth-targeted marketing.

1800 Diagonal Road, Suite 600
Alexandria, VA 22314
www.CASEforConsumers.org

An outright ban, which would be the result of a Schedule I classification, represents the most restrictive policy possible. As most Americans know, health and law-enforcement data show the vast majority of overdose deaths involve illicitly manufactured fentanyl and other synthetic drugs – not kratom or kratom-derived products.

Many adults report they currently use kratom products to cope with pain or opioid withdrawal. Compare that with the thousands of deaths involving heroin or opioids. If these products are suddenly made illegal, some will turn back to the illicit market where fentanyl is widespread and the odds of overdose very high.

While we greatly respect Governor DeWine's desire to protect the health and well-being of the great people of Ohio, his actions and those who support him are entirely misguided. There is insufficient data to demonstrate that the proposed ban will achieve its desired outcome, or that it won't cause far more harm than good. To the contrary, there is ample evidence that an outright ban of kratom-derived products will cause enormous suffering among its many thousands of users, who would have no choice but to either engage in criminal activity on the black market to obtain their desired kratom products or endure their afflictions with no relief given the absence of viable alternatives.

The stakes are enormous, especially for the victims of mental and physical illnesses. These are real Ohio residents, with names and faces, who will be denied perhaps the one product that makes their day bearable or provides their lives with hope of a better future. We cannot be so cruel as to ignore their pain and sacrifice their needs at the altar of political expediency and misguided public policy.

CASE urges the Ohio Board of Pharmacy to reject the proposed classification of mitragynine as a Schedule I Controlled Substance. Please consider developing a comprehensive and effective policy that will employ effective guardrails for public health without penalizing and punishing Ohioans seeking relief from their daily suffering.

Sincerely,

Gerard Scimeca
Chairman, CASE

1800 Diagonal Road, Suite 600
Alexandria, VA 22314
www.CASEforConsumers.org

The Ohio Council
Of Behavioral Health & Family Services Providers

17 S High Street, Suite 799, Columbus, OH 43215
614-228-0747 | www.TheOhioCouncil.org
@theohiocounci

Kratom & Mitragynine-Related Compounds Schedule I Reclassification Rule Comments

Melissa Green, MSW, LSW

January 27, 2026

The Ohio Council of Behavioral Health & Family Services Providers (The Ohio Council) appreciates the opportunity to comment on OAC 4729:9-1-01.1 and OAC 4729:9-1-01.2, the proposed rule package reclassifying Kratom and Mitragynine-related compounds as Schedule I drugs. We are pleased to express our strong support for these proposed rule changes.

The Ohio Council is a statewide advocacy and trade association representing 170 community behavioral health and family services providers who are nationally accredited and state certified businesses. Our members deliver high-quality prevention, mental health and substance use treatment, crisis intervention, and recovery support across the State of Ohio, serving more than 2.5 million Ohioans annually; many of whom are living with substance use disorders.

In recent years, the public health risks posed by Kratom and Mitragynine-related compounds have become increasingly apparent. Similar to opiate substances, Ohio Council member organizations have reported a growing number of individuals presenting for detoxification or treatment related to dependence on Kratom and Kratom-related products. These clinical observations align with the current research and concerns outlined by the Ohio Board of Pharmacy regarding the substances' potential for misuse and the development of dependence.

Beyond the growing anecdotal evidence of treatment providers, the known effects of Kratom and its active compounds raise serious clinical concerns that support reclassification. These substances interact with the same brain systems as opioid drugs, and can produce effects such as pain relief, sedation, and feelings of euphoria. With repeated or high-dose use, individuals may develop tolerance and dependence, followed by withdrawal symptoms when use is reduced or discontinued: reflecting patterns of harm consistent with other opioid-like substances.

These risks are heightened by the lack of regulation surrounding Kratom products. Unlike prescription medication or other controlled substances, Kratom is sold in a wide range of formulations and potencies, often without consistent labeling or ingredient disclosures. From a treatment perspective, this variability makes it difficult for clinicians to assess exposure, anticipate clinical effects, or provide appropriate interventions. Inconsistent potency and the potential presence of unknown additives increase the risk of adverse health effects, overdose, and dangerous interactions with other substances.

The unregulated availability of Kratom and Mitragynine-related compounds also pose significant risks to children and adolescents that can have life-long negative consequences. These products are widely available without age restrictions in gas stations, convenience stores, and online. Research consistently shows that early exposure to psychoactive substances increases the likelihood of developing substance use disorders later in life. Allowing easy access to substances with opioid-like effects increases the risk of early misuse and sets the stage for more severe and persistent addiction throughout adulthood.

As research and clinical experience continue to deepen our understanding of the risks posed by Kratom, it is critical that action is taken now to prevent the emergence of another substance-related public health crisis. From a systems-of-care perspective, an increase in individuals seeking treatment for Kratom-related substance use would place additional strain on Ohio's behavioral health infrastructure. These demands would stretch our already limited treatment capacity, particularly in communities presently experiencing workforce shortages and service gaps. Reclassifying Kratom and related compounds would support earlier intervention, clearer prevention messaging, and more consistent clinical response across the state.

The proposed rule changes are consistent with well-established principles used to evaluate controlled substances, including high potential for misuse, the risk of dependence, and the absence of accepted medical use under regulated conditions. Taken together, the clinical evidence, treatment system impact, risks to youth, and alignment with regulatory policy of similar substances strongly support reclassification. For these reasons, The Ohio Council strongly supports the Ohio Board of Pharmacy's proposed reclassification of Kratom and Mitragynine-related compounds as Schedule I controlled substances.

Thank you for the opportunity to comment on this proposed rule package. We welcome continued collaboration on this rule and would be glad to discuss these recommendations further. Please feel free to contact me at green@theohiocouncil.org.

Prevention
Action Alliance

Lifetime Prevention | Lifetime Wellness

January 27, 2026

Re: Proposed Classification of Mitragynine-Related Compounds as Schedule I Controlled Substances Rule 4729:9-1-01.1

Thank you for the opportunity to submit public comments on the Ohio Board of Pharmacy's proposed rule to classify mitragynine-related compounds as Schedule I controlled substances.

My name is Frances Gerbig, and I am the Executive Director of Prevention Action Alliance (PAA), a statewide nonprofit prevention organization based in Columbus, Ohio. For more than 30 years, PAA has supported communities across Ohio in preventing substance misuse, promoting mental health, and advancing evidence-based public health strategies that protect youth, families, and communities.

Prevention Action Alliance supports the Board's proposed rule addressing mitragynine-related compounds. These substances—designed to be structurally or pharmacologically similar to mitragynine—present serious and emerging public health concerns. Evidence indicates that such compounds are often developed or modified to evade regulation while retaining psychoactive effects, increasing the risk of misuse, dependence, and adverse health outcomes.

The data reviewed by the Board demonstrate that mitragynine-related compounds have no accepted medical use in treatment in Ohio and pose an imminent risk to public health, safety, and welfare. Reported harms include neurological, cardiovascular, and psychiatric effects, compounded by concerns related to toxicity, unpredictable potency, and the absence of consumer safeguards. The growing availability of kratom-derived and synthetic analog compounds further complicates enforcement and heightens risk, particularly for young people.

From a prevention and public health standpoint, the proposed classification provides necessary regulatory clarity and helps prevent the continued introduction of new, unregulated psychoactive substances into the marketplace. Experience has shown that partial or reactive regulatory approaches fail to adequately reduce harm as manufacturers rapidly modify chemical formulations to circumvent oversight.

Consistent with the criteria set forth in Ohio Revised Code 3719.44, the evidence supports the Board's determination that mitragynine-related compounds:

- Have demonstrated potential for abuse;

- Lack accepted medical use in treatment in this state; and
- Present safety risks that cannot be sufficiently mitigated through medical supervision or limited regulatory controls.

Prevention Action Alliance appreciates the Ohio Board of Pharmacy's comprehensive review and proactive approach to addressing these emerging substances. We support the proposed classification of mitragynine-related compounds as Schedule I controlled substances as an important step to protect public health, reduce harm, and prevent further misuse.

Thank you for your consideration and for your continued commitment to safeguarding the health and safety of Ohioans.

Respectfully submitted,
Frances R. Gerbig, MPH, OCPC, ICPS
Executive Director
Prevention Action Alliance

OHIO PSYCHIATRIC PHYSICIANS ASSOCIATION

A District Branch of the American Psychiatric Association

Dedicated to promoting the highest quality care for people with mental disorders and to serving the professional needs of Ohio's psychiatric physicians.

January 21, 2026

Cameron McNamee
Director of Policy and Communications
Ohio Board of Pharmacy
77 South High Street, 17th Floor
Columbus, OH 43215

Dear Members of the Ohio Board of Pharmacy,

On behalf of the Ohio Psychiatric Physicians Association (OPPA), representing more than 1,000 psychiatrists, we write to express our support for the Board's actions to classify mitragynine and certain mitragynine-related compounds as Schedule I controlled substances under Ohio law.

As psychiatrists committed to protecting the mental health and safety of Ohio patients, OPPA members are increasingly concerned about the unregulated availability and use of kratom (Mitragyna speciosa) and its psychoactive constituents. These substances are widely marketed as natural or benign products, despite mounting scientific and clinical evidence demonstrating opioid-like activity, abuse potential, and associated risks—particularly for individuals with substance use disorders or co-occurring mental health conditions.

Kratom and its derivatives have not been approved by the U.S. Food and Drug Administration for any medical use. Available research indicates that their active compounds interact with opioid receptors and can produce dependence, withdrawal symptoms, and other adverse effects. The proliferation of increasingly concentrated or chemically modified kratom products further compounds these risks, especially in the absence of standardized manufacturing, labeling, or medical oversight.

OPPA supports the Board's determination that these substances meet the statutory criteria for Schedule I classification, including high potential for abuse, lack of accepted medical use, and absence of demonstrated safety under medical supervision. We also recognize and appreciate the Board's careful evaluation of the relevant statutory factors and its consideration of public health and safety impacts in developing these rules.

In closing, OPPA urges the Board to proceed with finalizing the proposed rule and maintaining appropriate controls on mitragynine-related compounds. These actions represent a solid, evidence-informed approach to addressing emerging substance-related risks and preventing further harm to Ohio communities.

Thank you for your continued commitment to public health and patient safety.

Sincerely,

Nita Bhatt, MD, MPH
OPPA President

PO Box 400
Dublin, OH 43017
(614) 763-0040
(614) 481-7559 Fax

Email:
oppa@oppa.org

Website:
www.oppa.org

***(1/28/2026)* Regarding proposed ORC Section 4729:9-1-01.1 – Mitragynine-Related Compounds that classifies mitragynine- related compounds, as Schedule 1 Controlled Substances,**

Public Health - Dayton & Montgomery County's Community Overdose Action Team (COAT), a community coalition comprised of public health partners, treatment providers, harm-reduction organizations, recovery support services, healthcare professionals, first responders, and community stakeholders, we submit this comment in strong support of the proposed rule to classify mitraginine- related compounds as Schedule 1 controlled substances.

Our coalition's work is guided by the goal of preventing overdose deaths and improving long-term recovery outcomes through a coordinated continuum of prevention, harm reduction, evidence-based treatment, and recovery supports. We write to emphasize that widespread over the counter (OTC) availability of mitraginine-related compounds undermines community overdose-reduction progress and creates avoidable safety risks.

1. Community Overdose Reduction Depends on Rapid Linkage to Evidence-Based, Supervised Care

Our community has achieved meaningful progress in reducing opioid-related harms by building and sustaining an integrated system of care. Overdose deaths have declined 73% since their peak in 2017.[1] Our ability to reduce overdoses relies on reducing stigma associated with seeking help, identifying opioid use disorder (OUD) early, and connecting people to evidence based, medically supervised treatment pathways and established recovery networks. This includes low-barrier access to evidence-based treatment, including FDA-approved medications for opioid use disorder (MOUD), and robust wraparound supports (peer navigation, harm reduction services, mental health supports, social services linkage, and recovery services).

2. OTC Availability Sends a Misleading Safety Signal, Promotes New Initiation, and Undermines Engagement in Evidence-Based OUD Care

OTC availability of mitraginine creates a misleading perception of safety, suggesting standardization, quality control, and minimal risk. This framing encourages initiation among individuals who would not otherwise use addictive substances, including those seeking "natural" alternatives to self-manage chronic symptoms or opioid withdrawal—the result of a well-documented "naturalness bias."[2]

This perception of safety and effectiveness is particularly harmful when individuals begin using mitraginine-related compounds to manage withdrawal based on informal advice, marketing claims, or online information rather than engaging with clinicians, evidence-based treatments, and

[1] (COAT Data Unit)
[2] (Meier, Dillard, & Lappas, 2026)

established, comprehensive community supports that improve safety and long-term outcomes, including supervised stabilization, medical oversight, behavioral health care, peer services, infectious disease screening, and harm-reduction education.

The addictive potential of mitraginine-related compounds can lead to physiologic dependence, creating a cycle in which individuals substitute one dependence for another while believing they have chosen a safer option. This dynamic contributes to delayed diagnosis, delayed initiation of MOUD, fragmented care, and heightened vulnerability to relapse and overdose. In effect, mitraginine-related compounds undermine our community's efforts to reduce opioid-related harm.

3. Morbidity and Mortality Signals: Detection in Toxicology, Including Postmortem Reports
The prevalence of various substances in the drug supply changes over time. COAT collects extensive data on overdose deaths every year, including which drugs were present in each overdose death. COAT data comes from multiple sources, including Public Health – Dayton & Montgomery County, Dayton Police Department, ADAMHS, the Montgomery County Coroner' Office, the Montgomery County Probation Office, the Montgomery County Sheriff's Office, Project Dawn, and Wright State University.

According to COAT's data, mitraginine and 7-OH have been identified in our local toxicology findings, including in autopsy reports, both as a single substance and in combination with other substances.[3] While polysubstance exposure is common in overdose deaths, the detection of mitraginine and 7-OH underscore that these are not benign OTC products and that their presence can be associated with serious outcomes—as a single agent and particularly when combined with other sedating or psychoactive agents.

Conclusion
Schedule I placement is necessary to reduce broad commercial availability, curb initiation among individuals misled by OTC status, and prevent continued diversion away from established, evidence-based community treatment pathways. Our community has invested substantial resources in an accountable system that reduces opioid overdose deaths. Allowing a dependence-forming substance to remain widely available OTC undermines those gains and places community members at increased risk.

The Community Overdose Action Team respectfully urges the Board of Pharmacy to finalize the proposed rule and place mitraginine-related compounds in Schedule I. Doing so will protect communities by reducing exposure to an addictive substance currently marketed and perceived as benign, prevent unsafe self-treatment of opioid withdrawal, and promote connection to safe, effective, evidence-based OUD treatment and the robust harm reduction and recovery infrastructure our community has developed.

[3] (COAT Data Unit)

Respectfully submitted,

The Community Overdose Action Team

About the Community Overdose Action Team:
The Community Overdose Action Team seeks to reduce the number of people dying from drug overdoses and drug abuse. The Community Overdose Action Team was established in the fall of 2016 to address the opioid/heroin epidemic in Montgomery County. Montgomery County Alcohol, Drug Addiction & Mental Health Services, Public Health – Dayton & Montgomery County, and Montgomery County Administration are the lead agencies in the effort to combat the epidemic. COAT has over 200 members representing all sectors within our community including government, healthcare, faith-based, civic/volunteer organizations, law enforcement, fire/EMS, youth-serving organizations, schools, media, substance abuse organizations, concerned citizens, those in recovery, and families/friends of those in recovery. The COAT Project Manager is Dawn Schwartz, (937) 225-6026.

Organizational Public Comment

Submitted by: HAVEN Access Inc.

This comment applies to both proposed rules titled “CSI – BIA – Mitragynine” and “CSI – BIA – Mitragynine-Related Compounds.”

HAVEN Access Inc. formally opposes the proposed placement of mitragynine and mitragynine-related compounds into Schedule I.

HAVEN Access is a public-interest advocacy organization focused on protecting lawful access and ensuring evidence-based, procedurally sound drug policy. The parallel pursuit of two overlapping Schedule I proposals, released simultaneously with identical comment deadlines, creates fragmented public participation and prevents meaningful evaluation of cumulative impact.

Schedule I placement requires findings that a substance has a high potential for abuse, no accepted medical utility, and a lack of accepted safety even under medical supervision. The proposed rules do not demonstrate these findings using real-world, population-level evidence. Instead, they rely on speculative, indirect, or incomplete reasoning while disregarding the lived experiences of individuals who utilize kratom-derived products and the consequences of abruptly eliminating lawful access.

The mitragynine-related compounds proposal functions as a broad catch-all that effectively sweeps naturally occurring alkaloids and future derivatives into Schedule I without individualized analysis. Combined with the separate mitragynine proposal, this approach raises serious concerns regarding overbreadth, duplication, and the absence of a coherent, consolidated review.

We respectfully request that the Ohio Board of Pharmacy:

1. Hold a single public hearing that covers both proposed rules together

2. Allow testimony from affected individuals, clinicians, researchers, and other stakeholders relying on real-world evidence

3. Evaluate whether the rules should be denied or withdrawn, or at minimum consolidated and subjected to an extended comment period

Eliminating lawful access through permanent Schedule I placement would cause immediate and foreseeable harm, including driving individuals toward illicit markets or less safe alternatives, while failing to meet the statutory standards required for such classification.

HAVEN Access urges the Board to deny or withdraw these proposals and to pursue a transparent, evidence-driven process that meaningfully considers real-world impacts and procedural fairness.

WellLink™ | Northeast Ohio Opioid Consortium

January 28, 2026

Ohio Board of Pharmacy
77 South High Street
Columbus, OH 43215

RE: Support for Classification of Kratom and Synthetic Kratom Compounds as Schedule I Controlled Substances & Support for Research on Safety and Therapeutic Use

Dear Members of the Ohio Board of Pharmacy:

On behalf of the Northeast Ohio Opioid Consortium, we write to express our support for the classification of kratom and any synthetic kratom compounds, including mitragynine-related substances, as Schedule I controlled substances under Ohio law. We also urge the Board to support and enable rigorous scientific research and clinical trials to determine whether kratom or its derivatives may have safe and effective medical uses under controlled conditions.

Kratom (derived from the plant *Mitragyna speciosa*) and its primary alkaloids, including mitragynine and 7-hydroxymitragynine (7-OH), have come under increasing scrutiny due to their opioid-like effects and association with adverse outcomes. Although kratom has been marketed and used by some for purported benefits such as pain relief or managing withdrawal symptoms, there is currently no drug product containing kratom or its compounds that has received approval from the U.S. Food and Drug Administration for any medical indication. Moreover, adverse health events, including seizures, psychosis, and deaths, have been reported in association with kratom use, particularly with concentrated or synthetic derivatives.

Given these concerns, the Ohio Board of Pharmacy recently issued an emergency scheduling rule under Ohio Administrative Code Rule 4729:9-1-01.1, which classifies mitragynine-related compounds, including synthetic alkaloids like 7-OH and mitragynine pseudoindoxyl, as Schedule I controlled substances. This action reflects a precautionary approach in light of the absence of accepted medical use and the public health risks posed by these substances.

The Northeast Ohio Opioid Consortium, dedicated to reducing opioid misuse, overdose, and related harms across Northeast Ohio, supports this scheduling because it aligns with our mission to protect residents from substances that pose significant risk yet lack demonstrated medical utility. Controlling kratom and its potent derivatives as Schedule I will help prevent unregulated access and reduce the risk of misuse, dependency, and overdose among Ohioans.

At the same time, we recognize that some individuals and clinicians advocate for further exploration of kratom's potential therapeutic effects. We encourage the Board and policymakers to work with academic institutions, research bodies, and regulatory agencies to establish appropriate pathways that enable ethical, scientifically sound research, including necessary approvals from state and federal controlled substances authorities.

In closing, the Northeast Ohio Opioid Consortium:

1. Supports the classification of kratom and all synthetic kratom-related compounds as Schedule I controlled substances in Ohio to protect public health; and
2. Supports the advancement of controlled research and clinical trials to evaluate safety and efficacy in defined therapeutic contexts.

Thank you for your consideration of these important public health issues. We stand ready to assist the Board in its efforts to promote health and safety for all Ohioans. If you require additional information, please contact Jodi Mitchell, jodi.mitchell@mywelllink.com.

Respectfully,

Northeast Ohio Opioid Consortium Advisory Committee
Jennifer Johns, The Academy of Medicine of Cleveland & Northern Ohio (AMCNO)
Dr. Jeanne Lackamp, University Hospitals
Thom Olmstead, Sisters of Charity Health System
Dr. Joan Papp, The MetroHealth System
Dr. Ted Parran, Rosary Hall, St. Vincent Charity Community Health Center
Dr. David Streem, Cleveland Clinic
Daniel Lettenberger-Klein, WellLink Health Alliance

January 28, 2026

Ohio Board of Pharmacy
77 South High Street, 17th Floor
Columbus, OH 43215

RE: Support for Proposed Classification of Mitragynine-Related Compounds as Schedule I Controlled Substances

Dear Members of the Ohio Board of Pharmacy,

I appreciate the opportunity to provide comment in support of the proposed rule classifying mitragynine-related compounds as Schedule I controlled substances.

As a specialist in addiction medicine, I believe the proposed rule represents a necessary and timely response to an emerging public health concern.

Mitragynine-related compounds—particularly highly concentrated and semi-synthetic derivatives such as 7-hydroxymitragynine and mitragynine pseudoindoxyl—exhibit opioid-like pharmacologic effects, carry significant risk for abuse and dependence, and lack accepted medical use or established safety under medical supervision. The scientific evidence and surveillance data summarized in the Board's 8-factor analysis clearly demonstrate that these substances pose significant health risks.

Due to the opioid-like properties of mitragynine-related compounds, I treat withdrawal from mitragynine like withdrawal from fentanyl and other opioids. We have evidence-based treatments for opioid use disorder, including FDA-approved medication treatment with buprenorphine, methadone, or naltrexone. Mitragynine and mitragynine-related compounds have not undergone the rigorous FDA approval process that we expect for a medication to be used to treat a disorder, and do not have an accepted medical use.

Of particular concern is the manner in which these products have been marketed and distributed. The sale of potent mitragynine-related compounds in retail and online settings—often labeled or presented in ways that obscure their true pharmacologic effects—creates a substantial risk of unintentional exposure, especially among adolescents and young people.

While I recognize that the proposed rule may have economic implications for certain businesses, I believe these impacts are outweighed by the substantial and well-documented risks associated with continued over-the-counter availability of these compounds. Preventing avoidable drug-related harms is a critical priority for the state of Ohio.

For these reasons, I strongly support the proposed classification of mitragynine-related compounds as Schedule I controlled substances. I appreciate the Board's leadership on this important issue and its commitment to safeguarding the health of Ohioans.

Thank you for your consideration.

Sincerely,

Julie Teater, MD

Julie Teater, MD, DFAPA, FASAM
Professor, Clinical
Chief Psychiatrist
Medical Director of Addiction Medicine
Addiction Medicine Fellowship Program Director
Psychiatry Residency Associate Program Director
Department of Psychiatry and Behavioral Health
The Ohio State University Wexner Medical Center

COMMENTS OF THE GLOBAL KRATOM COALITION
Re: Proposed Rule 4729:9-1-01.1 – Mitragynine-Related Compounds
27 January 2026

Global Kratom Coalition ("GKC") hereby responds to the Ohio Board of Pharmacy's request for comments to its proposed rule 4729:9-1-01.1, addressing mitragynine-related compounds**.**

I. Statement of Support and Framing.

GKC supports Proposed Rule 4729:9-1-01.1 to the extent that it proposes for scheduling synthetic alkaloids isolated, concentrated, and chemically modified from the kratom plant. It proposes the scheduling of a distinct and emerging class of high-potency synthetic opioid products. Isolated, concentrated, and chemically modified from the kratom plant, individual kratom plant alkaloids, such as 7-hydroxymitragynine (7-OH) concentrates, present public-health risks that kratom in its natural botanical form does not. GKC Comments regarding Proposed Rule 4729:9-1-01.2 are incorporated here by reference and attached as **Exhibit A.**

1. In those comments, GKC presents scientific evidence, including clinical trial data, confirming that consumption of natural kratom leaf is not associated with any significant or unreasonable risks of illness or injury, including the potential for severe addiction.

GKC's support for this rule is based on the scientific evidence evaluating the risks associated with synthetic mitragynine-derived alkaloids, observed market behavior indicative of severe addictive potential, and explicit FDA public-health guidance, including its July 29, 2025 recommendation to DEA that it schedule concentrated synthetic 7-OH but not **natural kratom leaf**.[1] The evidence GKC marshals here differs from the Board's prior eight-factor analysis of mitragynine but results in a comparable conclusion. See Exh. 1. Bhe appropriateness of Board's rule does not depend on the validity of the Board's eight-factor analysis. For the reasons explained in the Henningfield et al. eight-factor analysis (attached as **Exhibit 2**), the scheduling of synthetic mitragynine-related alkaloids is amply justified for reasons under that analysis that differ from the Board's explanations. The Henningfield et al. reasons are set forth in Section VII below, which applies the statutory eight-factor test specifically to synthetic kratom-related compounds, including isolated and concentrated 7-hydroxymitragynine.

II. Purpose of Comment.

The purpose of this comment is to support the Board's effort to remove dangerous synthetic mitragynine-related products from the market, while avoiding an overbroad application of its

[1] *See* FDA / HHS Press Conference and Scheduling Recommendation Regarding Synthetic 7-Hydroxymitragynine (July 29, 2025), as summarized in Exhibit A.

scheduling authority to prohibit or restrict natural kratom leaf (which is not associated with any significant or unreasonable risk of illness or injury, including severe addictive risk).

III. Clarification of "Mitragynine-Related Compounds" as Used in the Proposed Rule.

As used in Proposed Rule 4729:9-1-01.1, the term "mitragynine-related compounds" is understood to refer to a subset of substances that are synthesized, isolated, or concentrated beyond levels naturally occurring in kratom leaf. These substances are pharmacologically and commercially distinct from kratom in its vegetation form. This comment uses the term "synthetic kratom-related compounds" to describe that subset of mitragynine-related compounds, which exclude natural kratom leaf.

IV. Distinction Between Synthetic Kratom-Related Compounds and Natural Kratom Leaf.

Synthetic kratom-related compounds differ fundamentally from kratom in its natural vegetation form, i.e., kratom leaf. The products targeted by Proposed Rule 4729:9-1-01.1 are defined by material differences in manufacture, which differences include:

- chemical synthesis or post-harvest chemical conversion
- isolation of single alkaloids
- concentration of alkaloid levels to many times that found in natural kratom leaf, reaching alkaloid daily dose amounts that transform the alkaloid into an opioid
- product formats engineered for rapid absorption free of moderating factors naturally occurring in kratom leaf such as fiber, antioxidants, and polyphenols.

By contrast, natural kratom leaf contains a complex alkaloid matrix, the entirety of which has been consumed for generations in tonics and teas, without significant or unreasonable risk of illness or injury.

V. FDA's Explicit Focus on Synthetic 7-OH Products.

Federal public-health authorities have drawn a clear distinction between natural kratom leaf, which FDA Commissioner Makary has deemed not of agency concern, and synthetic alkaloid isolate concentrates, such as 7-hydroxymitragynine (7-OH), which he has described as an opioid that poses a direct and substantial threat to public health. On July 29, 2025, FDA Commissioner Makary explained that unlike synthetic 7-OH, natural kratom leaf contains miniscule amounts, indeed trace amounts, of 7-OH (at levels substantially beneath that which causes adverse health effects). Dr. Makary explained that unlike kratom leaf, 7-OH presents a significant risk of severe addiction, respiratory depression, and overdose.

FDA's accompanying scientific assessment and educational materials explain that 7-OH is pharmacologically different from kratom leaf, often produced through chemical conversion or isolation, and frequently misrepresented to consumers as "kratom" despite producing opioid-like effects akin to scheduled substances. See **Exhibit 3**.

Importantly, Dr. Makary has not called for the scheduling or prohibition of kratom in its natural form. The **intent** of proposed Rule 4729:9-1-01.1 reflects this federal focus by targeting synthetic products rather than botanical kratom, however the wording of the rule does not reflect the stated intent because it appears to embrace natural kratom leaf.

VI. Intent of the Rule Versus Practical Effect of the Current Text.

GKC understands and supports the Board's stated intent to schedule synthetic kratom-related compounds while excluding kratom in its natural vegetation form. However, as written, portions of Proposed Rule 4729:9-1-01.1 create ambiguity that has already resulted in confusion among regulated parties and enforcement authorities.

In practice, similarly worded provisions and related agency communications have been interpreted to reach natural kratom leaf products, despite repeated statements that leaf is not the intended target. That ambiguity has contributed to enforcement actions and ongoing legal disputes concerning whether natural kratom leaf is being treated as a scheduled substance.

Clarifying the rule text at this stage would reduce enforcement and litigation risk, align the regulation with the Board's stated intent, complement, not work at cross purposes with, the FDA's scheduling recommendations, and avoid continued spillover effects onto botanical products that are not associated with the harms the rule seeks to prevent.

VII. The Eight-Factor Analysis Applied to Synthetic Kratom-Related Compounds (NEW).

This section applies the statutory eight-factor analysis to synthetic kratom-related compounds, including isolated and concentrated forms of 7-hydroxymitragynine (7-OH) and related analogs. This analysis is informed by established abuse-liability science that evaluates risk based on dose, formulation, exposure rate, and delivery, as commonly relied upon by federal public-health agencies, including peer-reviewed frameworks that distinguish whole-plant botanical preparations from isolated and concentrated opioid-active constituents. This analysis does not rely on, incorporate, or endorse the Board's prior eight-factor analysis of mitragynine, and it does not apply to kratom in its natural vegetation form, where relevant alkaloids occur only at trace, matrix-bound levels that materially limit exposure and abuse risk.[2]

[2] *See* **Jonathan E. Henningfield, PhD**, *Kratom 2026 Eight-Factor Analysis Prepared for the Ohio Board of Pharmacy* (Jan. 24, 2026)

1. Actual or Relative Potential for Abuse.

Synthetic kratom-related compounds exhibit a substantially higher potential for abuse than kratom leaf due to their isolation, concentration, and formulation. Concentrated 7-OH and related isolates are capable of delivering opioid-active doses with rapid onset and high bioavailability without the natural modulating features present in botanical preparations. These characteristics of the synthetics are well recognized as primary drivers of abuse liability for isolated opioid agonists.

2. Scientific Evidence of Pharmacological Effect.

At isolate and concentrate levels, 7-hydroxymitragynine functions as a potent μ-opioid receptor agonist, producing pharmacological effects that include reinforcement and respiratory depression. Those effects are dose- and formulation-dependent and differ materially from the pharmacological profile of natural kratom leaf, in which 7-OH occurs only in trace, matrix-bound amounts insufficient to produce opioid effects.

3. Current Scientific Knowledge Regarding the Substance.

Current scientific understanding recognizes that abuse liability is driven primarily by dose density, rate of delivery, and formulation, rather than botanical origin. Scientific literature consistently distinguishes whole-plant matrices—where competing constituents and physical structures limit exposure—from isolated opioid-active compounds lacking such constraints.

4. History and Current Pattern of Abuse.

Available evidence indicates that reports of misuse, compulsive use patterns, and adverse outcomes associated with "kratom-related" products are disproportionately associated with synthetic and concentrated formulations, particularly products containing isolated or enhanced 7-OH. These patterns are not observed with traditional kratom leaf products, which have a long-standing history of consumption without comparable abuse signals.

5. Scope, Duration, and Significance of Abuse.

Although relatively recent market entrants, synthetic kratom-related compounds demonstrate rapid market penetration, high per-user consumption, and elevated revenue concentration over a short time horizon. These characteristics indicate intensive patterns of use and support a finding of significant abuse liability, even in the absence of long-term epidemiological data, consistent with other emergent synthetic drug categories.

6. Risk to the Public Health.

Synthetic kratom-related compounds present a significant risk to public health due to high potency, narrow margins of safety, rapid tolerance escalation, and frequent misbranding as

"kratom," which obscures their opioid-like risk profile from consumers. Those risks include respiratory depression and overdose potential and are not associated with kratom in its natural vegetation form.

7. Psychic or Physiological Dependence Liability.

Concentrated opioid-active compounds are associated with heightened risk of rapid tolerance development and physiological dependence, particularly where repeated dosing is facilitated by high-potency, fast-acting formulations. Synthetic 7-OH products exhibit dependence liability comparable to other short-acting opioid agonists regulated under controlled-substance frameworks.

8. Whether the Substance Is an Immediate Precursor of a Controlled Substance.

Synthetic kratom-related compounds are often produced through chemical conversion, isolation, or modification pathways analogous to those used in the synthesis of other controlled opioid substances. These production characteristics raise enforcement and diversion concerns consistent with substances appropriately subject to scheduling.

VIII. Business and Consumer Impact Supports Targeted Scheduling.

While Proposed Rule 4729:9-1-01.1 is properly framed as a public-health intervention, market data provides useful context for understanding where intensity of use, consumption frequency, and economic concentration are occurring. This information is offered not as a toxicological assessment, but as a proxy relevant to the Board's evaluation of business and consumer impact under Senate Bill 2.

When market size, consumer prevalence, and time in market are evaluated together, a clear divergence emerges between natural kratom leaf products and recently introduced synthetic kratom-related products. Natural kratom leaf represents a long-standing consumer market characterized by broad participation, relatively low per-consumer spending, and stable use patterns. By contrast, synthetic kratom-related products, particularly concentrated 7-OH products, are a new market entrant marked by rapid revenue growth, elevated per-consumer spending, and product designs that promote frequent, high-intensity use.

[3]

As illustrated in Figure 1, synthetic kratom-related products have generated disproportionately high revenue over a short period of time despite substantially lower consumer prevalence. This pattern indicates significantly higher per-user spend and intensity of use, characteristics commonly associated with increased abuse risk and consumer harm. Regulatory action targeted at synthetic kratom-related compounds therefore ensures regulatory focus on the very segment of the market that poses the greatest public risk, while avoiding unnecessary disruption to lawful commerce involved in the marketing and sale of natural kratom leaf.

IX. Drafting Issues Requiring Clarification.

While GKC supports the objective of Proposed Rule 4729:9-1-01.1, several drafting issues should be remedied to ensure the rule functions as intended:

1. The phrase "synthetic or resinous extractives" is undefined and risks being interpreted more broadly than intended.
2. The rule does not specify the threshold at which isolation or concentration transforms a naturally occurring alkaloid into a scheduled synthetic substance.

[3] Source: Global Kratom Coalition market analysis submitted in support of Proposed Rule 4729:9-1-01.1

3. The rule text should clearly reflect the Board's stated position that kratom in its natural vegetation form, including products containing only trace naturally occurring 7-OH, is not scheduled.
4. Certain exclusions would benefit from clarification.

X. Requested Clarifications.

To strengthen the rule and ensure it achieves its intended purpose, GKC respectfully requests that the Board:

- define synthetic kratom-related compounds as alkaloids that are chemically synthesized or isolated and concentrated beyond levels occurring naturally in kratom leaf
- explicitly exclude kratom in its natural vegetation form, i.e., natural kratom leafd: products with naturally occurring alkaloid levels including trace amounts of otherwise banned alkaloids.
- align the rule text with the FDA Commissioner's statements concerning natural kratom leaf in his July 29, 2025 FDA/HHS press conference and the Governor's stated intent to except kratom in its vegetation form, i.e., kratom leaf.
- improve definitional precision to reduce enforcement ambiguity

Suggested rule amendment:

Section 5: Proposed Synthetics Rule

Changes are indicated in red.

4729:9-1-01.1–Synthetic Kratom-Related Compounds (NEW)

The following are classified as schedule I controlled substances:

(A) Synthetic kratom-related compounds, whether synthetic 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. Synthetic kratom-related compounds include, but are not limited to, isolates (which are single alkaloid extracts of kratom leaf) and concentrates (which are single alkaloid extracts enhanced through concentration to many times the levels naturally occurring in kratom leaf) of the following: 7- hydroxymitragynine; mitragynine pseudoindoxyl; dihydro-7-hydroxy mitragynine; and 7-acetoxymitragynine .

Synthetic kratom-related compounds do not include kratom in its vegetation form, which is natural kratom leaf whether in fresh leaf form, pulverized leaf form, powder form, or leaf or powder

infused with water. Kratom in its vegetation form is not scheduled hereunder and does 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 dietary ingredient that has been determined to be adulterated by the Food and Drug Administration;

(3) Any drug approved by the United States food and drug administration 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) Any synthetic kratom-related compound.

XI. Conclusion.

For the foregoing reasons, GKC supports Proposed Rule 4729:9-1-01.1. With the clarifications outlined above, the rule will effectively target dangerous synthetic kratom-related compounds while avoiding depriving consumers of the choice to obtain natural kratom leaf for which there is no evidence of significant or unreasonable risk of illness or injury.

Submitted by,

m lowe

Matthew Lowe

Global Kratom Coalition

1075705

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

Jack E. Henningfield, Daniel Wang, Lisa M. Zapawa, Mark A. Sembower, Steve Pype

January 24, 2026

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.

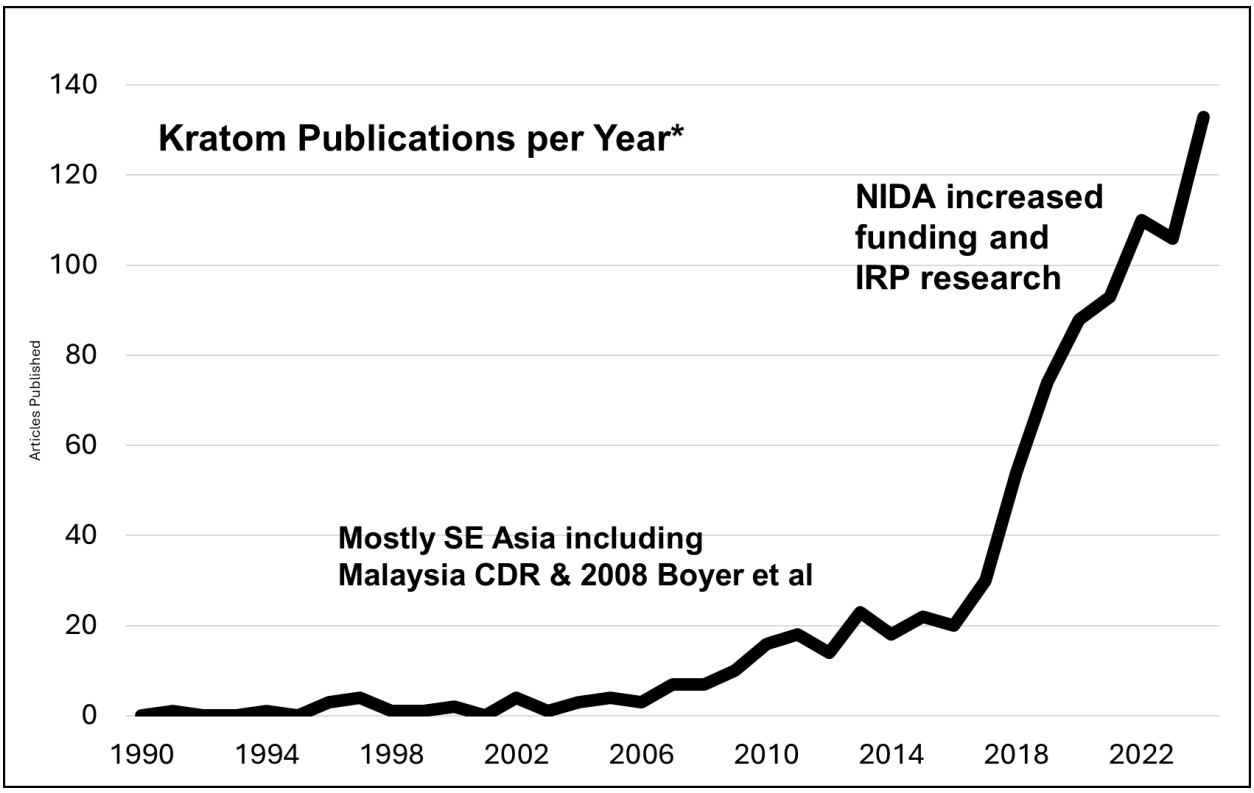
3 Evaluating Kratom and its Alkaloids Under the Eight Factors

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

---

[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.

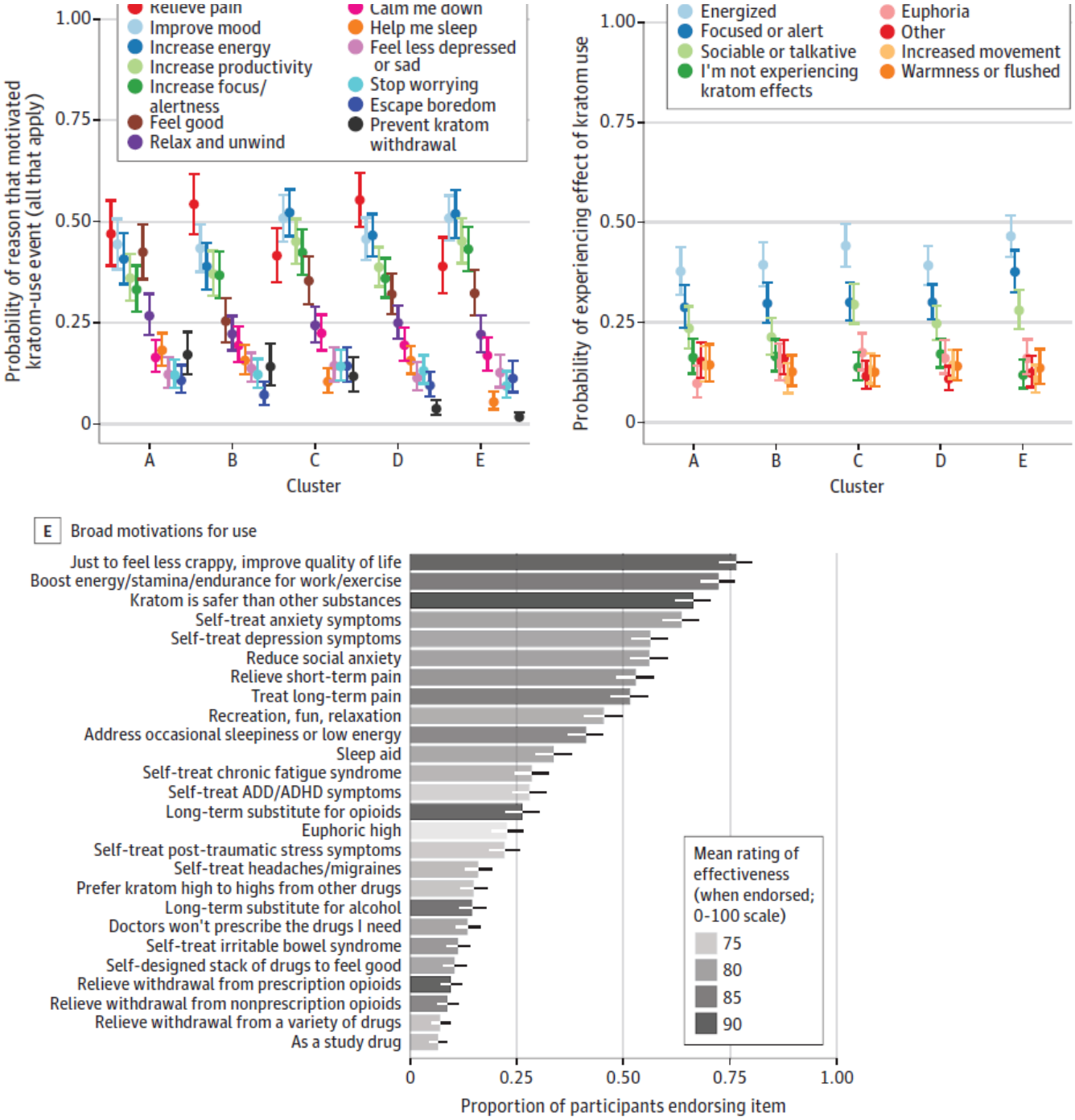
3.6.1 Reasons for Use and Benefits of Use

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.

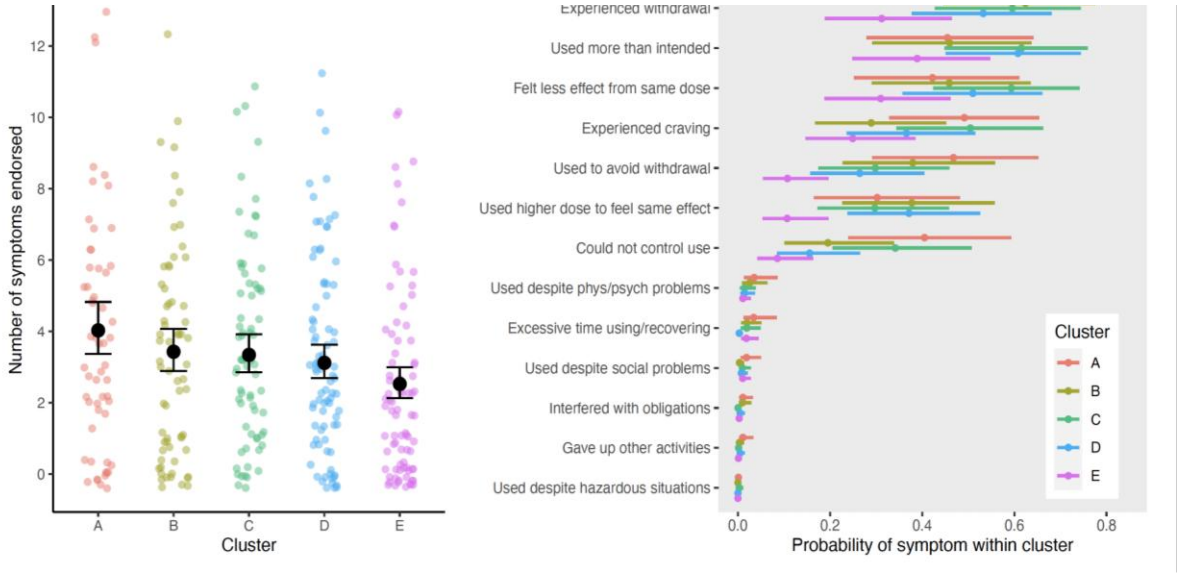
These results were largely confirmed in a much larger survey conducted by Hill et al. (2024), which assessed 2,061 current kratom consumers recruited between February and May 2023. In this sample, 25.5% of participants met DSM-5 criteria for current KUD, with most cases being classified as mild (66%) 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.

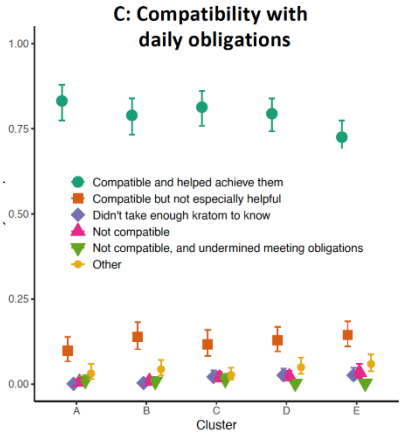
A study by Smith, Panlilio, Feldman, et al. (2024b) found in a 2022–2023 ecological momentary assessment (EMA) and survey study of 357 near-daily kratom users that 66.7% met DSM-5 criteria for KUD. However, this elevated prevalence must be interpreted in context: participants were specifically selected 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.

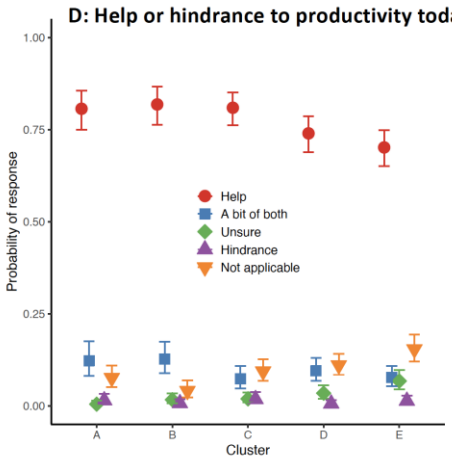
Across all clusters, kratom users reported low to moderate endorsement of DSM substance-use symptoms, with average symptom counts remaining modest and well below levels typically associated with severe substance use disorder (Figure A). The most commonly endorsed symptoms involved tolerance, withdrawal, 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.

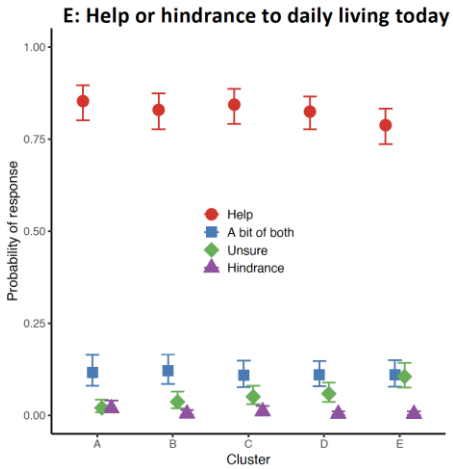
Consistent with this pattern, the large majority of respondents across clusters reported that kratom use was compatible with daily obligations and often helped them meet those obligations (Figure C), as well as improving productivity and daily living (Figures D and E). Reports of hindrance or incompatibility 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)

(Chichagi et al., 2024)

(Chinnappan et al., 2023)

(Choo et al., 2022)

(Dadamyan et al., 2025)

(Dasgupta & Ye, 2024)

(DeJonge et al., 2023)

(Dodulik et al., 2024)

(Donroe & Fiellin, 2022)

(Eckhardt & Nickel, 2023)

(Ellis et al., 2024)

(Eudaley et al., 2022)

(Evoy et al., 2025)

(Falise et al., 2023)

(Faucher et al., 2024)

(Gandhi et al., 2024)

(Gerona et al., 2025)

(Gnanasegaram et al., 2024)

(Gorelick, 2024)

(Govarthnapany et al., 2025)

(Grundmann, Veltri, Morcos, Knightes, et al., 2022)

(Grundmann, Veltri, Morcos, Knightes Iii, et al., 2022)

(Grundmann, Hendrickson, et al., 2023)

(Grundmann, Hill, et al., 2023)

(Grundmann, Veltri, et al., 2023)

(Grundmann, Smith, et al., 2024)

(Schmid et al., 2022)

(Settle et al., 2023)

(Schwensohn et al., 2022)

(Sekar et al., 2022)

(Settle & Yang, 2022)

(Settle et al., 2024)

(Sharron et al., 2025)

(Shi & Shea, 2024)

(Singh et al., 2023)

(Smith, Dunn, Epstein, et al., 2022)

(Smith, Dunn, Grundmann, et al., 2022b)

(Smith, Dunn, Grundmann, et al., 2022a)

(Smith, Dunn, Rogers, Garcia-Romeu, et al., 2022)

(Smith, Dunn, Rogers, Grundmann, et al., 2022)

(Smith, Rogers, Dunn, et al., 2022)

(Smith, Rogers, & Strickland, 2022)

(Smith, Feldman, Dunn, McCurdy, Grundmann, et al., 2023)

(Smith, Feldman, Dunn, McCurdy, Weiss, et al., 2023)

(Smith, Rogers, et al., 2023)

(Smith, Sharma, et al., 2023)

(Smith, Epstein, et al., 2024)

(Smith, Feldman, et al., 2024)

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

(Smith, Panlilio, Sharma, et al., 2024)

(Smith, Rogers, 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)
(Nsubuga et al., 2022)	(Y. Yang et al., 2024)
(Osawa & Johnson, 2025)	(Zamarripa et al., 2024)

References

Abdali, N., Nadipour Borujeni, M., Hosseini, S. A., Malekzadeh, R., Abolhasani, M., Mirzaei, S. A., & Elahian, F. (2024). Paynantheine more effectively reverses multidrug resistance in malignant EPG85.257RDB and MCF7MX cells than morphine and speciociliatine. *Cell Biol Int*, *48*(6), 861-871. https://doi.org/10.1002/cbin.12152

Abduraman, M. A., Amanah, A., Hamid, S. B. S., Abdullah, M., Sulaiman, S. F., & Tan, M. L. (2025). The regulatory effects of mitragynine on P-glycoprotein transporter. *J Pharm Pharmacol*, *77*(2), 321-334. https://doi.org/10.1093/jpp/rgae131

Adzrago, D., Obekpa, E. O., Suragh, T. A., John, E. R., Yeh, P. G., Gallardo, K. R., & Wilkerson, J. M. (2022). Kratom use categories and their associations with co-occurring substance use and mental health disorder symptoms during the COVID-19 pandemic. *Drug Alcohol Depend*, *239*, 109605. https://doi.org/10.1016/j.drugalcdep.2022.109605

Ahmad, I., Prabowo, W. C., Arifuddin, M., Fadraersada, J., Indriyanti, N., Herman, H., Purwoko, R. Y., Nainu, F., Rahmadi, A., Paramita, S., Kuncoro, H., Mita, N., Narsa, A. C., Prasetya, F., Ibrahim, A., Rijai, L., Alam, G., Mun'im, A., & Dej-Adisai, S. (2022). Mitragyna Species as Pharmacological Agents: From Abuse to Promising Pharmaceutical Products. *Life (Basel)*, *12*(2). https://doi.org/10.3390/life12020193

Ahmed, S., Tran, Q. V., & McLean, M. (2023). The Great Imitator: A Case of Accidental Kratom Overdose. *Cureus*, *15*(8), e43144. https://doi.org/10.7759/cureus.43144

Akbar, N. H., Suarantika, F., Fakih, T. M., Haniffadli, A., Muslimawati, K., & Putra, A. M. P. (2025). Screening, docking, and molecular dynamics analysis of Mitragyna speciosa (Korth.) compounds for targeting HER2 in breast cancer. *Curr Res Struct Biol*, *10*, 100171. https://doi.org/10.1016/j.crstbi.2025.100171

Alameh, I., Lebedev, M. V., Clark, J. M., Kamareddine, M., Ferrara, D., DeLorenzo, O., Sidhu, B. V., & Heric, A. (2025). Kratom-Associated Acute Right Ventricular Dysfunction: Diagnostic and Management Insights. *JACC Case Rep*, *30*(20), 104206. https://doi.org/10.1016/j.jaccas.2025.104206

Alford, A. S., Moreno, H. L., Benjamin, M. M., Dickinson, C. F., & Hamann, M. T. (2025). Exploring the Therapeutic Potential of Mitragynine and Corynoxeine: Kratom-Derived Indole and Oxindole Alkaloids for Pain Management. *Pharmaceuticals (Basel)*, *18*(2). https://doi.org/10.3390/ph18020222

Alghalith, A., Nguyen, H., & Tennant, R. (2024). The Complexities of Kratom: Insights on an Increasingly Frequent Clinical Encounter. *Cureus*, *16*(5), e59650. https://doi.org/10.7759/cureus.59650

Allison, D. R., Mubarak, M., Sharma, N., & Rao, D. S. (2022). Kratom (Mitragyna speciosa)-Induced Hepatitis. *ACG Case Rep J*, *9*(4), e00715. https://doi.org/10.14309/crj.0000000000000715

Alsbrook, S., Pro, G., & Koturbash, I. (2025). From kratom to 7-hydroxymitragynine: evolution of a natural remedy into a public-health threat. *Pharm Biol*, *63*(1), 896-911. https://doi.org/10.1080/13880209.2025.2590311

Ameline, A., Gheddar, L., Arbouche, N., Blanchot, A., Raul, J. S., & Kintz, P. (2024). Testing for Kratom alkaloids in fingernail clippings - not only mitragynine. *J Pharm Biomed Anal*, *243*, 116078. https://doi.org/10.1016/j.jpba.2024.116078

Anand, A., & Hosanagar, A. (2022). The Addictive Potential and Challenges with Use of the "Herbal Supplement" Kratom: A Case Report and Literature Review. *Pain Med*, *23*(1), 4-9. https://doi.org/10.1093/pm/pnab126

Anderer, S. (2025). What to Know About 7-OH, the New Vape Shop Hazard. *JAMA*. https://doi.org/10.1001/jama.2025.13592

Angyal, P., Hegedüs, K., Mészáros, B. B., Daru, J., Dudás, Á., Galambos, A. R., Essmat, N., Al-Khrasani, M., Varga, S., & Soós, T. (2023). Total Synthesis and Structural Plasticity of Kratom Pseudoindoxyl Metabolites. *Angew Chem Int Ed Engl*, *62*(35), e202303700. https://doi.org/10.1002/anie.202303700

Annuar, N. A. K., Azlan, U. K., Mediani, A., Tong, X., Han, R., Al-Olayan, E., Baharum, S. N., Bunawan, H., Sarian, M. N., Hamezah, H. S., & Jantan, I. (2024). An insight review on the neuropharmacological effects, mechanisms of action, pharmacokinetics and toxicity of mitragynine. *Biomed Pharmacother*, *171*, 116134. https://doi.org/10.1016/j.biopha.2024.116134

Arenson, A., Campbell, C. I., & Remler, I. (2023). Psychoactive plant derivatives (ayahuasca, ibogaine, kratom) and their application in opioid withdrawal and use disorder - a narrative review. *J Addict Dis*, 1-11. https://doi.org/10.1080/10550887.2023.2195777

Arenson, A., Campbell, C. I., & Remler, I. (2024). Psychoactive plant derivatives (ayahuasca, ibogaine, kratom) and their application in opioid withdrawal and use disorder - a narrative review. *J Addict Dis*, *42*(3), 253-263. https://doi.org/10.1080/10550887.2023.2195777

Arhin, M., Mobley, J., Hamad, H., & Remick, P. (2023). Successful Management of Kratom Use Disorder With Buprenorphine and Naloxone. *Cureus*, *15*(6), e41146. https://doi.org/10.7759/cureus.41146

Awad, M., Burke, H. H., & Oakman, S. A. (2024). Kratom-Induced Psychiatric Decompensation and Paranoid Delusions. *Cureus*, *16*(2), e54626. https://doi.org/10.7759/cureus.54626

Axelsson, M. A. B., Lovgren, H., Kronstrand, R., Green, H., & Bergstrom, M. A. (2022). Retrospective identification of new psychoactive substances in patient samples submitted for clinical drug analysis. *Basic Clin Pharmacol Toxicol*, *131*(5), 420-434. https://doi.org/10.1111/bcpt.13786

Axelsson, M. A. B., Lovgren, H., Kronstrand, R., Green, H., & Bergstrom, M. A. (2025). Epidemiology of New Psychoactive Substances in Relation to Traditional Drugs of Abuse in Clinical Oral Fluid Samples. *Basic Clin Pharmacol Toxicol*, *136*(2), e14117. https://doi.org/10.1111/bcpt.14117

Bachu, A. K., Singal, P., Griffin, B., Harbaugh, L., Prasad, S., Jain, L., Mohiuddin, S., Papudesi, B. N., Nagi, T., Youssef, N. A., Chopra, A., & Ahmed, S. (2023). Kratom use and mental health: A systematic literature review and case example. *J Addict Dis*, 1-12. https://doi.org/10.1080/10550887.2023.2273192

Bachu, A. K., Singal, P., Griffin, B., Harbaugh, L., Prasad, S., Jain, L., Mohiuddin, S., Papudesi, B. N., Nagi, T., Youssef, N. A., Chopra, A., & Ahmed, S. (2024). Kratom use and mental health: A systematic literature review and case example. *J Addict Dis*, *42*(4), 301-312. https://doi.org/10.1080/10550887.2023.2273192

Bade, R., van Herwerden, D., Rousis, N., Adhikari, S., Allen, D., Baduel, C., Bijlsma, L., Boogaerts, T., Burgard, D., Chappell, A., Driver, E. M., Sodre, F. F., Fatta-Kassinos, D., Gracia-Lor, E., Gracia-Marin, E., Halden, R. U., Heath, E., Jaunay, E., Krotulski,

A., . . . Mueller, J. (2024). Workflow to facilitate the detection of new psychoactive substances and drugs of abuse in influent urban wastewater. *J Hazard Mater*, *469*, 133955. https://doi.org/10.1016/j.jhazmat.2024.133955

Bakar, K. A., Lam, S. D., & Feroz, S. R. (2024). Binding characteristics of the major kratom alkaloid, mitragynine, towards serum albumin: Spectroscopic, calorimetric, microscopic, and computational investigations. *Chem Biol Interact*, *404*, 111264. https://doi.org/10.1016/j.cbi.2024.111264

Bakar, K. A., Lam, S. D., & Feroz, S. R. (2024). Binding characteristics of the major kratom alkaloid, mitragynine, towards serum albumin: Spectroscopic, calorimetric, microscopic, and computational investigations. *Chemico-Biological Interactions*, *404*, 111264. https://doi.org/https://doi.org/10.1016/j.cbi.2024.111264

Bakir, D., Konopka, C., Pisati, S., Shah, S., Maryala, S., Catalano, A., Ibrahim, F., & Allam, H. (2025). A case report of reversible ischemic MRI changes and discussion of possible link to kratom use. *NeuroImage: Reports*, *5*(2), 100261. https://doi.org/https://doi.org/10.1016/j.ynirp.2025.100261

Basheer, M., Hassan, Z., & Gam, L. H. (2023). Upregulation of Brain's Calcium Binding Proteins in Mitragynine Dependence: A Potential Cellular Mechanism to Addiction. *Int J Med Sci*, *20*(1), 102-113. https://doi.org/10.7150/ijms.78861

Bayu, A., Rahmawati, S. I., Karim, F., Panggabean, J. A., Nuswantari, D. P., Indriani, D. W., Ahmadi, P., Witular, R., Dharmayanti, N., & Putra, M. Y. (2024). An In Vitro Examination of Whether Kratom Extracts Enhance the Cytotoxicity of Low-Dose Doxorubicin against A549 Human Lung Cancer Cells. *Molecules*, *29*(6). https://doi.org/10.3390/molecules29061404

Beckerdite, E., & Wu, A. H. B. (2024). Untargeted High-Resolution Mass Spectrometry for Detection of Natural Products and Confiscated Powders and Pills. *Methods Mol Biol*, *2737*, 185-193. https://doi.org/10.1007/978-1-0716-3541-4_18

Begum, T., Arzmi, M. H., Helal Uddin, A. B. M., Khatib, A., Abbas, S. A., & Ahmed, Q. U. (2024). Mitragyna speciosa Korth toxicity: Experimental findings and future prospects. *J Taibah Univ Med Sci*, *19*(6), 1143-1156. https://doi.org/10.1016/j.jtumed.2024.12.002

Begum, T., Arzmi, M. H., Khatib, A., Uddin, A., Aisyah Abdullah, M., Rullah, K., Mat So'ad, S. Z., Zulaikha Haspi, N. F., Nazira Sarian, M., Parveen, H., Mukhtar, S., & Ahmed, Q. U. (2024). A review on Mitragyna speciosa (Rubiaceae) as a prominent medicinal plant based on ethnobotany, phytochemistry and pharmacological activities. *Nat Prod Res*, 1-17. https://doi.org/10.1080/14786419.2024.2371564

Behonick, G. S., Vu, C., Czarnecki, L., El-Ters, M., & Shanks, K. G. (2022). Two Single-Drug Fatal Intoxications by Mitragynine. *J Anal Toxicol*, *46*(5), e110-e114. https://doi.org/10.1093/jat/bkac016

Berthold, E. C., Kamble, S. H., Kanumuri, S. R. R., Kuntz, M. A., Senetra, A. S., Chiang, Y. H., Mukhopadhyay, S., McCurdy, C. R., & Sharma, A. (2024). Pharmacokinetic Interaction of Kratom and Cannabidiol in Male Rats. *Pharmaceutics*, *16*(3). https://doi.org/10.3390/pharmaceutics16030318

Berthold, E. C., Kamble, S. H., Raju, K. S., Kuntz, M. A., Senetra, A. S., Mottinelli, M., Leon, F., Restrepo, L. F., Patel, A., Ho, N. P., Hiranita, T., Sharma, A., McMahon, L. R., & McCurdy, C. R. (2022). The Lack of Contribution of 7-Hydroxymitragynine to the Antinociceptive Effects of Mitragynine in Mice: A Pharmacokinetic and

Pharmacodynamic Study. *Drug Metab Dispos*, *50*(2), 158-167. https://doi.org/10.1124/dmd.121.000640
Bonnet, U., Specka, M., Kanti, A. K., & Scherbaum, N. (2022). Differences between users' and addiction medicine experts' harm and benefit assessments of licit and illicit psychoactive drugs: Input for psychoeducation and legalization/restriction debates. *Front Psychiatry*, *13*, 1041762. https://doi.org/10.3389/fpsyt.2022.1041762
Bowe, A., & Kerr, P. L. (2024). Endogenous Opioid Activity as the Mechanism of Action for Mitragyna speciosa (Kratom): The Current State of the Evidence. *Adv Neurobiol*, *35*, 287-313. https://doi.org/10.1007/978-3-031-45493-6_15
Bowman, J., Lai, M., Charles, J. E., Gordon, A. J., & Smid, M. C. (2023). Kratom Use Among Pregnant and Lactating Individuals With Substance Use Disorder. *J Addict Med*, *17*(6), 722-724. https://doi.org/10.1097/ADM.0000000000001212
Brogdon, H. D., McPhee, M. M., Paine, M. F., Cox, E. J., & Burns, A. G. (2022). A Case of Potential Pharmacokinetic Kratom-drug Interactions Resulting in Toxicity and Subsequent Treatment of Kratom Use Disorder With Buprenorphine/Naloxone. *J Addict Med*, *16*(5), 606-609. https://doi.org/10.1097/ADM.0000000000000968
Broul, M., Rudenko, X., Bajus, A., Kral, J., Kyenge, D. M., Stankova, Z., & Albrecht, J. (2025). Case Report: Cannabis and kratom-induced self-amputation of ears and penis. *Front Psychiatry*, *16*, 1479863. https://doi.org/10.3389/fpsyt.2025.1479863
Broyan, V. R., Brar, J. K., Allgaier Student, T., & Allgaier, J. T. (2022). Long-term buprenorphine treatment for kratom use disorder: A case series. *Subst Abus*, *43*(1), 763-766. https://doi.org/10.1080/08897077.2021.2010250
Carlezon, W. A., Jr., & Krystal, A. D. (2016). Kappa-Opioid Antagonists for Psychiatric Disorders: From Bench to Clinical Trials. *Depress Anxiety*, *33*(10), 895-906. https://doi.org/10.1002/da.22500
Cauldron, K. R., Suchy, N., & Irwin, A. N. (2024). Characterization of kratom use and knowledge at a rural, Oregon community health center. *J Am Pharm Assoc (2003)*, 102138. https://doi.org/10.1016/j.japh.2024.102138
Charoenratana, S., Anukul, C., & Aramrattana, A. (2021). Attitudes towards Kratom use, decriminalization and the development of a community-based Kratom control mechanism in Southern Thailand. *Int J Drug Policy*, *95*, 103197. https://doi.org/10.1016/j.drugpo.2021.103197
Chathiran, W., Varatojo, L., Chimasangkanan, J., Saiyasombat, W., & Srichamnong, W. (2025). Effect of Heat Processing on Major Psychoactive Compounds and Total Phenolic Content in Psychotropic Plants: Cannabis (Cannabis Sativa) and Kratom (Mitragyna Speciosa) Leaves. *Cannabis Cannabinoid Res*. https://doi.org/10.1089/can.2024.0201
Chen, M. Y., Tu, Y. C., Shyu, H. Y., Lin, T. A., Juan, C. P., & Wu, F. C. (2025). Using rDNA ITS2 barcoding to identify kratom (Mitragyna speciosa) from the genus Mitragyna and Neolamarckia cadamba. *Electrophoresis*, *46*(3-4), 192-197. https://doi.org/10.1002/elps.202400003
Chiang, Y. H., Berthold, E. C., Kuntz, M. A., Kanumuri, S. R. R., Senetra, A. S., Mukhopadhyay, S., Hampson, A. J., McCurdy, C. R., & Sharma, A. (2024). Multiple-Dose Pharmacokinetics and Safety of Mitragynine, the Major Alkaloid of Kratom, in Rats. *ACS Pharmacol Transl Sci*, *7*(8), 2452-2464. https://doi.org/10.1021/acsptsci.4c00277

Chiang, Y. H., Kanumuri, S. R. R., Kuntz, M. A., Senetra, A. S., Berthold, E. C., Kamble, S. H., Mukhopadhyay, S., Hampson, A. J., McCurdy, C. R., & Sharma, A. (2025). In Vitro and In Vivo Pharmacokinetic Characterization of 7-Hydroxymitragynine, an Active Metabolite of Mitragynine, in Sprague-Dawley Rats. *Eur J Drug Metab Pharmacokinet*. https://doi.org/10.1007/s13318-025-00939-2

Chiappini, S., Vickers-Smith, R., Guirguis, A., Corkery, J. M., Martinotti, G., Harris, D. R., & Schifano, F. (2022). Pharmacovigilance Signals of the Opioid Epidemic over 10 Years: Data Mining Methods in the Analysis of Pharmacovigilance Datasets Collecting Adverse Drug Reactions (ADRs) Reported to EudraVigilance (EV) and the FDA Adverse Event Reporting System (FAERS). *Pharmaceuticals (Basel)*, *15*(6). https://doi.org/10.3390/ph15060675

Chichagi, F., Alikhani, R., & Beigi Harchegani, A. (2024). Cardiovascular health in kratom users; a narrative review. *J Addict Dis*, *42*(4), 313-325. https://doi.org/10.1080/10550887.2023.2282033

Chinnappan, J., Navari, Y., Casini, D., Palanisamy, N., Parikh, N., & Seedahmed, E. (2023). Kratom-Induced Acute Respiratory Distress Syndrome (ARDS). *Eur J Case Rep Intern Med*, *10*(4), 003835. https://doi.org/10.12890/2023_003835

Choo, L. L., Ahmad Zahari, M. M., Choy, S. K., Abdul Rahim, N., & Abd Rashid, R. (2022). The Prevalence and Psychosocial Correlates of Ketum (Mitragyna speciosa) Use among Individuals on Methadone Maintenance Therapy Programme in Hospital Taiping, Malaysia. *Healthcare (Basel)*, *10*(4). https://doi.org/10.3390/healthcare10040746

Chou, R., Wagner, J., Ahmed, A. Y., Morasco, B. J., Kansagara, D., Selph, S., Holmes, R., & Fu, R. (2022). *Living Systematic Review on Cannabis and Other Plant-Based Treatments for Chronic Pain: 2022 Update* (22-EHC042). https://www.ncbi.nlm.nih.gov/pubmed/36351096

Citti, C., Lagana, A., Capriotti, A. L., Montone, C. M., & Cannazza, G. (2023). Kratom: The analytical challenge of an emerging herbal drug. *J Chromatogr A*, *1703*, 464094. https://doi.org/10.1016/j.chroma.2023.464094

Coe, M. A., Pillitteri, J. L., Sembower, M. A., Gerlach, K. K., & Henningfield, J. E. (2019). Kratom as a substitute for opioids: Results from an online survey. *Drug and Alcohol Dependence*, *202*, 24-32. https://doi.org/https://doi.org/10.1016/j.drugalcdep.2019.05.005

Collar, A. L., & Barrett, E. D. (2024). Kratom: An Emerging Issue for Research and Physician Education. *Ann Intern Med*, *177*(9), 1267-1268. https://doi.org/10.7326/ANNALS-24-00209

Covvey, J. R., Vogel, S. M., Peckham, A. M., & Evoy, K. E. (2020). Prevalence and characteristics of self-reported kratom use in a representative US general population sample. *J Addict Dis*, *38*(4), 506-513. https://doi.org/10.1080/10550887.2020.1788914

Dadamyan, A. F., Barada, H., & Sablaban, I. M. (2025). The Hidden Perils of Kratom: A Case of Drug-Induced Psychosis Successfully Treated With a Second-Generation Antipsychotic. *Prim Care Companion CNS Disord*, *27*(4). https://doi.org/10.4088/PCC.25cr03935

Das, J. (2024). Kratom Alkaloids for the Treatment of Alcohol Use Disorder. *ACS Chem Neurosci*, *15*(24), 4352-4359. https://doi.org/10.1021/acschemneuro.4c00675

Dasgupta, A., & Ye, Z. (2024). Severe jaundice with life-threatening liver failure after Kratom use: Reversed by plasma exchange. *Transfus Apher Sci*, *63*(3), 103898. https://doi.org/10.1016/j.transci.2024.103898

DEA. (2023). *Schedules of Controlled Substances: Temporary Placement of MDMB-4en-PINACA, 4F-MDMB-BUTICA, ADB-4en-PINACA, CUMYL-PEGACLONE, 5F-EDMB-PICA, and MMB-FUBICA into Schedule I*. Retrieved 22 January from https://www.federalregister.gov/documents/2023/12/12/2023-27243/schedules-of-controlled-substances-temporary-placement-of-mdmb-4en-pinaca-4f-mdmb-butica

DEA. (2025a). *Schedules of Controlled Substances: Extension of Temporary Placement of CUMYL-PEGACLONE in Schedule I of the Controlled Substances Act*. Retrieved 22 January from https://www.federalregister.gov/documents/2025/12/11/2025-22496/schedules-of-controlled-substances-extension-of-temporary-placement-of-cumyl-pegaclone-in-schedule-i#footnote-1-p57542

DEA. (2025b). *Schedules of Controlled Substances: Placement of Three Specific Fentanyl-Related Substances in Schedule I*. Retrieved 22 January from https://www.federalregister.gov/documents/2025/06/10/2025-10372/schedules-of-controlled-substances-placement-of-three-specific-fentanyl-related-substances-in

Deebel, N. A., Scarberry, K., O'Connor, C. A., Dutta, R., Matz, E., Hanlon, C. A., & Terlecki, R. P. (2023). Investigating the Impact of Kratom (Mitragyna speciosa) Use Upon Male Sexual Health. *Res Rep Urol*, *15*, 69-76. https://doi.org/10.2147/RRU.S390094

DeJonge, P., Gummin, D., Titelbaum, N., & Meiman, J. (2023). Description of Kratom Exposure Events in Wisconsin as Reported to the Wisconsin Poison Center, January 1, 2010 to September 1, 2022. *WMJ*, *122*(3), 187-190. https://www.ncbi.nlm.nih.gov/pubmed/37494649

DHHS. (2025). *Press Conference on Opioid 7-OH Public Safety Measure*. https://www.youtube.com/live/FWHfeIgzVD4

Dhoble, L. R., Gour, A., McCurdy, C. R., & Sharma, A. (2025). Evaluating the drug interactions in kratom usage: clinical application. *Expert Opin Drug Metab Toxicol*, *21*(8), 949-959. https://doi.org/10.1080/17425255.2025.2521045

Dodulik, J., Plasek, J., Handlos, P., Gregorova, A., & Vaclavik, J., Jr. (2024). Ventricular fibrillation during football training as a consequence of kratom and caffeine use in an adolescent: case report. *Eur Heart J Case Rep*, *8*(8), ytae364. https://doi.org/10.1093/ehjcr/ytae364

Doharszky, A., Vagi, E. M., Konczol, A., Simon, A., Varnagy, E., Muratov, M., Steiger, K. I., Varnai, B., Beni, S., Riethmuller, E., & Fejos, I. (2024). Kratom Alkaloids: A Blood-Brain Barrier Specific Membrane Permeability Assay-Guided Isolation and Cyclodextrin Complexation Study. *Molecules*, *29*(22). https://doi.org/10.3390/molecules29225302

Donroe, J. H., & Fiellin, D. A. (2022). A Case of Kratom Use: Implications for Managing Addiction and Addressing Comorbidity in Overdose Survivors, and for the Education of Clinicians Who Are Not Addiction Specialists. *J Addict Med*, *16*(2), 138-140. https://doi.org/10.1097/ADM.0000000000000872

Dror, M. J., Misa, J., Yee, D. A., Chu, A. M., Yu, R. K., Chan, B. B., Aoyama, L. S., Chaparala, A. P., O'Connor, S. E., & Tang, Y. (2024). Engineered biosynthesis of plant heteroyohimbine and corynantheine alkaloids in Saccharomyces cerevisiae. *J Ind Microbiol Biotechnol*, *51*. https://doi.org/10.1093/jimb/kuad047

Dufour, J., Lin, X. L., Wang, J., Baisley, J., Atif, A., Berthold, E. C., & Atallah, R. (2024). The Safety of Multiple-Dose Liquid Blend Containing Kava and Kratom in Healthy Adults. *Cureus*, *16*(12), e75654. https://doi.org/10.7759/cureus.75654

Durkin, R., Grundmann, O., & Smith, K. E. (2025). Chapter 7 - Regulation and policy regarding kratom-derived dietary supplements and direct-to-consumer sales. In J. E. Henningfield, C. E. Beyer, & R. B. Raffa (Eds.), *Kratom: History, Science and Therapeutic Potential* (pp. 95-114). Academic Press. https://doi.org/10.1016/B978-0-443-27412-1.00007-9

Eckhardt, L. L., & Nickel, A. C. (2023). The Changing Complexities of Opioid-Related Sudden Death. *J Am Coll Cardiol*, *81*(23), 2269-2271. https://doi.org/10.1016/j.jacc.2023.04.024

Edinoff, A. N., Kaufman, S. E., Mahoney, T. C., Upshaw, W. C., Gong, J., Cornett, E. M., Murnane, K. S., Kaye, A. M., Varrassi, G., Shekoohi, S., & Kaye, A. D. (2024). Kratom: A Narrative Review of the Possible Clinical Uses and Dangers of This Opioid-Like Plant. *Cureus*, *16*(11), e73058. https://doi.org/10.7759/cureus.73058

Effendy, M. A., Yunusa, S., Mat, N. H., Has, A. T. C., Müller, C. P., & Hassan, Z. (2023). The role of AMPA and NMDA receptors in mitragynine effects on hippocampal synaptic plasticity. *Behav Brain Res*, *438*, 114169. https://doi.org/10.1016/j.bbr.2022.114169

Eggleston, W., Stoppacher, R., Suen, K., Marraffa, J. M., & Nelson, L. S. (2019). Kratom Use and Toxicities in the United States. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, *39*(7), 775-777. https://doi.org/https://doi.org/10.1002/phar.2280

Ellis, C. R., Racz, R., Kruhlak, N. L., Kim, M. T., Zakharov, A. V., Southall, N., Hawkins, E. G., Burkhart, K., Strauss, D. G., & Stavitskaya, L. (2020). Evaluating kratom alkaloids using PHASE. *PLoS One*, *15*(3), e0229646. https://doi.org/10.1371/journal.pone.0229646

Ellis, M. S., Buttram, M. E., Forber, A., & Black, J. C. (2024). Associations Between Kratom-Related State Policy Environments and Kratom Use in a Nationally Representative Population in the United States. *J Psychoactive Drugs*, *56*(3), 333-341. https://doi.org/10.1080/02791072.2023.2223622

Emerick, T., Durbhakula, S., Eibel, M. R., & Kohan, L. (2024). Kratom: a primer for pain physicians. *Curr Opin Anaesthesiol*, *37*(5), 575-580. https://doi.org/10.1097/ACO.0000000000001413

Eudaley, S. T., Brooks, S. P., & Hamilton, L. A. (2022). Case Report: Possible Serotonin Syndrome in a Patient Taking Kratom and Multiple Serotonergic Agents. *J Pharm Pract*, 8971900221116009. https://doi.org/10.1177/08971900221116009

Evoy, K. E., Acharya, S., Bloomfield, M., Torrez, S. B., Covvey, J. R., & Witry, M. (2025). Hemp-derived tetrahydrocannabinol (THC) and kratom related health claims provided by smoke shop employees: a secret shopper study. *Am J Drug Alcohol Abuse*, 1-9. https://doi.org/10.1080/00952990.2025.2502743

Falise, A. M., Hoeflich, C. C., Nutley, S. K., Lopez-Quintero, C., & Striley, C. W. (2023). Polysubstance use profiles among US adults using Kratom (Mitragyna speciosa): A latent class analysis using The National Survey on Drug Use and Health (NSDUH). *Am J Addict*, *32*(1), 76-80. https://doi.org/10.1111/ajad.13345

Farkas, D. J., Cooper, Z. D., Heydari, L. N., Hughes, A. C., Rawls, S. M., & Ward, S. J. (2025). Kratom Alkaloids, Cannabinoids, and Chronic Pain: Basis of Potential Utility

and Role in Therapy. *Cannabis Cannabinoid Res*, *10*(2), 187-199. https://doi.org/10.1089/can.2023.0064
Farkas, D. J., Inan, S., Heydari, L. N., Johnson, C. T., Zhao, P., Bradshaw, H. B., Ward, S. J., & Rawls, S. M. (2023). Cannabinoid mechanisms contribute to the therapeutic efficacy of the kratom alkaloid mitragynine against neuropathic, but not inflammatory pain. *Life Sci*, *328*, 121878. https://doi.org/10.1016/j.lfs.2023.121878
Faucher, M. A., Morillos, S., Cordova, P., McNeil-Santiel, J., Onisko, N., Adhikari, E. H., & Nelson, D. B. (2024). Kratom (Mitragyna speciosa): A Case Review of Use Before and During Pregnancy. *J Midwifery Womens Health*, *69*(1), 144-149. https://doi.org/10.1111/jmwh.13558
Fauzi, N. A. M., Tan, M. L., Hamid, S. B. S., Singh, D., & Abdullah, M. (2022). Regular Kratom (Mitragyna speciosa Korth.) Use and Its Association With Endoplasmic Reticulum Stress Response. *J Addict Med*, *16*(6), e374-e381. https://doi.org/10.1097/ADM.0000000000000988
FDA. (2017). *Assessment of Abuse Potential of Drugs Guidance for Industry*. https://www.fda.gov/media/116739/download
FDA. (2018). *Statement from FDA Commissioner Scott Gottlieb, M.D., on the agency's scientific evidence on the presence of opioid compounds in kratom, underscoring its potential for abuse*. Retrieved 22 January from https://web.archive.org/web/20190701173059/https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-agencys-scientific-evidence-presence-opioid-compounds
FDA. (2025). *FDA Takes Steps to Restrict 7-OH Opioid Products Threatening American Consumers*. Retrieved September 23, 2025 from https://www.fda.gov/news-events/press-announcements/fda-takes-steps-restrict-7-oh-opioid-products-threatening-american-consumers
Gandhi, I., Wang, X., & Fishman, S. (2024). Rare Case of Photodistributed Hyperpigmentation Linked to Kratom Consumption. *Cutis*, *114*(3), E7-E9. https://doi.org/10.12788/cutis.1100
Garba, S. A., Shaari, K., Abdul Manap, M. R., Lee, S. Y., Abdulazeez, I., & Mohd Faudzi, S. M. (2024). Quantitative analysis of selected alkaloids of Mitragyna speciosa using (1)H quantitative nuclear magnetic resonance spectroscopy. *Magn Reson Chem*, *62*(11), 803-813. https://doi.org/10.1002/mrc.5477
Garcia-Romeu, A., Cox, D. J., Smith, K. E., Dunn, K. E., & Griffiths, R. R. (2020). Kratom (Mitragyna speciosa): User demographics, use patterns, and implications for the opioid epidemic. *Drug and Alcohol Dependence*, *208*, 107849. https://doi.org/https://doi.org/10.1016/j.drugalcdep.2020.107849
Garmon, E. H., & Olson, K. (2022). Narrative Review of Kratom, an Emerging Psychoactive Substance With Perianesthetic Implications. *Anesth Analg*, *135*(6), 1180-1188. https://doi.org/10.1213/ANE.0000000000006177
Garza-Garcia, J. J. O., & Qu, Y. (2024). Chemical, pharmacological properties and biosynthesis of opioid mitragynine in Mitragyna speciosa (kratom). *Curr Opin Plant Biol*, *81*, 102600. https://doi.org/10.1016/j.pbi.2024.102600
Gerona, R., Tomer, D., Nielsen, D., Sage, A. C., French, D., Tolles, J., & Chenoweth, J. A. (2025). New psychoactive substances in roadway crash victims in California. *Front Toxicol*, *7*, 1572324. https://doi.org/10.3389/ftox.2025.1572324

Giroir, B. P. (2018). *Letter from the Assistant Secretary of Health to the Administrator of the Drug Enforcement Administration to Rescind Previous Support to Permanently Place Mitragynine and 7-hydroxymitragynine in Schedule I of the Controlled Substances Act 2018*. https://images.go02.informamarkets.com/Web/Informa02/%7b548e6d56-2ea4-4da4-9404-0348b56e9a88%7d_dhillon-8.16.2018-response-letter-from-ash-radm-giroir.pdf

Gnanasegaram, S. A., Sexton, L., & Stanciu, C. N. (2024). Kratom Consumption - The Tales of Three Patients. *J Psychoactive Drugs*, 1-4. https://doi.org/10.1080/02791072.2024.2424278

Gorelick, D. A. (2022). Kratom: Substance of Abuse or Therapeutic Plant? *Psychiatr Clin North Am*, *45*(3), 415-430. https://doi.org/10.1016/j.psc.2022.04.002

Gorelick, D. A. (2024). Response to: "Prevalence of Kratom Use Disorder Among Kratom Consumers". *J Addict Med*. https://doi.org/10.1097/ADM.0000000000001419

Govarthnapany, N., Gabrhelik, R., & Singh, D. (2025). Kratom (Mitragyna speciosa Korth.) Use Among Poly-Drug Users in Southeast Asia: A Systematic Review. *J Psychoactive Drugs*, 1-11. https://doi.org/10.1080/02791072.2025.2465797

Green, M., Vadiei, N., Veltri, C. A., Grundmann, O., & Evoy, K. E. (2024). Kratom as a potential substance use disorder harm reduction agent. *Front Public Health*, *12*, 1416689. https://doi.org/10.3389/fpubh.2024.1416689

Green, M., Veltri, C. A., Prozialeck, W. C., & Grundmann, O. (2025). The neuropharmacology of kratom, a novel psychoactive natural product. *Prog Neuropsychopharmacol Biol Psychiatry*, *136*, 111215. https://doi.org/10.1016/j.pnpbp.2024.111215

Groff, D., Stuckey, H., Philpott, C., Van Dyke, E., Silvis, M., Leong, S. L., & Bone, C. (2022). Kratom use disorder: a primer for primary care physicians. *J Addict Dis*, *40*(1), 131-141. https://doi.org/10.1080/10550887.2021.1950263

Grundmann, O. (2017). Patterns of Kratom use and health impact in the US—Results from an online survey. *Drug and Alcohol Dependence*, *176*, 63-70. https://doi.org/https://doi.org/10.1016/j.drugalcdep.2017.03.007

Grundmann, O., Garcia-Romeu, A., McCurdy, C. R., Sharma, A., Smith, K. E., Swogger, M. T., & Weiss, S. T. (2024). Not all kratom is equal: The important distinction between native leaf and extract products. *Addiction*, *119*(1), 202-203. https://doi.org/10.1111/add.16366

Grundmann, O., Green, M., Berthold, E., Yoon, S. L., & Ray, D. (2025). Prevalence and Use Patterns of Kratom (Mitragyna speciosa Korth.) in a US Nationally Representative Sample. *J Psychoactive Drugs*, 1-9. https://doi.org/10.1080/02791072.2025.2474249

Grundmann, O., Hendrickson, R. G., & Greenberg, M. I. (2023). Kratom: History, pharmacology, current user trends, adverse health effects and potential benefits. *Dis Mon*, *69*(6), 101442. https://doi.org/10.1016/j.disamonth.2022.101442

Grundmann, O., Hill, K., Al Barzanji, E., Hazrat, N. G., Kaur, G., Negeve, R. E., Shade, S., Weber, S., & Veltri, C. A. (2023). Correlations of kratom (Mitragyna speciosa Korth.) tea bag preparations and reported pharmacological effects. *J Ethnopharmacol*, *317*, 116779. https://doi.org/10.1016/j.jep.2023.116779

Grundmann, O., Smith, K. E., Prozialeck, W. C., Veltri, C. A., & Boyer, E. W. (2024). Commentary: Presence of kratom in opioid overdose deaths: findings from coroner

postmortem toxicological report. *Front Psychiatry*, *15*, 1411964. https://doi.org/10.3389/fpsyt.2024.1411964
Grundmann, O., Veltri, C. A., Morcos, D., Knightes, D., 3rd, Smith, K. E., Singh, D., Corazza, O., Cinosi, E., Martinotti, G., Walsh, Z., & Swogger, M. T. (2022). Exploring the self-reported motivations of kratom (Mitragyna speciosa Korth.) use: a cross-sectional investigation. *Am J Drug Alcohol Abuse*, *48*(4), 433-444. https://doi.org/10.1080/00952990.2022.2041026
Grundmann, O., Veltri, C. A., Morcos, D., Knightes Iii, D., Smith, K. E., & Rogers, J. M. (2022). How essential is kratom availability and use during COVID-19? Use pattern analysis based on survey and social media data. *Subst Abus*, *43*(1), 865-877. https://doi.org/10.1080/08897077.2021.2007517
Grundmann, O., Veltri, C. A., Morcos, S., Smith, K. E., Singh, D., Corazza, O., Cinosi, E., Martinotti, G., Walsh, Z., & Swogger, M. T. (2023). Correlations of kratom (Mitragyna speciosa Korth.) use behavior and psychiatric conditions from a cross-sectional survey. *Exp Clin Psychopharmacol*. https://doi.org/10.1037/pha0000632
Haider, M., Shah, N., & Yazdani, A. (2023). Kratom-induced common bile duct dilation. *Proc (Bayl Univ Med Cent)*, *36*(1), 116-117. https://doi.org/10.1080/08998280.2022.2119541
Hartley, C., 2nd, Bulloch, M., & Penzak, S. R. (2022). Clinical Pharmacology of the Dietary Supplement Kratom (Mitragyna speciosa). *J Clin Pharmacol*, *62*(5), 577-593. https://doi.org/10.1002/jcph.2001
Harun, N., Kamaruzaman, N. A., Mohamed Sofian, Z., & Hassan, Z. (2022). Mini review: Potential therapeutic values of mitragynine as an opioid substitution therapy. *Neurosci Lett*, *773*, 136500. https://doi.org/10.1016/j.neulet.2022.136500
Hassan, Z., Singh, D., Suhaimi, F. W., Chear, N. J., Harun, N., See, C. P., Kaur, G., Mat, N. H., Bakar, S. N. S., Yusof, N. S. M., Kasinather, V. B., Chawarski, M. C., Murugaiyah, V., & Ramanathan, S. (2023). Evaluation of toxicity profile of kratom (Mitragyna speciosa Korth) decoction in rats. *Regul Toxicol Pharmacol*, *143*, 105466. https://doi.org/10.1016/j.yrtph.2023.105466
Hatch, A., Gonzalez, E., & Hanna, K. (2024). Kratom: Facts, Fiction, and the Unknown. *J Am Board Fam Med*. https://doi.org/10.3122/jabfm.2023.230335R0
Helander, A., & Rylski, A. (2023). Drug testing for mitragynine and kratom: Analytical challenges and medico-legal considerations. *Drug Test Anal*, *15*(2), 213-219. https://doi.org/10.1002/dta.3391
Hemby, S. E., McIntosh, S., Leon, F., Cutler, S. J., & McCurdy, C. R. (2019). Abuse liability and therapeutic potential of the Mitragyna speciosa (kratom) alkaloids mitragynine and 7-hydroxymitragynine. *Addiction Biology*, *24*(5), 874-885. https://doi.org/https://doi.org/10.1111/adb.12639
Henningfield, J. E., Beyer, C. E., & Raffa, R. B. (2025). *Kratom: History, Science, and Therapeutic Potential*. Academic Press (Elsevier).
Henningfield, J. E., Chawarski, M. C., Garcia-Romeu, A., Grundmann, O., Harun, N., Hassan, Z., McCurdy, C. R., McMahon, L. R., Sharma, A., Shoaib, M., Singh, D., Smith, K. E., Swogger, M. T., Vicknasingam, B., Walsh, Z., Wang, D. W., & Huestis, M. A. (2023). Kratom withdrawal: Discussions and conclusions of a scientific expert forum. *Drug Alcohol Depend Rep*, *7*, 100142. https://doi.org/10.1016/j.dadr.2023.100142

Henningfield, J. E., Coe, M. A., Griffiths, R. R., Belouin, S. J., Berger, A., Coker, A. R., Comer, S. D., Heal, D. J., Hendricks, P. S., Nichols, C. D., Sapienza, F., Vocci, F. J., & Zia, F. Z. (2022). Psychedelic drug abuse potential assessment research for new drug applications and Controlled Substances Act scheduling. *Neuropharmacology*, *218*, 109220. https://doi.org/https://doi.org/10.1016/j.neuropharm.2022.109220

Henningfield, J. E., Comer, S. D., Banks, M., Coe, M. A., Collins, G., Cooper, Z. D., Fantegrossi, W., Durgin, C., Heal, D. J., Huskinson, S., Lanier, R., Lynch, W., Meisch, R., Rowlett, J., Strickland, J. C., & Gannon, B. (2025). Abuse Potential Assessment of Novel Central Nervous System Active and Psychedelic Substances for Controlled Substances Act Scheduling Recommendations. *Journal of Psychopharmacology – Special Issue on Psychedelics Dedicated to Roland R. Griffiths (In Press)*.

Henningfield, J. E., & Fant, R. V. (2016). *Assessment of Kratom under the CSA Eight Factors and Scheduling Recommendation*. P. Associates.

Henningfield, J. E., Fant, R. V., & Wang, D. W. (2018). The abuse potential of kratom according the 8 factors of the controlled substances act: implications for regulation and research. *Psychopharmacology*, *235*(2), 573-589. https://doi.org/10.1007/s00213-017-4813-4

Henningfield, J. E., Grundmann, O., Garcia-Romeu, A., & Swogger, M. T. (2022). We Need Better Estimates of Kratom Use Prevalence. *Am J Prev Med*, *62*(1), 132-133. https://doi.org/10.1016/j.amepre.2021.07.022

Henningfield, J. E., Grundmann, O., Huestis, M. A., & Smith, K. E. (2024). Kratom safety and toxicology in the public health context: research needs to better inform regulation. *Front Pharmacol*, *15*, 1403140. https://doi.org/10.3389/fphar.2024.1403140

Henningfield, J. E., Rodricks, J. V., Magnuson, A. M., & Huestis, M. A. (2022). Respiratory effects of oral mitragynine and oxycodone in a rodent model. *Psychopharmacology (Berl)*, *239*(12), 3793-3804. https://doi.org/10.1007/s00213-022-06244-z

Henningfield, J. E., Wang, D., Sembower, M. A., Pype, S., & Foxon, F. (2025). *Eight Factor Analysis for 7-Hydroxymitragynine (7-OH)*.

Henningfield, J. E., Wang, D. W., & Huestis, M. A. (2021). Kratom Abuse Potential 2021: An Updated Eight Factor Analysis. *Front Pharmacol*, *12*, 775073. https://doi.org/10.3389/fphar.2021.775073

Henningfield, J. E., Wang, D. W., & Huestis, M. A. (2022a). Kratom Abuse Potential 2021: An Updated Eight Factor Analysis [Review]. *Front Pharmacol*, *12*, 775073. https://doi.org/10.3389/fphar.2021.775073

Henningfield, J. E., Wang, D. W., & Huestis, M. A. (2022b). Kratom Abuse Potential 2021: An Updated Eight Factor Analysis [Review]. *Frontiers in Pharmacology*, *Volume 12 - 2021*. https://doi.org/10.3389/fphar.2021.775073

Heywood, J., Smallets, S., & Paustenbach, D. (2024). Beneficial and adverse health effects of kratom (Mitragyna speciosa): A critical review of the literature. *Food Chem Toxicol*, *192*, 114913. https://doi.org/10.1016/j.fct.2024.114913

Hill, K., Boyer, E. W., Grundmann, O., & Smith, K. E. (2025). De facto opioids: Characterization of novel 7-hydroxymitragynine and mitragynine pseudoindoxyl product marketing. *Drug Alcohol Depend*, *272*, 112701. https://doi.org/10.1016/j.drugalcdep.2025.112701

Hill, K., Gibson, S., Grundmann, O., Smith, K. E., Ballard, J., & Stanciu, C. N. (2023). Evaluating health information provided to kratom consumers by good manufacturing practice-qualified vendors. *Subst Abuse Treat Prev Policy*, *18*(1), 21. https://doi.org/10.1186/s13011-023-00531-4
Hill, K., Grundmann, O., Smith, K. E., & Stanciu, C. N. (2024). Prevalence of Kratom Use Disorder Among Kratom Consumers. *J Addict Med*, *18*(3), 306-312. https://doi.org/10.1097/ADM.0000000000001290
Hill, K., Henderson, A., Sharma, A., Kanumuri, S. R. R., Mukhopadhyay, S., Veltri, C., Smith, K. E., McCurdy, C. R., & Grundmann, O. (2025). Diversification of Kratom in US Markets: Results from an Online Survey and Chemical Assay of Products. *Subst Use Misuse*, 1-10. https://doi.org/10.1080/10826084.2025.2551707
Hill, R., Kruegel, A. C., Javitch, J. A., Lane, J. R., & Canals, M. (2022). The respiratory depressant effects of mitragynine are limited by its conversion to 7-OH mitragynine. *Br J Pharmacol*, *179*(14), 3875-3885. https://doi.org/10.1111/bph.15832
Hiranita, T., Obeng, S., Sharma, A., Wilkerson, J. L., McCurdy, C. R., & McMahon, L. R. (2022). In vitro and in vivo pharmacology of kratom. *Adv Pharmacol*, *93*, 35-76. https://doi.org/10.1016/bs.apha.2021.10.001
Hong, S., Zimmerman, P. E., Rao, V., & Markwalter, D. W. (2023). Buprenorphine-Naloxone in the Setting of Kratom Withdrawal, Opioid Use Disorder, and Stage IV Lung Adenocarcinoma. *J Palliat Med*, *26*(5), 734-736. https://doi.org/10.1089/jpm.2022.0491
Hoshina, Y., & Liang, J. Z. (2024). Kratom Neurotoxicity: T1 Hyperintensity in the Basal Ganglia. *Neurohospitalist*, *14*(4), 462-463. https://doi.org/10.1177/19418744241257724
Hossain, R., Sultana, A., Nuinoon, M., Noonong, K., Tangpong, J., Hossain, K. H., & Rahman, M. A. (2023). A Critical Review of the Neuropharmacological Effects of Kratom: An Insight from the Functional Array of Identified Natural Compounds. *Molecules*, *28*(21). https://doi.org/10.3390/molecules28217372
Huestis, M. A., Brett, M. A., Bothmer, J., & Atallah, R. (2024). Human Mitragynine and 7-Hydroxymitragynine Pharmacokinetics after Single and Multiple Daily Doses of Oral Encapsulated Dried Kratom Leaf Powder. *Molecules*, *29*(5). https://doi.org/10.3390/molecules29050984
Hughes, S., van de Klashorst, D., Veltri, C. A., & Grundmann, O. (2022). Acute, Sublethal, and Developmental Toxicity of Kratom (Mitragyna speciosa Korth.) Leaf Preparations on Caenorhabditis elegans as an Invertebrate Model for Human Exposure. *Int J Environ Res Public Health*, *19*(10). https://doi.org/10.3390/ijerph19106294
Hughs, M., Kish-Trier, E., O'Brien, A., & McMillin, G. A. (2023). Analysis of Mitragynine and Speciociliatine in Umbilical Cord by LC-MS-MS for Detecting Prenatal Exposure to Kratom. *J Anal Toxicol*, *46*(9), 957-964. https://doi.org/10.1093/jat/bkac064
Huisman, G., Menke, M., Grundmann, O., Schreiber, R., & Mason, N. (2023). Examining the Psychoactive Differences between Kratom Strains. *Int J Environ Res Public Health*, *20*(14). https://doi.org/10.3390/ijerph20146425
Indriani, D. W., Rahmawati, S. I., Bayu, A., Ahmadi, P., Sari, A. N., Zuraida, Z., Dharmayanti, N., & Putra, M. Y. (2025). Serotonin release mediates analgesia via opioidergic system and withdrawal symptoms in chronic kratom extract-treated mice.

BMC Complement Med Ther, *25*(1), 205. https://doi.org/10.1186/s12906-025-04947-2

Ismail, R., Abdul Manaf, M. R., Hassan, M. R., Mohammed Nawi, A., Ibrahim, N., Lyndon, N., Amit, N., Zakaria, E., Abd Razak, M. A., Zaiedy Nor, N. I., Shukor, M. S., & Kamarubahrin, A. F. (2022). Prevalence of Drug and Substance Use among Malaysian Youth: A Nationwide Survey. *Int J Environ Res Public Health*, *19*(8). https://doi.org/10.3390/ijerph19084684

Jain, V., & Lloyd, M. S. (2025). A Kratomic Bomb: Cardiotoxicities From Mitragyna speciosa Extract. *JACC Case Rep*, *30*(5), 103110. https://doi.org/10.1016/j.jaccas.2024.103110

Janthongkaw, A., Klaophimai, S., Khampaya, T., Yimthiang, S., Yang, Y., Ma, R., Bumyut, A., & Pouyfung, P. (2023). Effect of Green and Red Thai Kratom (Mitragyna speciosa) on pancreatic digestive enzymes (alpha-glucosidase and lipase) and acetyl-carboxylase 1 activity: A possible therapeutic target for obesity prevention. *PLoS One*, *18*(9), e0291738. https://doi.org/10.1371/journal.pone.0291738

Janthongkaw, A., Klaophimai, S., Khamphaya, T., Yimthiang, S., Yang, Y., Ma, R., Bumyut, A., & Pouyfung, P. (2024). Correction: Effect of Green and Red Thai Kratom (Mitragyna speciosa) on pancreatic digestive enzymes (alpha-glucosidase and lipase) and acetyl-carboxylase 1 activity: A possible therapeutic target for obesity prevention. *PLoS One*, *19*(6), e0305988. https://doi.org/10.1371/journal.pone.0305988

Japarin, R. A., Harun, N., Hassan, Z., & Shoaib, M. (2023). Mitragynine, a primary constituent of kratom reinstates morphine-seeking behaviour in rats. *Behav Pharmacol*, *34*(2-3), 123-130. https://doi.org/10.1097/FBP.0000000000000715

Jarka, C., & Gregoire, K. (2023). Precipitated withdrawal with kratom use following naltrexone administration. *Ment Health Clin*, *13*(3), 155-158. https://doi.org/10.9740/mhc.2023.06.155

Jaunay, E. L., Bade, R., Paxton, K. R., Nadarajan, D., Barry, D. C., Zhai, Y., Tscharke, B. J., O'Brien, J. W., Mueller, J., White, J. M., Simpson, B. S., & Gerber, C. (2024). Monitoring the use of novel psychoactive substances in Australia by wastewater-based epidemiology. *Sci Total Environ*, *919*, 170473. https://doi.org/10.1016/j.scitotenv.2024.170473

Johnson, K. M., Lause, M., Chung, C., & Massick, S. (2023). Kratom ingestion associated with photodistributed hyperpigmentation. *Int J Dermatol*, *62*(9), e494-e496. https://doi.org/10.1111/ijd.16650

Kamble, S. H., Berthold, E. C., King, T. I., Raju Kanumuri, S. R., Popa, R., Herting, J. R., Leon, F., Sharma, A., McMahon, L. R., Avery, B. A., & McCurdy, C. R. (2021). Pharmacokinetics of Eleven Kratom Alkaloids Following an Oral Dose of Either Traditional or Commercial Kratom Products in Rats. *J Nat Prod*, *84*(4), 1104-1112. https://doi.org/10.1021/acs.jnatprod.0c01163

Kamble, S. H., León, F., King, T. I., Berthold, E. C., Lopera-Londoño, C., Siva Rama Raju, K., Hampson, A. J., Sharma, A., Avery, B. A., McMahon, L. R., & McCurdy, C. R. (2020). Metabolism of a Kratom Alkaloid Metabolite in Human Plasma Increases Its Opioid Potency and Efficacy. *ACS Pharmacology & Translational Science*, *3*(6), 1063-1068. https://doi.org/10.1021/acsptsci.0c00075

Kamble, S. H., Obeng, S., Leon, F., Restrepo, L. F., King, T. I., Berthold, E. C., Kanumuri, S. R. R., Gamez-Jimenez, L. R., Pallares, V. L. C., Patel, A., Ho, N. P., Hampson,

A., McCurdy, C. R., McMahon, L. R., Wilkerson, J. L., Sharma, A., & Hiranita, T. (2023). Pharmacokinetic and Pharmacodynamic Consequences of Cytochrome P450 3A Inhibition on Mitragynine Metabolism in Rats. *J Pharmacol Exp Ther*, *385*(3), 180-192. https://doi.org/10.1124/jpet.122.001525

Karunakaran, T., Ganasan, J., Rusmadi, N. N., Santhanam, R., & Mordi, M. N. (2025). In-vitro hepatotoxic activity of mitragynine and paynantheine isolated from the leaves of Mitragyna speciosa Korth. (Kratom). *Nat Prod Res*, *39*(17), 5131-5135. https://doi.org/10.1080/14786419.2024.2375760

Karunakaran, T., Marimuthu, Y., Vicknasingam, B., & Chawarski, M. C. (2025). The scientific evolution of kratom: a historical overview. In J. E. Henningfield, C. E. Beyer, & R. B. Raffa (Eds.), *Kratom: History, Science and Therapeutic Potential*. Academic Press.

Karunakaran, T., Ngew, K. Z., Zailan, A. A. D., Mian Jong, V. Y., & Abu Bakar, M. H. (2022). The Chemical and Pharmacological Properties of Mitragynine and Its Diastereomers: An Insight Review. *Front Pharmacol*, *13*, 805986. https://doi.org/10.3389/fphar.2022.805986

Kedzierski, N., & Mata, D. (2023). Mitragynine in the Orange County DUID population. *J Anal Toxicol*, *47*(8), 770-785. https://doi.org/10.1093/jat/bkad066

Khalid, K., Ku Md Saad, S., Soelar, S. A., Mohamed Yusof, Z., & Warijo, O. (2023). Exploring adolescents' practice and perspective on the use and misuse of kratom in northwest Malaysia. *J Ethn Subst Abuse*, *22*(1), 121-132. https://doi.org/10.1080/15332640.2021.1906816

Kikura-Hanajiri, R., Kawamura, M., Maruyama, T., Kitajima, M., Takayama, H., & Goda, Y. (2009). Simultaneous analysis of mitragynine, 7-hydroxymitragynine, and other alkaloids in the psychotropic plant “kratom” (Mitragyna speciosa) by LC-ESI-MS. *Forensic Toxicology*, *27*(2), 67-74. https://doi.org/10.1007/s11419-009-0070-5

Kim, K., Shahsavarani, M., Garza-García, J. J. O., Carlisle, J. E., Guo, J., De Luca, V., & Qu, Y. (2023). Biosynthesis of kratom opioids. *New Phytol*, *240*(2), 757-769. https://doi.org/10.1111/nph.19162

Kiyokawa, M., Kwon, A. K., Cape, M. C., & Streltzer, J. M. (2023). Kratom use disorder: case reports on successful treatment with home induction of buprenorphine-naloxone. *Fam Pract*. https://doi.org/10.1093/fampra/cmad081

Koturbash, I., Yeager, R. P., Mitchell, C. A., Ferguson, S., Navarro, V. J., Paine, M. F., & Roe, A. L. (2024). Botanical-induced toxicity: Liver injury and botanical-drug interactions. A report on a society of Toxicology Annual Meeting symposium. *Regul Toxicol Pharmacol*, *153*, 105708. https://doi.org/10.1016/j.yrtph.2024.105708

Krantz, M. J., Rudo, T. J., Haigney, M. C. P., Stockbridge, N., Kleiman, R. B., Klein, M., & Kao, D. P. (2023). Ventricular Arrhythmias Associated With Over-the-Counter and Recreational Opioids. *J Am Coll Cardiol*, *81*(23), 2258-2268. https://doi.org/10.1016/j.jacc.2023.04.009

Krotulski, A. J., Denn, M. T., Brower, J. O., Papsun, D. M., & Logan, B. K. (2025). *Evaluation of Commercially Available Smoke Shop Products Marketed as “7-Hydroxy Mitragynine” & Related Alkaloids*. Center for Forensic Science Research and Education. Retrieved 22 January from https://www.cfsre.org/images/content/reports/public_alerts/7-Hydroxy_Mitragynine_NPS_Discovery_033125.pdf

Kruegel, A. C., Gassaway, M. M., Kapoor, A., Váradi, A., Majumdar, S., Filizola, M., Javitch, J. A., & Sames, D. (2016). Synthetic and Receptor Signaling Explorations of the Mitragyna Alkaloids: Mitragynine as an Atypical Molecular Framework for Opioid Receptor Modulators. *Journal of the American Chemical Society*, *138*(21), 6754-6764. https://doi.org/10.1021/jacs.6b00360

Kruegel, A. C., Uprety, R., Grinnell, S. G., Langreck, C., Pekarskaya, E. A., Le Rouzic, V., Ansonoff, M., Gassaway, M. M., Pintar, J. E., Pasternak, G. W., Javitch, J. A., Majumdar, S., & Sames, D. (2019). 7-Hydroxymitragynine Is an Active Metabolite of Mitragynine and a Key Mediator of Its Analgesic Effects. *ACS Central Science*, *5*(6), 992-1001. https://doi.org/10.1021/acscentsci.9b00141

Laforest, L. C., Kuntz, M. A., Kanumuri, S. R. R., Mukhopadhyay, S., Sharma, A., O'Connor, S. E., McCurdy, C. R., & Nadakuduti, S. S. (2023). Metabolite and Molecular Characterization of Mitragyna speciosa Identifies Developmental and Genotypic Effects on Monoterpene Indole and Oxindole Alkaloid Composition. *J Nat Prod*, *86*(4), 1042-1052. https://doi.org/10.1021/acs.jnatprod.3c00092

Lampe, J. R. (2021). *The controlled substances act (CSA): a legal overview for the 117th congress*. C. R. Service. https://sgp.fas.org/crs/misc/R45948.pdf

Larsen, I., Zhang, E., & Farahmand, P. (2022). Current Understanding of the Effects and Potential Clinical Utility of Kratom: A Review. *J Psychiatr Pract*, *28*(2), 92-97. https://doi.org/10.1097/PRA.0000000000000609

Le, T. T., McGrath, S. R., & Fasinu, P. S. (2022). Herb-drug Interactions in Neuropsychiatric Pharmacotherapy - A Review of Clinically Relevant Findings. *Curr Neuropharmacol*, *20*(9), 1736-1751. https://doi.org/10.2174/1570159X19666210809100357

Leksungnoen, N., Andriyas, T., Ngernsaengsaruay, C., Uthairatsamee, S., Racharak, P., Sonjaroon, W., Kjelgren, R., Pearson, B. J., McCurdy, C. R., & Sharma, A. (2022). Variations in mitragynine content in the naturally growing Kratom (Mitragyna speciosa) population of Thailand. *Front Plant Sci*, *13*, 1028547. https://doi.org/10.3389/fpls.2022.1028547

LeSaint, K. T., Yin, S., Sharma, A., Avery, B. A., McCurdy, C. R., & Waksman, J. C. (2022). Acute Renal Insufficiency Associated With Consumption of Hydrocodone- and Morphine-Adulterated Kratom (Mitragyna Speciosa). *J Emerg Med*, *63*(1), e28-e30. https://doi.org/10.1016/j.jemermed.2022.02.004

Leyrer-Jackson, J. M., Acuna, A. M., & Olive, M. F. (2022). Current and emerging pharmacotherapies for opioid dependence treatments in adults: a comprehensive update. *Expert Opin Pharmacother*, *23*(16), 1819-1830. https://doi.org/10.1080/14656566.2022.2140039

Li, X., Ndungu, P., Taneja, S. B., Chapin, M. R., Egbert, S. B., Akenapalli, K., Paine, M. F., Kane-Gill, S. L., & Boyce, R. D. (2023). An evaluation of adverse drug reactions and outcomes attributed to kratom in the US Food and Drug Administration Adverse Event Reporting System from January 2004 through September 2021. *Clin Transl Sci*, *16*(6), 1002-1011. https://doi.org/10.1111/cts.13505

Liang, Z., Guo, Y., Ellin, N., King, T. I., Berthold, E. C., Mukhopadhyay, S., Sharma, A., McCurdy, C. R., & Prentice, B. M. (2024). Formation of multiple ion types during MALDI imaging mass spectrometry analysis of Mitragyna speciosa alkaloids in dosed rat brain tissue. *Talanta*, *274*, 125923. https://doi.org/10.1016/j.talanta.2024.125923

Limcharoen, T., Pouyfung, P., Ngamdokmai, N., Prasopthum, A., Ahmad, A. R., Wisdawati, W., Prugsakij, W., & Warinhomhoun, S. (2022). Inhibition of α-Glucosidase and Pancreatic Lipase Properties of Mitragyna speciosa (Korth.) Havil. (Kratom) Leaves. *Nutrients*, *14*(19), 3909. https://www.mdpi.com/2072-6643/14/19/3909
LoParco, C. R., Bone, C., Berg, C. J., Rossheim, M. E., Peeri, N. C., Tillett, K. K., & Seo, D. C. (2024). Associations Between Opioid and Kratom Use in the USA: Differences by Race/Ethnicity and Sexual Orientation. *J Racial Ethn Health Disparities*. https://doi.org/10.1007/s40615-024-02142-6
LoParco, C. R., Yockey, R. A., Sekhon, V. K., Olsson, S., Galindo, R., Balasundaram, R., Agwuncha, T., & Rossheim, M. E. (2024). Kratom Retail Availability in Fort Worth, Texas. *J Psychoactive Drugs*, *56*(1), 8-13. https://doi.org/10.1080/02791072.2023.2181243
Lund, E., Low, A. B., Allan, J. D., Puentes, J. A., & Flynn, D. N. (2022). Anesthetic Challenges Posed by Heavy Kratom Users. *Cureus*, *14*(3), e22864. https://doi.org/10.7759/cureus.22864
Mahaprom, K., Chokpaisarn, J., Kunworarath, N., Paduka, W., Phoopha, S., Limsuwan, S., & Neamsuvan, O. (2025). In vivo analgesic, anti-inflammatory activities, and phytochemical profile of Thai herbal Kratom recipe, a traditional Thai herbal medicine for muscle pain relief. *J Ethnopharmacol*, *343*, 119442. https://doi.org/10.1016/j.jep.2025.119442
Makary, M. A. (2025). *"Dear Colleague" Letter, July 29, 2025*. https://www.ahpa.org/Files/Media/FDA/final_updated_7-oh_dear_colleague_letter_7-28-2025.pdf
Manus, J. P., Crenshaw, R. C., Ringer, L. C., Towers, S. A., Paige, N. B., Leon, F., McCurdy, C. R., & Lester, D. B. (2025). Effects of kratom alkaloids on mesolimbic dopamine release. *Neurosci Lett*, *850*, 138153. https://doi.org/10.1016/j.neulet.2025.138153
Manwill, P. K., Flores-Bocanegra, L., Khin, M., Raja, H. A., Cech, N. B., Oberlies, N. H., & Todd, D. A. (2022). Kratom (Mitragyna speciosa) Validation: Quantitative Analysis of Indole and Oxindole Alkaloids Reveals Chemotypes of Plants and Products. *Planta Med*, *88*(9-10), 838-857. https://doi.org/10.1055/a-1795-5876
Martin, G., Collins, D. P., & Valenzuela, H. (2022). Life-Threatening Hyponatremia Secondary to Chronic Kratom Use: A Case Presentation. *Cureus*, *14*(9), e29073. https://doi.org/10.7759/cureus.29073
Mat, N. H., Bakar, S. N. S., Murugaiyah, V., Chawarski, M. C., & Hassan, Z. (2023). Analgesic effects of main indole alkaloid of kratom, mitragynine in acute pain animal model. *Behav Brain Res*, *439*, 114251. https://doi.org/10.1016/j.bbr.2022.114251
Matsumoto, K., Horie, S., Ishikawa, H., Takayama, H., Aimi, N., Ponglux, D., & Watanabe, K. (2004). Antinociceptive effect of 7-hydroxymitragynine in mice: Discovery of an orally active opioid analgesic from the Thai medicinal herb Mitragyna speciosa. *Life Sciences*, *74*(17), 2143-2155. https://doi.org/https://doi.org/10.1016/j.lfs.2003.09.054
McCurdy, C. (2025). Kratom (Mitragyna speciosa): Recent Advances in Understanding the Chemistry, Pharmacology, and Human Use. In D. J. McKenna (Ed.), *Ethnopharmacologic Search for Psychoactive Drugs* (pp. 331-353). Synergetic Press.
McCurdy, C. R., Sharma, A., Smith, K. E., Veltri, C. A., Weiss, S. T., White, C. M., & Grundmann, O. (2024). An update on the clinical pharmacology of kratom: uses,

abuse potential, and future considerations. *Expert Rev Clin Pharmacol*, *17*(2), 131-142. https://doi.org/10.1080/17512433.2024.2305798
Miller, A. H. F., Krotulski, A. J., Walton, S. E., Dulaney, A. R., Frolichstein, A. P., Dusek, H. L., & Murphy, C. (2025). Kratom Cardiotoxicity: Reversible Brugada Pattern and QTc Prolongation. *JACC Case Rep*, *30*(5), 103109. https://doi.org/10.1016/j.jaccas.2024.103109
Mongar, P., Jaisi, A., Inkviya, T., Wungsintaweekul, J., & Wiwattanawongsa, K. (2024). Effects of Itraconazole on Pharmacokinetics of Mitragynine and 7-Hydroxymitragynine in Healthy Volunteers. *ACS Pharmacol Transl Sci*, *7*(3), 823-833. https://doi.org/10.1021/acsptsci.3c00335
Muhamad, N. A., Chemi, N., Ma'amor, N. H., Rosli, I. A., Leman, F. N., Mohamad Isa, M. F., Johari, M. Z., Abdullah, N., Ibrahim, N. A., Chan, H. K., Abu Hassan, M. R., & My Substance Abuse Study, G. (2024). Substance abuse among new patients attending main government hospitals in Malaysia from 2018-2021: A comparison between before and during COVID-19 pandemic. *PLoS One*, *19*(10), e0309422. https://doi.org/10.1371/journal.pone.0309422
Mun, C. J., Panlilio, L. V., Dunn, K. E., Thrul, J., McCurdy, C. R., Epstein, D. H., & Smith, K. E. (2025). Kratom (Mitragyna speciosa) use for self-management of pain: Insights from cross-sectional and ecological momentary assessment data. *J Pain*, *26*, 104726. https://doi.org/10.1016/j.jpain.2024.104726
Mun, C. J., Timmons, P., Panlilio, L. V., Verrico, C. D., Thomas, Y. T., Zamarripa, C. A., Epstein, D. H., & Smith, K. E. (2025). Is bedtime use of kratom (Mitragyna speciosa) a sleep aid or disruptor? Examining its daily effects and individual differences. *Exp Clin Psychopharmacol*. https://doi.org/10.1037/pha0000794
Nadarajan, D., O'Brien, J., Cresswell, S., Kele, B., Mueller, J., & Bade, R. (2024). Application of design of experiment for quantification of 71 new psychoactive substances in influent wastewater. *Anal Chim Acta*, *1321*, 343036. https://doi.org/10.1016/j.aca.2024.343036
Nakajima, M., Nagasawa, S., Yamazaki, K., Yazawa, T., Yoneyama, H., Kotaka, Y., & Nemoto, T. (2024). Direct S(0) → T(n) Transition under Visible Light Irradiation Enabling Synthesis of a Pseudoindoxyl Scaffold. *Org Lett*, *26*(15), 3289-3293. https://doi.org/10.1021/acs.orglett.4c00957
Nam, Y., Tam, A. T., Miller, E. R., & Scheidt, K. A. (2024). A Platform for the Synthesis of Corynantheine-Type Corynanthe Alkaloids. *J Am Chem Soc*, *146*(1), 118-124. https://doi.org/10.1021/jacs.3c12556
Ng, K., & Ha, T. (2024). Extraction and detection of mitragynine in Kratom leaves by high-performance liquid chromatography. *Nat Prod Res*, 1-6. https://doi.org/10.1080/14786419.2024.2331602
Nsubuga, J., Baugher, J., Dahl, E., Schwensohn, C., Blessington, T., Aguillon, R., Whitney, B., Goldman, S., Brewster, M., Humbert, J., Crosby, A., Gieraltowski, L., Singleton, L. S., & Hilgendorf, J. (2022). Multistate Outbreak Investigation of Salmonella Infections Linked to Kratom: A Focus on Traceback, Laboratory, and Regulatory Activities. *J Food Prot*, *85*(5), 747-754. https://doi.org/10.4315/JFP-21-319
Nukitram, J., Cheaha, D., Sengnon, N., Wungsintaweekul, J., Limsuwanchote, S., & Kumarnsit, E. (2022). Ameliorative effects of alkaloid extract from Mitragyna speciosa (Korth.) Havil. Leaves on methamphetamine conditioned place preference in mice. *J Ethnopharmacol*, *284*, 114824. https://doi.org/10.1016/j.jep.2021.114824

Obeng, S., Crowley, M. L., Mottinelli, M., Leon, F., Zuarth Gonzalez, J. D., Chen, Y., Gamez-Jimenez, L. R., Restrepo, L. F., Ho, N. P., Patel, A., Martins Rocha, J., Alvarez, M. A., Thadisetti, A. M., Park, C. R., Pallares, V. L. C., Milner, M. J., Canal, C. E., Hampson, A. J., McCurdy, C. R., . . . Hiranita, T. (2024). The Mitragyna speciosa (kratom) alkaloid mitragynine: Analysis of adrenergic alpha(2) receptor activity in vitro and in vivo. *Eur J Pharmacol*, *980*, 176863. https://doi.org/10.1016/j.ejphar.2024.176863

Obeng, S., Leon, F., Patel, A., Zuarth Gonzalez, J. D., Chaves Da Silva, L., Restrepo, L. F., Gamez-Jimenez, L. R., Ho, N. P., Guerrero Calvache, M. P., Pallares, V. L. C., Helmes, J. A., Shiomitsu, S. K., Soto, P. L., McCurdy, C. R., McMahon, L. R., Wilkerson, J. L., & Hiranita, T. (2022). Interactive Effects of micro-Opioid and Adrenergic-alpha (2) Receptor Agonists in Rats: Pharmacological Investigation of the Primary Kratom Alkaloid Mitragynine and Its Metabolite 7-Hydroxymitragynine. *J Pharmacol Exp Ther*, *383*(3), 182-198. https://doi.org/10.1124/jpet.122.001192

Obeng, S., Wilkerson, J. L., Leon, F., Reeves, M. E., Restrepo, L. F., Gamez-Jimenez, L. R., Patel, A., Pennington, A. E., Taylor, V. A., Ho, N. P., Braun, T., Fortner, J. D., Crowley, M. L., Williamson, M. R., Pallares, V. L. C., Mottinelli, M., Lopera-Londono, C., McCurdy, C. R., McMahon, L. R., & Hiranita, T. (2021). Pharmacological Comparison of Mitragynine and 7-Hydroxymitragynine: In Vitro Affinity and Efficacy for mu-Opioid Receptor and Opioid-Like Behavioral Effects in Rats. *J Pharmacol Exp Ther*, *376*(3), 410-427. https://doi.org/10.1124/jpet.120.000189

ODS. (1994). *Dietary Supplement Health and Education Act of 1994 Public Law 103-417 103rd Congress*. Retrieved 22 January from https://ods.od.nih.gov/About/DSHEA_Wording.aspx

Ogozalek, S. (2023). *The Tampa Bay Times tested 20 kratom products. Here's what we found.* (Tampa Bay, Issue. https://www.tampabay.com/investigations/2023/12/09/tampa-bay-times-tested-20-kratom-products-heres-what-we-found/

Ortiz, Y. T., Bilbrey, J. A., Felix, J. S., Kienegger, E. A., Mottinelli, M., Mukhopadhyay, S., McCurdy, C. R., McMahon, L. R., & Wilkerson, J. L. (2023). Cannabidiol and mitragynine exhibit differential interactive effects in the attenuation of paclitaxel-induced mechanical allodynia, acute antinociception, and schedule-controlled responding in mice. *Pharmacol Rep*, *75*(4), 937-950. https://doi.org/10.1007/s43440-023-00498-w

Osawa, K. A., & Johnson, R. D. (2025). Postmortem distribution of mitragynine and 7-hydroxymitragynine in 51 cases. *J Anal Toxicol*, *49*(2), 122-128. https://doi.org/10.1093/jat/bkae099

Owaid, S. J., Yunusa, S., Gam, L. H., & Hassan, Z. (2025). Comparative brain proteome analysis of an Indole Alkaloid of Kratom, Mitragynine and Kratom juice in rats. *Behav Brain Res*, *493*, 115709. https://doi.org/10.1016/j.bbr.2025.115709

Paankhao, N., Sangsawang, A., Kantha, P., Paankhao, S., Promsee, K., Soontara, C., Kongsriprapan, S., Srisapoome, P., Kumwan, B., Meachasompop, P., Phrompanya, P., Buncharoen, W., & Uchuwittayakul, A. (2024). Antioxidant and antibacterial efficiency of the ethanolic leaf extract of Kratom (Mitragyna speciosa (Korth.) Havil) and its effects on growth, health, and disease resistance against Edwardsiella tarda infection in Nile tilapia (Oreochromis niloticus). *Fish Shellfish Immunol*, *152*, 109771. https://doi.org/10.1016/j.fsi.2024.109771

Palamar, J. J. (2021). Past-Year Kratom Use in the U.S.: Estimates From a Nationally Representative Sample. *Am J Prev Med*, *61*(2), 240-245. https://doi.org/10.1016/j.amepre.2021.02.004
Palamar, J. J. (2022). Kratom Use Is Underestimated, but Prevalence Still Appears to Be Low. *Am J Prev Med*, *62*(1), 133-134. https://doi.org/10.1016/j.amepre.2021.07.021
Pansai, N., Wungsintaweekul, J., & Wichienchot, S. (2024). The effects of Mitragyna speciosa extracts on intestinal microbiota and their metabolites in vitro fecal fermentation. *J Sci Food Agric*, *104*(14), 8500-8510. https://doi.org/10.1002/jsfa.13677
Papadi, G., Bakhiya, N., & Ildico Hirsch-Ernst, K. (2022). Assessment of the possible health risks associated with the consumption of botanical preparations of Mitragyna speciosa (kratom). *EFSA J*, *20*(Suppl 1), e200415. https://doi.org/10.2903/j.efsa.2022.e200415
Papsun, D., Schroeder, W., Brower, J., & Logan, B. (2023). Forensic Implications of Kratom: Kratom Toxicity, Correlation with Mitragynine Concentrations, and Polypharmacy. *Current Addiction Reports*, *10*(2), 272-281. https://doi.org/10.1007/s40429-023-00477-4
Parent, M. C., Woznicki, N. W., & Yang, J. (2022). Demographic and behavioral factors associated with kratom use among U.S. college students. *J Am Coll Health*, 1-5. https://doi.org/10.1080/07448481.2022.2112584
Parent, M. C., Woznicki, N. W., & Yang, J. (2024). Demographic and behavioral factors associated with kratom use among U.S. college students. *J Am Coll Health*, *72*(7), 1983-1987. https://doi.org/10.1080/07448481.2022.2112584
Penzak, S. R., Durham, S. H., Phillippe, H. M., & Fox, B. I. (2023). Knowledge of Kratom among Alabama Pharmacists. *Pharmacy (Basel)*, *12*(1). https://doi.org/10.3390/pharmacy12010006
Peran, D., Stern, M., Cernohorsky, P., Sykora, R., Popela, S., & Duska, F. (2023). Mitragyna speciosa (Kratom) poisoning: Findings from ten cases. *Toxicon*, *225*, 107054. https://doi.org/10.1016/j.toxicon.2023.107054
Perez, J. (2023). Kratom and opioid use disorder in the perioperative period: A case report on the expanding role of buprenorphine. *J Opioid Manag*, *19*(1), 91-93. https://doi.org/10.5055/jom.2023.0762
Piercey, C. J., Bunch, J., Cameron, J., Ahern, R., Packwood, I., Bruning, C., Henry, D., Ruehrmund, J., Weldon, K., Smith, K. E., & Karoly, H. C. (2025). Kratom use among ethnobotanical tea bar patrons in Colorado: Subjective drug effects, adverse reactions, and perceived benefits of use. *Drug Alcohol Depend Rep*, *16*, 100361. https://doi.org/10.1016/j.dadr.2025.100361
Pont-Fernandez, S., Kheyfets, M., Rogers, J. M., Smith, K. E., & Epstein, D. H. (2023). Kava (Piper methysticum) in the United States: the quiet rise of a substance with often subtle effects. *Am J Drug Alcohol Abuse*, *49*(1), 85-96. https://doi.org/10.1080/00952990.2022.2140292
Post, S., Spiller, H. A., Chounthirath, T., & Smith, G. A. (2019). Kratom exposures reported to United States poison control centers: 2011-2017. *Clin Toxicol (Phila)*, *57*(10), 847-854. https://doi.org/10.1080/15563650.2019.1569236
Prevete, E., Kuypers, K. P. C., Theunissen, E. L., Esposito, G., Ramaekers, J. G., Pasquini, M., & Corazza, O. (2023). Clinical Implications of Kratom (Mitragyna

speciosa) Use: a Literature Review. *Curr Addict Rep*, *10*(2), 317-334. https://doi.org/10.1007/s40429-023-00478-3
Prevete, E., Theunissen, E. L., Kuypers, K. P. C., Paci, R., Reckweg, J. T., Cavarra, M., Toennes, S. W., Ritscher, S., Bersani, G., Corazza, O., Pasquini, M., & Ramaekers, J. G. (2025). An exploratory study of the safety profile and neurocognitive function after single doses of mitragynine in humans. *Psychopharmacology (Berl)*, *242*(6), 1363-1376. https://doi.org/10.1007/s00213-024-06734-2
Prozialeck, W., Fowler, A., & Edwards, J. (2022). Public Health Implications and Possible Sources of Lead (Pb) as a Contaminant of Poorly Regulated Kratom Products in the United States. *Toxics*, *10*(7). https://doi.org/10.3390/toxics10070398
Qureshi, S., Iqbal, S. M. Z., Ameer, A., Karrila, S., Ghadi, Y. Y., & Shah, S. A. (2024). Enhancing drug-target interaction predictions in context of neurodegenerative diseases using bidirectional long short-term memory in male Swiss albino mice pharmaco-EEG analysis. *Heliyon*, *10*(21), e39279. https://doi.org/10.1016/j.heliyon.2024.e39279
Raffa, R. B. (2014). *Kratom and Other Mitragynines*. CRC Press. https://doi.org/10.1201/b17666
Rayanakorn, A., Apisitwittaya, P., Lee, S. W. H., Yaja, K., Inpan, R., Na Takuathung, M., & Koonrungsesomboon, N. (2025). The effects of kratom (Mitragyna speciosa) on metabolic syndrome-related parameters: a systematic review and meta-analysis. *Front Pharmacol*, *16*, 1587528. https://doi.org/10.3389/fphar.2025.1587528
Reich, N., Salvo, G., Leong, D., Wan, V., & Kosatsky, T. (2022). Kratom exposures managed by the British Columbia poison centre, 2012-2019: a descriptive analysis. *CMAJ Open*, *10*(3), E755-E761. https://doi.org/10.9778/cmajo.20210252
Reissig, C. J. (2024). *Pilot, Dose-Finding Study of Kratom Alkaloids: Study Design Updates*. https://cdn.prod.website-files.com/61858fcfc6543059f0617522/660ad17db7408f1953ba73ed_dosefinding.pdf
Reissig, C. J., Chiapperino, D., Seitz, A., Lee, R., Radin, R., & McAninch, J. (2025). *7-Hydroxymitragynine (7-OH) An Assessment of the Scientific Data and Toxicological Concerns Around an Emerging Opioid Threat* https://www.fda.gov/media/187899/download?attachment
Rhee, J., Shin, I., Kim, J., Lee, J., Cho, B., Kim, J., Park, M., & Kim, E. (2024). LC-MS-MS method for mitragynine and 7-hydroxymitragynine in hair and its application in authentic hair samples of suspected kratom abusers. *J Anal Toxicol*, *48*(6), 429-438. https://doi.org/10.1093/jat/bkae041
Rianprakaisang, T. N., Moss, M. J., Gerona, R., & Hendrickson, R. G. (2023). Plasma concentrations of phenibut and mitragynine in a single patient. *Clin Toxicol (Phila)*, *61*(7), 561-562. https://doi.org/10.1080/15563650.2023.2227996
Riley, A. P. (2025). Semi-synthesis in the exploration of opioid-targeting natural products. *Nat Prod Rep*. https://doi.org/10.1039/d5np00029g
Rodzlan Hasani, W. S., Robert Lourdes, T. G., Ganapathy, S. S., Ab Majid, N. L., Abd Hamid, H. A., & Mohd Yusoff, M. F. (2023). Patterns of polysubstance use among adults in Malaysia-A latent class analysis. *PLoS One*, *18*(1), e0264593. https://doi.org/10.1371/journal.pone.0264593
Rogers, J. M., Colvin, K., Epstein, D. H., Grundmann, O., McCurdy, C. R., & Smith, K. E. (2024). Growing pains with kratom: experiences discussed in subreddits contrast

with satisfaction expressed in surveys. *Front Pharmacol*, *15*, 1412397. https://doi.org/10.3389/fphar.2024.1412397
Rogers, J. M., Smith, K. E., Schriefer, D., & Epstein, D. H. (2022). For Better or Worse: Self-reported Changes in Kratom and Other Substance Use as a Result of the COVID-19 Pandemic. *Substance Abuse: Research and Treatment*, *16*, 11782218221123977. https://doi.org/10.1177/11782218221123977
Rogers, J. M., Smith, K. E., Schriefer, D., & Epstein, D. H. (2022). For Better or Worse: Self-reported Changes in Kratom and Other Substance Use as a Result of the COVID-19 Pandemic. *Subst Abuse*, *16*, 11782218221123977. https://doi.org/10.1177/11782218221123977
Rogers, J. M., Weiss, S. T., Epstein, D. H., Grundmann, O., Hill, K., & Smith, K. E. (2024). Kratom addiction per DSM-5 SUD criteria, and kratom physical dependence: Insights from dosing amount versus frequency. *Drug Alcohol Depend*, *260*, 111329. https://doi.org/10.1016/j.drugalcdep.2024.111329
Roma, K., Mohammed, S., Sieck, B., Naik, K., & Wahid, S. (2023). Kratom-induced acute liver injury: A case study and the importance of herbal supplement regulation. *J Hepatol*, *79*(2), 581-584. https://doi.org/10.1016/j.jhep.2023.04.026
Rossheim, M. E., LoParco, C. R., Tillett, K. K., Yockey, R. A., Lin, H. C., & Berg, C. J. (2024). Kratom Products Are Widely Available Throughout the United States. *Am J Public Health*, *114*(11), 1188-1190. https://doi.org/10.2105/AJPH.2024.307824
Sablaban, I. M., & Gautam, M. (2023). Kratom & Stimulant Co-Addiction: A Case Series and Brief Review. *J Addict Dis*, *41*(2), 181-184. https://doi.org/10.1080/10550887.2022.2066459
Saengmolee, W., Cheaha, D., Sa-Ih, N., & Kumarnsit, E. (2022). Exploring of cardiac autonomic activity with heart rate variability in long-term kratom (Mitragyna speciosa Korth.) users: a preliminary study. *PeerJ*, *10*, e14280. https://doi.org/10.7717/peerj.14280
Saingam, D., Singh, D., Geater, A. F., Assanangkornchai, S., Jitpiboon, W., & Latkin, C. (2023). The Health Impact of Long-Term Kratom (Mitragyna Speciosa) Use in Southern Thailand. *Subst Use Misuse*, *58*(10), 1212-1225. https://doi.org/10.1080/10826084.2023.2215301
Sakamoto, J., Kitajima, M., & Ishikawa, H. (2022). Asymmetric Total Syntheses of Mitragynine, Speciogynine, and 7-Hydroxymitragynine. *Chem Pharm Bull (Tokyo)*, *70*(9), 662-668. https://doi.org/10.1248/cpb.c22-00441
SAMHSA. (2025). *Key substance use and mental health indicators in the United States: Results from the 2024 National Survey on Drug Use and Health*. S. A. a. M. H. S. A. Center for Behavioral Health Statistics and Quality. https://www.samhsa.gov/data/data-we-collect/nsduh-national-survey-drug-use-and-health/national-releases
Schmid, P., Leibfarth, M., & Uhlmann, C. (2022). [An Outpatient Withdrawal Treatment of Kratom in Social Phobia: Psychotherapeutic Surgery Meets Addiction Psychiatric Outpatient Clinic]. *Psychiatr Prax*, *49*(4), 217-220. https://doi.org/10.1055/a-1787-4122 (Eine ambulante Entzugsbehandlung von Kratom bei sozialer Phobie: psychotherapeutische Praxis trifft suchtpsychiatrische Institutsambulanz.)
Schotte, C., Jiang, Y., Grzech, D., Dang, T. T., Laforest, L. C., León, F., Mottinelli, M., Nadakuduti, S. S., McCurdy, C. R., & O'Connor, S. E. (2023). Directed Biosynthesis

of Mitragynine Stereoisomers. *J Am Chem Soc*, *145*(9), 4957-4963. https://doi.org/10.1021/jacs.2c13644
Schwensohn, C., Nsubuga, J., Cronquist, L., Jose, G., Mastel, L., McCullough, L., Smith, L., Powell, M., Booth, H., Allen, K., Classon, A., & Gieraltowski, L. (2022). A Multiple-Serotype Outbreak of Salmonella Infections Linked to Kratom, United States, 2017-2018. *Foodborne Pathog Dis*, *19*(9), 648-653. https://doi.org/10.1089/fpd.2022.0013
Sekar, A., Velani, S., Katzman, S., O'Donnell, M., & Conway, K. S. (2022). Suspected Fanconi syndrome from cadmium toxicity exacerbated by heavy kratom use. A rare occurrence. *Clin Toxicol (Phila)*, *60*(7), 888-889. https://doi.org/10.1080/15563650.2022.2046774
Settle, A. G., & Yang, C. (2022). A Case of Severe Kratom Addiction Contributing to a Suicide Attempt. *Cureus*, *14*(9), e29698. https://doi.org/10.7759/cureus.29698
Settle, J. R., Smith, A., Rausch, P., & Rw, R. (2023). A social media analysis of kratom use to discontinue stimulants. *J Addict Dis*, 1-7. https://doi.org/10.1080/10550887.2023.2292304
Settle, J. R., Smith, A., Rausch, P., & Rw, R. (2024). A social media analysis of kratom use to discontinue stimulants. *J Addict Dis*, *42*(4), 508-514. https://doi.org/10.1080/10550887.2023.2292304
Sharron, K., Diallo, I. B., Witmer, A. M., & Nestadt, P. S. (2025). Kratom Use and Suicidal Thoughts and Behaviors in the United States. *Subst Use Addctn J*, *46*(4), 972-980. https://doi.org/10.1177/29767342251345229
Shi, T., & Shea, J. L. (2024). A case of fatal overdose involving both hydromorphone and kratom. *J Forensic Sci*, *69*(1), 355-358. https://doi.org/10.1111/1556-4029.15394
Singh, D., Azuan, M. A., & Narayanan, S. (2023). Kratom (Mitragyna speciosa) use in a sample of drug-dependent adolescents in rehabilitation for drug use in Malaysia. *J Ethn Subst Abuse*, 1-16. https://doi.org/10.1080/15332640.2023.2293941
Singh, D., Azuan, M. A., & Narayanan, S. (2025). Kratom (Mitragyna speciosa) use in a sample of drug-dependent adolescents in rehabilitation for drug use in Malaysia. *J Ethn Subst Abuse*, *24*(4), 930-945. https://doi.org/10.1080/15332640.2023.2293941
Singh, D., Mathandaver, D., Müller, C. P., & Smith, K. E. (2025). Kratom (Mitragyna speciosa) as a Replacement for Alcohol Among a Sample of Malaysian Adults with a History of Alcohol Use Problems. *Subst Use Misuse*, 1-7. https://doi.org/10.1080/10826084.2025.2600634
Smith, K. E., Boyer, E. W., Grundmann, O., McCurdy, C. R., & Sharma, A. (2025). The rise of novel, semi-synthetic 7-hydroxymitragnine products. *Addiction*, *120*(2), 387-388. https://doi.org/10.1111/add.16728
Smith, K. E., Dunn, K. E., Epstein, D. H., Feldman, J. D., Garcia-Romeu, A., Grundmann, O., Henningfield, J. E., McCurdy, C. R., Rogers, J. M., Schriefer, D., Singh, D., & Weiss, S. T. (2022). Need for clarity and context in case reports on kratom use, assessment, and intervention. *Subst Abus*, *43*(1), 1221-1224. https://doi.org/10.1080/08897077.2022.2074608
Smith, K. E., Dunn, K. E., Grundmann, O., Garcia-Romeu, A., Rogers, J. M., Swogger, M. T., & Epstein, D. H. (2022a). Social, psychological, and substance use characteristics of U.S. adults who use kratom: Initial findings from an online, crowdsourced study. *Experimental and Clinical Psychopharmacology*, *30*(6), 983-996. https://doi.org/10.1037/pha0000518

Smith, K. E., Dunn, K. E., Grundmann, O., Garcia-Romeu, A., Rogers, J. M., Swogger, M. T., & Epstein, D. H. (2022b). Social, psychological, and substance use characteristics of U.S. adults who use kratom: Initial findings from an online, crowdsourced study. *Exp Clin Psychopharmacol*, *30*(6), 983-996. https://doi.org/10.1037/pha0000518

Smith, K. E., Dunn, K. E., Rogers, J. M., Garcia-Romeu, A., Strickland, J. C., & Epstein, D. H. (2022). Assessment of Kratom Use Disorder and Withdrawal Among an Online Convenience Sample of US Adults. *J Addict Med*, *16*(6), 666-670. https://doi.org/10.1097/ADM.0000000000000986

Smith, K. E., Dunn, K. E., Rogers, J. M., Grundmann, O., McCurdy, C. R., Garcia-Romeu, A., Schriefer, D., Swogger, M. T., & Epstein, D. H. (2022). Kratom use as more than a "self-treatment". *Am J Drug Alcohol Abuse*, *48*(6), 684-694. https://doi.org/10.1080/00952990.2022.2083967

Smith, K. E., Epstein, D. H., & Weiss, S. T. (2024). Controversies in Assessment, Diagnosis, and Treatment of Kratom Use Disorder. *Curr Psychiatry Rep*, *26*(9), 487-496. https://doi.org/10.1007/s11920-024-01524-1

Smith, K. E., Feldman, J. D., Dunn, K. E., McCurdy, C. R., Grundmann, O., Garcia-Romeu, A., Panlilio, L. V., Rogers, J. M., Sharma, A., Pont-Fernandez, S., Kheyfets, M., & Epstein, D. H. (2023). Novel methods for the remote investigation of emerging substances: Application to kratom. *Exp Clin Psychopharmacol*. https://doi.org/10.1037/pha0000656

Smith, K. E., Feldman, J. D., Dunn, K. E., McCurdy, C. R., Grundmann, O., Garcia-Romeu, A., Panlilio, L. V., Rogers, J. M., Sharma, A., Pont-Fernandez, S., Kheyfets, M., & Epstein, D. H. (2024). Novel methods for the remote investigation of emerging substances: Application to kratom. *Exp Clin Psychopharmacol*, *32*(2), 215-227. https://doi.org/10.1037/pha0000656

Smith, K. E., Feldman, J. D., Dunn, K. E., McCurdy, C. R., Weiss, S. T., Grundmann, O., Garcia-Romeu, A., Nichels, J., & Epstein, D. H. (2023). Examining the paradoxical effects of kratom: a narrative inquiry. *Front Pharmacol*, *14*, 1174139. https://doi.org/10.3389/fphar.2023.1174139

Smith, K. E., & Lawson, T. (2017). Prevalence and motivations for kratom use in a sample of substance users enrolled in a residential treatment program. *Drug and Alcohol Dependence*, *180*, 340-348. https://doi.org/https://doi.org/10.1016/j.drugalcdep.2017.08.034

Smith, K. E., Panlilio, L. V., Feldman, J. D., Grundmann, O., Dunn, K. E., McCurdy, C. R., Garcia-Romeu, A., & Epstein, D. H. (2024a). Ecological Momentary Assessment of Self-Reported Kratom Use, Effects, and Motivations Among US Adults. *JAMA Network Open*, *7*(1), e2353401-e2353401. https://doi.org/10.1001/jamanetworkopen.2023.53401

Smith, K. E., Panlilio, L. V., Feldman, J. D., Grundmann, O., Dunn, K. E., McCurdy, C. R., Garcia-Romeu, A., & Epstein, D. H. (2024b). Ecological Momentary Assessment of Self-Reported Kratom Use, Effects, and Motivations Among US Adults. *JAMA Netw Open*, *7*(1), e2353401. https://doi.org/10.1001/jamanetworkopen.2023.53401

Smith, K. E., Panlilio, L. V., Sharma, A., McCurdy, C. R., Feldman, J. D., Mukhopadhyay, S., Kanumuri, S. R. R., Kuntz, M. A., Hill, K., & Epstein, D. H. (2024). Time course of kratom effects via ecological momentary assessment, by product type, dose amount,

and assayed alkaloid content. *Drug Alcohol Depend*, *264*, 112460. https://doi.org/10.1016/j.drugalcdep.2024.112460
Smith, K. E., Rogers, J. M., Dunn, K. E., Grundmann, O., McCurdy, C. R., Schriefer, D., & Epstein, D. H. (2022). Searching for a Signal: Self-Reported Kratom Dose-Effect Relationships Among a Sample of US Adults With Regular Kratom Use Histories. *Front Pharmacol*, *13*, 765917. https://doi.org/10.3389/fphar.2022.765917
Smith, K. E., Rogers, J. M., & Feldman, J. D. (2023). Kratom's Emergence and Persistence Within the US Polydrug Epidemic. *Curr Addict Rep*, *10*(2), 262-271. https://doi.org/10.1007/s40429-023-00476-5
Smith, K. E., Rogers, J. M., Schriefer, D., & Grundmann, O. (2021). Therapeutic benefit with caveats?: Analyzing social media data to understand the complexities of kratom use. *Drug Alcohol Depend*, *226*, 108879. https://doi.org/10.1016/j.drugalcdep.2021.108879
Smith, K. E., Rogers, J. M., Sharma, A., McCurdy, C. R., Weiss, S. T., Dunn, K. E., Feldman, J. D., Kuntz, M. A., Mukhopadhyay, S., Raju, K. S. R., Taylor, R. C., & Epstein, D. H. (2024). Responses to a "Typical" Morning Dose of Kratom in People Who Use Kratom Regularly: A Direct-Observation Study. *J Addict Med*, *18*(2), 144-152. https://doi.org/10.1097/ADM.0000000000001259
Smith, K. E., Rogers, J. M., & Strickland, J. C. (2022). Associations of Lifetime Nonmedical Opioid, Methamphetamine, and Kratom Use within a Nationally Representative US Sample. *J Psychoactive Drugs*, *54*(5), 429-439. https://doi.org/10.1080/02791072.2021.2006374
Smith, K. E., Sharma, A., Grundmann, O., & McCurdy, C. R. (2023). Kratom Alkaloids: A Blueprint? *ACS Chem Neurosci*, *14*(2), 195-197. https://doi.org/10.1021/acschemneuro.2c00704
Smith, K. E., Singh, D., & Grundmann, O. (2025). Chapter 5 - Kratom-related physical dependence and addiction. In J. E. Henningfield, C. E. Beyer, & R. B. Raffa (Eds.), *Kratom: History, Science and Therapeutic Potential* (pp. 59-78). Academic Press. https://doi.org/https://doi.org/10.1016/B978-0-443-27412-1.00005-5
Spungen, H. H., Mody, K., Micetic, B., Wade, C., & Kang, A. M. (2024). Neonatal and Maternal Ichthyosiform Dermopathy in Association with Kava Use during Pregnancy. *J Med Toxicol*, *20*(3), 308-313. https://doi.org/10.1007/s13181-024-01016-x
Stanciu, C., Ahmed, S., Gnanasegaram, S., Gibson, S., Penders, T., Grundmann, O., & McCurdy, C. (2022). Kratom as an opioid alternative: harm, or harm reduction? A systematic review of literature. *Am J Drug Alcohol Abuse*, *48*(5), 509-528. https://doi.org/10.1080/00952990.2022.2111685
Stanciu, C. N., Ahmed, S., Sarfraz, Z., Nimavat, N., Healey, C. J., Grundmann, O., Ballard, J. R., & Henningfield, J. (2024). Prevalence, Characteristics, and Reasons for Kratom Use among Psychiatrically Ill Inpatients Who Use Substances. *J Dual Diagn*, *20*(2), 87-97. https://doi.org/10.1080/15504263.2023.2289456
Stefanello, N., Spanevello, R. M., Passamonti, S., Porciúncula, L., Bonan, C. D., Olabiyi, A. A., Teixeira da Rocha, J. B., Assmann, C. E., Morsch, V. M., & Schetinger, M. R. C. (2019). Coffee, caffeine, chlorogenic acid, and the purinergic system. *Food and Chemical Toxicology*, *123*, 298-313. https://doi.org/https://doi.org/10.1016/j.fct.2018.10.005
Striley, C. W., Hoeflich, C. C., Viegas, A. T., Berkowitz, L. A., Matthews, E. G., Akin, L. P., Iheanyi-Okeahialam, C., Mansoor, U., & McCurdy, C. R. (2022). Health Effects

Associated With Kratom (Mitragyna speciosa) and Polysubstance Use: A Narrative Review. *Subst Abuse*, *16*, 11782218221095873. https://doi.org/10.1177/11782218221095873
Sudmoon, R., Tanee, T., Wonok, W., Ameamsri, U., Liehr, T., Daduang, S., Siripiyasing, P., & Chaveerach, A. (2025). Discovery of rhynchophylline and mitraphylline in two Thai Mitragyna species and the investigation of their biological activity via opioid gene expression analysis. *Sci Rep*, *15*(1), 5865. https://doi.org/10.1038/s41598-025-89715-5
Suhaimi, F. W., Khari, N. H. M., Hassan, Z., & Müller, C. P. (2025). Exploring the cognitive effects of kratom: A review. *Behavioural Brain Research*, *480*, 115387. https://doi.org/https://doi.org/10.1016/j.bbr.2024.115387
Suhaimi, F. W., Zul Aznal, A. N., Mohamad Nor Hazalin, N. A., Teh, L. K., Hassan, Z., & Salleh, M. Z. (2023). Kratom (M. speciosa) exposure during adolescence caused long-lasting cognitive behavioural deficits associated with perturbated brain metabolism pathways in adult rats. *Behav Brain Res*, *446*, 114411. https://doi.org/10.1016/j.bbr.2023.114411
Suriaga, A. A., Tappen, R. M., McCurdy, C. R., Newman, D., Grundmann, O., & Kelly, J. F. (2024). The Associations of Kratom (Mitragynine), Opioids, Other Substances, and Sociodemographic Variables to Drug Intoxication-related Mortality. *J Addict Med*. https://doi.org/10.1097/ADM.0000000000001417
Swart, B. B., Reznikoff, C., & Steen, K. (2024a). Isolated Kratom Use Disorder Treated With Extended-Release Buprenorphine Taper. *J Addict Med*, *18*(5), 602-604. https://doi.org/10.1097/ADM.0000000000001328
Swart, B. B., Reznikoff, C., & Steen, K. (2024b). Isolated Kratom Use Disorder Treated with Extended-Release Buprenorphine Taper. *J Addict Med*. https://doi.org/10.1097/ADM.0000000000001328
Swatek, J. L., & Peterson, B. L. (2024). Drug Trends in the Teenage Postmortem Population From 2017 to 2021. *Am J Forensic Med Pathol*. https://doi.org/10.1097/PAF.0000000000000977
Swogger, M. T., Hart, E., Erowid, F., Erowid, E., Trabold, N., Yee, K., Parkhurst, K. A., Priddy, B. M., & Walsh, Z. (2015). Experiences of Kratom Users: A Qualitative Analysis. *Journal of Psychoactive Drugs*, *47*(5), 360-367. https://doi.org/10.1080/02791072.2015.1096434
Swogger, M. T., Smith, K. E., Garcia-Romeu, A., Grundmann, O., Veltri, C. A., Henningfield, J. E., & Busch, L. Y. (2022). Understanding Kratom Use: A Guide for Healthcare Providers. *Front Pharmacol*, *13*, 801855. https://doi.org/10.3389/fphar.2022.801855
Sykora, H. (2025). Home Care and the Patient Taking Kratom. *Home Healthc Now*, *43*(2), 122-124. https://doi.org/10.1097/NHH.0000000000001323
Tampanna, N., Wanitsuwan, W., Chewatanakornkul, S., Wangkulangkul, P., Theapparat, Y., Detarun, P., & Wichienchot, S. (2025). The role of kratom (Mitragyna speciosa Korth.) extract in medical foods for obese patients: Effects on gut microbiota in a colon model. *Food Res Int*, *204*, 115935. https://doi.org/10.1016/j.foodres.2025.115935
Tanna, R. S., Cech, N. B., Oberlies, N. H., Rettie, A. E., Thummel, K. E., & Paine, M. F. (2023). Translating Kratom-Drug Interactions: From Bedside to Bench and Back. *Drug Metab Dispos*, *51*(8), 923-935. https://doi.org/10.1124/dmd.122.001005

Tanna, R. S., Nguyen, J. T., Hadi, D. L., Layton, M. E., White, J. R., Cech, N. B., Oberlies, N. H., Rettie, A. E., Thummel, K. E., & Paine, M. F. (2023). Clinical Assessment of the Drug Interaction Potential of the Psychotropic Natural Product Kratom. *Clin Pharmacol Ther*, *113*(6), 1315-1325. https://doi.org/10.1002/cpt.2891

Tanna, R. S., Nguyen, J. T., Hadi, D. L., Manwill, P. K., Flores-Bocanegra, L., Layton, M. E., White, J. R., Cech, N. B., Oberlies, N. H., Rettie, A. E., Thummel, K. E., & Paine, M. F. (2022). Clinical Pharmacokinetic Assessment of Kratom (Mitragyna speciosa), a Botanical Product with Opioid-like Effects, in Healthy Adult Participants. *Pharmaceutics*, *14*(3). https://doi.org/10.3390/pharmaceutics14030620

Tassavor, B., Young Eun, C., Nikolskaia, O., & Jobarteh-Williams, R. (2025). Hyperpigmentation From Chronic Kratom Use: A Case Report and Review of the Literature. *Cureus*, *17*(2), e79804. https://doi.org/10.7759/cureus.79804

Thepthien, B. O., Jayasvasti, I., & Ham, E. (2024). The prevalence of kratom use and association with co-occurring substance use among adolescents: a 2022 Bangkok behavioral surveillance survey, Thailand. *J Ethn Subst Abuse*, 1-15. https://doi.org/10.1080/15332640.2024.2367233

Thewjitcharoen, Y., Krittiyawong, S., Nakasatien, S., & Himathongkam, T. (2022). Kratom-Associated Mixed Cholestatic-Hepatocellular Liver Injury in a Patient With Long COVID: A case Report. *Clin Med Insights Case Rep*, *15*, 11795476221132824. https://doi.org/10.1177/11795476221132824

Thongsepee, N., Amonyingcharoen, S., Chamod, P., Himakhun, W., Sangpairoj, K., Martviset, P., Chantree, P., & Sornchuer, P. (2025). Modulatory effects of Kratom extract on the gut microbiota of rats: implications for health. *BMC Complement Med Ther*, *25*(1), 85. https://doi.org/10.1186/s12906-025-04836-8

Tobacyk, J., Parks, B. J., Lovelady, N., & Brents, L. K. (2022). Qualitative content analysis of public responses to an FDA inquiry on the impact of scheduling changes to kratom. *Int J Drug Policy*, *108*, 103817. https://doi.org/10.1016/j.drugpo.2022.103817

Tobarran, N., Wolf, C., Cumpston, K. L., & Wills, B. K. (2022). Pressure Necrosis Requiring Fasciotomy After Kratom Overdose. *J Addict Med*, *16*(2), 252-253. https://doi.org/10.1097/ADM.0000000000000873

Torres-Ortiz, A., Al Zein, S., & Alqudsi, M. (2022). A Case of Hyperkalemia Induced by Kratom (Mitragyna speciosa). *Cureus*, *14*(4), e24036. https://doi.org/10.7759/cureus.24036

Torrico, T., Patel, K., Nikolov, N., Salam, M. T., Padhy, R., & Weinstein, D. (2023). Presence of kratom in opioid overdose deaths: findings from coroner postmortem toxicological report. *Front Psychiatry*, *14*, 1332999. https://doi.org/10.3389/fpsyt.2023.1332999

Uchaipichat, V. (2025). Inhibitory effects of Kratom constituents, mitragynine and 7-hydroxymitragynine, on 4-methylumbelliferone glucuronidation by human UDP-glucuronosyltransferases. *Toxicol Rep*, *14*, 101951. https://doi.org/10.1016/j.toxrep.2025.101951

Umbehr, G., & Lukaszewicz, M. (2022). Acute liver injury following short-term use of the herbal supplement kratom. *JAAPA*, *35*(2), 39-41. https://doi.org/10.1097/01.JAA.0000805820.94245.3d

UNODC. (2021). *Summary of assessments, findings and recommendations of the 44th World Health Organization's (WHO) Expert Committee on Drug Dependence*

(ECDD), 11–15 October 2021. Retrieved September 24, 2025 from https://www.unodc.org/documents/commissions/CND/CND_Sessions/CND_64Reconvened/ECN72021_CRP12_V2108992.pdf

UNODC. (2025). *August 2025 - Emergence of potent kratom-related products containing 7-hydroxymitragynine and/or mitragynine pseudoindoxyl*. Retrieved 22 January from https://www.unodc.org/LSS/Announcement/Details/d0c66623-b200-4537-9f25-7df89fbdbf8b

Vadiei, N., Evoy, K. E., & Grundmann, O. (2025). The Impact of Diverse Kratom Products on Use Patterns, Dependence, and Toxicity. *Curr Psychiatry Rep*, *27*(10), 584-592. https://doi.org/10.1007/s11920-025-01631-7

Valle, K., Wingate, K., Tinker, D., & Dilworth, D. (2025). Unveiling kratom's dark side: Case report implicating the botanical ingredient as a culprit in recalcitrant photo-exposed hyperpigmentation. *JAAD Case Rep*, *59*, 101-104. https://doi.org/10.1016/j.jdcr.2025.02.017

Vanani, N. B., Stevanovic, S. G., & Stevanovic, N. (2023). Adverse Drug Interaction Between Kratom and Amitriptyline With Gastrointestinal and Mild Hepatic Effects. *Cureus*, *15*(1), e33809. https://doi.org/10.7759/cureus.33809

Vicknasingam, B., Karunakaran, T., & Chawarski, M. C. (2024). Research and publication gaps on kratom and kratom products: a scoping review of current literature. *Curr Opin Psychiatry*, *37*(4), 282-291. https://doi.org/10.1097/YCO.0000000000000950

Viwatpinyo, K., Mukda, S., & Warinhomhoun, S. (2023). Effects of mitragynine on viability, proliferation, and migration of C6 rat glioma, SH-SY5Y human neuroblastoma, and HT22 immortalized mouse hippocampal neuron cell lines. *Biomed Pharmacother*, *166*, 115364. https://doi.org/10.1016/j.biopha.2023.115364

Wei, L. C. (2024). Addressing the Challenges of Kratom Regulation in Taiwan: A Public Health Perspective. *J Dual Diagn*, *20*(2), 98. https://doi.org/10.1080/15504263.2024.2320692

White, C. M. (2025). Kratom's Use and Impact on Pediatric Populations. *J Pediatr Pharmacol Ther*, *30*(2), 289-293. https://doi.org/10.5863/1551-6776-30.2.289

White, C. M., Belcourt, J., & Sedensky, A. (2025). A Descriptive Assessment of Products Containing the Opioid Receptor Stimulator Mitragynine Pseudoindoxyl. *Subst Use Misuse*, *60*(12), 1950-1954. https://doi.org/10.1080/10826084.2025.2522162

WHO. (2021). *Summary of assessments, findings and recommendations of the 44th ECDD, 11-15 October 2021* Retrieved 22 January from https://cdn.who.int/media/docs/default-source/controlled-substances/44ecdd_unsg_annex1.pdf?sfvrsn=9c380ac2_5

Wightman, R. S., & Hu, D. (2025). A Case of 7-OH Mitragynine Use Requiring Inpatient Medically Managed Withdrawal. *J Addict Med*. https://doi.org/10.1097/ADM.0000000000001558

Xu, K. Y., Mintz, C. M., Borodovsky, J. T., Glaser, P. E. A., Bierut, L. J., & Grucza, R. A. (2021). Prevalence of Kratom Use and Co-Occurring Substance Use Disorders in the United States. *Prim Care Companion CNS Disord*, *23*(4). https://doi.org/10.4088/PCC.21br02930

Yang, B., Tan, M. L., Zhang, R., Singh, D., & Leong Bin Abdullah, M. F. I. (2023). Kratom use disorder and unfolded protein response: Evaluating their relationship in a case control study. *PLoS One*, *18*(6), e0287466. https://doi.org/10.1371/journal.pone.0287466

Yang, B., Zhang, R., & Leong Bin Abdullah, M. F. I. (2024). The association between neuropsychiatric effects of substance use and occurrence of endoplasmic reticulum and unfolded protein response: A systematic review. *Toxicol Lett*, *391*, 71-85. https://doi.org/10.1016/j.toxlet.2023.12.008

Yang, Y., Muller, C. P., & Singh, D. (2024). Kratom (Mitragyna speciosa) Use and Mental Health: A Systematic Review and Multilevel Meta-Analysis. *Eur Addict Res*, *30*(4), 252-274. https://doi.org/10.1159/000539338

You, C. Y., Hassan, Z., Muller, C. P., & Suhaimi, F. W. (2022). Mitragynine improves cognitive performance in morphine-withdrawn rats. *Psychopharmacology (Berl)*, *239*(1), 313-325. https://doi.org/10.1007/s00213-021-05996-4

Yue, K., Katz, J. L., & Shu, X. (2022). Physiological dependence to mitragynine indicated by a rapid cross-dependence procedure with heroin-dependent mice. *Psychopharmacology (Berl)*, *239*(3), 897-908. https://doi.org/10.1007/s00213-022-06080-1

Yunusa, S., Hassan, Z., & Muller, C. P. (2023). Mitragynine inhibits hippocampus neuroplasticity and its molecular mechanism. *Pharmacol Rep*, *75*(6), 1488-1501. https://doi.org/10.1007/s43440-023-00541-w

Yunusa, S., Muller, C. P., & Hassan, Z. (2024). Mitragynine (Kratom)-Withdrawal behaviour and cognitive impairments can be ameliorated by an epigenetic mechanism. *Br J Pharmacol*, *181*(13), 2070-2084. https://doi.org/10.1111/bph.16352

Yusoff, N. H. M., Hassan, Z., Murugaiyah, V., & Muller, C. P. (2022). The effect of mitragynine on extracellular activity of brain dopamine and its metabolites. *Brain Res Bull*, *178*, 1-8. https://doi.org/10.1016/j.brainresbull.2021.11.002

Zainudin, N. A. B., Zulkifli, N. N., Abdul Hamid, K., Hashim, H., & Mansor, S. (2023). A Pilot Study of the Striatal Dopamine Transporter Levels in Kratom-Dependent and Normal Subjects Using 99mTc-TRODAT-1 Single Photon Emission Computed Tomography-Computed Tomography (SPECT-CT). *Cureus*, *15*(8), e43251. https://doi.org/10.7759/cureus.43251

Zamarripa, C. A., Spindle, T. R., Panlilio, L. V., Strickland, J. C., Feldman, J. D., Novak, M. D., Epstein, D. H., Dunn, K. E., McCurdy, C. R., Sharma, A., Kuntz, M. A., Mukhopadhyay, S., Raju, K. S. R., Rogers, J. M., & Smith, K. E. (2024). Effects of kratom on driving: Results from a cross-sectional survey, ecological momentary assessment, and pilot simulated driving Study. *Traffic Inj Prev*, *25*(4), 594-603. https://doi.org/10.1080/15389588.2024.2327827

Zhang, P., Wei, W., Zhang, X., Wen, C., Ovatlarnporn, C., & Olatunji, O. J. (2023). Antidiabetic and antioxidant activities of Mitragyna speciosa (kratom) leaf extract in type 2 diabetic rats. *Biomed Pharmacother*, *162*, 114689. https://doi.org/10.1016/j.biopha.2023.114689

Zuarth Gonzalez, J. D., Ragsdale, A. K., Mukhopadhyay, S., McCurdy, C. R., McMahon, L. R., Obeng, S., & Wilkerson, J. L. (2025). Mitragynine and 7-Hydroxymitragynine: Bidirectional Effects on Breathing in Rats. *bioRxiv*. https://doi.org/10.1101/2025.05.16.654392

Zul Aznal, A. N., Mohamad Nor Hazalin, N. A., Hassan, Z., Mat, N. H., Chear, N. J., Teh, L. K., Salleh, M. Z., & Suhaimi, F. W. (2022). Adolescent kratom exposure affects cognitive behaviours and brain metabolite profiles in Sprague-Dawley rats. *Front Pharmacol*, *13*, 1057423. https://doi.org/10.3389/fphar.2022.1057423

1 Appendix 1: Kratom Abuse Potential 2021: An Updated Eight Factor Analysis

frontiers in Pharmacology

REVIEW
published: 28 January 2022
doi: 10.3389/fphar.2021.775073

Kratom Abuse Potential 2021: An Updated Eight Factor Analysis

Jack E. Henningfield, Daniel W. Wang and Marilyn A. Huestis*

PinneyAssociates, Inc., Bethesda, MD, United States

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

OPEN ACCESS

Edited by:
Valentina Echeverria Moran, Bay Pines VA Healthcare System, United States

Reviewed by:
Walter Prozialeck, Midwestern University, United States
C. White, University of Connecticut, United States

****Correspondence:***
Jack E. Henningfield
jhenning@pinneyassociates.com

Specialty section:
This article was submitted to Ethnopharmacology, a section of the journal Frontiers in Pharmacology

Received: *13 September 2021*
Accepted: *22 November 2021*
Published: *28 January 2022*

Citation:
Henningfield JE, Wang DW and Huestis MA (2022) Kratom Abuse Potential 2021: An Updated Eight Factor Analysis. Front. Pharmacol. 12:775073. doi: 10.3389/fphar.2021.775073

1 INTRODUCTION

This is an update to the Henningfield et al. (2018) assessment of the abuse potential of kratom based on the eight factors of the United States Controlled Substances Act (US CSA) (Henningfield et al., 2018a) and summarizes new scientific findings from January 2018 through August 2021. The CSA eight factors evaluate pharmacological actions in the brain or central nervous system (CNS) that may lead to dependence, substance use disorders, or addictions (American Psychiatric Association, 2013; National Institute on Drug Abuse, 2019; World Health Organization, 1994; O'Brien et al., 2011). Abuse potential assessments determine whether substances and medicinal products should be controlled by the CSA (scheduled), and if so the restrictiveness or level of control. Substances are only placed in Schedule I (heroin, LSD, cannabis) when there is no FDA approved therapeutic use and sufficient abuse potential to merit control. Substances with approved therapeutic uses and sufficient abuse potential must be placed in Schedules II–V. By law, an eight-factor analysis (8-FA) provides the primary pharmacological and public health basis for drug scheduling (Food and Drug Administration, 2017a; Belouin and Henningfield, 2018; Johnson et al., 2018). This assessment focuses on kratom and its alkaloids, in particular mitragynine (MG), the primary alkaloid in kratom present in sufficient amounts to account for its effects.

Kratom and its alkaloids are not approved for any therapeutic use by the FDA, are not federally controlled in the US, nor in the International Drug Control Conventions; however some countries do control kratom and/or its two primary alkaloids, MG and 7-OH-MG (Prozialeck et al., 2019; International Narcotics C, 2020a; International Narcotics C, 2020b). Six states in the US (Alabama, Arkansas, Indiana, Tennessee, Vermont and Wisconsin) have banned kratom, while five have passed consumer protection legislation to ensure consumer access to kratom with a framework for regulatory oversight (Arizona, Georgia, Nevada, Oklahoma and Utah). Maryland rejected a proposed ban and passed a minimum age of purchase law (age 21), and at this writing, several states are considering their own kratom consumer protection laws to ensure consumer access but with regulatory oversight. In 2021, Thailand decriminalized kratom farming, possession and sales. In December, 2021, the World Health Organization Expert Committee on Drug Dependence concluded "there is insufficient evidence to recommend a critical review of kratom mitragynine and 7-hydroxymitragynine" [for potential scheduling] but should be kept under surveillance (Commission on Narcotic Drugs, 2021).

In August 2016 the US Drug Enforcement Agency (DEA) proposed scheduling kratom on a temporary "emergency" basis but withdrew the proposal due to thousands of comments from kratom consumers and bipartisan members of Congress, and out of concern that people who were managing their opioid use disorder with the aid of kratom would return to opioid use. The DEA requested that FDA perform a full 8-FA and develop its own independent recommendations related to scheduling (Ingraham, 2016a; Ingraham, 2016b). Subsequently, Dr. Henningfield and his colleagues at PinneyAssociates were commissioned by the American Kratom Association's legal regulatory counsel to develop an 8-FA (Pinney Associates (2016)) for submission to DEA by December 2, 2016. In November 2017, FDA Commissioner Scott Gottlieb announced that kratom carried "narcotic like" risks of addiction and death but did not make public its October 17th recommendation to DEA to permanently place MG and 7-OH-MG in Schedule I of the CSA (Food and Drug Administration, 2017b; Food and Drug Administration, 2017c).

DEA typically responds to formal 8-FA scheduling requests within 90 days, though there is no legal timeline; however, a formal scheduling rescission order was issued on August 18, 2018 from the Assistant Secretary of Health, US Department of Health and Human Services (DHHS) (Giroir, 2018). The order included conclusions based on a DHHS review consistent with those of the Henningfield et al. (2018) 8-FA (Henningfield et al., 2018a). The DHHS rescission letter stated "mitragynine does not satisfy the first of the three statutory requisites for Schedule I"; "There is still debate among reputable scientists over whether kratom by itself is associated with fatal overdoses"; and "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." The letter also raised concerns about "the stifling effect of classification in Schedule I on critical research needed on the complex and potentially useful chemistry of components of kratom." This letter was not made public until January 2021.

In 2017, the National Institute on Drug Abuse (NIDA) substantially increased its active research program on kratom's alkaloids and derivatives as potentially safer and less abusable medicines for pain and addiction and other disorders. The purpose of this review is to provide an update of our 2018 article on the abuse potential of kratom. It includes more than 100 new studies related to kratom abuse potential, safety, patterns of use, and potential therapeutic and public health benefits.

2 METHODS

The intent was to include all new studies published in English relevant to kratom abuse potential, safety and mechanisms of action published in since January 1, 2018 with some essential earlier studies mentioned and referenced to our 2018 review.[1] This was by comprehensive online literature searches, and direct requests to leading kratom researchers worldwide. To be concise, factors 4, 5, and 6 are considered a single group of public health related factors.[2] (Henningfield et al., 2018a; Johnson et al., 2018). Factor 8 is unchanged as neither kratom nor its constituents are scheduled.

[1] The authors welcome communications from readers on abuse-potential and safety related kratom research published since 2018 that we might have missed.

[2] For formal FDA submissions Factors 4, 5, and 6 are considered separately (see Henningfield et al., 2018a and Johnson, Griffiths, Hendricks and Henningfield, 2018 as examples), however, for temporary (also known as "emergency") scheduling, determining if a substance poses an imminent health risk is based on the analysis of all three factors combined similarly to our approach in this review.

3 RESULTS

3.1 Factor 1: Actual or Relative Potential for Abuse

A summary of the references used, along with main findings and comments from the authors of this review are included in **Table 1.**

3.1.1 Summary of 2018 Findings

There were no animal intravenous drug self-administration (IV DSA), intracranial self-stimulation (ICSS) brain reward, or physical dependence/withdrawal studies of kratom's alkaloids; however, other data suggested relatively low abuse potential as compared to opioids and other drugs of abuse (Henningfield et al., 2018a). There was evidence of morphine opioid receptor (MOR) mediated effects, and preliminary drug discrimination and conditioned place preference (CPP) studies with rats suggested abuse related effects at high intolerable human dose equivalents.

Survey data from the US and field studies in Southeast Asia (SEA) showed most kratom use was for health-related benefits, and to facilitate occupational performance. Data indicated that problem abuse and addiction were not common and was generally more tolerable and readily self-manageable as compared to opioids. A frequent reason for use was as an opioid substitute for pain and self-management of opioid, alcohol, and other drug dependence.

3.1.2 Factor 1 Science Updates

3.1.2.1 Intravenous Drug Self-Administration Trials

Rates of MG self-administration were similar to those of saline, and MG pretreatment produced dose-related reductions in morphine self-administration rates (Hemby et al., 2019). The authors concluded "The present findings indicate that MG does not have abuse potential and reduces morphine intake, desired characteristics of candidate pharmacotherapies for opiate addiction and withdrawal ... ". 7-OH-MG was self-administered at high doses and pretreatment increased morphine self-administration.

MG self-administration rates in rats did not exceed those obtained with saline and MG pretreatment decreased heroin self-administration, with little effect on methamphetamine self-administration (Yue et al., 2018). The authors noted "These results suggest limited abuse liability of mitragynine and the potential for mitragynine treatment to specifically reduce opioid abuse. With the current prevalence of opioid abuse and misuse, it appears currently that mitragynine is deserving of more extensive exploration for its development or that of an analog as a medical treatment for opioid abuse." These results are consistent with human reports that kratom is useful in the management of opioid craving and withdrawal and to support opioid abstinence (Grundmann et al., 2018; Coe et al., 2019; Prozialeck et al., 2019; Garcia-Romeu et al., 2020).

Intracranial Self-Stimulation

In the ICSS model, rats equipped with brain electrodes self-deliver rewarding electrical brain stimulation. Opioids, amphetamine-like stimulants, cocaine, and other classic drugs of abuse reduce the stimulation threshold and increase the strength of the rewarding effects of drugs on ICSS (Negus and Miller, 2014). Neither MG nor 7-OH-MG showed evidence of brain rewarding effects, whereas morphine robustly and dose-dependently decreased the stimulation threshold (Behnood-Rod et al., 2020). Thus, the ICSS results suggest lower brain rewarding effects of MG as compared to morphine.

Drug Discrimination Studies

The discriminative stimulus effects of MG were evaluated in studies designed to assess generalization to morphine as well as the delta-opioid receptor agonist SNC80 and kappa-opioid receptor agonist U69593, alpha adrenergic agonists lofexidine, clonidine and phenylephrine, alpha adrenergic antagonists yohimbine and atipamezole, and the cannabinoid agonist Δ-9-tetrahydrocannabinol (Reeve et al., 2020). The strongest generalization was to lofexidine and phenylephrine, both unscheduled drugs: phenylephrine is in some over-the-counter cold medicines; lofexidine is approved for several indications including the first nonopioid for alleviating opioid withdrawal.

In a comparison of MG and 7-OH-MG across studies that included *in vitro* receptor binding and an antinociception test, MG partially generalized to morphine, whereas 7-OH-MG fully generalized to morphine in rats (Obeng et al., 2021). Similarly, Hiranita et al. (2020) found only partial generalization of oral MG to i.p. morphine in rats (Hiranita et al., 2020).

3.1.2.4 Conditioned Place Preference

Various MG preparations produced mixed CPP effects with some suggesting abuse potential at high doses. A low priming injection of MG or morphine reinstated CPP after establishment with either drug, suggesting rewarding effects for both (Japarin et al., 2021). Baclofen pretreatment prevented the acquisition and expression of MG-induced CPP (Yusoff et al., 2018). CPP was achieved in mice with a high dose methanolic extract of kratom leaves (Vijeepallam et al., 2019). In a fourth study (see also Factor 2), lyophilized (freeze-dried) kratom tea (LKT), a potential treatment for pain and opioid dependence, did not induce CPP in mice (Wilson et al., 2020).

3.1.2.5 Physical Dependence and Withdrawal

Discontinuation of morphine administration produced response rate disruptions indicating significant signs of spontaneous withdrawal, whereas discontinuation of MG administration did not produce significant signs of spontaneous withdrawal. Naloxone administration did precipitate response rate disruptions indicating withdrawal in both MG and morphine treated rats, however, this withdrawal effect was weaker and shorter lived in MG treated rats as compared to morphine treated rats (Harun et al., 2020). MG treatment also reduced naloxone precipitated withdrawal in animals receiving chronic morphine, consistent with human reports. Hassan, Pike, See, Sreenlivasan et al. (2020) compared the efficacy of MG to methadone for treating morphine withdrawal in rats concluding that MG treatment attenuated withdrawal symptoms significantly, similar to methadone and buprenorphine, and potentially with less undesired effects (Hassan et al., 2020).

TABLE 1 | Summary of references.

Factor/Description	Citations	Main findings	Comments
Factor 1: Actual or relative potential for abuse			
Intravenous Self-Administration (IV SA)	(Prozialeck et al., 2019), (Grundmann et al., 2018; Yue et al., 2018; Coe et al., 2019; Hemby et al., 2019; Garcia-Romeu et al., 2020)	No evidence of reward	MG pretreatment reduced morphine self-administration
Intracranial Self-Stimulation (ICSS)	(Negus and Miller, 2014)-(Behnood-Rod et al., 2020)	No evidence of reward for MG or 7-OH-MG	
Drug Discrimination	(Hiranita et al., 2020; Reeve et al., 2020; Obeng et al., 2021)	MG showed partial generalization to multiple drugs, including morphine 7-OH-MG showed full generalization to morphine	Strongest generalization of MG was to unscheduled drugs: phenylephrine and lofexidine
Conditioned Place Preference (CPP)	(Yusoff et al., 2018; Vijeepallam et al., 2019; Wilson et al., 2020; Japarin et al., 2021)	Mixed evidence of CPP	
Physical Dependence/ Withdrawal	(Harun et al., 2020; Hassan et al., 2020; Johari et al., 2021; Hassan et al., 2021; Hassan et al., 20211778; Harun et al., 2021a)	Mixed evidence of weak withdrawal across studies relative to morphine	MG reduces morphine withdrawal and differs from morphine withdrawal on some measures
Survey Data	(Prozialeck et al., 2019), (Grundmann et al., 2018; Coe et al., 2019; Garcia-Romeu et al., 2020), (Singh et al., 2014; Galbis-Reig, 2016; Swogger and Walsh, 2018; Smith et al., 2019; Harun et al., 2021b)	Majority use is for health benefits, not recreational use or to get high. Use is almost exclusively oral, without the tendency of many recreational substance to smoke, inject, and/or nasally insufflate	Most people reporting "kratom addiction" found it weaker and more tolerable and acceptable than "drug" addiction and were more likely so use it to manage other addictions than to use addictively
Factor 2: Scientific evidence of pharmacological effect			
Potential Therapeutic Effects	(Behnood-Rod et al., 2020; Obeng et al., 2021), (Vicknasingam et al., 2020; Chakraborty et al., 2021a)	Kratom's antinociceptive effects appear to be mediated at least partly by 7-OH-MG metabolite formation	Animal study findings are consistent for use to manage opioid use disorder and withdrawal, pain and suggest exploration for other disorders
Mechanisms of Action	(Prozialeck et al., 2019), (Behnood-Rod et al., 2020), (Hassan et al., 2019; Hiranita et al., 2019; Kruegel et al., 2019; Gutridge et al., 2020; Todd et al., 2020; Suhaimi et al., 2021)	Kratom alkaloids, including 7-OH-MG may interact with opioid receptors, but do not recruit β-arrestin 2	These are consistent with little or no respiratory depression across a broad range of doses and conditions
Kratom Minor Alkaloids and Metabolites	(Kruegel et al., 2019; Chakraborty et al., 2021a; León et al., 2021; Sharma and McCurdy, 2021), (Newman and Cragg, 2016; Sharma et al., 2019; Domnic et al., 2021a; Domnic et al., 2021b; Chear et al., 2021)	Most minor kratom alkaloids and metabolites are in de minimis levels	Some minor alkaloids might influence kratom's pharmacological effects and merit evaluation for potential therapeutic uses at much higher doses than provided by kratom
Metabolism and Metabolite Profiling	(Kamble et al., 2019; Kamble et al., 2020a; Kamble et al., 2020b)	7-OH-MG appears to metabolize differently in humans than in other species (e.g., rats, dogs, monkeys)	Animal models for kratom alone may not be fully predictive of human effects
Factor 3: Current state of scientific knowledge			
MG and 7-OH-MG PK/PD	(Hiranita et al., 2020), (Avery et al., 2019; Jagaballan et al., 2019; Maxwell et al., 2020)	Greater exposure observed with natural kratom formulations than with oral MG	
Minor Alkaloids PK/PD	(King et al., 2020; Berthold et al., 2021; Kamble et al., 2021)	Approximately one third of minor alkaloids are characterized	
Clinical Studies	(Singh et al., 2018a; Singh et al., 2018b; Singh et al., 2019a; Singh et al., 2020a; Leong Bin Abdullah et al., 2020; Leong Abdullah et al., 2021)	Long term users of kratom have no significant differences in most physiological measures compared to nonusers	These should not be considered definitive safety data but provide a foundation for further studies
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			
U.S. National and Federal Survey Data	(National Institute on Drug Abuse, 2019), (Coe et al., 2019)-(Garcia-Romeu et al., 2020), (U.S. Department of health and Human Services, 2020; Schimmel et al., 2021; Covey et al., 2020; Grundmann, 2017; Drug Abuse Warning Network, 2020; Drug Enforcement Adm, 2020a; Substance Abuse and Menta,	NSDUH Lifetime Use: 1.4%; Past Year Use0.7%. Little evidence of use on other federal surveys either because kratom was not specifically included or did not meet the threshold for reporting	Federal survey data provide no evidence that kratom poses an imminent threat to public health but merits continuing monitoring to better understand trends in use

(Continued on following page)

TABLE 1 | *(Continued)* Summary of references.

Factor/Description	Citations	Main findings	Comments
	2020; Drug Enforcement Adm, 2020b; Grundmann et al., 2021; Miech et al., 2021)		
Kratom Use Prevalence	(U.S. Department of Health and Human Services, 2020; Schimmel et al., 2021; Covey et al., 2020), (Botanical Education Alliance, 2016)	Estimates range from 1.8 million to over 16 million users in the US	It appears likely that there are at least 10 million kratom users in the US but more definitive studies are needed
Kratom Use Associated Mortality	(National Institute on Drug Abuse, 2019), (Giroir, 2018), (Food and Drug Admini, 2018; Gershman et al., 2019; Henningfield et al., 2019; Olsen et al., 2019)	Risk of kratom associated death appears to be at least a thousand times lower than for morphine-like opioids	Approximately 80% of kratom positive or "involved" deaths also detected other drugs of abuse or the decedent had a history of substance use disorders in one study contribution by other drugs not possible to rule out
Mortality Risks Projected as a Result of Banning Licit Kratom	(Henningfield et al., 2018a), (Ingraham, 2016b), (Giroir, 2018), (Grundmann et al., 2018; Coe et al., 2019; Garcia-Romeu et al., 2020), (Grundmann, 2017), (Henningfield et al., 2018b; Henningfield et al., 2018c; Henningfield et al., 2018d; Prozialeck et al., 2020)	Surveys suggest that it is likely that some kratom users would return to opioid use if kratom use and possession is banned	Fears of relapse to opioid use was a serious concern voiced by thousands of users in surveys and comments to DEA and FDA
Public Health and Individual Benefits of Kratom	(Henningfield et al., 2018a), (Prozialeck et al., 2019), (Coe et al., 2019)-(Garcia-Romeu et al., 2020), (Swogger and Walsh, 2018), (Grundmann, 2017), (Drug Enforcement Adm, 2016), (Raffa, 2014)-(Pain News Network, 2018)	Kratom is used by millions of people in the US to manage substance use disorders, pain, mood disorder, and for energy and improved mental focus and alertness	Reasons for use of kratom rather than FDA approved medications included better efficacy, presumed lower risks and because it is more accessible and tolerable, and/or preferred as a "natural product". Note: such data should not be used to support therapeutic claims in labeling or marketing
Kratom Use for Managing Opioid Use/Withdrawal and Other Health Reasons	(Coe et al., 2019), (Grundmann, 2017), (Singh et al., 2019b; Singh et al., 2020b; Singh et al., 2020c)	Surveys in US and SEA report kratom is used mostly for its health benefits, including opioid withdrawal	Although management of opioid use and withdrawal is prominent, nonclinical data suggest that use for other substance use disorder management and many other disorders merit further exploration
Comment on Therapeutic Use in Context of FDA Standards	(Katz, 2004; DiMasi et al., 2016; Food and Drug Admini, 2016; Dabrowska and Thaul, 2018; Wouters et al., 2020)	While research has yet to meet FDA's standard for therapeutic efficacy (NDA), there is substantial evidence of its use and efficacy in treating opioid withdrawal symptoms, and other disorders	
Factor 7—The psychic or physiological dependence liability			
Science Updates	(Hemby et al., 2019), (Coe et al., 2019)-(Garcia-Romeu et al. 2020), (Swogger and Walsh, 2018), (Harun et al., 2021b)-(Vicknasingam et al., 2020), (Grundmann, 2017), (Grundmann et al., 2021), (Swogger et al., 2015; Smith and Lawson, 2017; Singh et al., 2018c; Leong Bin Abdullah et al., 2021)	Some chronic, frequent kratom users report dependence/addition and/or withdrawal, but this is generally more readily self-managed compared to use disorders of other drugs of abuse	

Although MG withdrawal signs are weak in rats compared to those from morphine withdrawal, there does appear to be evidence of physical dependence; however, MG withdrawal unlike morphine was not associated with anxiogenic-like subjective symptoms. When using a pentylenetetrazol (PTZ) discrimination trial to evaluate anxiogenic signs in rats after MG or morphine withdrawal precipitated by naloxone, MG showed no substitution to the PTZ discriminative stimulus, while morphine produced a dose-related PTZ-like stimulus, further supporting MG as a novel pharmacotherapeutic intervention for managing opioid use disorder (Johari et al., 2021).

Other studies of opioid or MG withdrawal suggested that specific brain proteins might serve as more sensitive biomarkers for physiological dependence in rats as compared to behavioral signs (Hassan et al., 2021). Clonidine treatment may attenuate MG withdrawal signs in rats (Hassan et al., 2021). Another recent study employed an open-field test and an elevated-plus maze test to evaluate naloxone-precipitated withdrawal from MG as compared to morphine, and provided additional evidence confirming that MG can induce physical dependence and measurable signs of withdrawal in rats (Harun et al., 2021a). Overall, the research is consistent with human reports that

kratom withdrawal is generally more modest and more readily self-manageable than that produced by opioids (e.g., 22 and as discussed in Factor 7).

3.1.2.6 Real World Evidence of Abuse and Dependence

Factors 4–6 discuss the public health aspects of kratom use; however, many of the same studies address Factor 1 concerning evidence for abuse and are mentioned here.

As reported by Henningfield, et al. (2018), although surveys and anecdotal reports in the US and SEA confirm that some kratom consumers reported "addiction" those studies also indicated that use "to get high" is relatively low as compared to opioids and other recreational drugs of abuse, and that use by smoking, injecting, and/or insufflating was rare as compared to opioids, stimulants and other recreational drugs (Henningfield et al., 2018a). Recent studies confirm that kratom intake can lead to dependence and withdrawal in some kratom users, but these are substantially less likely to interfere with family, social and occupational life and commitments as compared to opioid dependence. Moreover, kratom is widely viewed as a healthier and less life-impairing substance to replace drugs such as opioids, alcohol, and stimulants (Singh et al., 2014; Galbis-Reig, 2016; Swogger and Walsh, 2018; Prozialeck et al., 2019).

A variety of reports confirm kratom use to self-manage opioid withdrawal and that abstinence from high chronic kratom use is typically associated with milder symptomatology than abstinence from classical opioids (Grundmann et al., 2018; Smith et al., 2019; Garcia-Romeu et al., 2020). The conclusion of Prozialeck et al. (2019) and Grundmann et al. (2018) (Grundmann et al., 2018; Prozialeck et al., 2019) were further strengthened by two published US surveys which found that the overwhelming majority of kratom consumers reported that their use was for various health benefits and not for recreational purposes (Coe et al., 2019; Garcia-Romeu et al., 2020; Harun et al., 2021b).

3.1.3 Factor 1 Updated Conclusion

Diverse scientific approaches were employed to profile MG's abuse potential, finding no evidence of rewarding effects in the IV self-administration and ICSS models, and weak evidence of potential reward in the CPP procedure. MG 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'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 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). New studies discussed in Factors 2–7 contribute further to the understanding of kratom's abuse potential, including its public health risks and benefits, that are part of the 8-factor abuse potential assessment.

3.2 Factor 2—Scientific Evidence of its Pharmacological Effects

3.2.1 Summary of 2018 Findings

MG and 7-OH-MG have some MOR mediated effects, but 7-OH-MG occurs at low concentrations in kratom leaves and is absent in many kratom product derivatives suggesting that the effects reported by kratom consumers are due primarily to MG. Some kratom effects were shown to be naloxone reversible (e.g., "pain" tolerance); however, MG and 7-OH-MG mechanisms of action were diverse and mediated by non-opioid transmitters and pathways (Kruegel and Grundmann, 2018). Thus, characterization of MG as an opioid "analog" or "narcotic like opioid" is not consistent with the overall evidence, leading Henningfield et al. (2018) to conclude "More research is clearly needed to elucidate receptor binding profiles and the diverse and probably complex mechanisms of action of the kratom alkaloids singly, in combination, and as commonly occur in marketed products and brewed extracts" (Henningfield et al., 2018a).

3.2.2 Factor 2 Science Updates

3.2.2.1 Potential Therapeutic Effects

Although neither kratom nor any of its alkaloids are approved for therapeutic use for any disorder, surveys discussed in *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* and elsewhere (Henningfield et al., 2018a; Grundmann et al., 2018; Swogger and Walsh, 2018; Coe et al., 2019; Prozialeck et al., 2019; Garcia-Romeu et al., 2020) show individuals in the US and around the world describe using kratom for its health benefits. Research characterizing kratom's effects, mechanisms of action, and therapeutic kratom alkaloid use rapidly advanced since 2018. In a placebo-controlled cold pressor task evaluating anti-nociceptive effects, pain tolerance was significantly increased following consumption of a kratom tea-type decoction similar to Malaysian preparations (Vicknasingam et al., 2020). These data provided "the first objectively measured evidence obtained in controlled research with human subjects that are preliminarily supporting or confirming previously published reports of kratom pain relieving properties based on self-reports collected in observational studies".

Consistent with Vicknasingam et al. (2020)'s clinical findings, oral LKT administration to mice produced dose-related antinociceptive effects at doses that did not alter locomotion or produce CPP; there were brief, non-life threatening decreases in respiration (Behnood-Rod et al., 2020). Repeated LKT administration produced no physical dependence, but significantly decreased naloxone-precipitated withdrawal in morphine dependent mice, confirming MOR agonist activity and therapeutic LKT effect for treating pain and opioid physical dependence.

After investigating *in vitro* receptor binding affinity and *in vivo* morphine discrimination, antinociception in the "heated plate" pain test, and naloxone challenge tests in rats, the authors concluded "At human m-opioid receptor (MOR) *in vitro*, mitragynine has low affinity and is an antagonist … ". Overall, 7-OH-MG had stronger MOR mediated effects including antinociception (Obeng et al., 2021). An extensive series of tests characterized several minor indole and oxindole alkaloids that the authors suggest are insufficient in abundance to account for the biological effects of kratom but may show promise for the development of potential medicines including potential new chemical entities (Chakraborty et al., 2021a).

Several of these studies showed MOR mediated antinociceptive effects with little evidence of respiratory depression suggesting the potential to contribute to new generations of nonopioid analgesics.

3.2.2.2 Mechanisms of Action

Although kratom produces some effects in common with opioids, and some of its alkaloid's actions are mediated by MOR receptors, its effects and mechanisms of action are diverse and include non-opioid mechanisms of action and non-opioid acting constituent alkaloids, as discussed in earlier reviews (Henningfield et al., 2018a; Kruegel and Grundmann, 2018; Prozialeck et al., 2019). In 2021, Leon et al. (2021) investigated several alkaloids, including mitragynine, paynantheine and speciogynine that produce serotonergic effects potentially mediated by their metabolites. As the authors discuss, such actions would be consistent with some of the mood enhancing effects attributed to kratom (Kruegel and Grundmann, 2018; Sharma and McCurdy, 2021).

Kratom contains approximately 1–2% MG by weight, as well as other alkaloids (including 7-OH-MG) that typically are present at such low levels in kratom leaf material that it is uncertain if they contribute to kratom effects (Prozialeck et al., 2019). 7-OH-MG is present in low concentrations in natural kratom products, but gradually emerges *in vivo* as a MG metabolite. Kruegel et al. (2019) studied its role as a mediator of MG effects (Kruegel et al., 2019) summarizing "7-hydroxymitragynine is formed from mitragynine in mice and … brain concentrations of this metabolite are sufficient to explain most or all of the opioid-receptor-mediated analgesic activity of mitragynine … it suggests a possible explanation for the seemingly improved safety profile of mitragynine compared to classical opioid agonists … We believe mitragynine and related compounds have great potential as future therapeutics, but metabolic processes must be carefully considered as the field continues to advance." Hiranita, Sharma, Oyola et al. (2020) reported although "the conversion rate of 7-hydroxymitragynine from p.o. mitragynine is low, 7-hydroxymitragynine is a more potent and efficacious μ-opioid receptor agonist than mitragynine, suggesting that conversion to this metabolite may contribute to the *in vivo* μ-opioid activity of mitragynine" (Behnood-Rod et al., 2020).

Kratom is commonly consumed to enhance occupational performance and as a coffee substitute for energy at low doses. In an animal model of spatial learning and memory, high doses impaired memory (Hassan et al., 2019). Suhaimi, Hassan, Mansor and Müller (2021) reported changes in brain electroencephalogram (EEG) activity after acute and chronic MG exposure in rats, with strong effects on some measures at high doses, supporting the importance of more research on brain function and potential cognitive effects (Suhaimi et al., 2021).

Gutridge et al. (2020) pharmacologically characterized interactions between kratom extracts, kratom alkaloids, and synthetic carfentanil-amide opioids with G-proteins and beta-arrestin at mu, delta and kappa opioid receptors *in vitro*, and assessed whether they had rewarding properties and the degree to which they reduced alcohol intake (Gutridge et al., 2020). The authors concluded that "kratom alkaloids do not recruit β-arrestin 2 at the μOP, δOP, and κOP and can significantly reduce both moderate and binge alcohol intake in male and female mice. This pharmacological profile and effect on alcohol intake in rodents may explain why some find kratom useful to self-medicate for alcohol use disorder." These findings were further supported by the findings by Todd et al. (2020) who concluded "mitragynine and 7-hydroxymitragynine demonstrate functional selectivity for G-protein signaling, with no measurable recruitment of β-arrestin. Overall, the study demonstrates the unique binding and functional profiles of the kratom alkaloids, suggesting potential utility for managing pain, but further studies are needed to follow up on these *in vitro* findings" (Todd et al., 2020).

Hiranita et al. (2019) compared the effects of MG to morphine in behavioral and antinociception assays in rat models finding "Opioid receptors do not appear to mediate the disruptive effects of mitragynine on learned behavior. Mitragynine had lesser antinociceptive effects than morphine, and these did not appear to be mediated by opioid receptors. The pharmacology of mitragynine includes a substantial non-opioid mechanism" (Hiranita et al., 2019).

3.2.2.3 Studies of Kratom Minor Alkaloids and Their Metabolites, and Analogs

Advances in analytical methods are accelerating our understanding of the effects of numerous kratom alkaloids including liquid chromatography–tandem mass spectrometry assays that quantify kratom alkaloids in kratom leaf extracts and commercial products (Sharma et al., 2019).

Most of these alkaloids are present at de minimis levels with respect to human experience, effects, and safety; however, it is possible that while the majority of natural plant-based kratom preparation effects are mediated by MG, one or more minor alkaloids may also play a minor role and account for differences in kratom strains (Kruegel et al., 2019; Chear et al., 2021).

An *in vitro* pharmacological characterization of five kratom based minor alkaloids found that their low abundance made it unlikely that these alkaloids play a major mediating role in the biological actions of kratom consumed by humans, but this research may contribute to furthering the understanding of kratom mechanisms of action and opioid receptor function (Chakraborty et al., 2021a).

Kratom alkaloids are of interest as templates for novel synthesized molecules (i.e., analogs) for new medicines. One third to one half of FDA-approved medicines are based on natural plant product substances from which novel chemical entities were developed (Newman and Cragg, 2016; Domnic et al., 2021a). Such efforts are actively in progress characterizing a variety of indole and oxindole alkaloids, determining their chemical structures, and binding affinities for opioid and other receptors (Chear et al., 2021). One approach to the synthesis of novel MG analogs produced several partial MOR agonists with low G-protein activation (Chakraborty et al., 2021b). These analogs demonstrated robust analgesic effects but low respiratory depressant, locomotor, and conditioned place preference suggesting lower adverse effects including abuse potential.

Combinations of kratom alkaloids may inhibit cell proliferation and migration of nasopharyngeal carcinoma cells suggesting alkaloid or new analogs as potential cancer treatments (Domnic et al., 2021b).

3.2.2.4 MG Metabolism and Metabolite Profiling

Thirteen MG metabolites were identified in human liver microsomes (HLM) and S9 fraction studies (Kamble et al., 2019), and potential MG and other kratom alkaloids drug interactions were investigated including with pharmaceutic products (Kamble et al., 2020a).

7-OH-MG can be converted to pseudoindoxyl-MG in human plasma to a greater extent than is produced in mice, rats, dogs and cynomolgus monkeys, possibly explaining potential human effects and benefits that may not be predicted in animal studies alone (Kamble et al., 2020b).

3.2.3 Factor 2 Updated Conclusion

Kratom's main effects are due to the consumption of MG, but other minor alkaloids and metabolites, including 7-OH-MG, 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.

3.3 Factor 3—The State of Current Scientific Knowledge Regarding the Drug

3.3.1 Summary of 2018 Findings

The 2018 8-FA highlighted kratom's pharmacodynamic effects. Preclinical anti-nociceptive studies suggested that MG and 7-OH-MG produced such effects mediated by MOR receptors. Most information about the effects of long-term use in humans on various physiological, and cognitive parameters was based on anecdotal reports, case histories, and preliminary field studies in SEA. A two-compartment model best described human oral MG pharmacokinetics (Trakulsrichai et al., 2015).

3.3.2 Factor 3 Science Updates

New kratom pharmacokinetics studies in rats, mice and dogs document plasma MG, 7-OH-MG, and other alkaloids and minor metabolites over 12 h or more, with accompanying safety assessments. Six new clinical studies following long-term kratom use provide safety data on health, and organ and brain function were also conducted.

3.3.2.1 Pharmacokinetics and Pharmacodynamics Findings Related to MG and 7-OH-MG Safety

After oral administration of traditional or other natural kratom formulations to rats, greater systemic exposure was observed than that of an equivalent oral MG dose alone; no adverse events were reported (Avery et al., 2019).

Administration of 5 mg/kg oral MG (equivalent to approximately 3 mg/kg in humans) and 0.1 mg/kg IV MG to beagle dogs was well tolerated and produced no adverse events or major abnormalities in clinical parameters (Maxwell et al., 2020).

The estimated MG clearance (CL/F) was 2.21 L/h, absorption rate (Ka) 0.82/h, and volume of distribution (Vd) 30.8 L after oral 20, 40, and 80 mg/kg MG doses to rats (Jagabalan et al., 2019). Oral 55 mg/kg MG produced 85 ng/ml Cmax for 7-OH-MG, 14 times lower than the MG Cmax. Anti-nociception after IV MG and 7-OH-MG suggested that 7-OH-MG was more potent and efficacious than MG, and metabolic formation of 7-OH-MG contributes to *in vivo* MOR mediated effects of oral MG (Hiranita et al., 2020).

3.3.2.2 Pharmacokinetic and Pharmacodynamic Findings With Kratom's Minor Alkaloids

MG, 7-OH-MG, corynantheidine, speciogynine, speciociliatine, paynantheine, corynoxine, corynoxine-B, mitraphylline, ajmalicine, and isospeciofoline were analyzed in rat plasma after a variety of oral kratom products, with only MG, 7-OH-MG, speciociliatine, and corynantheidine quantifiable at 8 h (Kamble et al., 2021).

Speciociliatine pharmacokinetics were characterized following IV and oral dosing to help understand the potential contribution of this alkaloid to *in vivo* kratom administration effects (Berthold et al., 2021). Speciociliatine had higher systemic exposure and lower clearance compared to the other kratom alkaloids mitragynine and corynantheidine. Similarly, the pharmacokinetics of corynanthidine, a minor kratom alkaloid and perhaps a MOR antagonist, were determined after 2.5 mg/kg IV and 20 mg/kg oral doses to rats, yielding a 50% oral bioavailability, a 4.1 h Tmax and extensive distribution including in brain corpus callosum and hippocampus regions (King et al., 2020).

3.3.2.3 *Safety Assessments From Clinical Studies*

Kratom's anti-nociceptive effects in the cold pressor test are described in Factor 2 and its potential for physiological dependence and withdrawal are discussed in Factor 7 (Vicknasingam et al., 2020). This section summarizes six new clinical studies that assessed health and safety endpoints.

Leong Bin Abdullah et al. (2020) studied the lipid profiles, liver function and blood chemistries in 100 chronic kratom users and 100 healthy nonusers in Malaysia finding that the "liver parameters of the study participants were within normal range. The serum total cholesterol and LDL of kratom users were significantly lower than those of healthy subjects who do not use kratom. There were no significant differences in the serum triglyceride and HDL levels. However, higher average daily frequency of kratom use and increasing age were associated with increased serum total cholesterol among kratom users."

Singh, Muller, Murugaiyah et al. (2018) studied various hematological and clinical-chemistry parameters of kratom users in Malaysia (Singh et al., 2018a). They interviewed and collected blood samples from 58 "regular kratom users" and 19 "healthy controls." Findings showed there were no significant differences in the hematological and clinical-chemistry parameters of traditional kratom users and healthy controls, except for HDL and LDL cholesterol values; these were found to be above the normal reference range for the users. Similarly, long-term kratom consumption (>5 years), and quantity of daily kratom use (≥3 ½ glasses; mitragynine content 76.3–114.8 mg) did not appear to alter the hematological and biochemical parameters of kratom users. These data suggest that even long-term and heavy kratom consumption did not significantly alter the hematological and clinical-chemistry parameters of kratom users in a traditional setting.

Singh, Narayanan, Grundmann et al. (2020), studied the long-term effects of kratom use in thirteen people in Malaysia who used kratom longer than 20 years in a cross-sectional pilot study (Singh et al., 2020a). They summarized their results as follows: "Respondents were required to undergo a blood-test and laboratory analysis was conducted to determine the mitragynine content in an acquired street sample of kratom. The regular, long-term consumption of brewed kratom decoction did not cause any significant alterations in haematological, kidney, liver, thyroid, inflammatory and gastrointestinal analytes in a cohort of kratom users who had no history of substance misuse. However, those who had a higher intake (>3 glasses per day) of kratom exhibited higher lipid values (except for HDL-cholesterol), and a moderate elevation of homocysteine level. Long-term (>20 years with a daily intake of ≥87.54 mg mitragynine) kratom consumption was not associated with altered biochemical levels, although prolonged and chronic, frequent use (>3 glasses daily) may result in cardiovascular risks." Note that this study was not designed to determine if kratom or other factors contributed to higher lipid values.

Singh, Chye, Suo et al. (2018) conducted a preliminary study of the impact of kratom use on brain function, as assessed by brain magnetic resonance imaging, among chronic kratom users in Malaysia. They reported "There were no significant differences ($p > 0.05$) in the intracranial volume (ICV), cortical volumes (frontal, parietal, temporal, occipital, or cingulate lobe), or subcortical volumes (striatum, hippocampus, or amygdala), as well as in the diffusion tensor imaging (DTI) metrics, fractional anisotropy (FA) and mean diffusivity (MD) between kratom users and the controls. This preliminary study showed long-term consumption of kratom decoction is not significantly associated with altered brain structures in regular kratom users in traditional settings" (Singh et al., 2018b).

Singh, Narayanan, Muller et al. (2019) studied potential long-term cognitive effects associated with kratom use in kratom uses in Malaysia with assessments performed using the Cambridge Neuropsychological Test Automated Battery (Singh et al., 2019a). Relative to control participants, higher consumption (>3 glasses daily or mitragynine doses between 72.5 and 74.9 mg) of kratom tea was selectively associated with impaired performance on the Paired Associates Learning task of the Cambridge Neuropsychological Test Automated Battery, reflecting deficits in visual episodic memory and new learning.

Leong Bin Abdullah, Tan, et al., evaluated the prevalence of ECG abnormalities and QTc intervals in kratom users without histories of illicit drug use. Sinus tachycardia was higher in kratom users. Daily kratom consumption was associated with borderline QTc intervals (Leong Abdullah et al., 2021). Another study by Leong Bin Abdullah and Singh found that people who consumed four or more glasses of kratom tea daily had higher MG concentrations than lower intake consumers and this higher intake was associated with prolonged QTc intervals (Leong Bin Abdullah and Singh, 2021a). The same authors published a comprehensive review of the cardiovascular and cardiotoxic effects of kratom and came to the conclusion that limitations in studies to date do not permit definitive conclusions about the cardiovascular risks (Leong Bin Abdullah and Singh, 2021b).

3.3.3 Factor 3 Updated Conclusion

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 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.

3.4 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

3.4.1 Summary of 2018 Findings

Note that for this update, Factors 4, 5, and 6 are considered together because they all contribute to understanding nonmedical use, recreational use and abuse, and public health impact, relying on some of the same surveys across factors. The Henningfield et al., 2018 8-FA considered all major relevant federal surveys, as well as data from internet monitoring, and more than 20,200 comments to the DEA, and concluded that there was no evidence of an imminent public health threat associated with kratom (Henningfield et al., 2018a). To the contrary, the review concluded that there were foreseeable health risks including opioid overdose and deaths if lawful kratom was banned and possession criminalized. Moreover, although kratom is not approved as safe and effective for therapeutic use, it was evident that most kratom use in the US was for health and well-being by people who personally found kratom to be more effective, tolerable, accessible and/or preferred a natural product as compared to FDA approved medicines.

3.4.2 Factors 4, 5, and 6 Science Updates

3.4.2.1 U.S. National and Federal Survey Data

Table 2 summarizes the main findings from the major national and federal surveys and other data sources. Overall, there are more similarities than differences with respect to demographics reported in this table as well as in other demographics reported in the published survey results. Prevalence appears to be substantially underestimated by the NSDUH and RADARS surveys (U.S. Department of health and Human Services, 2020; Schimmel et al., 2021).

NSDUH, RADARS, and Covvey et al. did not report reasons for use; however, many kratom users reported past or present use of opioids and/or drug addiction treatment consistent with past findings that self-management of addiction and withdrawal is a common reason for kratom use (National Institute on Drug Abuse, 2019; Coe et al., 2019; Garcia-Romeu et al., 2020; U.S. Department of health and Human Services, 2020; Schimmel et al., 2021; Covvey et al., 2020; Grundmann, 2017). Survey data incidence reports for DAWN, MTFS, NFLIS, and TEDS are apparently below the threshold for reporting as confirmed in an inquiry to NFLIS (Drug Enforcement Administration, 2020a; Drug Abuse Warning Network, 2020; Substance Abuse and Mental, 2020).

These findings do not support the conclusion that kratom use represents an imminent health threat and in fact kratom is not listed in the most recent DEA National Drug Threat Assessment (Drug Enforcement Administration, 2020b). There is no evidence that kratom is "fueling" or otherwise contributing to the opioid epidemic, though the survey data suggest that it is an informal self-management approach supporting the efforts of many opioid users to reduce and discontinue opioid use (Grundmann, 2017; Coe et al., 2019; Garcia-Romeu et al., 2020; Grundmann et al., 2021).

3.4.2.2 Kratom Use Prevalence

As mentioned in Table 2, the NSDUH and RADARS surveys may greatly underestimate the US prevalence and incidence of kratom use, with estimates of past year kratom use of 1,790,00–2,040,000.[3] (U.S. Department of health and Human Services, 2020; Schimmel et al., 2021). In contrast, a credible estimate based on market data suggested prevalence of 3–5 million in 2014–2015 (Botanical Education Allia, 2016).

Experts and marketers agree that the kratom market substantially expanded since that time, with kratom export data from Indonesia to the US and major marketer consensus finding that the US consumer base was likely 10–16 million. This is consistent with a nationally projectable survey estimate from 2020 concluding past year kratom use as 4.1% or 10,500,000 kratom users (Covvey et al., 2020).

3.4.2.3 Kratom Use Associated Mortality

The two most widely cited estimates of kratom associated mortality are based on world-wide reports over nearly 10 years (Food and Drug Administration, 2018; Olsen et al., 2019). FDA's statement noted that all but one involved other substances, and that case was under further investigation.[4] Medical examiners or coroners reported kratom as the cause of death in 91 (59.9%) of 152 kratom positive decedents (out of 27,338 overdose deaths in 27 states), including seven for whom kratom was the only substance positive on postmortem toxicology, although other substances could not be ruled out (Olsen et al., 2019). In approximately 80% of kratom positive or "involved" deaths, decedents had a history of "substance misuse", with 65% of cases listing fentanyl as the cause of death, 32.9% heroin, followed by benzodiazepines, prescription opioids, and cocaine. An earlier study (Gershman et al., 2019) cautioned that comprehensive toxicology might identify other substances contributing or causing death. We are not aware that any of the 93,000 drug overdoses estimated for 2020 included deaths due to kratom. That does not mean that there were no deaths in which kratom was the primary cause or a contributing factor; however, the signal is clearly low.

An assessment of various survey data concluded that the risk of kratom associated death was at least a thousand times lower than for morphine-like opioids (Henningfield et al., 2019). This is consistent with NIDA's position (National Institute on Drug Abuse, 2019) and with the 2018 DHHS kratom scheduling rescission letter and the conclusions drawn by Assistant Secretary of Health Brett P. Giroir, MD, ADM who stated:

[3]Note in a summary of RADARS data presented a few months after the Schimmel et al., 2020 publication, it was reported that the national projected past year prevalence estimate was 3.35 million.

[4]FDA never reported the results of that investigation, however, the US DHHS review that led to the 2018 withdrawal of the 2017 MG and 7-OH-MG CSA scheduling recommendation determined that the incident in question was an automobile crash not attributable to kratom use.

TABLE 2 | Summary of data sources.

Survey/Data source	Main results and comment	Other comments
Drug Abuse Warning Network (Drug Abuse Warning Networ, 2020)	No reports in DAWN from 1970 to 2011 "New DAWN" began in 2019 and has not listed kratom	
Monitoring the Future Study (Miech et al., 2021)	Kratom use is not assessed	Note that 9% of NSDUH Reports were from age 12–17 year olds
National Forensic Laboratory Information Service (Drug Enforcement Adm, 2020a)	Since 2016 NFLIS did not include MG/kratom reports because the rates are below the threshold for inclusion	
National Survey on Drug Use and Health (U.S. Department of health and Human Services, 2020)	Paid responders on national panel (n = 67,625).[6] 2019 Prevalence Lifetime Use: 1.4%; Past Year Use: 0.7%	See Grundmann et al., 2021 and Henningfield et al., 2021 comment on apparent underestimation of kratom use prevalence (Grundmann et al., 2021; Henningfield et al., 2021)
Treatment Episodes Data Set (Substance Abuse and Menta, 2020)	No reports. This does not mean there were no reports but suggests subthreshold signal	Internet chatrooms and SUD treatment clinic advertising suggests some kratom users are seeking cessation assistance
Coe et al. (2019) (Coe et al., 2019)	Internet Survey of self-identified kratom users age ≥18 (n = 2,867) 48% use for self-management of pain 10% for self-management of opioid UD or withdrawal 22% use for mood management 2.4% use to get high	
Garcia-Romeu et al. (2020) (Garcia-Romeu et al., 2020)	Internet Survey of self-identified kratom users, age ≥18 (n = 2,798) 91% use for self-management of pain 41% for self-management of opioid UD or withdrawal 67% for management of anxiety 65% for depression <3% report kratom dependence	2% met DSM-5 criteria for past-year moderate or severe kratom-related SUD, but it was rated very low on scale of concern and adverse impact
Cowey et al. (2020) (Cowey et al., 2020)	Nationally representative Internet survey of persons aged 18–59 (n = 1842) 112 (6%) reported lifetime kratom use 72% were 25–44 years old, male, employed, and at higher educational levels 24–47% of respondents indicated self-reported diagnoses for any addiction, and 43% reported previously received treatment for addiction	Similar demographics as Grundmann 2017, Coe et al., 2019 and Garcia-Romeu et al., 2020 but may have underestimated % over 50 due to 59 year old upper age limit of survey. ((Coe et al., 2019), (Garcia-Romeu et al., 2020), (Grundmann, 2017)) Reasons for use were not asked, e.g., to self-manage pain, addiction, mood
Schimmel et al. (2021) (Schimmel et al., 2021)	RADARS® survey of paid survey responder on national panel age >18 (n = 59,714) 0.8% lifetime use 44% age >35 61% male 59% past year opioid use	Reasons for use were not asked, e.g., pain, addiction, mood. See Grundmann et al., 2021 and Henningfield et al., 2021 comment on apparent under estimation of kratom use prevalence (Grundmann et al., 2021; Henningfield et al., 2021)

"There is still debate among reputable scientists over whether kratom by itself is associated with fatal overdoses" (Giroir, 2018).

3.4.2.4 Mortality Risks Projected as a Result of Banning Licit Kratom

Surveys and more than 20,000 comments to the DEA suggest that many kratom users fear resumption of opioid use and the need to resort to illicit kratom markets (Drug Enforcement Adm, 2016; Grundmann, 2017; Coe et al., 2019; Garcia-Romeu et al., 2020). It is not possible to project how many people would relapse to opioids and potentially overdose (Henningfield et al., 2018a; Henningfield et al., 2018b; Henningfield et al., 2018c; Henningfield et al., 2018d; Grundmann et al., 2018; Prozialeck et al., 2020). This was a concern of the DEA in withdrawing its 2016 kratom scheduling proposal (Ingraham, 2016b) and in the US DHHS kratom scheduling recission letter (Giroir, 2018).

3.4.2.5 Public Health and Individual Benefits of Kratom

In 2018, a systematic review of kratom use and mental health by Swogger and Walsh concluded ". . .kratom use appears to have several important mental health benefits that warrant further study. Kratom dependence is a risk for some people, though the dependence syndrome appears to be mild in its psychosocial and physiological effects relative to that of opioids. More and better research, including well-controlled, prospective studies, is necessary to further elucidate kratom's potential for good and harm and the moderators of its effects" (Swogger and Walsh, 2018). The

therapeutic potential of kratom based on surveys, anecdotal reports, and nonclinical research supports the plausibility of such benefits as discussed by other reviewers (Prozialeck et al., 2019; Hemby et al., 2019; Yue et al., 2018; Grundmann et al., 2018; Kruegel and Grundmann, 2018; Sharma and McCurdy, 2021; Swogger et al., 2018; Prozialeck et al., 2021).

The most important public health benefits with respect to mortality are widely agreed upon by kratom experts and surveys, and that is its use to self-manage opioid and other drug addiction and withdrawal symptoms, and thereby reduce use and overdose from far deadlier substances. This type of use is not unique in the US but was long reported in SEA (Raffa, 2014; Henningfield et al., 2018a). This was also reported in the first major US Internet survey of kratom use (Grundmann, 2017), as well as in subsequent surveys (Coe et al., 2019; Garcia-Romeu et al., 2020; Pain News Network (2018)). This was also a conclusion of a systematic review of 13 studies addressing kratom use and mental health in the US, SEA, and other countries and regions of the world, and a review by an international consortium of kratom researchers (Swogger and Walsh, 2018; Prozialeck et al., 2019).

While the opioid epidemic represents a highly visible and deadly epidemic in its own right, it is important to recognize that many millions use kratom as their preferred approach to managing other life-threatening disorders including pain, depression, anxiety, post-traumatic stress, fibromyalgia and more (Drug Enforcement Adm, 2016; Grundmann, 2017; Coe et al., 2019; Garcia-Romeu et al., 2020).

3.4.2.6 Kratom Use for Managing Opioid Use/Withdrawal and Other Health Reasons

In the first half-year of the COVID-19 pandemic, there was uncertainty about kratom supply by vendors and consumers, however, overall US supply was not affected. The main reasons for kratom use are pain relief (48%), anxiety, "PTSD" or depression (22%), increase energy or focus (10%), and "help cut down on opioid use and/or relieve withdrawal" (10%) (Coe et al., 2019). Side effects were generally minor, e.g., stomach upset, rarely required medical attention and rates and severity of "bad reactions" were generally similar to those reported by Grundmann (Grundmann, 2017).

Field studies with face-to-face interviews in Malaysia provide complementary evidence to US Internet surveys regarding reasons for use and potential benefits (Singh et al., 2019b). Motives related to mood and other factors in 116 regular kratom users employed the Drinking Motives Questionnaire (DMQ) to measure motives for kratom use, reported "heavy" kratom use as drinking more than three glasses daily (estimating that 1 glass contains 48.24–50.4 mg of mitragynine), with use associated with significantly higher means scores on the Coping and Enhancement scales. A field face-to-face survey of 92 long-term male kratom users found that 72 participants (78%) reported using kratom to "enhance sexual performance" and all but one found did their sexual performance did improve. Interestingly, among participants who described kratom intake for other reasons, 35% reported enhanced sexual performance (Singh et al., 2020b).

Patterns and reasons for use and demographics were investigated in 142 current and 62 former opioid polydrug users in Malaysia (Singh et al., 2020c). The alkaloid content of a kratom street sample was primarily MG, followed by paynantheine, speciociliatine, speciogynine, and "low levels" of 7-OH-MG. There were no significant differences in demographic characteristics between current and former opioid polydrug users except with respect to marital status, with current kratom users having a higher odds ratio of being single. While both current and former opioid users reported using kratom to ameliorate opioid withdrawal, current users had significantly higher likelihood of using kratom for that purpose; however, former opioid users were more likely to use kratom for mood elevating effects.

3.4.2.7 Comment on Therapeutic Use in Context of FDA Standards

It is important to note that the benefits documented in published surveys do not constitute the basis for therapeutic claims and no kratom product or kratom alkaloid is approved for therapeutic use in the US. The FDA and other federal agencies state that there is no proven therapeutic use for kratom despite evidence that millions of people in the US and many more in SEA use kratom primarily for therapeutic, beneficial use. That evidence includes peer reviewed surveys and field studies in the US and SEA, clinical and preclinical studies showing that MG's mechanisms of action are consistent with such effects. Moreover, several animal models used to predict efficacy for treating opioid use disorder, opioid withdrawal and pain demonstrated efficacy.

None of this research meets FDA's standard for therapeutic efficacy that is determined by evaluation of a New Drug Application (NDA). The NDA must be supported by "substantial evidence of effectiveness," and is defined as "evidence consisting of adequate and well-controlled investigations" (Katz, 2004; Dabrowska and Thaul, 2018). The time and cost to develop and achieve FDA approval of a product as therapeutically effective and acceptably safe varies widely but is often approximated at 10 years and 1 billion dollars (DiMasi et al., 2016; Wouters et al., 2020). Only two botanical substances, Veregen® (sinecatechins) and Mytesi™ (crofelemer), were developed as drug products consistent with FDA's Botanical Drug Guidance and both are available only as prescription drugs that is typical of new drug approvals (Food and Drug Admini, 2016).

3.4.3 Factor 4, 5, and 6 Updated Conclusions

The most important finding from new US survey evidence is that the conclusion that kratom products and kratom's primary active alkaloid, MG, pose a "serious imminent threat to public health" is not supported. This extensive survey update agrees with the Henningfield et al. (2018) conclusion: "There has been no documented threat to public health that would appear to warrant emergency scheduling of the products and placement in Schedule I of the CSA carries risks of creating serious public health problems.... Although kratom appears to have pharmacological properties that support some level of scheduling, if it was an approved drug, placing it into Schedule I, thus banning it, risks creating public health problems that do not presently exist" (Henningfield et al., 2018a).

The evidence shows that millions of people in the US purchase and use kratom products for improving health and are preferred to FDA approved medicines because for them, kratom products are more effective, accessible, and tolerable. Furthermore, many prefer managing health problems with natural products.

For those using kratom products in place of opioids, which appears to be approximately 1/3 of all kratom users, it is foreseeable that removing kratom from the legal marketplace would put many at risk of returning to opioid use and risking opioid overdose death. This was clearly stated in comments to the DEA and public hearings as reported in the 2018 8-FA, and in surveys. Assistant Secretary Dr. Giroir noted "... 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: ... 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 IV drug use ..." (Giroir, 2018).

3.5 Factor 7—The Psychic or Physiological Dependence Liability

3.5.1 Summary of 2018 Findings

Recently, psychic dependence is referred to simply as "dependence" or "substance use disorder" and more commonly as "addiction" though definitions of addiction vary widely (American Psychiatric Asso, 1994; World Health Organization, 1994). Physiological dependence is often used interchangeably with the most common measure of physiological dependence, namely "withdrawal" which is also considered a clinical disorder (American Psychiatric Asso, 2013).

In the 2018 8-FA, Henningfield, Fant and Wang (2018) concluded "There have not been laboratory studies of physical or psychological dependence or abuse potential in humans caused by kratom." Nor had classic animal studies employing the drug self-administration and physical dependence/withdrawal model been conducted (see Factor 2 in this report)".

Nonetheless, the real-world evidence in the published literature supported the following conclusions: "...abrupt discontinuation [of kratom use] may be accompanied by withdrawal symptoms that are qualitatively similar but generally weaker than those observed following discontinuation of opioids. However, such reports make it difficult to disentangle the emergence of preexisting symptoms that had been mitigated by kratom use from those that occur as a physiological rebound accompanying the abrupt discontinuation of kratom use in kratom-dependent people. More studies of kratom's potential to produce physical dependence, tolerance, and withdrawal are needed to characterize the nature and severity, and determinants of abstinence-associated symptoms."

3.5.2 Factor 7 Science Updates

In addition to the animal laboratory studies predictive of abuse potential, dependence, and withdrawal summarized in Factor 1, there are several new studies, surveys, and expert reviews addressing the risk and factors associated with dependence and withdrawal. A major category of kratom use is related to the typically mild and tolerable dependence and withdrawal that occurs in some frequent kratom users and the resulting use of kratom as an approach to self-management. In this context, kratom provides a harm reduction alternative to opioids in particular, but also potentially for alcohol, methamphetamine, and other drugs.

Dependence and withdrawal were addressed in a systematic review of kratom use for mental health reasons that concluded "Kratom dependence is a risk for some people, though the dependence syndrome appears to be mild in its psychosocial and physiological effects relative to that of opioids ... kratom use does not appear to result in significant respiratory depression" (Swogger and Walsh, 2018). A major category of kratom use globally was to self-manage substance use disorders, consistent with the findings discussed in Factor 1 that demonstrated low abuse and physical dependence potential, and that MG administration reduced morphine and heroin self-administration, and withdrawal signs (Hemby et al., 2019; Harun et al., 2021b).

The Vicknasingam et al. (2021) study included in Factor 2 also assessed potential withdrawal signs using the Clinical Opiate Withdrawal Scale (COWS), comparing scores when participants were administered placebo or a kratom concoction (Vicknasingam et al., 2020). Although this study was not designed to be a definitive withdrawal assessment study, and did not include an opioid comparator, it was likely that people using kratom multiple times per day for many years would have experienced pronounced withdrawal symptoms. The authors concluded "None of the participants reported withdrawal symptoms either using spontaneous self-report or had significant withdrawal symptoms based on the COWS scores... All participants reported long histories of daily kratom consumption, with high frequency of daily consumption and substantial amounts consumed. It is not possible to quantify these reports into markers that could be used to approximate amounts of plant material or active ingredients consumed. However, despite the reported long duration and high levels of daily kratom consumption, during documented kratom discontinuation lasting from 10 to 20 h, no participant reported or displayed discomfort, symptoms, or signs of potential withdrawal symptoms."

100 long term kratom users and 100 non-users in Malaysia were interviewed to assess potential symptoms related to kratom dependence and withdrawal (Leong Bin Abdullah et al., 2021). Kratom use longer than 6 years and 3 or more times per day were more likely to be associated with dependence, reduced quality of life and/or withdrawal symptoms when kratom use is discontinued. However, the authors noted that the study did not allow causative conclusions as to whether quality of life reductions are a

result of increased kratom use or if such quality of life and other demographic factors contribute to more frequent kratom use.

An internet survey assessing reasons for use and effects of use in 2,798 present and past kratom users included questions about kratom dependence, withdrawal symptoms associated with discontinuation, and use to self-manage opioid dependence (Garcia-Romeu et al., 2020). Kratom-related withdrawal symptoms were reported by 9.5% of respondents with another 17.5% reporting possible kratom-related withdrawal. This supports results of previous studies (Swogger et al., 2015; Grundmann, 2017; Smith and Lawson, 2017; Coe et al., 2019) by suggesting that kratom has a relatively benign risk profile compared to typical opioids, with only a minority of respondents endorsing kratom-related adverse effects, withdrawal symptoms, or problematic use.

Coe et al. (2019) conducted an internet survey (2,867 current, 157 former kratom users) that included similar questions as Garcia-Romeu et al. and Grundmann (2017) (Grundmann, 2017; Garcia-Romeu et al., 2020), related to opioid use and effects. Kratom use was less likely to interfere with social, family, and occupational functioning compared to conventional opioids. Kratom was used by many to reduce or completely replace prescription and nonprescription opioid withdrawal and was generally considered "very effective" for managing opioid withdrawal. Relief of anxiety (including associated with post-traumatic stress disorder), depression, as well as to increase focus or energy were other major reasons for use. The foregoing conclusions are also consistent with those of Grundmann, Babin, Henningfield et al. (2021) who stated: "Some user reports suggest that regular kratom consumption carries risks of dependency and addiction, though with generally self-manageable withdrawal" (Grundmann et al., 2021).

Singh, Narayanan, Muller et al. (2018) employed widely used psychiatric instruments (Beck Depression Inventory and Beck Anxiety Inventory) to assess potential symptoms of anxiety and depression that may accompany abrupt discontinuation of kratom use in apparently frequent chronic kratom consumers in Malaysia (Singh et al., 2018c). Most respondents (70%) experienced symptoms of mild anxiety, while 81% reported symptoms of mild depression during kratom cessation. Those who consumed higher quantities of kratom tea daily (≥4 glasses) had "higher odds of reporting longer duration of kratom use history . . . , higher frequency of daily kratom use (≥4 times), . . . and were more likely to experience moderate symptoms of depression during kratom cessation" than those who consumed less. Cessation from regular and long-term kratom tea consumption was not associated with symptoms of high anxiety or depression.

3.5.3 Factor 7 Updated Conclusion

Kratom's potential to produce psychic dependence (aka "dependence" or "use disorder") and physiological dependence (aka, "withdrawal") advanced considerably due to surveys, and preclinical and clinical studies. Several surveys in the US, field studies in Malaysia, and a clinical trial of pain relief efficacy that included assessment of withdrawal support the conclusions of the 2018 8-FA (Henningfield et al., 2018a). Some kratom users report dependence/addiction and/or withdrawal with a greater likelihood with higher levels of chronic daily consumption. In general, it is more readily self-managed and less likely to interfere with occupational, social and family activities and responsibilities compared to dependencies to opioids, alcohol, stimulants and other drugs of abuse.

It is also important to note that there is wide individual variability, and some people do experience what they consider to be strong addiction and withdrawal to kratom. At present, it appears likely that many if not most individuals had prior histories of dependence to opioids and/or other drugs. Their conditions remain of concern nonetheless and is another area warranting further study. People for whom kratom use is considered a serious problem should have the same access to treatment as anyone with a substance use disorder. Many addiction treatment providers already advertise and offer kratom use disorder treatment assistance.

Use of opioids such as methadone and buprenorphine should be judicious in people seeking help to manage their kratom use disorder and/or withdrawal. If they formerly or are perhaps still using opioids, then the possibility of treatment with buprenorphine or methadone may be more helpful and appropriate if kratom is not satisfactory. However, for people without prior histories of recreational opioid use and dependence, treating with buprenorphine or methadone may introduce individuals to opioids and may not be the best option. This could be like treating unwanted caffeine dependence with amphetamine to replace the caffeine.

4 DISCUSSION AND CONCLUSION

In 2018, there was sufficient evidence to conclude that there was no imminent public health threat nor high degree of pharmacological abuse potential that would justify scheduling, taking into consideration the serious foreseeable adverse public health consequences of thousands of former opioid users returning to opioids and risking overdose, as well as the *de facto* criminalization of millions of US citizens. Approximately 8 months after the Henningfield et al. 8-FA was published, the US DHHS came to the same conclusion and rescinded the 2017 recommendation to place MG and 7-OH-MG in Schedule I of the CSA (Giroir, 2018). Since January 2018, there was remarkable research relevant to the abuse potential and safety of kratom from the perspective of the CSA eight factors.

Two intravenous drug self-administration studies showed that MG did not substitute for morphine (Hemby et al., 2019) or heroin (Yue et al., 2018), and that MG pretreatment reduced morphine and heroin self-administration. An intracranial brain self-stimulation (ICSS) study showed that whereas morphine produced robust decreases in the brain stimulation threshold, MG and 7-OH-MG did not (Behnood-Rod et al., 2020).

In the evaluation of physical dependence and withdrawal potential, four studies showed MG did not carry morphine-like physical dependence or withdrawal potential (Harun et al., 2020; Hassan et al., 2020; Wilson et al., 2020; Johari et al., 2021). Moreover, MG pretreatment of animals reduced spontaneous

morphine withdrawal (Hassan et al., 2020). In MG physically dependent animals, withdrawal signs were qualitatively different and much weaker than morphine, consistent with its mixed mechanisms of action (Johari et al., 2021). In a mouse physical dependence model (Wilson et al., 2020), naloxone precipitated withdrawal in morphine- but not MG LKT-maintained animals, while LKT pretreatment significantly reduced withdrawal in the morphine-maintained mice.

These findings are consistent with new US survey data showing relatively low self-reported kratom addiction rates, with most people describing MG use to manage pain, depression, anxiety, opioid and other drug use disorders and withdrawal, and to increase alertness, focus and work performance. In addition, kratom dependence and withdrawal are generally weaker and more readily self-managed relative to opioids.

Extensive *in vitro* and *in vivo* animal neuropharmacology studies of the mechanisms of action of MG, 7-OH-MG and other alkaloids illustrate that they are not appropriately designated as opioids, opioid analogs, or "atypical opioids," though some are partial agonists with low potential to recruit beta arrestin and produce respiratory depression. 7-OH-MG produces stronger MOR mediated opioid effects on abuse potential related measures and antinociception, but naturally occurs at levels so low as to not contribute meaningfully to kratom effects. This supports recommendations that regulations should prohibit kratom products with 7-OH-MG concentrations greater than occur safely in nature.[5]

Safety assessments in pharmacokinetic and pharmacodynamic studies confirm that kratom based extracts and individual alkaloids at far higher doses than consumed by humans do not appear to carry substantial mortality risk, with one analysis suggesting a mortality risk at least 1000 times less than illicit opioids (Henningfield et al., 2019). Results support the US DHHS conclusion that "experts disagree on whether kratom by itself causes overdose deaths" (Giroir, 2018; National Institute on Drug Abuse, 2019). This does not imply that kratom does not carry a mortality risk—most substances do under certain conditions and exposure levels, another important area for further research.

As to the question of whether or not kratom poses an imminent public health threat, no analysis of factors 4–6 of the 8 CSA factors, including the FDA analysis (Food and Drug Administration, 2017b), revealed kratom to pose an imminent public health risk. The US has the most comprehensive survey data to address the need for temporary or "emergency" placement of substances into CSA Schedule I. Yet none of the major surveillance systems identified such a public health threat. This includes the old and new Drug Abuse Warning Network, Monitoring the Future, National Survey on Drug Use and Health, RADARS®, or the Treatment Evaluation Data Set. DEA's National Forensic Laboratory Information System mentioned kratom reports from 2010–2016 but none thereafter because the signal remained low. Neither has kratom been included in any DEA Annual National Drug Threat Reports.

The primary public health consequences of kratom use are well documented by four surveys of more than 20,000 kratom consumers summarized in this review, by Henningfield et al., 2018 (Henningfield et al., 2018a), and more than 20,000 comments to DEA (Drug Enforcement Adm, 2016) suggesting that millions of US citizens use kratom for health and well-being and many to self-manage opioid and other drug withdrawal and use disorders as their preferred approach. Many kratom users believe kratom is more effective, tolerable and/or accessible than other pharmaceuticals (Grundmann et al., 2018; Swogger and Walsh, 2018; Prozialeck et al., 2019; Prozialeck et al., 2020).

There are problems with kratom product purity (e.g., Prozialeck et al., 2020) (Prozialeck et al., 2020) and adulteration (Prozialeck et al., 2019) in the consumer marketplace. A scheduling imposed kratom ban would likely worsen these problems because kratom marketing would not discontinue and consumer demand would not cease, rather marketing would switch from regulatable lawful to illicit kratom suppliers. More states and ideally the US federal government could address these issues by product performance standards and regulatory approaches guided by science and informed through a federal rule-making approach.

Remarkably, as discussed in several reports (Henningfield et al., 2019; Prozialeck et al., 2019; Henningfield et al., 2021), there has yet to emerge a generally accepted estimate of the number of current US kratom consumers, which current ranges from approximately 2 to more than 10 million (see factors 4–6 and Henningfield et al., 2021) (Henningfield et al., 2021). As noted by Henningfield et al., 2018 and bluntly stated in the US DHHS scheduling rescission letter (Giroir, 2018), surveys need to address such issues before any action to ban consumer kratom sales and possession is contemplated. As stated in the DHHS letter:

"Further analysis and public input regarding kratom and its chemical components are needed before any scheduling should be undertaken. It is important that we have additional information to justify scheduling, such as:

- A scientific assessment of how many Americans utilize *kratom*, and an understanding of the geographic and demographic distribution of these users (Factors 4, 5);
- A scientific assessment of the actual scale and degree of dependence and/or addiction of Americans utilizing *kratom* (Factors 1, 5, 7);
- A scientific determination based on data whether *kratom* actually serves as a gateway drug that promotes further use of more dangerous opioids (Factors 1, 4, 5).
- A valid prediction of how many kratom users will suffer adverse consequences if kratom is no longer available, including among people with intractable pain, psychological distress, risk for suicide; and/or people who might transition to proven deadly opioids such as prescription opioids, heroin, or fentanyl.

[5]Five states (AZ, GA, NV, OK, and UT) have taken this approach in their kratom consumer protection regulations and law but setting actual performance standards to address the variety of kratom based products would be seem best done by FDA which has extensive experience in such matters and could take a federal rule making approach that ensures input from diverse stakeholders representing science, public health, consumers, and the industry that prepares and manufactures kratom products.

- A scientifically valid assessment of causality in the current few deaths in which *kratom* was co-utilized with known lethal drugs such as fentanyl (Factors 1, 2, 3, 5 and 6)" (Giroir, 2018).

By law, scheduling considers diverse evidence including chemistry and pharmacology, level of abuse potential, physiological dependence determined in animal and human studies, as well as assessment of individual and public health risks and benefits. Taking all of these factors into account, this review provides stronger evidence than was available to Henningfield et al., or the US DHHS in 2018 (Henningfield et al., 2018a; Giroir, 2018) to recommend not only that CSA scheduling is not warranted but that CSA scheduling carries a substantial foreseeable risk of thousands of opioid overdose deaths as well as depriving millions of US citizens of one of their preferred health management assets. The fact that possession of kratom by millions of US citizens would be criminalized as a heroin-like drug felony offense is not a CSA consideration but should not be ignored.

In conclusion, we do not recommend scheduling kratom or any of its alkaloids in the CSA. We do recommend accelerated research to address the many questions raised in this review, including support of the potential development of new medicines with potential better safety and/or efficacy profiles for a variety of diseases. Finally, we recommend that the US federal government and other nations consider approaches to kratom regulation as are presently being pioneered in five US states.

AUTHOR CONTRIBUTIONS

JH was the primary scientist/investigator, and lead the identification of articles, writing, and analysis. DW supported writing, research, and analysis. MH provided toxicological analysis of articles and supported writing and analysis.

ACKNOWLEDGMENTS

This report is an update of the Henningfield et al., 2018 kratom abuse potential assessment review and comprises an annotated bibliography and review of kratom-related scientific studies published since January 1, 2018. The AKA and its affiliate, the Center for Plant Science and Health that funds new research into kratom, supported an earlier independent summary of kratom research that is posted on the AKA website. AKA did not support the preparation of this review article. The AKA did not have any input into approach, assessments or conclusions of the earlier summary postop on the AKA website or this article. Acknowledgement we are greatly appreciative of the efforts of our PinneyAssociates colleagues who contributed to this article: Yolanda Green; Rachel Beck, PhD; and August Buchhalter, PhD. We also acknowledge the thinking embodied in this document by our former colleague and co-author of earlier kratom abuse potential assessments, Reggie Fant, PhD. Dr. Fant died in September 2020 and we miss him dearly. See more about our team and Dr. Fant at www.pinneyassociates.com.

REFERENCES

American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders*. 4th Edition. Arlington, VA: DSM-IV.

American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders*. 5th Edition. Arlington, VA: DSM-5.

Avery, B. A., Boddu, S. P., Sharma, A., Furr, E. B., Leon, F., Cutler, S. J., et al. (2019). Comparative Pharmacokinetics of Mitragynine after Oral Administration of Mitragyna Speciosa (Kratom) Leaf Extracts in Rats. *Planta Med.* 85 (4), 340–346. doi:10.1055/a-0770-3683

Behnood-Rod, A., Chellian, R., Wilson, R., Hiranita, T., Sharma, A., Leon, F., et al. (2020). Evaluation of the Rewarding Effects of Mitragynine and 7-hydroxymitragynine in an Intracranial Self-Stimulation Procedure in Male and Female Rats. *Drug Alcohol Depend* 215, 108235. doi:10.1016/j.drugalcdep.2020.108235

Belouin, S. J., and Henningfield, J. E. (2018). Psychedelics: Where We Are Now, Why We Got Here, what We Must Do. *Neuropharmacology* 142, 7–19. doi:10.1016/j.neuropharm.2018.02.018

Berthold, E. C., Kamble, S. H., Raju, K. S., King, T. I., Popa, R., Sharma, A., et al. (2021). Preclinical Pharmacokinetic Study of Speciociliatine, a Kratom Alkaloid, in Rats Using an UPLC-MS/MS Method. *J. Pharm. Biomed. Anal.* 194, 113778. doi:10.1016/j.jpba.2020.113778

Botanical Education Alliance (2016). *Results of Survey of Kratom Venders to Estimate the Number of Venders, and Size of the Market by Consumers and Kratom Product Venders*. Washington, DC.

Chakraborty, S., DiBerto, J. F., Faouzi, A., Bernhard, S. M., Gutridge, A. M., Ramsey, S., et al. (2021). A Novel Mitragynine Analog with Low-Efficacy Mu Opioid Receptor Agonism Displays Antinociception with Attenuated Adverse Effects. *J. Med. Chem.* 64 (18), 13873–13892. doi:10.1021/acs.jmedchem.1c01273

Chakraborty, S., Uprety, R., Daibani, A. E., Rouzic, V. L., Hunkele, A., Appourchaux, K., et al. (2021). Kratom Alkaloids as Probes for Opioid Receptor Function: Pharmacological Characterization of Minor Indole and Oxindole Alkaloids from Kratom. *ACS Chem. Neurosci.* 12 (14), 2661–2678. doi:10.1021/acschemneuro.1c00149

Chear, N. J., León, F., Sharma, A., Kanumuri, S. R. R., Zwolinski, G., Abboud, K. A., et al. (2021). Exploring the Chemistry of Alkaloids from Malaysian Mitragyna Speciosa (Kratom) and the Role of Oxindoles on Human Opioid Receptors. *J. Nat. Prod.* 84 (4), 1034–1043. doi:10.1021/acs.jnatprod.0c01055

Coe, M. A., Pillitteri, J. L., Sembower, M. A., Gerlach, K. K., and Henningfield, J. E. (2019). Kratom as a Substitute for Opioids: Results from an Online Survey. *Drug Alcohol Depend* 202, 24–32. doi:10.1016/j.drugalcdep.2019.05.005

Commission on Narcotic Drugs (2021). Summary of assessments, findings and recommendations of the 44th World Health Organization's (WHO) Expert Committee on Drug Dependence (ECDD). Available at: https://www.unodc.org/documents/commissions/CND/CND_Sessions/CND_64Reconvened/ECN72021_CRP12_V2108992.pdf (Accessed October 11–15, 2021).

Covey, J. R., Vogel, S. M., Peckham, A. M., and Evoy, K. E. (2020). Prevalence and Characteristics of Self-Reported Kratom Use in a Representative US General Population Sample. *J. Addict. Dis.* 38 (4), 506–513. doi:10.1080/10550887.2020.1788914

Dabrowska, A., and Thaul, S. (2018). How FDA Approves Drugs and Regulates Their Safety and Effectiveness: Congressional Research Service. Case Report Prepared for Members and Committees of Congress. Available from: https://fas.org/sgp/crs/misc/R41983.pdf.

DiMasi, J. A., Grabowski, H. G., and Hansen, R. W. (2016). Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs. *J. Health Econ.* 47, 20–33. doi:10.1016/j.jhealeco.2016.01.012

Domnic, G., Narayanan, S., Mohana-Kumaran, N., and Singh, D. (2021). Kratom (Mitragyna Speciosa Korth.) an Overlooked Medicinal Plant in Malaysia. *J. Substance Use* 26 (1), 1–6. doi:10.1080/14659891.2021.1885515

Domnic, G., Jeng-Yeou Chear, N., Abdul Rahman, S. F., Ramanathan, S., Lo, K. W., Singh, D., et al. (2021). Combinations of Indole Based Alkaloids from Mitragyna Speciosa (Kratom) and Cisplatin Inhibit Cell Proliferation and

Migration of Nasopharyngeal Carcinoma Cell Lines. *J. Ethnopharmacol* 279, 114391. doi:10.1016/j.jep.2021.114391

Drug Abuse Warning Network (2020). *Preliminary DAWN Data Review*. Rockville, Maryland, United States: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration.

Galbis-Reig, D. (2016). A Case Report of Kratom Addiction and Withdrawal. *WMJ* 115 (1), 49–53.

Garcia-Romeu, A., Cox, D. J., Smith, K. E., Dunn, K. E., and Griffiths, R. R. (2020). Kratom (Mitragyna Speciosa): User Demographics, Use Patterns, and Implications for the Opioid Epidemic. *Drug Alcohol Depend* 208, 107849. doi:10.1016/j.drugalcdep.2020.107849

Gershman, K., Timm, K., Frank, M., Lampi, L., Melamed, J., Gerona, R., et al. (2019). Deaths in Colorado Attributed to Kratom. *N. Engl. J. Med.* 380 (1), 97–98. doi:10.1056/NEJMc1811055

Giroir, B. P. (2018). Letter from the Assistant Secretary of Health to the Administrator of the Drug Enforcement Administration to Rescind Previous Support to Permanently Place Mitragynine and 7-hydroxymitragynine in Schedule I of the Controlled Substances Act 2018. Available from: https://images.go02.informamarkets.com/Web/Informa02/%7b548e6d56-2ea4-4da4-9404-0348b56e9a88%7d_dhillon-8.16.2018-response-letter-from-ash-radm-giroir.pdf.

Grundmann, O., Babin, J. K., Henningfield, J. E., Garcia-Romeu, A., Kruegel, A. C., Prozialeck, W. C., et al. (2021). Kratom Use in the United States: a Diverse and Complex Profile. *Addiction* 116 (1), 202–203. doi:10.1111/add.15173

Grundmann, O., Brown, P. N., Henningfield, J., Swogger, M., and Walsh, Z. (2018). The Therapeutic Potential of Kratom. *Addiction* 113 (10), 1951–1953. doi:10.1111/add.14371

Grundmann, O. (2017). Patterns of Kratom Use and Health Impact in the US-Results from an Online Survey. *Drug Alcohol Depend* 176, 63–70. doi:10.1016/j.drugalcdep.2017.03.007

Gutridge, A. M., Robins, M. T., Cassell, R. J., Uprety, R., Mores, K. L., Ko, M. J., et al. (2020). G Protein-Biased Kratom-Alkaloids and Synthetic Carfentanil-Amide Opioids as Potential Treatments for Alcohol Use Disorder. *Br. J. Pharmacol.* 177 (7), 1497–1513. doi:10.1111/bph.14913

Harun, N., Johari, I. S., Japarin, R. A., Bakar, S. N. S., Mat, N. H., Hassan, Z., et al. (2021). Naloxone-precipitated Mitragynine Withdrawal Did Not Associate with Increased Anxiety-like Behaviour in Rats. *Malays J. Biochem. Mol. Biol.* 24 (1), 100–107.

Harun, N., Johari, I. S., Japarin, R. A., Suhaimi, F. W., Hassan, Z., and Shoaib, M. (2021). Current Perspectives on the Therapeutic Potential of Mitragyna Speciosa and its Derivatives on Animal Model. *TJPS* 45 (3), 195–201.

Harun, N., Johari, I. S., Mansor, S. M., and Shoaib, M. (2020). Assessing Physiological Dependence and Withdrawal Potential of Mitragynine Using Schedule-Controlled Behaviour in Rats. *Psychopharmacology (Berl)* 237 (3), 855–867. doi:10.1007/s00213-019-05418-6

Hassan, R., Othman, N., Mansor, S. M., Müller, C. P., and Hassan, Z. (2021). Proteomic Analysis Reveals Brain Rab35 as a Potential Biomarker of Mitragynine Withdrawal in Rats. *Brain Res. Bull.* 172, 139–150. doi:10.1016/j.brainresbull.2021.04.018

Hassan, R., Pike See, C., Sreenivasan, S., Mansor, S. M., Müller, C. P., and Hassan, Z. (2020). Mitragynine Attenuates Morphine Withdrawal Effects in Rats-A Comparison with Methadone and Buprenorphine. *Front. Psychiatry* 11, 411. doi:10.3389/fpsyt.2020.00411

Hassan, R., Sreenivasan, S., Müller, C. P., and Hassan, Z. (2021). Methadone, Buprenorphine, and Clonidine Attenuate Mitragynine Withdrawal in Rats. *Front. Pharmacol.* 12, 708019. doi:10.3389/fphar.2021.708019

Hassan, Z., Suhaimi, F. W., Ramanathan, S., Ling, K. H., Effendy, M. A., Müller, C. P., et al. (2019). Mitragynine (Kratom) Impairs Spatial Learning and Hippocampal Synaptic Transmission in Rats. *J. Psychopharmacol.* 33 (7), 908–918. doi:10.1177/0269881119844186

Hemby, S. E., McIntosh, S., Leon, F., Cutler, S. J., and McCurdy, C. R. (2019). Abuse Liability and Therapeutic Potential of the Mitragyna Speciosa (Kratom) Alkaloids Mitragynine and 7-hydroxymitragynine. *Addict. Biol.* 24 (5), 874–885. doi:10.1111/adb.12639

Henningfield, J. E., Babin, J., Boyer, E. W., Brown, P., Garcia-Romeu, A., Griffiths, R. R., et al. Critique of the FDA's 8-Factor Analysis of Kratom, Specifically, Mitragynine and 7-hydroxymitragyine 2018. Available from: https://www.americankratom.org/images/file/Scientists-Response-to-FDA-Kratom-8FA-28-Nov-2018-FINAL.pdf.

Henningfield, J. E., Fant, R. V., and Wang, D. W. (2018). The Abuse Potential of Kratom According the 8 Factors of the Controlled Substances Act: Implications for Regulation and Research. *Psychopharmacology (Berl)* 235 (2), 573–589. doi:10.1007/s00213-017-4813-4

Henningfield, J. E., Grundmann, O., Babin, J. K., Fant, R. V., Wang, D. W., and Cone, E. J. (2019). Risk of Death Associated with Kratom Use Compared to Opioids. *Prev. Med.* 128, 105851. doi:10.1016/j.ypmed.2019.105851

Henningfield, J. E., Grundmann, O., Garcia-Romeu, A., and Swogger, M. T. (2021). We Need Better Estimates of Kratom Use Prevalence. *Am. J. Prev. Med* 62 (1), 132–133. doi:10.1016/j.amepre.2021.07.022

Henningfield, J. E., Swogger, M. T., Walsh, Z., Kruegel, A. C., Grundmann, O., Garcia-Romeu, A., et al. (2018). Kratom Science Letter to Congressional Leaders. Available from: https://www.americankratom.org/images/16_Kratom_Scientist_Letter_to_Congressional_Leaders_June_21_2018_FINAL.pdf.

Henningfield, J. E., Swogger, M. T., Walsh, Z., Kruegel, A. C., Grundmann, O., Garcia-Romeu, A., et al. (2018). *Kratom Science Letter to the White House*. US: American Kratom Association. Available from: http://www.americankratom.org/images/file/Document%2019%20Science%20Letter%20on%20Kratom%20Sent%20to%20WH%20and%20DEA%20Feb%208%202018.pdf.

Hiranita, T., Leon, F., Felix, J. S., Restrepo, L. F., Reeves, M. E., Pennington, A. E., et al. (2019). The Effects of Mitragynine and Morphine on Schedule-Controlled Responding and Antinociception in Rats. *Psychopharmacology (Berl)* 236 (9), 2725–2734. doi:10.1007/s00213-019-05247-7

Hiranita, T., Sharma, A., Oyola, F. L., Obeng, S., Reeves, M. E., Restrepo, L. F., et al. (2020). Potential Contribution of 7-Hydroxymitragynine, a Metabolite of the Primary Kratom (Mitragyna Speciosa) Alkaloid Mitragynine, to the μ-Opioid Activity of Mitragynine in Rats. *FASEB J.* 34 (S1), 1. doi:10.1096/fasebj.2020.34.s1.05180

Ingraham, C. (2016). DEA Defies Senators' Appeal to Reconsider 'unprecedented' Kratom Ban. *The Wash. Post.*

Ingraham, C. (2016). The DEA Is Withdrawing a Proposal to Ban Another Plant after the Internet Got Really Mad. *Wash. Post.*

International Narcotics Control Board (2020). *List of Narcotic Drugs under International Control: Yellow List*. 59th ed. Vienna, Austria: International Narcotics Control Board.

International Narcotics Control Board (2020). *List of Psychotropic Substances under International Control: Green List*. Vienna, Austria: International Narcotics Control Board.

Jagabalan, Y., Zainal, H., Al Ganaby, A., Murugaiyah, V., and Ramanathan, S. (2019). "Pharmacokinetic Modeling of Single Dose Kratom (Mitragynine) in Rats. Front Pharmacol," in International Conference on Drug Discovery and Translational Medicine 2018 (ICDDTM '18) "Seizing Opportunities and Addressing Challenges of Precision Medicine, Putrajaya, Malaysia, 03 Dec 2018.

Japarin, R. A., Yusoff, N. H., Hassan, Z., Müller, C. P., and Harun, N. (2021). Cross-reinstatement of Mitragynine and Morphine Place Preference in Rats. *Behav. Brain Res.* 399, 113021. doi:10.1016/j.bbr.2020.113021

Johari, I. S., Harun, N., Sofian, Z. M., and Shoaib, M. (2021). Pentylenetetrazol-like Stimulus Is Not Produced Following Naloxone-Precipitated Mitragynine Withdrawal in Rats. *Psychopharmacology Berl* 238, 3183–3191. doi:10.1007/s00213-021-05934-4

Johnson, M. W., Griffiths, R. R., Hendricks, P. S., and Henningfield, J. E. (2018). The Abuse Potential of Medical Psilocybin According to the 8 Factors of the Controlled Substances Act. *Neuropharmacology* 142, 143–166. doi:10.1016/j.neuropharm.2018.05.012

Kamble, S. H., Berthold, E. C., King, T. I., Raju Kanumuri, S. R., Popa, R., Herting, J. R., et al. (2021). Pharmacokinetics of Eleven Kratom Alkaloids Following an Oral Dose of Either Traditional or Commercial Kratom Products in Rats. *J. Nat. Prod.* 84 (4), 1104–1112. doi:10.1021/acs.jnatprod.0c01163

Kamble, S. H., León, F., King, T. I., Berthold, E. C., Lopera-Londoño, C., Siva Rama Raju, K., et al. (2020). Metabolism of a Kratom Alkaloid Metabolite in Human Plasma Increases its Opioid Potency and Efficacy. *ACS Pharmacol. Transl Sci.* 3 (6), 1063–1068. doi:10.1021/acsptsci.0c00075

Kamble, S. H., Sharma, A., King, T. I., Berthold, E. C., León, F., Meyer, P. K. L., et al. (2020). Exploration of Cytochrome P450 Inhibition Mediated Drug-Drug

Interaction Potential of Kratom Alkaloids. *Toxicol. Lett.* 319, 148–154. doi:10.1016/j.toxlet.2019.11.005

Kamble, S. H., Sharma, A., King, T. I., León, F., McCurdy, C. R., and Avery, B. A. (2019). Metabolite Profiling and Identification of Enzymes Responsible for the Metabolism of Mitragynine, the Major Alkaloid of Mitragyna Speciosa (Kratom). *Xenobiotica* 49 (11), 1279–1288. doi:10.1080/00498254.2018.1552819

Katz, R. (2004). FDA: Evidentiary Standards for Drug Development and Approval. *NeuroRx* 1 (3), 307–316. doi:10.1602/neurorx.1.3.307

King, T. I., Sharma, A., Kamble, S. H., León, F., Berthold, E. C., Popa, R., et al. (2020). Bioanalytical Method Development and Validation of Corynantheidine, a Kratom Alkaloid, Using UPLC-MS/MS, and its Application to Preclinical Pharmacokinetic Studies. *J. Pharm. Biomed. Anal.* 180, 113019. doi:10.1016/j.jpba.2019.113019

Kruegel, A. C., and Grundmann, O. (2018). The Medicinal Chemistry and Neuropharmacology of Kratom: A Preliminary Discussion of a Promising Medicinal Plant and Analysis of its Potential for Abuse. *Neuropharmacology* 134 (Pt A), 108–120. doi:10.1016/j.neuropharm.2017.08.026

Kruegel, A. C., Uprety, R., Grinnell, S. G., Langreck, C., Pekarskaya, E. A., Le Rouzic, V., et al. (2019). 7-Hydroxymitragynine Is an Active Metabolite of Mitragynine and a Key Mediator of its Analgesic Effects. *ACS Cent. Sci.* 5 (6), 992–1001. doi:10.1021/acscentsci.9b00141

León, F., Obeng, S., Mottinelli, M., Chen, Y., King, T. I., Berthold, E. C., et al. (2021). Activity of Mitragyna Speciosa ("kratom") Alkaloids at Serotonin Receptors. *J. Med. Chem.* 64 (18), 13510–13523. doi:10.1021/acs.jmedchem.1c00726

Leong Abdullah, M. F. I., Tan, K. L., Narayanan, S., Yuvashnee, N., Chear, N. J. Y., Singh, D., et al. (2021). Is Kratom (Mitragyna Speciosa Korth.) Use Associated with ECG Abnormalities? Electrocardiogram Comparisons between Regular Kratom Users and Controls. *Clin. Toxicol. (Phila)* 59 (5), 400–408. doi:10.1080/15563650.2020.1812627

Leong Bin Abdullah, M. F. I., and Singh, D. (2021). Assessment of Cardiovascular Functioning Among Regular Kratom (Mitragyna Speciosa Korth) Users: A Case Series. *Front. Pharmacol.* 12, 723567. doi:10.3389/fphar.2021.723567

Leong Bin Abdullah, M. F. I., and Singh, D. (2021). The Adverse Cardiovascular Effects and Cardiotoxicity of Kratom (Mitragyna Speciosa Korth.): A Comprehensive Review. *Front. Pharmacol.* 12, 726003. doi:10.3389/fphar.2021.726003

Leong Bin Abdullah, M. F. I., Tan, K. L., Mohd Isa, S., Yusoff, N. S., Chear, N. J. Y., and Singh, D. (2020). Lipid Profile of Regular Kratom (Mitragyna Speciosa Korth.) Users in the Community Setting. *PLoS One* 15 (6), e0234639. doi:10.1371/journal.pone.0234639

Leong Bin Abdullah, M. F. I., Yuvashnee, N., and Singh, D. (2021). Effect of Regular Kratom (Mitragyna Speciosa Korth.) Use on Quality of Life of People Who Use Kratom. *Subst. Abus.*, 1–12. doi:10.1080/08897077.2021.1876809

Maxwell, E. A., King, T. I., Kamble, S. H., Raju, K. S. R., Berthold, E. C., León, F., et al. (2020). Pharmacokinetics and Safety of Mitragynine in Beagle Dogs. *Planta Med.* 86 (17), 1278–1285. doi:10.1055/a-1212-5475

Miech, R. A., Johnston, L. D., O'Malley, P. M., Bachman, J. G., Schulenberg, J. E., and Patrick, M. E. (2021). *Monitoring the Future National Survey Results on Drug Use, 1975–2020: Volume I, Secondary School Students.* Ann Arbor: Institute for Social Research, The University of Michigan.

National Institute on Drug Abuse (2019). *Kratom DrugFacts.* Bethesda, MD: National Institutes of Health. Available from: https://www.drugabuse.gov/publications/drugfacts/kratom.

Negus, S. S., and Miller, L. L. (2014). Intracranial Self-Stimulation to Evaluate Abuse Potential of Drugs. *Pharmacol. Rev.* 66 (3), 869–917. doi:10.1124/pr.112.007419

Newman, D. J., and Cragg, G. M. (2016). Natural Products as Sources of New Drugs from 1981 to 2014. *J. Nat. Prod.* 79 (3), 629–661. doi:10.1021/acs.jnatprod.5b01055

O'Brien, C. P. (2011). "Drug Addiction," in *Goodman & Gilman's the Pharmacological Basis of Therapeutics.* Editors L. L. Brunton, B. A. Chabner, and B. C. Knollman 12th ed. (New York: McGraw Hill Medical), 649–668.

Obeng, S., Wilkerson, J. L., León, F., Reeves, M. E., Restrepo, L. F., Gamez-Jimenez, L. R., et al. (2021). Pharmacological Comparison of Mitragynine and 7-Hydroxymitragynine: *In Vitro* Affinity and Efficacy for μ-Opioid Receptor and Opioid-like Behavioral Effects in Rats. *J. Pharmacol. Exp. Ther.* 376 (3), 410–427. doi:10.1124/jpet.120.000189

Olsen, E. O., O'Donnell, J., Mattson, C. L., Schier, J. G., and Wilson, N. (2019). Notes from the Field: Unintentional Drug Overdose Deaths with Kratom Detected - 27 States, July 2016-December 2017. *MMWR Morb Mortal Wkly Rep.* 68 (14), 326–327. doi:10.15585/mmwr.mm6814a2

Pain News Network (2018). Kratom Survey. Available from: https://www.painnewsnetwork.org/kratom-survey.

Pinney Associates (2016). *Assessment of Kratom under the CSA Eight Factors and Scheduling Recommendation*, Bethesda, MD.

Proxialeck, W. C., Avery, B. A., Boyer, E. W., Grundmann, O., Henningfield, J. E., Kruegel, A. C., et al. (2019). Kratom Policy: The challenge of Balancing Therapeutic Potential with Public Safety. *Int. J. Drug Pol.* 70, 70–77. doi:10.1016/j.drugpo.2019.05.003

Proxialeck, W. C., Edwards, J. R., Lamar, P. C., Plotkin, B. J., Sigar, I. M., Grundmann, O., et al. (2020). Evaluation of the Mitragynine Content, Levels of Toxic Metals and the Presence of Microbes in Kratom Products Purchased in the Western Suburbs of Chicago. *Int. J. Environ. Res. Public Health* 17 (15). doi:10.3390/ijerph17155512

Proxialeck, W. C., Lamar, P. C., Krupp, M., 2nd, Moon, M., Phelps, L. E., and Grundmann, O. (2021). Kratom Use within the Context of the Evolving Opioid Crisis and the COVID-19 Pandemic in the United States. *Front. Pharmacol.* 12, 729220. doi:10.3389/fphar.2021.729220

R. B. Raffa (Editor) (2014). *Kratom and Other Mitragynines: The Chemistry and Pharmacology of Opioids from a Non-opium Source* (Boca Raton: CRC Press, Taylor & Francis).

Reeve, M. E., Obeng, S., Oyola, F. L., Behnke, M., Restrepo, L. F., Patel, A., et al. (2020). The Adrenergic α 2 Receptor-Mediated Discriminative-Stimulus Effects of Mitragynine, the Primary Alkaloid in Kratom (Mitragyna Speciosa) in Rats. *FASEB J.* 34 (S1), 1. doi:10.1096/fasebj.2020.34.s1.05233

Schimmel, J., Amioka, E., Rockhill, K., Haynes, C. M., Black, J. C., Dart, R. C., et al. (2021). Prevalence and Description of Kratom (Mitragyna Speciosa) Use in the United States: a Cross-Sectional Study. *Addiction* 116 (1), 176–181. doi:10.1111/add.15082

Sharma, A., Kamble, S. H., León, F., Chear, N. J., King, T. I., Berthold, E. C., et al. (2019). Simultaneous Quantification of Ten Key Kratom Alkaloids in Mitragyna Speciosa Leaf Extracts and Commercial Products by Ultra-performance Liquid Chromatography-Tandem Mass Spectrometry. *Drug Test. Anal.* 11 (8), 1162–1171. doi:10.1002/dta.2604

Sharma, A., and McCurdy, C. R. (2021). Assessing the Therapeutic Potential and Toxicity of Mitragyna Speciosa in Opioid Use Disorder. *Expert Opin. Drug Metab. Toxicol.* 17 (3), 255–257. doi:10.1080/17425255.2021.1853706

Singh, D., Chye, Y., Suo, C., Yücel, M., Grundmann, O., Ahmad, M. Z., et al. (2018). Brain Magnetic Resonance Imaging of Regular Kratom (Mitragyna Speciosa Korth.) Users: a Preliminary Study. *Malays J. Med. Heal Sci.* 14 (Suppl. 1), 65–70.

Singh, D., Müller, C. P., Murugaiyah, V., Hamid, S. B. S., Vicknasingam, B. K., Avery, B., et al. (2018). Evaluating the Hematological and Clinical-Chemistry Parameters of Kratom (Mitragyna Speciosa) Users in Malaysia. *J. Ethnopharmacol* 214, 197–206. doi:10.1016/j.jep.2017.12.017

Singh, D., Müller, C. P., and Vicknasingam, B. K. (2014). Kratom (Mitragyna Speciosa) Dependence, Withdrawal Symptoms and Craving in Regular Users. *Drug Alcohol Depend* 139, 132–137. doi:10.1016/j.drugalcdep.2014.03.017

Singh, D., Narayanan, S., Grundmann, O., Chear, N. J. Y., Murugaiyah, V., Hamid, S. B. S., et al. (2020). Long-term Effects of Kratom [mitragyna Speciosa] Use. *Mal J. Med. Health Sci.* 16 (4), 64–72.

Singh, D., Narayanan, S., Müller, C. P., Swogger, M. T., Chear, N. J. Y., Dzulkapli, E. B., et al. (2019). Motives for Using Kratom (Mitragyna Speciosa Korth.) Among Regular Users in Malaysia. *J. Ethnopharmacol* 233, 34–40. doi:10.1016/j.jep.2018.12.038

Singh, D., Narayanan, S., Müller, C. P., Swogger, M. T., Rahim, A. A., Leong Bin Abdullah, M. F. I., et al. (2018). Severity of Kratom (Mitragyna Speciosa Korth.) Psychological Withdrawal Symptoms. *J. Psychoactive Drugs* 50 (5), 445–450. doi:10.1080/02791072.2018.1511879

Singh, D., Narayanan, S., Müller, C. P., Vicknasingam, B., Yücel, M., Ho, E. T. W., et al. (2019). Long-term Cognitive Effects of Kratom (Mitragyna Speciosa

Korth.) Use. *J. Psychoactive Drugs* 51 (1), 19–27. doi:10.1080/02791072.2018.1555345

Singh, D., Yeou Chear, N. J., Narayanan, S., Leon, F., Sharma, A., McCurdy, C. R., et al. (2020). Patterns and Reasons for Kratom (Mitragyna Speciosa) Use Among Current and Former Opioid Poly-Drug Users. *J. Ethnopharmacol* 249, 112462. doi:10.1016/j.jep.2019.112462

Singh, D., Grundmann, O., Murugaiyah, V., Rahim, A. B. M., Chawarski, M., and Balasingam, V. (2020). Improved Sexual Functioning of Long-Term Daily Users of Mitragyna Speciosa (Korth.). *J. Herbal Med.* 19, 100293. doi:10.1016/j.hermed.2019.100293

Smith, K. E., and Lawson, T. (2017). Prevalence and Motivations for Kratom Use in a Sample of Substance Users Enrolled in a Residential Treatment Program. *Drug Alcohol Depend* 180, 340–348. doi:10.1016/j.drugalcdep.2017.08.034

Smith, L. C., Lin, L., Hwang, C. S., Zhou, B., Kubitz, D. M., Wang, H., et al. (2019). Lateral Flow Assessment and Unanticipated Toxicity of Kratom. *Chem. Res. Toxicol.* 32 (1), 113–121. doi:10.1021/acs.chemrestox.8b00218

Substance Abuse and Mental Health Services Administration (2020). *Center for Behavioral Health Statistics and Quality. Treatment Episode Data Set (TEDS): 2018. Admissions to and Discharges from Publicly Funded Substance Use Treatment.* Rockville, MD: Substance Abuse and Mental Health Services Administration.

Suhaimi, F. W., Hassan, Z., Mansor, S. M., and Müller, C. P. (2021). The Effects of Chronic Mitragynine (Kratom) Exposure on the EEG in Rats. *Neurosci. Lett.* 745, 135632. doi:10.1016/j.neulet.2021.135632

Swogger, M. T., Hart, E., Erowid, F., Erowid, E., Trabold, N., Yee, K., et al. (2015). Experiences of Kratom Users: A Qualitative Analysis. *J. Psychoactive Drugs* 47 (5), 360–367. doi:10.1080/02791072.2015.1096434

Swogger, M. T., Smith, K. E., Garcia-Romeu, A., Grundmann, O., Veltri, C., Henningfield, J., et al. Understanding Kratom Use: A Guide for Healthcare Providers. *Front. Pharmacol.*

Swogger, M. T., and Walsh, Z. (2018). Kratom Use and Mental Health: A Systematic Review. *Drug Alcohol Depend* 183, 134–140. doi:10.1016/j.drugalcdep.2017.10.012

Todd, D. A., Kellogg, J. J., Wallace, E. D., Khin, M., Flores-Bocanegra, L., Tanna, R. S., et al. (2020). Chemical Composition and Biological Effects of Kratom (Mitragyna Speciosa): *In Vitro* Studies with Implications for Efficacy and Drug Interactions. *Sci. Rep.* 10 (1), 19158. doi:10.1038/s41598-020-76119-w

Trakulsrichai, S., Sathirakul, K., Auparakkitanon, S., Krongvorakul, J., Suesjai, J., Noumjad, N., et al. (2015). Pharmacokinetics of Mitragynine in Man. *Drug Des. Devel Ther.* 9, 2421–2429. doi:10.2147/DDDT.S79658

U.S. Department of health and Human Services (2020). *U.S. Departmentof Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality*. National Survey on Drug Use and Health 2019 (NSDUH-2019-DS0001). Rockville, MD.

U.S. Drug Enforcement Administration (2020). National Drug Threat Assessment: U.S. Department of Justice. [Available from: https://www.dea.gov/sites/default/files/2021-02/DIR-008-21%202020%20National%20Drug%20Threat%20Assessment_WEB.pdf.

U.S. Drug Enforcement Administration (2020). *National Forensic Laboratory Information System: NFLIS-Drug 2019 Annual Report*. Springfield, VA: U.S. Drug Enforcement Administration.

U.S. Drug Enforcement Administration Temporary Placement of Mitragynine and 7-Hydroxymitragynine into Schedule I; Withdrawal. Docket No. DEA-2016-0015-0006 2016 Available from: https://www.regulations.gov/document/DEA-2016-0015-0006.

U.S. Food and Drug Administration (2017). *Assessment of Abuse Potential of Drugs: Guidance for Industry. Silver Spring*. MD,US: Center for Drug Evaluation and Research, Food and Drug Administration.

U.S. Food and Drug Administration (2016). *Botanical Drug Development: Guidance for Industry. Silver Spring*. MD,US: U.S. Department of Health and Human Services, Center for Drug Evaluation and Research. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/botanical-drug-development-guidance-industry.

U.S. Food and Drug Administration (2017). Letter from the Assistant Secretary of Health to the Administrator of the Drug Enforcement Administration to Permanently Place Mitragynine and 7-hydroxymitragynine in Schedule I of the Controlled Substances Act 2017. Available from: https://www.documentcloud.org/documents/5031552-HHS-kratom-letter.html.

U.S. Food and Drug Administration (2018). Statement from FDA Commissioner Scott Gottlieb. M.D., on the agency's scientific evidence on the presence of opioid compounds in kratom, underscoring its potential for abuse 2018 Available from: https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-agencys-scientific-evidence-presence-opioid-compounds.

U.S. Food and Drug Administration (2017). Statement from FDA Commissioner Scott Gottlieb, M.D. On FDA Advisory about Deadly Risks Associated with Kratom. Available from: https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-fda-advisory-about-deadly-risks-associated-kratom.

Vicknasingam, B., Chooi, W. T., Rahim, A. A., Ramachandram, D., Singh, D., Ramanathan, S., et al. (2020). Kratom and Pain Tolerance: A Randomized, Placebo-Controlled, Double-Blind Study. *Yale J. Biol. Med.* 93 (2), 229–238.

Vijeepallam, K., Pandy, V., Murugan, D. D., and Naidu, M. (2019). Methanolic Extract of Mitragyna Speciosa Korth Leaf Inhibits Ethanol Seeking Behaviour in Mice: Involvement of Antidopaminergic Mechanism. *Metab. Brain Dis.* 34 (6), 1713–1722. doi:10.1007/s11011-019-00477-2

Warner, M. L., Kaufman, N. C., and Grundmann, O. (2016). The Pharmacology and Toxicology of Kratom: from Traditional Herb to Drug of Abuse. *Int. J. Leg. Med* 130 (1), 127–138. doi:10.1007/s00414-015-1279-y

Wilson, L. L., Harris, H. M., Eans, S. O., Brice-Tutt, A. C., Cirino, T. J., Stacy, H. M., et al. (2020). Lyophilized Kratom tea as a Therapeutic Option for Opioid Dependence. *Drug Alcohol Depend* 216, 108310. doi:10.1016/j.drugalcdep.2020.108310

World Health Organization (WHO) (1994). *The ICD-10 Classification of Mental and Behavioural Disorders: Conversion Tables between ICD-8, ICD-9 and ICD-10, Rev*, 1. Geneva, Switzerland: World Health Organization.

Wouters, O. J., McKee, M., and Luyten, J. (2020). Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. *JAMA* 323 (9), 844–853. doi:10.1001/jama.2020.1166

Yue, K., Kopajtic, T. A., and Katz, J. L. (2018). Abuse Liability of Mitragynine Assessed with a Self-Administration Procedure in Rats. *Psychopharmacology (Berl)* 235 (10), 2823–2829. doi:10.1007/s00213-018-4974-9

Yusoff, N. H. M., Mansor, S. M., Müller, C. P., and Hassan, Z. (2018). Baclofen Blocks the Acquisition and Expression of Mitragynine-Induced Conditioned Place Preference in Rats. *Behav. Brain Res.* 345, 65–71. doi:10.1016/j.bbr.2018.02.039

Conflict of Interest: Authors JH, DW, and MH were employed by the company Pinney Associates, Inc. Through Pinney Associates, JH, MH, DW, and colleagues provide scientific and regulatory consulting to support new drug applications (NDAs) and risk management programs for a broad range of CNS active substances and drug products including psychedelic substances, new chemical entities, and alternative formulations and routes of delivery, as well as dietary ingredient notifications, cannabinoid assessment, and noncombustible tobacco/nicotine products for FDA regulation. This includes advising the American Kratom Association and its affiliate, the Center for Plant Science and Health, on kratom science and regulation. MH is also a Professor at Thomas Jefferson University & President, Huestis & Smith Toxicology LLC, a toxicology consulting company working with pharmaceutical & diagnostic companies. No clients had any contribution or input into this assessment or its conclusions.

The reviewer WP declared a past co-authorship with one of the authors JH to the handling editor.

2 Appendix 2: The Abuse Potential of 7-Hydroxymitragynine (7-OH) According to the 8 Factors of the Controlled Substances Act

Pinney Associates

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

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

Jack E. Henningfield, Daniel W. Wang, Mark A. Sembower, Steve Pype, Floe Foxon

September 29, 2025

Table of Contents

List of Abbreviations

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

Disclosure

This report was funded without restrictions by the Center for Plant Science and Health (CPSH). CPSH had no input into the writing of this report, its methods, or its conclusions.

Through Pinney Associates, JEH, DWW, MS, SP, and FF consult to CPSH. In addition to CPSH, in the last 36 months, Pinney Associates has consulted to the Holistic Alternative Recovery Trust, NP Pharma, and Botanic Tonics LLC (the last uncompensated) on kratom science and regulatory issues and studies. Through Pinney Associates, in support of CPSH, JH has commented on kratom pharmacology, public health, and regulatory needs for state hearings and for a judicial hearing to address questions raised by the court on these same matters. JEH has also developed reports and given depositions addressing kratom addictiveness, and risks and benefits to kratom users, along with regulatory needs on behalf of several defendants in kratom litigation.

Acknowledgements

The authors are grateful for the care and efforts of Megan S. Harris in the editing and formatting of the report.

1 Introduction

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

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

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

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

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

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

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

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

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

---

[1] In 21 U.S. Code § 802 – Definitions

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

(A) Opium, opiates, derivatives of opium and opiates, including their isomers, esters, ethers, salts, and salts of isomers, esters, and ethers, whenever the existence of such isomers, esters, ethers,

and salts is possible within the specific chemical designation. Such term does not include the isoquinoline alkaloids of opium.

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

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

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

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

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

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

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

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

2 Factor 1: Actual or Relative Potential for Abuse

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

2.1 Pharmacology

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

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

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

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

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

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

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

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

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

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

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

2.2 Nonclinical Abuse Potential Models (Rewarding Effects)

2.2.1 Self-Administration

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

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

2.2.2 Intracranial Self-Stimulation

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

2.2.3 Drug Discrimination

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

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

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

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

2.2.4 Conditioned Place Preference

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

2.3 Clinical Studies and Evidence of Abuse Potential in Humans

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

2.4 Implications for Abuse Potential

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

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

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

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

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

3 Factor 2: Scientific Evidence of its Pharmacological Effects

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

3.1 Mechanism of Action and Opioid Binding

7-OH's interactions with opioid receptors appear to be the predominate cause of at least its abuse related effects. For example, 7-OH consistently demonstrates high affinity for the MOR, with reported inhibitor constant (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 β-arrestin-2 pathway. This is a significant finding, as β-arrestin-2 recruitment is strongly associated

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

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

3.2 Effects on Other Neurotransmitter Systems

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

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

3.3 Antinociception

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

3.4 Respiratory Depression

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

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

3.5 Comparison to Morphine

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

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

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

3.6 Implications for Abuse Potential

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

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

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

4 Factor 3: Current State of Scientific Knowledge

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

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

4.1 Pharmacokinetics

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

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

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

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

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

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

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

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

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

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

4.2 Mitragynine Pseudoindoxyl

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

4.3 Conclusions

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

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

5.1 Factor 4: History and Current Patterns of Abuse

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

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

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

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

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

5.1.1 Reasons for Use

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

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

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

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

5.1.2 Dosing, Routes of Administration, and Trajectory of Use

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

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

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

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

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

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

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

5.2.1 National Surveillance Systems

5.2.1.1 FAERS

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

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

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

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

5.2.1.2 National Poison Data System

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

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

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

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

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

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

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

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

a Excludes cases classified as 'confirmed non-exposure'.
b Cases may involve other substances, besides 7-OH.
Source: Adapted from NPDS dataset.

5.2.1.3 National Forensic Laboratory Information System (NFLIS)

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

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

5.2.1.4 DEA Toxicology Testing Program (DEA TOX)

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

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

5.2.1.5 Other National Surveillance Data

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

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

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

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

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

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

And in its Conclusions section:

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

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

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

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

5.2.2 Published Case Reports

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

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

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

5.2.3 Social Media Discussion

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

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

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

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

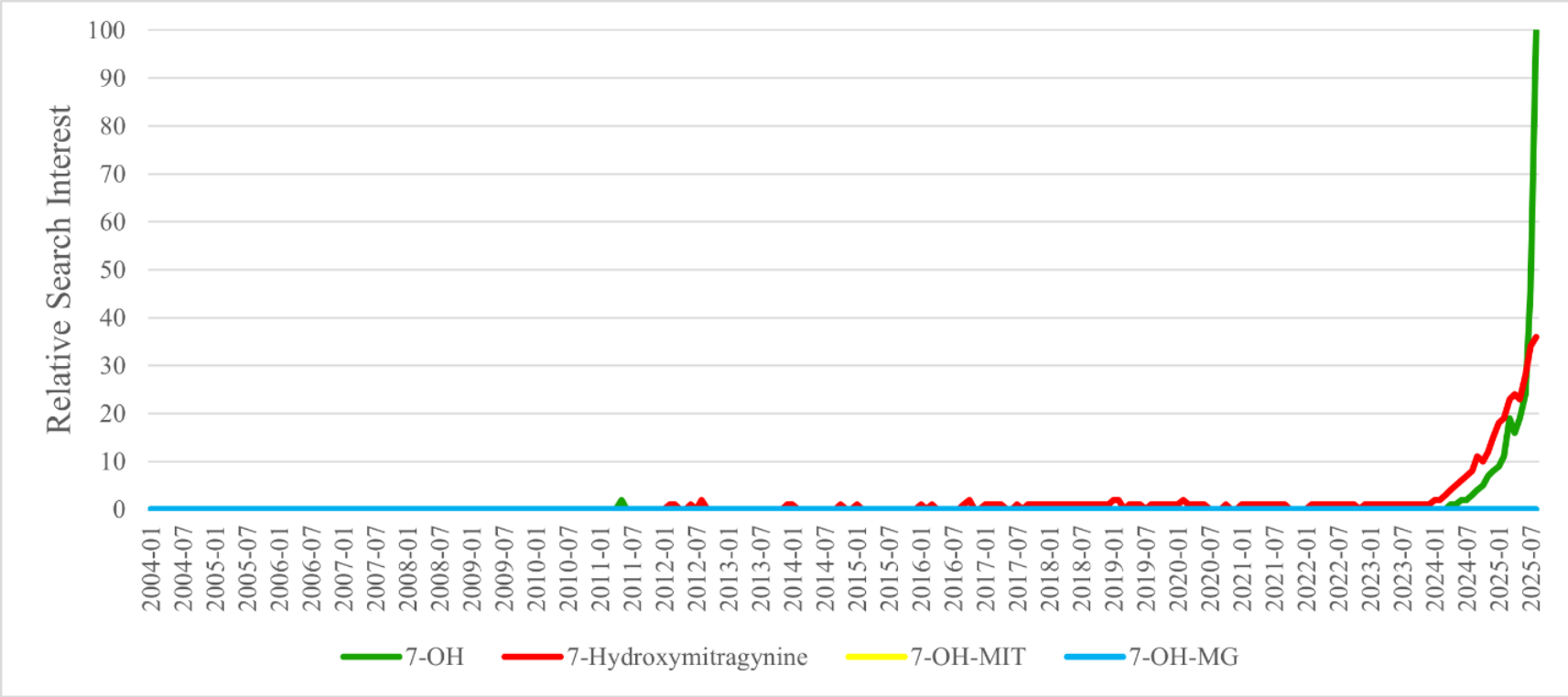
The following review of Reddit posts and comments on 7-OH is non-exhaustive. On Reddit, 7-OH was discussed in the Quitting Kratom subreddit (www.reddit.com/r/quittingkratom). Reddit posts and comments were much less descriptive than Erowid experience reports making inferences difficult. Nevertheless,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

posts and comments were missing data on dose. Among comments reporting withdrawal symptoms and dose, these ranged from 30 mg/day to 500 mg/day.

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

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

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



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

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

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

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

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

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

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

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

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

5.3.1 Pharmacological Risks

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

5.3.2 Abuse, Dependence, and Withdrawal Risk

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

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

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

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

5.3.3 Potential Benefits to Consumers and Public Health

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

5.4 Implications

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

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

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

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

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

6 Factor 7: The Psychic or Physiological Dependence Liability

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

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

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

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

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

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

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

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

8 Scheduling Recommendation

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

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

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

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

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

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

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

8.1 Policy Implementation Considerations to Minimize Unintended Consequences

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

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

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

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

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

9 Research Priorities and Policy Considerations

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

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

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

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

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

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

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

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

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

DHHS therefore developed an alternative test wherein:

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

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

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

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

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

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

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

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

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

9.1 Comparison of 7-OH to Kratom and other Substances

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

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

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

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

9.2 Potential Unintended Consequences of Schedule I Placement and Policy Implications

9.2.1 Potential Unintended Consequences of Scheduling

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

9.2.1.1 Relapse by Patients and Consumers to Harmful Opioids

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

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

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

9.2.1.2 Restrictions and Impediments to Scientific Research

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

9.2.1.3 Criminalization and Enforcement

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

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

10 References

Abbott, A. (2010). Levodopa: the story so far. *Nature*, *466*(7310), S6–S7. https://doi.org/10.1038/466S6a

Akbar, N. H., Suarantika, F., Fakih, T. M., Haniffadli, A., Muslimawati, K., & Putra, A. M. P. (2025). Screening, docking, and molecular dynamics analysis of Mitragyna speciosa (Korth.) compounds for targeting HER2 in breast cancer. *Curr Res Struct Biol*, *10*, 100171. https://doi.org/10.1016/j.crstbi.2025.100171

Andreae, M. H., Rhodes, E., Bourgoise, T., Carter, G. M., White, R. S., Indyk, D., Sacks, H., & Rhodes, R. (2016). An Ethical Exploration of Barriers to Research on Controlled Drugs. *Am J Bioeth*, *16*(4), 36–47. https://doi.org/10.1080/15265161.2016.1145282

Balster, R. (1983). *COMMENTS ON ABUSE LIABILITY OF NICORETTE FDA Drug Abuse Advisory Committee*.

Behnood-Rod, A., Chellian, R., Wilson, R., Hiranita, T., Sharma, A., Leon, F., McCurdy, C. R., McMahon, L. R., & Bruijnzeel, A. W. (2020). Evaluation of the rewarding effects of mitragynine and 7-hydroxymitragynine in an intracranial self-stimulation procedure in male and female rats. *Drug and Alcohol Dependence*, *215*, 108235. https://doi.org/https://doi.org/10.1016/j.drugalcdep.2020.108235

Berthold, E. C., Kamble, S. H., Kanumuri, S. R. R., Kuntz, M. A., Senetra, A. S., Chiang, Y. H., Mukhopadhyay, S., McCurdy, C. R., & Sharma, A. (2024). Pharmacokinetic Interaction of Kratom and Cannabidiol in Male Rats. *Pharmaceutics*, *16*(3). https://doi.org/10.3390/pharmaceutics16030318

Broul, M., Rudenko, X., Bajus, A., Král, J., Kyenge, D. M., Staňková, Z., & Albrecht, J. (2025). Case Report: Cannabis and kratom-induced self-amputation of ears and penis. *Front Psychiatry*, *16*, 1479863. https://doi.org/10.3389/fpsyt.2025.1479863

Carlezon, W. A., Jr., & Krystal, A. D. (2016). Kappa-Opioid Antagonists for Psychiatric Disorders: From Bench to Clinical Trials. *Depress Anxiety*, *33*(10), 895–906. https://doi.org/10.1002/da.22500

Chakraborty, S., DiBerto, J. F., Faouzi, A., Bernhard, S. M., Gutridge, A. M., Ramsey, S., Zhou, Y., Provasi, D., Nuthikattu, N., Jilakara, R., Nelson, M. N. F., Asher, W. B., Eans, S. O., Wilson, L. L., Chintala, S. M., Filizola, M., van Rijn, R. M., Margolis, E. B., Roth, B. L.,…Majumdar, S. (2021). A Novel Mitragynine Analog with Low-Efficacy Mu Opioid Receptor Agonism Displays Antinociception with Attenuated Adverse Effects. *J Med Chem*, *64*(18), 13873–13892. https://doi.org/10.1021/acs.jmedchem.1c01273

Chakraborty, S., Uprety, R., Slocum, S. T., Irie, T., Le Rouzic, V., Li, X., Wilson, L. L., Scouller, B., Alder, A. F., Kruegel, A. C., Ansonoff, M., Varadi, A., Eans, S. O., Hunkele, A., Allaoa, A., Kalra, S., Xu, J., Pan, Y. X., Pintar, J.,…Majumdar, S. (2021). Oxidative Metabolism as a Modulator of Kratom's Biological Actions. *J Med Chem*, *64*(22), 16553–16572. https://doi.org/10.1021/acs.jmedchem.1c01111

Chiang, Y. H., Berthold, E. C., Kuntz, M. A., Kanumuri, S. R. R., Senetra, A. S., Mukhopadhyay, S., Hampson, A. J., McCurdy, C. R., & Sharma, A. (2024). Multiple-Dose Pharmacokinetics and Safety of Mitragynine, the Major Alkaloid of Kratom, in Rats. *ACS Pharmacol Transl Sci*, *7*(8), 2452–2464.

https://doi.org/10.1021/acsptsci.4c00277

Chiang, Y. H., Kanumuri, S. R. R., Kuntz, M. A., Senetra, A. S., Berthold, E. C., Kamble, S. H., Mukhopadhyay, S., Hampson, A. J., McCurdy, C. R., & Sharma, A. (2025). In Vitro and In Vivo Pharmacokinetic Characterization of 7-Hydroxymitragynine, an Active Metabolite of Mitragynine, in Sprague-Dawley Rats. *Eur J Drug Metab Pharmacokinet*, *50*(3), 205–218. https://doi.org/10.1007/s13318-025-00939-2

Cicero, T. J., Ellis, M. S., & Surratt, H. L. (2012). Effect of abuse-deterrent formulation of OxyContin. *New England Journal of Medicine*, *367*(2), 187–189.

DEA. (2024). *Schedules of Controlled Substances: Rescheduling of Marijuana*. Retrieved September 24, 2025 from https://www.federalregister.gov/documents/2024/05/21/2024-11137/schedules-of-controlled-substances-rescheduling-of-marijuana

DHHS. (2023a) Letter from Office of the Assistant Secretary of Health to the FDA Commissioner regarding the Department of Health and Human Services' evaluation of marijuana's currently accepted medical use in treatment in the United States. https://www.scribd.com/document/714969286/HHS-252-Page-Rescheduling-Recommendation

DHHS. (2025a). *Press Conference on Opioid 7-OH Public Safety Measure*. https://www.youtube.com/live/FWHfeIgzVD4

DHHS. (2025b). *Secretary Kennedy, Deputy Secretary O'Neill, Commissioner Makary, and U.S. Senator Mullin to Host Press Conference on Measures to Safeguard American Public from Dangerous Opioid 7-OH*. https://www.hhs.gov/press-room/hhs-opioid-7oh-press-conference-kennedy.html

Ellis, C. R., Racz, R., Kruhlak, N. L., Kim, M. T., Zakharov, A. V., Southall, N., Hawkins, E. G., Burkhart, K., Strauss, D. G., & Stavitskaya, L. (2020). Evaluating kratom alkaloids using PHASE. *PLoS One*, *15*(3), e0229646. https://doi.org/10.1371/journal.pone.0229646

Ermer, J. C., Pennick, M., & Frick, G. (2016). Lisdexamfetamine Dimesylate: Prodrug Delivery, Amphetamine Exposure and Duration of Efficacy. *Clinical Drug Investigation*, *36*(5), 341–356. https://doi.org/10.1007/s40261-015-0354-y

FDA. (2017). *Assessment of Abuse Potential of Drugs Guidance for Industry*. https://www.fda.gov/media/116739/download

FDA. (2025a). *FDA Takes Steps to Restrict 7-OH Opioid Products Threatening American Consumers*. Retrieved September 23, 2025 from https://www.fda.gov/news-events/press-announcements/fda-takes-steps-restrict-7-oh-opioid-products-threatening-american-consumers

FDA. (2025b). *Preventing The Next Wave of the Opioid Epidemic: What You Need to Know About 7-OH*. https://www.fda.gov/media/187900/download

Giroir, B. P. (2018). *Letter from the Assistant Secretary of Health to the Administrator of the Drug Enforcement Administration to Rescind Previous Support to Permanently Place Mitragynine and 7-hydroxymitragynine in Schedule I of the Controlled Substances Act 2018*. https://images.go02.informamarkets.com/Web/Informa02/%7b548e6d56-2ea4-

4da4-9404-0348b56e9a88%7d_dhillon-8.16.2018-response-letter-from-ash-radm-giroir.pdf

Gonzalez, J. D. Z., Ragsdale, A. K., Mukhopadhyay, S., McCurdy, C. R., McMahon, L. R., Obeng, S., & Wilkerson, J. L. (2025). Mitragynine and 7-Hydroxymitragynine:

Bidirectional Effects on Breathing in Rats. *bioRxiv*. https://doi.org/10.1101/2025.05.16.654392

Grundmann, O., Green, M., Berthold, E., Yoon, S. L., & Ray, D. (2025). Prevalence and Use Patterns of Kratom (Mitragyna speciosa Korth.) in a US Nationally Representative Sample. *J Psychoactive Drugs*, 1–9. https://doi.org/10.1080/02791072.2025.2474249

Grundmann, O., Smith, K. E., Prozialeck, W. C., Veltri, C. A., & Boyer, E. W. (2024). Commentary: Presence of kratom in opioid overdose deaths: findings from coroner postmortem toxicological report. *Front Psychiatry*, *15*, 1411964. https://doi.org/10.3389/fpsyt.2024.1411964

Grundmann, O., Veltri, C. A., Morcos, D., Knightes, D., 3rd, Smith, K. E., Singh, D., Corazza, O., Cinosi, E., Martinotti, G., Walsh, Z., & Swogger, M. T. (2022). Exploring the self-reported motivations of kratom (Mitragyna speciosa Korth.) use: a cross-sectional investigation. *Am J Drug Alcohol Abuse*, *48*(4), 433–444. https://doi.org/10.1080/00952990.2022.2041026

Gummin, D. D., Mowry, J. B., Beuhler, M. C., Spyker, D. A., Rivers, L. J., Feldman, R., Brown, K., Pham, N. P. T., Bronstein, A. C., & DesLauriers, C. (2024). 2023 Annual Report of the National Poison Data System® (NPDS) from America's Poison Centers®: 41st Annual Report. *Clinical Toxicology*, *62*(12), 793–1027. https://doi.org/10.1080/15563650.2024.2412423

Gutridge, A. M., Robins, M. T., Cassell, R. J., Uprety, R., Mores, K. L., Ko, M. J., Pasternak, G. W., Majumdar, S., & van Rijn, R. M. (2020). G protein-biased kratom-alkaloids and synthetic carfentanil-amide opioids as potential treatments for alcohol use disorder. *British Journal of Pharmacology*, *177*(7), 1497–1513. https://doi.org/https://doi.org/10.1111/bph.14913

Harun, N., Hassan, Z., Navaratnam, V., Mansor, S. M., & Shoaib, M. (2015). Discriminative stimulus properties of mitragynine (kratom) in rats. *Psychopharmacology*, *232*(13), 2227–2238. https://doi.org/10.1007/s00213-015-3866-5

Heflin, J. O. (2023). *Kratom Regulation: Federal Status and State Approaches*. Retrieved September 24, 2025 from https://www.congress.gov/crs-product/LSB11082.

Hemby, S. E., McIntosh, S., Leon, F., Cutler, S. J., & McCurdy, C. R. (2019). Abuse liability and therapeutic potential of the Mitragyna speciosa (kratom) alkaloids mitragynine and 7-hydroxymitragynine. *Addiction Biology*, *24*(5), 874–885. https://doi.org/https://doi.org/10.1111/adb.12639

Henningfield, J. E., Ashworth, J. B., Gerlach, K. K., Simone, B., & Schnoll, S. H. (2019). The nexus of opioids, pain, and addiction: Challenges and solutions. *Preventive medicine*, *128*, 105852.

Henningfield, J. E., Beyer, C. E., & Raffa, R. B. (2025). *Kratom: History, Science, and Therapeutic Potential*. Academic Press (Elsevier).

Henningfield, J. E., Coe, M. A., Griffiths, R. R., Belouin, S. J., Berger, A., Coker, A. R., Comer, S. D., Heal, D. J., Hendricks, P. S., Nichols, C. D., Sapienza, F., Vocci, F. J., & Zia, F. Z. (2022). Psychedelic drug abuse potential assessment research for new drug applications and Controlled Substances Act scheduling.

Neuropharmacology, *218*, 109220. https://doi.org/https://doi.org/10.1016/j.neuropharm.2022.109220

Henningfield, J. E., Comer, S., Banks, M., Coe, M., Collins, G., Cooper, Z., Fantegrossi, W., Durgin, C., Heal, D., Huskinson, S., Lanier, R., Lynch, W., Meisch, R., Rowlett, J., Strickland, J., & Gannon, B. (2025). Abuse Potential Assessment of Novel Central Nervous System Active and Psychedelic Substances for Controlled Substances Act Scheduling Recommendations. *Journal of Psychopharmacology – Special Issue on Psychedelics Dedicated to Roland R. Griffiths (In Press)*.

Henningield, J.E., Fant, R.V. (2016). Assessment of Kratom under the CSA Eight Factors and Scheduling Recommendation. Pinney Associates. Retreived September 23, 32025 from https://d3n8a8pro7vhmx.cloudfront.net/americankratomassociation/pages/21/attachments/original/1485630505/Henningfield_Eight_Factor_Analysis.pdf?1485630505

Henningfield, J. E., Fant, R. V., & Wang, D. W. (2018). The abuse potential of kratom according the 8 factors of the controlled substances act: implications for regulation and research. *Psychopharmacology*, *235*(2), 573–589. https://doi.org/10.1007/s00213-017-4813-4

Henningfield, J. E., Grundmann, O., Babin, J. K., Fant, R. V., Wang, D. W., & Cone, E. J. (2019). Risk of death associated with kratom use compared to opioids. *Preventive medicine*, *128*, 105851. https://doi.org/https://doi.org/10.1016/j.ypmed.2019.105851

Henningfield, J. E., Grundmann, O., Garcia-Romeu, A., & Swogger, M. T. (2022). We Need Better Estimates of Kratom Use Prevalence. *Am J Prev Med*, *62*(1), 132–133. https://doi.org/10.1016/j.amepre.2021.07.022

Henningfield, J. E., Grundmann, O., Huestis, M. A., & Smith, K. E. (2024). Kratom safety and toxicology in the public health context: research needs to better inform regulation. *Frontiers in pharmacology*, *15*, 1403140. https://doi.org/10.3389/fphar.2024.1403140

Henningfield, J. E., Rodricks, J. V., Magnuson, A. M., & Huestis, M. A. (2022). Respiratory effects of oral mitragynine and oxycodone in a rodent model. *Psychopharmacology (Berl)*, *239*(12), 3793–3804. https://doi.org/10.1007/s00213-022-06244-z

Henningfield, J. E., Wang, D. W., & Huestis, M. A. (2021). Kratom Abuse Potential 2021: An Updated Eight Factor Analysis. *Front Pharmacol*, *12*, 775073. https://doi.org/10.3389/fphar.2021.775073

Henningfield, J. E., Wang, D. W., & Huestis, M. A. (2022). Kratom Abuse Potential 2021: An Updated Eight Factor Analysis [Review]. *Frontiers in Pharmacology*, *Volume 12 - 2021*. https://doi.org/10.3389/fphar.2021.775073

Hill, K., Boyer, E. W., Grundmann, O., & Smith, K. E. (2025). De facto opioids: Characterization of novel 7-hydroxymitragynine and mitragynine pseudoindoxyl product marketing. *Drug Alcohol Depend*, *272*, 112701. https://doi.org/10.1016/j.drugalcdep.2025.112701

Hill, K., Henderson, A., Sharma, A., Kanumuri, S. R. R., Mukhopadhyay, S., Veltri, C., Smith, K. E., McCurdy, C. R., & Grundmann, O. (2025). Diversification of Kratom

in US Markets: Results from an Online Survey and Chemical Assay of Products. *Subst Use Misuse*, 1–10. https://doi.org/10.1080/10826084.2025.2551707
Hiranita, T., Sharma, A., Oyola, F. L., Obeng, S., Reeves, M. E., Restrepo, L. F., Patel, A., Behnke, M., Ho, N. P., Williamson, M. R., Gamez Jimenez, L. R., McCurdy, C. R., & McMahon, L. R. (2020). Potential Contribution of 7-Hydroxymitragynine, a Metabolite of the Primary Kratom (Mitragyna Speciosa) Alkaloid Mitragynine, to the μ-Opioid Activity of Mitragynine in Rats. *The FASEB Journal*, *34*(S1), 1–1. https://doi.org/https://doi.org/10.1096/fasebj.2020.34.s1.05180
Horie, S., Koyama, F., Takayama, H., Ishikawa, H., Aimi, N., Ponglux, D., Matsumoto, K., & Murayama, T. (2005). Indole alkaloids of a Thai medicinal herb, Mitragyna speciosa, that has opioid agonistic effect in guinea-pig ileum. *Planta Med*, *71*(3), 231–236. https://doi.org/10.1055/s-2005-837822
Hossain, R., Sultana, A., Nuinoon, M., Noonong, K., Tangpong, J., Hossain, K. H., & Rahman, M. A. (2023). A Critical Review of the Neuropharmacological Effects of Kratom: An Insight from the Functional Array of Identified Natural Compounds. *Molecules*, *28*(21). https://doi.org/10.3390/molecules28217372
Huestis, M. A., Brett, M. A., Bothmer, J., & Atallah, R. (2024). Human Mitragynine and 7-Hydroxymitragynine Pharmacokinetics after Single and Multiple Daily Doses of Oral Encapsulated Dried Kratom Leaf Powder. *Molecules*, *29*(5). https://doi.org/10.3390/molecules29050984
Kamble, S. H., Berthold, E. C., King, T. I., Raju Kanumuri, S. R., Popa, R., Herting, J. R., Leon, F., Sharma, A., McMahon, L. R., Avery, B. A., & McCurdy, C. R. (2021). Pharmacokinetics of Eleven Kratom Alkaloids Following an Oral Dose of Either Traditional or Commercial Kratom Products in Rats. *J Nat Prod*, *84*(4), 1104–1112. https://doi.org/10.1021/acs.jnatprod.0c01163
Kamble, S. H., León, F., King, T. I., Berthold, E. C., Lopera-Londoño, C., Siva Rama Raju, K., Hampson, A. J., Sharma, A., Avery, B. A., McMahon, L. R., & McCurdy, C. R. (2020). Metabolism of a Kratom Alkaloid Metabolite in Human Plasma Increases Its Opioid Potency and Efficacy. *ACS Pharmacology & Translational Science*, *3*(6), 1063–1068. https://doi.org/10.1021/acsptsci.0c00075
Karunakaran, T., Vicknasingam, B., & Chawarski, M. C. (2025). Phytochemical analysis of water and ethanol liquid extracts prepared using freshly harvested leaves of Mitragyna speciosa (Korth.). *Natural Product Research*, *39*(15), 4480–4487. https://doi.org/10.1080/14786419.2024.2362428
Kikura-Hanajiri, R., Kawamura, M., Maruyama, T., Kitajima, M., Takayama, H., & Goda, Y. (2009). Simultaneous analysis of mitragynine, 7-hydroxymitragynine, and other alkaloids in the psychotropic plant “kratom” (Mitragyna speciosa) by LC-ESI-MS. *Forensic Toxicology*, *27*(2), 67–74. https://doi.org/10.1007/s11419-009-0070-5
Kruegel, A. C., Gassaway, M. M., Kapoor, A., Váradi, A., Majumdar, S., Filizola, M., Javitch, J. A., & Sames, D. (2016). Synthetic and Receptor Signaling Explorations of the Mitragyna Alkaloids: Mitragynine as an Atypical Molecular Framework for Opioid Receptor Modulators. *Journal of the American Chemical Society*, *138*(21), 6754–6764. https://doi.org/10.1021/jacs.6b00360
Kruegel, A. C., Uprety, R., Grinnell, S. G., Langreck, C., Pekarskaya, E. A., Le Rouzic, V., Ansonoff, M., Gassaway, M. M., Pintar, J. E., Pasternak, G. W., Javitch, J. A.,

Majumdar, S., & Sames, D. (2019). 7-Hydroxymitragynine Is an Active Metabolite of Mitragynine and a Key Mediator of Its Analgesic Effects. *ACS Central Science*, *5*(6), 992–1001. https://doi.org/10.1021/acscentsci.9b00141

Makary, M. A. (2025). *"Dear Colleague" Letter, July 29, 2025*. https://www.ahpa.org/Files/Media/FDA/final_updated_7-oh_dear_colleague_letter_7-28-2025.pdf

Manus, J. P., Crenshaw, R. C., Ringer, L. C., Towers, S. A., Paige, N. B., Leon, F., McCurdy, C. R., & Lester, D. B. (2025). Effects of kratom alkaloids on mesolimbic dopamine release. *Neuroscience Letters*, *850*, 138153. https://doi.org/https://doi.org/10.1016/j.neulet.2025.138153

Manus, J. P., Crenshaw, R. C., Ringer, L. C., Towers, S. A., Paige, N. B., Leon, F., McCurdy, C. R., & Lester, D. B. (2025). Effects of kratom alkaloids on mesolimbic dopamine release. *Neurosci Lett*, *850*, 138153. https://doi.org/10.1016/j.neulet.2025.138153

Matsumoto, K., Horie, S., Ishikawa, H., Takayama, H., Aimi, N., Ponglux, D., & Watanabe, K. (2004). Antinociceptive effect of 7-hydroxymitragynine in mice: Discovery of an orally active opioid analgesic from the Thai medicinal herb Mitragyna speciosa. *Life Sciences*, *74*(17), 2143–2155. https://doi.org/https://doi.org/10.1016/j.lfs.2003.09.054

Matsumoto, K., Takayama, H., Narita, M., Nakamura, A., Suzuki, M., Suzuki, T., Murayama, T., Wongseripipatana, S., Misawa, K., Kitajima, M., Tashima, K., & Horie, S. (2008). MGM-9 [(E)-methyl 2-(3-ethyl-7a,12a-(epoxyethanoxy)-9-fluoro-1,2,3,4,6,7,12,12b-octahydro-8-methoxyindolo[2,3-a]quinolizin-2-yl)-3-methoxyacrylate], a derivative of the indole alkaloid mitragynine: A novel dual-acting μ- and κ-opioid agonist with potent antinociceptive and weak rewarding effects in mice. *Neuropharmacology*, *55*(2), 154–165. https://doi.org/https://doi.org/10.1016/j.neuropharm.2008.05.003

Maxwell, E. A., King, T. I., Kamble, S. H., Raju, K. S. R., Berthold, E. C., Leon, F., Hampson, A., McMahon, L. R., McCurdy, C. R., & Sharma, A. (2021). Oral Pharmacokinetics in Beagle Dogs of the Mitragynine Metabolite, 7-Hydroxymitragynine. *Eur J Drug Metab Pharmacokinet*, *46*(3), 459–463. https://doi.org/10.1007/s13318-021-00684-2

Mongar, P., Jaisi, A., Inkviya, T., Wungsintaweekul, J., & Wiwattanawongsa, K. (2024). Effects of Itraconazole on Pharmacokinetics of Mitragynine and 7-Hydroxymitragynine in Healthy Volunteers. *ACS Pharmacol Transl Sci*, *7*(3), 823–833. https://doi.org/10.1021/acsptsci.3c00335

Obeng, S., Kamble, S. H., Reeves, M. E., Restrepo, L. F., Patel, A., Behnke, M., Chear, N. J., Ramanathan, S., Sharma, A., León, F., Hiranita, T., Avery, B. A., McMahon, L. R., & McCurdy, C. R. (2020). Investigation of the Adrenergic and Opioid Binding Affinities, Metabolic Stability, Plasma Protein Binding Properties, and Functional Effects of Selected Indole-Based Kratom Alkaloids. *J Med Chem*, *63*(1), 433–439. https://doi.org/10.1021/acs.jmedchem.9b01465

Obeng, S., Leon, F., Patel, A., Zuarth Gonzalez, J. D., Chaves Da Silva, L., Restrepo, L. F., Gamez-Jimenez, L. R., Ho, N. P., Guerrero Calvache, M. P., Pallares, V. L. C., Helmes, J. A., Shiomitsu, S. K., Soto, P. L., McCurdy, C. R., McMahon, L. R., Wilkerson, J. L., & Hiranita, T. (2022). Interactive Effects of micro-Opioid and

Adrenergic-alpha (2) Receptor Agonists in Rats: Pharmacological Investigation of the Primary Kratom Alkaloid Mitragynine and Its Metabolite 7-Hydroxymitragynine. *J Pharmacol Exp Ther*, *383*(3), 182–198. https://doi.org/10.1124/jpet.122.001192

Obeng, S., Wilkerson, J. L., Leon, F., Reeves, M. E., Restrepo, L. F., Gamez-Jimenez, L. R., Patel, A., Pennington, A. E., Taylor, V. A., Ho, N. P., Braun, T., Fortner, J. D., Crowley, M. L., Williamson, M. R., Pallares, V. L. C., Mottinelli, M., Lopera-Londono, C., McCurdy, C. R., McMahon, L. R., & Hiranita, T. (2021). Pharmacological Comparison of Mitragynine and 7-Hydroxymitragynine: In Vitro Affinity and Efficacy for mu-Opioid Receptor and Opioid-Like Behavioral Effects in Rats. *J Pharmacol Exp Ther*, *376*(3), 410–427. https://doi.org/10.1124/jpet.120.000189

Ogozalek, S. (2023). *The Tampa Bay Times tested 20 kratom products. Here's what we found.* (Tampa Bay, Issue. https://www.tampabay.com/investigations/2023/12/09/tampa-bay-times-tested-20-kratom-products-heres-what-we-found/

Osawa, K. A., & Johnson, R. D. (2025). Postmortem distribution of mitragynine and 7-hydroxymitragynine in 51 cases. *J Anal Toxicol*, *49*(2), 122–128. https://doi.org/10.1093/jat/bkae099

Palamar, J. J. (2021). Past-Year Kratom Use in the U.S.: Estimates From a Nationally Representative Sample. *Am J Prev Med*, *61*(2), 240–245. https://doi.org/10.1016/j.amepre.2021.02.004

Papsun, D., Schroeder, W., Brower, J., & Logan, B. (2023). Forensic Implications of Kratom: Kratom Toxicity, Correlation with Mitragynine Concentrations, and Polypharmacy. *Current Addiction Reports*, *10*(2), 272–281. https://doi.org/10.1007/s40429-023-00477-4

Puckett, Y., Patel, P., & Bokhari, A. A. (2025). Prednisone. [Updated 2025 Apr 26]. In *StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available: https://www.ncbi.nlm.nih.gov/books/NBK534809/*.

Pullman, M., Kanumuri, S. R. R., Leon, J. F., Cutler, S., McCurdy, C., & Sharma, A. (2025). Cardio-pulmonary arrest in a patient revived with naloxone following reported use of 7-hydroxymitragynine. *Clinical Toxicology*. Advance online publication. https://doi.org/10.1080/15563650.2025.2565428

Reissig, C. J., Chiapperino, D., Seitz, A., Lee, R., Radin, R., & McAninch, J. (2025). *7-Hydroxymitragynine (7-OH) An Assessment of the Scientific Data and Toxicological Concerns Around an Emerging Opioid Threat* https://www.fda.gov/media/187899/download?attachment

SAMHSA. (2023). *2022 NSDUH Detailed Tables: Table 8.21A – Illicit Drug, Illegally Made Fentanyl, or Other Substance Use in Lifetime: Among People Aged 12 or Older; by Age Group, Numbers in Thousands, 2021 and 2022*. https://www.samhsa.gov/data/sites/default/files/reports/rpt42728/NSDUHDetailedTabs2022/NSDUHDetailedTabs2022/NSDUHDetTabsSect8pe2022.htm#tab8.21a

SAMHSA. (2024). *2023 NSDUH Detailed Tables: Table 8.21A – Illicit Drug, Illegally Made Fentanyl, or Other Substance Use in Lifetime: Among People Aged 12 or Older; by Age Group, Numbers in Thousands, 2022 and 2023*.

https://www.samhsa.gov/data/sites/default/files/reports/rpt47100/NSDUHDetailedTabs2023_v1/NSDUHDetailedTabs2023_v1/2023-nsduh-detailed-tables-sect8pe.htm#tab8.21a
Schimmel, J., & Dart, R. C. (2020). Kratom (Mitragyna Speciosa) Liver Injury: A Comprehensive Review. *Drugs*, *80*(3), 263–283. https://doi.org/10.1007/s40265-019-01242-6
Singh, D., Yeou Chear, N. J., Narayanan, S., Leon, F., Sharma, A., McCurdy, C. R., Avery, B. A., & Balasingam, V. (2020). Patterns and reasons for kratom (Mitragyna speciosa) use among current and former opioid poly-drug users. *Journal of Ethnopharmacology*, *249*, 112462. https://doi.org/https://doi.org/10.1016/j.jep.2019.112462
Smith, K. E., Boyer, E. W., Grundmann, O., McCurdy, C. R., & Sharma, A. (2025). The rise of novel, semi-synthetic 7-hydroxymitragnine products. *Addiction*, *120*(2), 387–388. https://doi.org/10.1111/add.16728
Smith, K. E., & Lawson, T. (2017). Prevalence and motivations for kratom use in a sample of substance users enrolled in a residential treatment program. *Drug and Alcohol Dependence*, *180*, 340–348. https://doi.org/https://doi.org/10.1016/j.drugalcdep.2017.08.034
Smith, K. E., Panlilio, L. V., Sharma, A., McCurdy, C. R., Feldman, J. D., Mukhopadhyay, S., Kanumuri, S. Rama R., Kuntz, M. A., Hill, K., & Epstein, D. H. (2024). Time course of kratom effects via ecological momentary assessment, by product type, dose amount, and assayed alkaloid content. *Drug and Alcohol Dependence*, *264*, 112460. https://doi.org/10.1016/j.drugalcdep.2024.112460
Strickler, G. K., Kreiner, P. W., Halpin, J. F., Doyle, E., & Paulozzi, L. J. (2020). Opioid Prescribing Behaviors - Prescription Behavior Surveillance System, 11 States, 2010-2016. *MMWR Surveill Summ*, *69*(1), 1–14. https://doi.org/10.15585/mmwr.ss6901a1
Sudmoon, R., Tanee, T., Wonok, W., Ameamsri, U., Liehr, T., Daduang, S., Siripiyasing, P., & Chaveerach, A. (2025). Discovery of rhynchophylline and mitraphylline in two Thai Mitragyna species and the investigation of their biological activity via opioid gene expression analysis. *Sci Rep*, *15*(1), 5865. https://doi.org/10.1038/s41598-025-89715-5
Takayama, H., Ishikawa, H., Kurihara, M., Kitajima, M., Aimi, N., Ponglux, D., Koyama, F., Matsumoto, K., Moriyama, T., Yamamoto, L. T., Watanabe, K., Murayama, T., & Horie, S. (2002). Studies on the Synthesis and Opioid Agonistic Activities of Mitragynine-Related Indole Alkaloids: Discovery of Opioid Agonists Structurally Different from Other Opioid Ligands. *Journal of Medicinal Chemistry*, *45*(9), 1949–1956. https://doi.org/10.1021/jm010576e
Takayama, H. (2004). Chemistry and pharmacology of analgesic indole alkaloids from the Rubiaceous plant *Mitragyna speciosa*. *Chemical and Pharmaceutical Bulletin, 52*(8), 916–928. https://doi.org/10.1248/cpb.52.916
Tanna, R. S., Nguyen, J. T., Hadi, D. L., Manwill, P. K., Flores-Bocanegra, L., Layton, M. E., White, J. R., Cech, N. B., Oberlies, N. H., Rettie, A. E., Thummel, K. E., & Paine, M. F. (2022). Clinical Pharmacokinetic Assessment of Kratom (Mitragyna speciosa), a Botanical Product with Opioid-like Effects, in Healthy Adult

Participants. *Pharmaceutics*, *14*(3). https://doi.org/10.3390/pharmaceutics14030620

Todd, D. A., Kellogg, J. J., Wallace, E. D., Khin, M., Flores-Bocanegra, L., Tanna, R. S., McIntosh, S., Raja, H. A., Graf, T. N., Hemby, S. E., Paine, M. F., Oberlies, N. H., & Cech, N. B. (2020). Chemical composition and biological effects of kratom (Mitragyna speciosa): In vitro studies with implications for efficacy and drug interactions. *Scientific Reports*, *10*(1), 19158. https://doi.org/10.1038/s41598-020-76119-w

Uchaipichat, V. (2025). Inhibitory effects of Kratom constituents, mitragynine and 7-hydroxymitragynine, on 4-methylumbelliferone glucuronidation by human UDP-glucuronosyltransferases. *Toxicol Rep*, *14*, 101951. https://doi.org/10.1016/j.toxrep.2025.101951

UNODC. (2021). *Summary of assessments, findings and recommendations of the 44th World Health Organization's (WHO) Expert Committee on Drug Dependence (ECDD), 11–15 October 2021*. Retrieved September 24, 2025 from https://www.unodc.org/documents/commissions/CND/CND_Sessions/CND_64Reconvened/ECN72021_CRP12_V2108992.pdf

UNODC. (2025). *August 2025 - Emergence of potent kratom-related products containing 7-hydroxymitragynine and/or mitragynine pseudoindoxyl*. Retrieved September 23, 2025 from https://www.unodc.org/LSS/Announcement/Details/d0c66623-b200-4537-9f25-7df89fbdbf8b

Vadiei, N., Evoy, K. E., & Grundmann, O. (2025). The Impact of Diverse Kratom Products on Use Patterns, Dependence, and Toxicity. *Curr Psychiatry Rep*, *27*(10), 584–592. https://doi.org/10.1007/s11920-025-01631-7

White, C. M. (2025). Kratom's Use and Impact on Pediatric Populations. *J Pediatr Pharmacol Ther*, *30*(2), 289–293. https://doi.org/10.5863/1551-6776-30.2.289

Wightman, R. S., & Hu, D. (2025). A Case of 7-OH Mitragynine Use Requiring Inpatient Medically Managed Withdrawal. *J Addict Med*. https://doi.org/10.1097/ADM.0000000000001558

11 Appendices

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

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

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

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

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

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

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

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

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

Publication or Source	Short Title or Description	Comparators Studied or Mentioned	Abuse-related Variables	Physical Dependence & Withdrawal	Safety Individual Population	Comments
Obeng et al. (2022)	Interactive Effects of m-Opioid and Adrenergic a2 Receptor Agonists in Rats Pharmacological investigation of the primary kratom alkaloid mitragynine and its metabolite 7-hydroxymitragynine	MG, 7-OH-MG, morphine, methadone, clonidine, lofexidine, U69,593, naltrexone, yohimbine	MG showed low affinity at α2A and α2C receptors MG bound MOR with Ki ~1700 nM. 7-OH-MG showed stronger MOR affinity (Ki ~78 nM) but no α2 binding at ≤10 μM.	NA	No toxicity or lethality reported.	MG has weak affinity for MOR but meaningful interactions with α2-adrenergic systems. Combined activity may account for kratom's mixed reported stimulant/analgesic profile. In hot plate tests, MG did not produce significant antinociception across routes (IP, SC, oral). In contrast, 7-OH-MG produced robust, naloxone-sensitive antinociception. MG and 7-OH-MG enhanced potency of α2 agonists (clonidine/lofexidine)
Maxwell et al. (2021)	Oral pharmacokinetics in beagle dogs of the mitragynine metabolite, 7-hydroxymitragynine.	MG, 7-OH-MG	NA	NA	NA	Following a single oral dose (1 mg/kg) of 7-HMG, plasma samples were obtained from healthy female beagle dogs. Absorption of 7-HMG was rapid, with a peak plasma concentration (C_{max}, 56.4 ± 1.6 ng/mL) observed within 15 min post-dose. In contrast, 7-HMG elimination was slow, exhibiting a mono-exponential distribution and mean $t_{1/2}$ of 3.6 ± 0.5 h. Oral dosing of 1 mg/kg 7-HMG was well-tolerated with no observed AEs or significant changes to clinical laboratory tests. The exposure of 7-HMG after MG dosing due to metabolism corresponds to a 0.24 mg/kg dose of 7-HMG indicating a 23.1%

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

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

Publication or Source	Short Title or Description	Comparators Studied or Mentioned	Abuse-related Variables	Physical Dependence & Withdrawal	Safety Individual Population	Comments
						of 7-OH-MG, though this may be due to poor water solubility. The concentration of 7-HMG fell below the LLOQ after 8 h following IV administration and 4 h following oral administration.
Uchaipichat (2025)	Inhibitory effects of Kratom constituents, mitragynine and 7-hydroxymitragynine, on 4-methylumbelliferone glucuronidation by human UDP-glucuronosyltransferases.	MG, 7-OH-MG	NA	NA	NA	7-OH exhibited the highest inhibitory potency on UGT1A9, with IC_{50} value of 51 μM, while moderate potency was observed for UGT1A1 and UGT1A3, with IC_{50} value of 196 and 141 μM, respectively. The inhibitory potency of 7-OH on UGT2B15 was low (IC_{50} > 200 μM), while negligible effects were observed for UGT1A6 and UGT2B7. 7-OH competitively inhibited UGT1A3 (Ki = 33 μM) and noncompetitively inhibited UGT1A9 (Ki = 29 μM). Values are relatively high compared to the maximum plasma concentrations reported in humans, suggesting an unlikely potential for herb-drug interactions via UGT inhibition.
Berthold et al. (2024)	Pharmacokinetic Interaction of Kratom and Cannabidiol in Male Rats	MG, 7-OH-MG, speciociliaine, paynantheine, speciogynine, corynantheidine measured	NA	NA	NA	The metabolite to parent (i.e., mitragynine) exposure ratio percentage of 7-OH-MG remained similar (3.5 and 3.1 with and without cannabidiol, respectively). As there was an increase in MG exposure during this study, it was expected that this would be due to a decrease

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

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

Publication or Source	Short Title or Description	Comparators Studied or Mentioned	Abuse-related Variables	Physical Dependence & Withdrawal	Safety Individual Population	Comments
					No patients experienced severe AEs.	distribution and clearance than 3R alkaloids; exhibited longer terminal $t_{1/2}$, higher CL/F and Vz/F, lower dose-normalized AUC_{inf} and C_{max}, shorter T_{max} than 3R alkaloids. 3R alkaloids (mitraciliatine, speciociliatine, isopaynantheine) followed monophasic concentration-time profile.
Kamble et al. (2021)	Pharmacokinetics of Eleven Kratom Alkaloids Following an Oral Dose of Either Traditional or Commercial Kratom Products in Rats	Traditional Kratom (lyophilized kratom tea) Commercial Kratom (OPMS liquid shot)	NA	NA	NA	Among the 11 alkaloids, only MG, 7-OH-MG, speciociliatine, and corynantheidine showed systemic exposure 8 h postdose, and the dose-normalized systemic exposure of these four alkaloids was higher (1.6−2.4-fold) following the administration of the commercial OPMS liquid. Paynantheine and speciogynine levels were quantifiable up to 1 h postdose, whereas none of the other alkaloids were detected.
Hiranita et al. (2020)	Potential Contribution of 7-Hydroxymitragynine, a Metabolite of the Primary Kratom (Mitragyna Speciosa) Alkaloid Mitragynine, to the μ-Opioid Activity of	MG and 7-OH binding activity and efficacy at the MOR were compared Plasma levels following PO MG administration were measured Antinociception in	In rats discriminating morphine (3.2 mg/kg, IP) from vehicle, the discriminative stimulus effects of MG were assessed 90 min after PO administration.	NA	32 mg/kg MG was lethal.	Binding activity of 7-OH at MOR (Ki = 78 nm) was 22-fold lower than morphine and 9-0 fold higher than MG. Following PO administration of MG (HCl salt, 55 mg/kg), C_{max} of 7-OH (85 ng/mL) was 14-fold less than MG. T_{max} of 7-OH and MG were 30 and 84 min, respectively. 7-OH is a more potent and efficacious MOR agonist than MG,

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

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

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

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

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

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

Abbreviations: 7-OH-MG (7-HMG; 7-OH) = 7-hydroxymitragynine; AE(s) = adverse event(s)/adverse effect(s); BBB = blood brain barrier; C_{max} = maximum concentration; CNS = central nervous system; COWS = Clinical Opiate Withdrawal Scale; CPP = conditioned place preference; CYP = cytochrome; DOR = delta (δ)- opioid receptor; GI

= gastrointestinal; IC_{50} = half maximal inhibitory concentration; IP = intraperitoneal; Ki = inhibitor constant; IV = intravenous; KOR = kappa (ƙ)- opioid receptor; LLOQ = lower limit of quantitation; MG (MTG) = mitragynine; MGP (MP) = mitragynine pseudoindoxyl; MOR = mu (μ)- opioid receptor; NA = not available; Oxy = oxycodone; P-gp

= P-glycoprotein; PK = pharmacokinetic; SC = subcutaneous; SOWS = Subjective Opiate Withdrawal Scale; $t_{1/2}$ = half life; T_{max} = time to maximum concentration.

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

FDA NEWS RELEASE

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

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

More Press Announcements (/news-events/newsroom/press-announcements)

For Immediate Release:

July 29, 2025

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

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

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

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

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

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

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

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

Related Information

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

Media:
HHS Request for Comment (https://www.hhs.gov/request-for-comment-form/index.html?Agency=ASPA)
202-690-6343

Consumer:
888-INFO-FDA

###

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

U.S. FOOD & DRUG ADMINISTRATION

7-Hydroxymitragynine (7-OH):

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

7-Hydroxymitragynine (7-OH):

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

FDA Center for Drug Evaluation and Research Authors

Chad J. Reissig, PhD, Supervisory Pharmacologist, Controlled Substance Staff (CSS), CDER
Dominic Chiapperino, PhD, Director, CSS, CDER
Amy Seitz, PhD, MPH, Team Lead for Nonmedical Drug Use Team 3, Division of Epidemiology II (DEPI), Office of Pharmacovigilance and Epidemiology (OPE), Office of Surveillance and Epidemiology (OSE), CDER
Regina Lee, Pharm.D., Safety Evaluator, Division of Pharmacovigilance II, OPE, OSE, CDER
Rose Radin, PhD, Associate Director for Science, DEPI, OPE, OSE, CDER
Jana McAninch, MD, MPH, MS, Associate Director for Public Health Initiatives, OSE, CDER

Acknowledgments

Matthew Daubresse, DrPH, MHS, Epidemiologist, DEPI, OPE, OSE, CDER
Tamra Meyer, PhD, MPH, Associate Director for Nonmedical Drug Use, DEPI, OPE, OSE, CDER
Marta Sokolowska, PhD, Deputy Center Director for Substance Use and Behavioral Health, CDER

Table of Contents

EXECUTIVE SUMMARY

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

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

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

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

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

INTRODUCTION

The Context for 7-OH Concerns

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

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

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

Contemporary Outlook

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

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

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

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

7-OH Sources and Products vs. Kratom

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

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

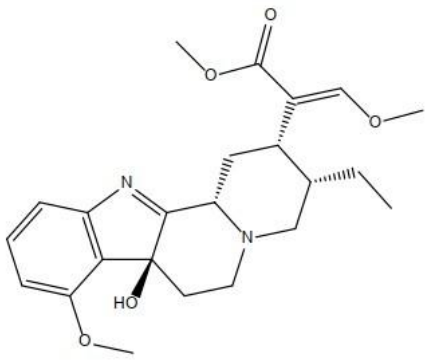


Figure 1. 7-Hydroxymitragynine Chemical Structure

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

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

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

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

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

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

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

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

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

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

National Drug Early Warning System (NDEWS)

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

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

Social Media

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

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

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

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

Drug Enforcement Administration Toxicology Testing Program (DEA TOX)

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

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

Human Exposures in Pharmacokinetic Studies

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

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

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

Tanna et. al., assessed the PK of a single orally administered dose of kratom (2 g), in the form of a tea, to healthy adult subjects (n = 5 completers). According to the authors, there were only trace amounts of 7-OH (< LOQ) in the starting product, therefore, the assumption was made that 7-OH was generated from the metabolism of mitragynine *in vivo.* The authors identified a PK difference between enantiomers of kratom alkaloids in either the 3S or 3R configuration. 7-OH has a 3S configuration which, according to the authors, leads to a shorter T_{max}, lower exposure (AUC), longer terminal half-life, and a higher volume of distribution during the terminal phase compared to the 3R alkaloids. Measured 7-OH in plasma samples demonstrated that 7-OH had a C_{max} = 16.1 nM, T_{max} = 1h, half-life = 5.67h, and an AUC0-120h = 103nM x h.(Tanna et al., 2022).

Epidemiological Data Sources

Limitations with the Epidemiological Data Sources

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

FDA's Adverse Event Reporting System

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

America's Poison Centers, National Poison Data System

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

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

	Number of exposure cases**	Number of abuse cases**	Single substance exposure cases	Single substance abuse cases
Total cases involving 7-OH	53	24	37	16
Reason				
Adverse drug reaction	4		2	
Intentional- abuse	24		16	
Intentional- misuse	4		3	
Intentional - Suspected suicide	2		0	
Other – Withdrawal	8		6	
Unintentional – general	4		4	
Unintentional- misuse	1		1	
Unintentional therapeutic error	4		3	
Unknown reason	2		2	
Related clinical outcomes				
Minor			6	3
Moderate			13	6
Major			3	1
Not followed, minimal clinical effects possible			5	3
Unable to follow, judged as potentially toxic exposure			1	0
Age				
<18 years	6	1	5	0
≥ 18 years	46	23	32	16
Unknown age	1	0	0	0

*Excludes cases classified as 'confirmed non-exposure'
**Cases may involve other substances, besides 7-OH
Related clinical outcomes include cases with clinical effects deemed "related" to exposure based on timing, severity, and assessment of clinical effects by Poison Center Specialists. Definitions available from America's Poison Centers: NPDS Full Report 2023. Page 235.

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

Summary of Epidemiological Data and 7-OH Concerns

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

Preclinical Data Characterizing 7-OH Pharmacology

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

In Vitro Data

Receptor Binding Studies

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

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

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

Functional Studies

Many of the studies referenced above performed additional assessments of 7-OH to determine its functional activity after binding (i.e., agonist or antagonist effects). These studies have consistently demonstrated that 7-OH produces mu-opioid agonist effects. For example, Kruegel and colleagues examined the functional activity of 7-OH and mitragynine in HEK cells expressing opioid receptors using a bioluminescence resonance energy transfer (BRET) assay. Both mitragynine and 7-OH functioned as partial agonists, producing Emax values of 34% and 47% respectively and EC_{50} values of 339 ± 178 nM and 34.5 ± 4.5 nM (Kruegel et al., 2016). Activation of the mu opioid receptor pathway was also investigated using forskolin-stimulated cyclic adenosine monophosphate (cAMP) accumulation in Chinese Hamster Ovary (CHO) cells expressing mu opioid receptors. In this assay, 7-OH produced a maximal activation (Emax) of 85.9%, a value similar to that produced by the positive control comparators DAMGO (86.2%) and morphine (86.9%). These data suggest 7-OH acts a full mu opioid agonist (Todd et al., 2020). Similarly, Matsumoto and colleagues concluded that 7-OH was "found to have an opioid agonist property on μ- and/or κ-opioid receptors" based on its ability to inhibit contraction of isolated guinea pig ileum. In this assay, 7-OH displayed approximately 13-fold greater potency than morphine and 46-fold greater potency than mitragynine. The inhibition was reversed by naloxone, suggesting the effects are mediated via mu opioid receptors (Matsumoto et al., 2004). Other functional assays produced results that are aligned with Matsumoto and colleagues. For example, using a cAMP mobilization assay as a measure of functional effects, 7-OH acted as a full agonist with an EC_{50} of 7.6 nM, and was more potent than mitragynine (EC_{50} 307.5 nM) (Obeng et al., 2020). Likewise, when evaluating the agonist activity of 7-OH in an electrically stimulated guinea pig ileum, 7-OH acted as a full agonist and was more potent than morphine (Takayama et al., 2002). Finally, using a [^{35}S] GTPγS functional assay, 7-OH produced an Emax of 77% with an EC_{50} of 53.4 nM, further demonstrating its agonist effects (Varadi et al., 2016).

Animal Data on Behavioral and Physiological Effects

Conditioned Place Preference

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

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

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

Drug Discrimination

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

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

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

In a second study, the discriminative stimulus effects of 7-OH were examined in separate groups of rats trained to discriminate either morphine (3.2 mg/kg i.p., 15 min pretreatment) or mitragynine (32 mg/kg i.p., 30 min pretreatment) from saline. After successful acquisition of discrimination training 7-OH was administered in substitution tests. 7-OH was administered i.p., with a 15 min pretreatment time in a dose range of 0.1-17.8 mg/kg. In the morphine-trained rats, 7-OH produced complete substitution at doses above 0.56 mg/kg, with the 1.0 mg/kg dose producing 100% drug-lever-appropriate responding and a resultant ED_{50} of 0.28 mg/kg. Notably, the dose-response curve was shifted to the left, demonstrating an increased potency of 7-OH relative to morphine. In addition, pretreatment with 0.032 mg/kg naltrexone shifted the dose-response curve to the right suggesting substitution was mediated via mu-opioid receptors (Obeng et al., 2021). Taken together, the drug discrimination data demonstrate the ability of 7-OH to substitute and mimic the stimulus effects of morphine, and that 7-OH is more potent in doing so. These data are a strong indication that 7-OH produces subjective effects in humans that are similar to opioids, along with an associated abuse potential.

Self-Administration

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

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

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

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

There are some pharmacokinetic (PK) data available from animal studies involving the administration of isolated, i.e., single entity, 7-OH. Following a single oral dose (1 mg/kg 7-OH) to beagle dogs, absorption was rapid, with a peak plasma concentration (i.e., Cmax) of 56 ± 1.6 ng/mL 15 minutes post-dose. The elimination half-life was slower, producing a mean of 3.6 ± 0.5 h. No AEs were observed, and no abnormal laboratory findings were reported (Maxwell et al., 2021). In adult male and female mice, the PK parameters of 7-OH were investigated after a single oral dose of 50 mg/kg 7-OH. The tissue distribution of 7-OH was observed in descending order: liver > kidney > spleen > lung > brain. Plasme C_{max} values were 0.6 and 09 µg/mL in males and females with a T max value of 0.5 hr. Area under the curve (AUC) values over 48 hours (AUC_{0-48} hr* µg/mL) were 1.4 and 2.9 in male and female mice (Berthold et al., 2022).

Antinociceptive Effects

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

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

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

Respiratory Depression

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

Physical Dependence and Withdrawal

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

Summary of Preclinical Data

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

CONCLUSIONS

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

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

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

REFERENCES

Ator, N. A., & Griffiths, R. R. (2003). Principles of drug abuse liability assessment in laboratory animals. *Drug Alcohol Depend*, *70*(3 Suppl), S55-72. https://doi.org/10.1016/s0376-8716(03)00099-1

Baldo, B. A., & Rose, M. A. (2022). Mechanisms of opioid-induced respiratory depression. *Arch Toxicol*, *96*(8), 2247-2260. https://doi.org/10.1007/s00204-022-03300-7

Balster, R. L., & Bigelow, G. E. (2003). Guidelines and methodological reviews concerning drug abuse liability assessment. *Drug Alcohol Depend*, *70*(3 Suppl), S13-40. https://doi.org/10.1016/s0376-8716(03)00097-8

Bateman, J. T., Saunders, S. E., & Levitt, E. S. (2023). Understanding and countering opioid-induced respiratory depression. *Br J Pharmacol*, *180*(7), 813-828. https://doi.org/10.1111/bph.15580

Berthold, E. C., Kamble, S. H., Raju, K. S., Kuntz, M. A., Senetra, A. S., Mottinelli, M., Leon, F., Restrepo, L. F., Patel, A., Ho, N. P., Hiranita, T., Sharma, A., McMahon, L. R., & McCurdy, C. R. (2022). The Lack of Contribution of 7-Hydroxymitragynine to the Antinociceptive Effects of Mitragynine in Mice: A Pharmacokinetic and Pharmacodynamic Study. *Drug Metab Dispos*, *50*(2), 158-167. https://doi.org/10.1124/dmd.121.000640

Brady, J. V., Griffiths, R. R., Hienz, R. D., Ator, N. A., Lukas, S. E., & Lamb, R. J. (1987). Assessing Drugs for Abuse Liability and Dependence Potential in Laboratory Primates. In M. A. Bozarth (Ed.), *Methods of Assessing the Reinforcing Properties of Abused Drugs* (pp. 45-85). Springer New York. https://doi.org/10.1007/978-1-4612-4812-5_3

Chakraborty, S., Uprety, R., Slocum, S. T., Irie, T., Le Rouzic, V., Li, X., Wilson, L. L., Scouller, B., Alder, A. F., Kruegel, A. C., Ansonoff, M., Varadi, A., Eans, S. O., Hunkele, A., Allaoa, A., Kalra, S., Xu, J., Pan, Y. X., Pintar, J.,…Majumdar, S. (2021). Oxidative Metabolism as a Modulator of Kratom's Biological Actions. *J Med Chem*, *64*(22), 16553-16572. https://doi.org/10.1021/acs.jmedchem.1c01111

Chear, N. J., Leon, F., Sharma, A., Kanumuri, S. R. R., Zwolinski, G., Abboud, K. A., Singh, D., Restrepo, L. F., Patel, A., Hiranita, T., Ramanathan, S., Hampson, A. J., McMahon, L. R., & McCurdy, C. R. (2021). Exploring the Chemistry of Alkaloids from Malaysian Mitragyna speciosa (Kratom) and the Role of Oxindoles on Human Opioid Receptors. *J Nat Prod*, *84*(4), 1034-1043. https://doi.org/10.1021/acs.jnatprod.0c01055

Cinosi, E., Martinotti, G., Simonato, P., Singh, D., Demetrovics, Z., Roman-Urrestarazu, A., Bersani, F. S., Vicknasingam, B., Piazzon, G., Li, J. H., Yu, W. J., Kapitany-Foveny, M., Farkas, J., Di Giannantonio, M., & Corazza, O. (2015). Following "the Roots" of Kratom (Mitragyna speciosa): The Evolution of an Enhancer from a Traditional Use to Increase Work and Productivity in Southeast Asia to a Recreational Psychoactive Drug in Western Countries. *Biomed Res Int*, *2015*, 968786. https://doi.org/10.1155/2015/968786

D'Amour, F. E., & Smith, D. L. (1941). A METHOD FOR DETERMINING LOSS OF PAIN SENSATION. *The Journal of Pharmacology and Experimental Therapeutics*, *72*(1), 74-79. https://doi.org/10.1016/S0022-3565(25)03823-6

Ellis, C. R., Racz, R., Kruhlak, N. L., Kim, M. T., Zakharov, A. V., Southall, N., Hawkins, E. G., Burkhart, K., Strauss, D. G., & Stavitskaya, L. (2020). Evaluating kratom alkaloids using PHASE. *PLoS One*, *15*(3), e0229646. https://doi.org/10.1371/journal.pone.0229646

Garcia-Romeu, A., Cox, D. J., Smith, K. E., Dunn, K. E., & Griffiths, R. R. (2020). Kratom (Mitragyna speciosa): User demographics, use patterns, and implications for the opioid

epidemic. *Drug Alcohol Depend*, *208*, 107849. https://doi.org/10.1016/j.drugalcdep.2020.107849
Grundmann, O., Garcia-Romeu, A., McCurdy, C. R., Sharma, A., Smith, K. E., Swogger, M. T., & Weiss, S. T. (2024). Not all kratom is equal: The important distinction between native leaf and extract products. *Addiction*, *119*(1), 202-203. https://doi.org/10.1111/add.16366
Gutridge, A. M., Robins, M. T., Cassell, R. J., Uprety, R., Mores, K. L., Ko, M. J., Pasternak, G. W., Majumdar, S., & van Rijn, R. M. (2020). G protein-biased kratom-alkaloids and synthetic carfentanil-amide opioids as potential treatments for alcohol use disorder. *Br J Pharmacol*, *177*(7), 1497-1513. https://doi.org/10.1111/bph.14913
Harun, N., Hassan, Z., Navaratnam, V., Mansor, S. M., & Shoaib, M. (2015). Discriminative stimulus properties of mitragynine (kratom) in rats. *Psychopharmacology (Berl)*, *232*(13), 2227-2238. https://doi.org/10.1007/s00213-015-3866-5
Hemby, S. E., McIntosh, S., Leon, F., Cutler, S. J., & McCurdy, C. R. (2019). Abuse liability and therapeutic potential of the Mitragyna speciosa (kratom) alkaloids mitragynine and 7-hydroxymitragynine. *Addict Biol*, *24*(5), 874-885. https://doi.org/10.1111/adb.12639
Hill, K., Boyer, E. W., Grundmann, O., & Smith, K. E. (2025). De facto opioids: Characterization of novel 7-hydroxymitragynine and mitragynine pseudoindoxyl product marketing. *Drug Alcohol Depend*, *272*, 112701. https://doi.org/10.1016/j.drugalcdep.2025.112701
Hossain, R., Sultana, A., Nuinoon, M., Noonong, K., Tangpong, J., Hossain, K. H., & Rahman, M. A. (2023). A Critical Review of the Neuropharmacological Effects of Kratom: An Insight from the Functional Array of Identified Natural Compounds. *Molecules*, *28*(21). https://doi.org/10.3390/molecules28217372
Huestis, M. A., Brett, M. A., Bothmer, J., & Atallah, R. (2024). Human Mitragynine and 7-Hydroxymitragynine Pharmacokinetics after Single and Multiple Daily Doses of Oral Encapsulated Dried Kratom Leaf Powder. *Molecules*, *29*(5). https://doi.org/10.3390/molecules29050984
Johanson, C. E., & Schuster, C. R. (1981). Animal models of drug self-administration. *Advances in Substance Abuse*, *2*, 219-297.
Kamble, S. H., Leon, F., King, T. I., Berthold, E. C., Lopera-Londono, C., Siva Rama Raju, K., Hampson, A. J., Sharma, A., Avery, B. A., McMahon, L. R., & McCurdy, C. R. (2020). Metabolism of a Kratom Alkaloid Metabolite in Human Plasma Increases Its Opioid Potency and Efficacy. *ACS Pharmacol Transl Sci*, *3*(6), 1063-1068. https://doi.org/10.1021/acsptsci.0c00075
Karunakaran, T., Vicknasingam, B., & Chawarski, M. C. (2024). Phytochemical analysis of water and ethanol liquid extracts prepared using freshly harvested leaves of Mitragyna speciosa (Korth.). *Nat Prod Res*, 1-8. https://doi.org/10.1080/14786419.2024.2362428
Kikura-Hanajiri, R., Kawamura, M., Maruyama, T., Kitajima, M., Takayama, H., & Goda, Y. (2009). Simultaneous analysis of mitragynine, 7-hydroxymitragynine, and other alkaloids in the psychotropic plant "kratom" (Mitragyna speciosa) by LC-ESI-MS. *Forensic Toxicology*, *27*(2), 67-74. https://doi.org/10.1007/s11419-009-0070-5
Kruegel, A. C., Gassaway, M. M., Kapoor, A., Varadi, A., Majumdar, S., Filizola, M., Javitch, J. A., & Sames, D. (2016). Synthetic and Receptor Signaling Explorations of the Mitragyna Alkaloids: Mitragynine as an Atypical Molecular Framework for Opioid Receptor Modulators. *J Am Chem Soc*, *138*(21), 6754-6764. https://doi.org/10.1021/jacs.6b00360
Leon, F., Habib, E., Adkins, J. E., Furr, E. B., McCurdy, C. R., & Cutler, S. J. (2009). Phytochemical characterization of the leaves of Mitragyna speciosa grown in U.S.A. *Nat Prod Commun*, *4*(7), 907-910. https://www.ncbi.nlm.nih.gov/pubmed/19731590

Lydecker, A. G., Sharma, A., McCurdy, C. R., Avery, B. A., Babu, K. M., & Boyer, E. W. (2016). Suspected Adulteration of Commercial Kratom Products with 7-Hydroxymitragynine. *J Med Toxicol*, *12*(4), 341-349. https://doi.org/10.1007/s13181-016-0588-y

Matsumoto, K., Horie, S., Ishikawa, H., Takayama, H., Aimi, N., Ponglux, D., & Watanabe, K. (2004). Antinociceptive effect of 7-hydroxymitragynine in mice: Discovery of an orally active opioid analgesic from the Thai medicinal herb Mitragyna speciosa. *Life Sci*, *74*(17), 2143-2155. https://doi.org/10.1016/j.lfs.2003.09.054

Matsumoto, K., Horie, S., Takayama, H., Ishikawa, H., Aimi, N., Ponglux, D., Murayama, T., & Watanabe, K. (2005). Antinociception, tolerance and withdrawal symptoms induced by 7-hydroxymitragynine, an alkaloid from the Thai medicinal herb Mitragyna speciosa. *Life Sci*, *78*(1), 2-7. https://doi.org/10.1016/j.lfs.2004.10.086

Matsumoto, K., Takayama, H., Narita, M., Nakamura, A., Suzuki, M., Suzuki, T., Murayama, T., Wongseripipatana, S., Misawa, K., Kitajima, M., Tashima, K., & Horie, S. (2008). MGM-9 [(E)-methyl 2-(3-ethyl-7a,12a-(epoxyethanoxy)-9-fluoro-1,2,3,4,6,7,12,12b-octahydro-8-methoxyindolo[2,3-a]quinolizin-2-yl)-3-methoxyacrylate], a derivative of the indole alkaloid mitragynine: a novel dual-acting mu- and kappa-opioid agonist with potent antinociceptive and weak rewarding effects in mice. *Neuropharmacology*, *55*(2), 154-165. https://doi.org/10.1016/j.neuropharm.2008.05.003

Maxwell, E. A., King, T. I., Kamble, S. H., Raju, K. S. R., Berthold, E. C., Leon, F., Hampson, A., McMahon, L. R., McCurdy, C. R., & Sharma, A. (2021). Oral Pharmacokinetics in Beagle Dogs of the Mitragynine Metabolite, 7-Hydroxymitragynine. *Eur J Drug Metab Pharmacokinet*, *46*(3), 459-463. https://doi.org/10.1007/s13318-021-00684-2

McCurdy, C. R., Sharma, A., Smith, K. E., Veltri, C. A., Weiss, S. T., White, C. M., & Grundmann, O. (2024). An update on the clinical pharmacology of kratom: uses, abuse potential, and future considerations. *Expert Rev Clin Pharmacol*, *17*(2), 131-142. https://doi.org/10.1080/17512433.2024.2305798

Mombelli, E. (2022). Animal Models of Drug Addiction. In S. Della Sala (Ed.), *Encyclopedia of Behavioral Neuroscience, 2nd edition (Second Edition)* (pp. 674-681). Elsevier. https://doi.org/https://doi.org/10.1016/B978-0-12-819641-0.00118-3

Mongar, P., Jaisi, A., Inkviya, T., Wungsintaweekul, J., & Wiwattanawongsa, K. (2024). Effects of Itraconazole on Pharmacokinetics of Mitragynine and 7-Hydroxymitragynine in Healthy Volunteers. *ACS Pharmacol Transl Sci*, *7*(3), 823-833. https://doi.org/10.1021/acsptsci.3c00335

NDEWS. (2024). National Drug Early Warning System Weekly Briefing. (195). https://ndews.org/newsletter/weekly-briefing-issue-195/

Obeng, S., Kamble, S. H., Reeves, M. E., Restrepo, L. F., Patel, A., Behnke, M., Chear, N. J., Ramanathan, S., Sharma, A., Leon, F., Hiranita, T., Avery, B. A., McMahon, L. R., & McCurdy, C. R. (2020). Investigation of the Adrenergic and Opioid Binding Affinities, Metabolic Stability, Plasma Protein Binding Properties, and Functional Effects of Selected Indole-Based Kratom Alkaloids. *J Med Chem*, *63*(1), 433-439. https://doi.org/10.1021/acs.jmedchem.9b01465

Obeng, S., Wilkerson, J. L., Leon, F., Reeves, M. E., Restrepo, L. F., Gamez-Jimenez, L. R., Patel, A., Pennington, A. E., Taylor, V. A., Ho, N. P., Braun, T., Fortner, J. D., Crowley, M. L., Williamson, M. R., Pallares, V. L. C., Mottinelli, M., Lopera-Londono, C., McCurdy, C. R., McMahon, L. R., & Hiranita, T. (2021). Pharmacological Comparison of Mitragynine and 7-Hydroxymitragynine: In Vitro Affinity and Efficacy for mu-Opioid Receptor and Opioid-Like Behavioral Effects in Rats. *J Pharmacol Exp Ther*, *376*(3), 410-427. https://doi.org/10.1124/jpet.120.000189

Ogozalek, S. (2023, December 9). The Tampa Bay Times tested 20 kratom products. Here's what we found. *Tampa Bay Times*. https://www.tampabay.com/investigations/2023/12/09/tampa-bay-times-tested-20-kratom-products-heres-what-we-found/

Panlilio, L. V., & Goldberg, S. R. (2007). Self-administration of drugs in animals and humans as a model and an investigative tool. *Addiction*, *102*(12), 1863-1870. https://doi.org/10.1111/j.1360-0443.2007.02011.x

Ponglux, D., Wongseripipatana, S., Takayama, H., Kikuchi, M., Kurihara, M., Kitajima, M., Aimi, N., & Sakai, S. (1994). A New Indole Alkaloid, 7 alpha-Hydroxy-7H-mitragynine, from Mitragyna speciosa in Thailand. *Planta Med*, *60*(6), 580-581. https://doi.org/10.1055/s-2006-959578

Prus, A. J., James, J. R., & Rosecrans, J. A. (2009). Conditioned Place Preference. In J. J. Buccafusco (Ed.), *Methods of Behavior Analysis in Neuroscience* (2nd ed.). https://www.ncbi.nlm.nih.gov/pubmed/21204336

Rogers, J. M., Weiss, S. T., Epstein, D. H., Grundmann, O., Hill, K., & Smith, K. E. (2024). Kratom addiction per DSM-5 SUD criteria, and kratom physical dependence: Insights from dosing amount versus frequency. *Drug Alcohol Depend*, *260*, 111329. https://doi.org/10.1016/j.drugalcdep.2024.111329

Sengnon, N., Vonghirundecha, P., Chaichan, W., Juengwatanatrakul, T., Onthong, J., Kitprasong, P., Sriwiriyajan, S., Chittrakarn, S., Limsuwanchote, S., & Wungsintaweekul, J. (2023). Seasonal and Geographic Variation in Alkaloid Content of Kratom (Mitragyna speciosa (Korth.) Havil.) from Thailand. *Plants (Basel)*, *12*(4). https://doi.org/10.3390/plants12040949

Sharma, A., Smith, K. E., Kuntz, M. A., Berthold, E. C., Elashkar, O. I., Guadagnoli, N., Kanumuri, S. R. R., Mukhopadhyay, S., Panlilio, L. V., Epstein, D. H., & McCurdy, C. R. (2025). Chemical Analysis and Alkaloid Intake for Kratom Products Available in the United States. *Drug Test Anal*. https://doi.org/10.1002/dta.3906

Singh, D., Narayanan, S., & Vicknasingam, B. (2016). Traditional and non-traditional uses of Mitragynine (Kratom): A survey of the literature. *Brain Res Bull*, *126*(Pt 1), 41-46. https://doi.org/10.1016/j.brainresbull.2016.05.004

Singh, D., Narayanan, S., Vicknasingam, B., Corazza, O., Santacroce, R., & Roman-Urrestarazu, A. (2017). Changing trends in the use of kratom (Mitragyna speciosa) in Southeast Asia. *Hum Psychopharmacol*, *32*(3). https://doi.org/10.1002/hup.2582

Smith, K. E., Boyer, E. W., Grundmann, O., McCurdy, C. R., & Sharma, A. (2024). The rise of novel, semi-synthetic 7-hydroxymitragnine products. *Addiction*. https://doi.org/10.1111/add.16728

Smith, K. E., Panlilio, L. V., Sharma, A., McCurdy, C. R., Feldman, J. D., Mukhopadhyay, S., Kanumuri, S. R. R., Kuntz, M. A., Hill, K., & Epstein, D. H. (2024). Time course of kratom effects via ecological momentary assessment, by product type, dose amount, and assayed alkaloid content. *Drug Alcohol Depend*, *264*, 112460. https://doi.org/10.1016/j.drugalcdep.2024.112460

Smith, K. E., Rogers, J. M., Dunn, K. E., Grundmann, O., McCurdy, C. R., Schriefer, D., & Epstein, D. H. (2022). Searching for a Signal: Self-Reported Kratom Dose-Effect Relationships Among a Sample of US Adults With Regular Kratom Use Histories. *Front Pharmacol*, *13*, 765917. https://doi.org/10.3389/fphar.2022.765917

Solinas, M., Panlilio, L. V., Justinova, Z., Yasar, S., & Goldberg, S. R. (2006). Using drug-discrimination techniques to study the abuse-related effects of psychoactive drugs in rats. *Nat Protoc*, *1*(3), 1194-1206. https://doi.org/10.1038/nprot.2006.167

Swedberg, M. D. (2016). Drug discrimination: A versatile tool for characterization of CNS safety pharmacology and potential for drug abuse. *J Pharmacol Toxicol Methods*, *81*, 295-305. https://doi.org/10.1016/j.vascn.2016.05.011

Takayama, H., Ishikawa, H., Kurihara, M., Kitajima, M., Aimi, N., Ponglux, D., Koyama, F., Matsumoto, K., Moriyama, T., Yamamoto, L. T., Watanabe, K., Murayama, T., & Horie, S. (2002). Studies on the synthesis and opioid agonistic activities of mitragynine-related indole alkaloids: discovery of opioid agonists structurally different from other opioid ligands. *J Med Chem*, *45*(9), 1949-1956. https://doi.org/10.1021/jm010576e

Tanna, R. S., Nguyen, J. T., Hadi, D. L., Manwill, P. K., Flores-Bocanegra, L., Layton, M. E., White, J. R., Cech, N. B., Oberlies, N. H., Rettie, A. E., Thummel, K. E., & Paine, M. F. (2022). Clinical Pharmacokinetic Assessment of Kratom (Mitragyna speciosa), a Botanical Product with Opioid-like Effects, in Healthy Adult Participants. *Pharmaceutics*, *14*(3). https://doi.org/10.3390/pharmaceutics14030620

Todd, D. A., Kellogg, J. J., Wallace, E. D., Khin, M., Flores-Bocanegra, L., Tanna, R. S., McIntosh, S., Raja, H. A., Graf, T. N., Hemby, S. E., Paine, M. F., Oberlies, N. H., & Cech, N. B. (2020). Chemical composition and biological effects of kratom (Mitragyna speciosa): In vitro studies with implications for efficacy and drug interactions. *Sci Rep*, *10*(1), 19158. https://doi.org/10.1038/s41598-020-76119-w

Varadi, A., Marrone, G. F., Palmer, T. C., Narayan, A., Szabo, M. R., Le Rouzic, V., Grinnell, S. G., Subrath, J. J., Warner, E., Kalra, S., Hunkele, A., Pagirsky, J., Eans, S. O., Medina, J. M., Xu, J., Pan, Y. X., Borics, A., Pasternak, G. W., McLaughlin, J. P., & Majumdar, S. (2016). Mitragynine/Corynantheidine Pseudoindoxyls As Opioid Analgesics with Mu Agonism and Delta Antagonism, Which Do Not Recruit beta-Arrestin-2. *J Med Chem*, *59*(18), 8381-8397. https://doi.org/10.1021/acs.jmedchem.6b00748

Walker, E. A. (2018). A Prospective Evaluation of Drug Discrimination in Pharmacology. *Curr Top Behav Neurosci*, *39*, 319-328. https://doi.org/10.1007/7854_2018_59

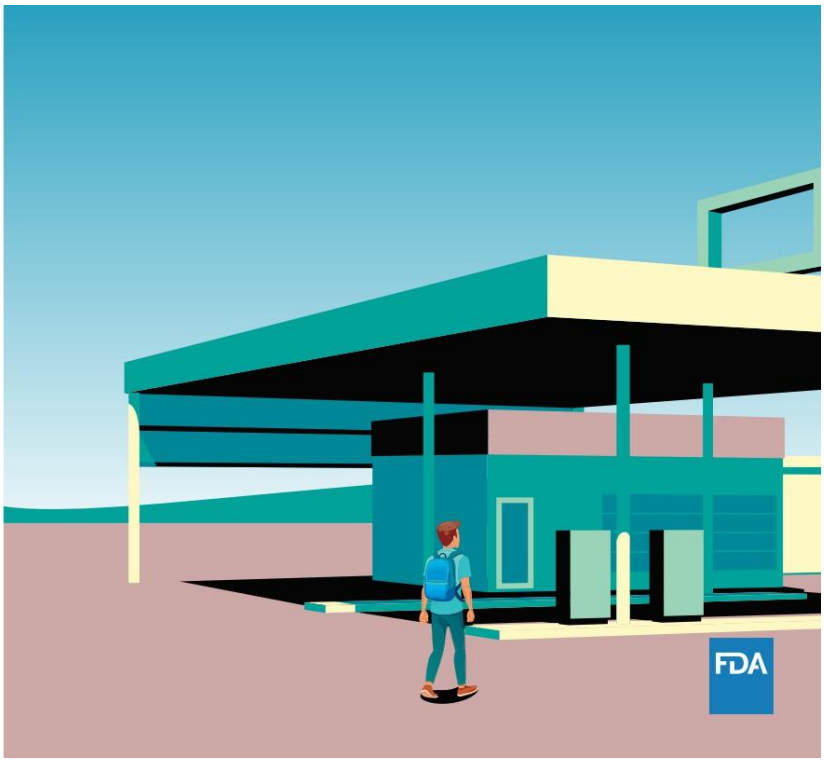
Young, R. (2009). Drug Discrimination. In J. J. Buccafusco (Ed.), *Methods of Behavior Analysis in Neuroscience* (2nd ed.). https://www.ncbi.nlm.nih.gov/pubmed/21204332

Zuarth Gonzalez, J. D., Ragsdale, A. K., Mukhopadhyay, S., McCurdy, C. R., McMahon, L. R., Obeng, S., & Wilkerson, J. L. (2025). Mitragynine and 7-Hydroxymitragynine: Bidirectional Effects on Breathing in Rats. *bioRxiv*. https://doi.org/10.1101/2025.05.16.654392

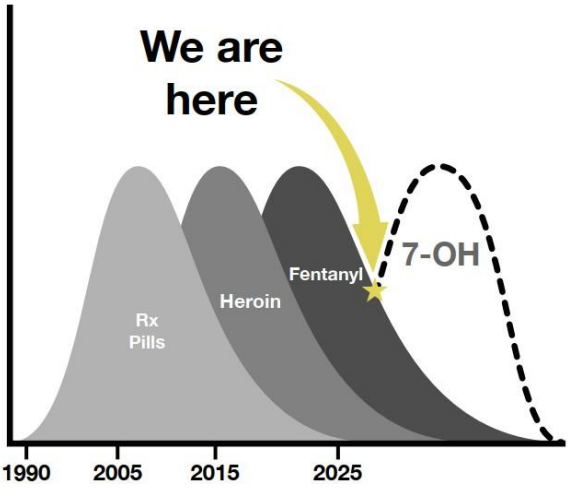
11.4 Appendix 4: FDA Slide Set: Preventing The Next Wave of the Opioid Epidemic: What You Need to Know About 7-OH

Preventing The Next Wave of the Opioid Epidemic:

What You Need to Know About 7-OH

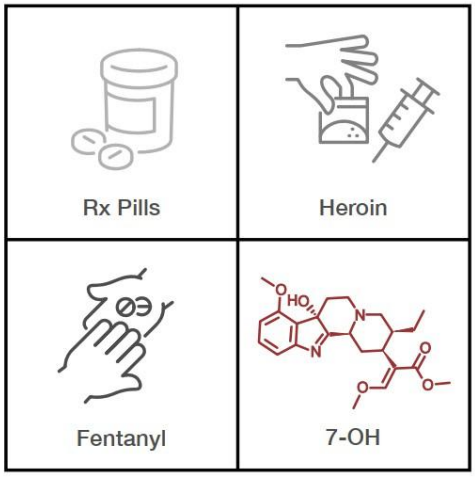


The Opioid Epidemic is Evolving with 7-OH. We Can and Must Act Now to Prevent a New Wave.



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

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



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

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

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

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

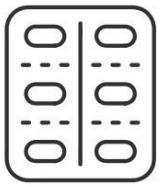
What began as doctor-prescribed painkillers migrated to back-alley dealers when prescriptions dried up. Opioids have disturbingly gone mainstream with 7-OH—no prescription needed, no dealer required. This dangerous opioid is sitting on store shelves, making gas stations and convenience stores risky places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

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

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

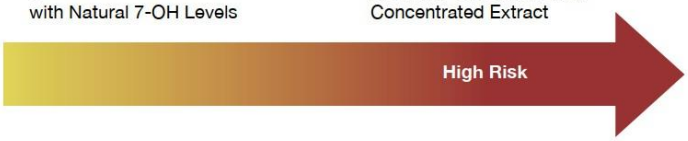
While Some 7-OH Products are Marketed as Natural Kratom, They are Not the Same. 7-OH Presents Significant Risks.

Crushed/Powdered Leaves with Natural 7-OH Levels



Kratom 7-OH Significantly Concentrated Extract

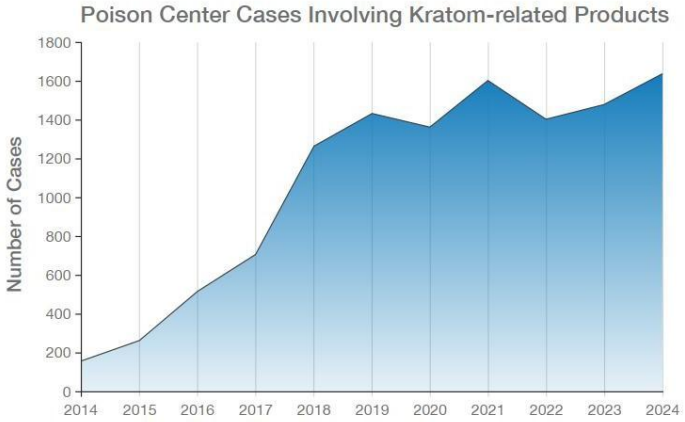
7-OH is 13x more potent than morphine.



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

Poison Control is Sounding the Alarm on 7-OH.

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



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

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

**Data reflect partial year.*

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

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

FDA APPROVED THERAPIES

Protect You and Your Family

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

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

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

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

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

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

FDA U.S. FOOD & DRUG ADMINISTRATION

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

Measures to Safeguard American Public from Dangerous Opioid 7-OH

2.1 Participants:

HHS Secretary Robert F. Kennedy, Jr.

HHS Deputy Secretary Jim O'Neill

FDA Commissioner Dr. Marty Makary

Melody Woolf (chronic pain survivor).

Hubert H. Humphrey Building Auditorium

200 Independence Ave SW Washington, D.C.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Tom, if you could come up here?

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

Thank you, Tom.

MR. PREVOZNIK: Thanks, Marty.

DR. MAKARY: Thank you.

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

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

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

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

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

Thank you, Melody.

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

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

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

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

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

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

things just turned around for my family.

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

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

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

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

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

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

MR. MAKARY: Thank you, Melody.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

generation that was hooked on that.

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

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

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

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

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

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

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

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

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

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

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

STEPHANIE: Thank you, Secretary Kennedy.

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

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

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

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

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

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

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

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

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

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

to start that process.

Thank you, Lizzy.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

STEPHANIE: Okay, last question right here.

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

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

STEPHANIE: Thank you so much.

(End of press conference)

CERTIFICATE

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

/s/ Vivian Saxe 9/2/25

VIVIAN SAXE, CERT**D 631 DATE

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

July 29, 2025

Dear Colleague,

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

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

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

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

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

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

Sincerely,

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

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20903
www.fda.gov

ZEIGER, TIGGES & LITTLE LLP

TELEPHONE: (614) 365-9900
FACSIMILE: (614) 365-7900

ATTORNEYS AT LAW
8000 WALTON PARKWAY
SUITE 260
NEW ALBANY, OHIO 43054

WRITER'S DIRECT NUMBER:
(614) 365-4113
LITTLE@LITOHIO.COM

January 28, 2026

Re: Comments of Botanic Tonics, LLC in
Ohio Board of Pharmacy Scheduling Proceedings
Proposed Rule 4729.9-1-01.1 (Mitragynine-Related Compounds);
Proposed Rule 4729.9-1-01.2 (Mitragynine)

Dear Board of Pharmacy:

I represent Botanic Tonics, LLC ("BT"), manufacturer of a whole kratom leaf (whole kratom leaf infused in water) dietary supplement, *feel free* CLASSIC® ("Feel Free"). BT submits this comment for inclusion in both above-referenced proceedings. By it, BT endorses both the argument presented and the conclusions reached in the comments filed in each respective proceeding by Global Kratom Coalition (GKC). BT therefore urges the Board to adopt GKC's recommendations in its comments.

As explained and corroborated in the GKC comments, the applicable science and law favors the scheduling of concentrated kratom alkaloid isolates ("synthetics"), but not the scheduling of natural kratom leaf ("kratom leaf"). The former (the synthetics) are indistinguishable from opioids in their addictive potential and risk of injury. The latter (kratom leaf) have been proven in clinical trials not to present any significant or unreasonable risk of illness or injury, including the risk of severe addiction.

BT has a direct and substantial interest in each of these proceedings. BT currently sells Feel Free in Ohio through distributors. Its annual revenues from the sale of Feel Free exceed $5 million. If the Proposed Rules are adopted in a way that would cause kratom leaf to be scheduled along with the synthetics, the effect would be to cause BT to suffer a complete loss of revenues, as it would no longer be able to sell Feel Free in Ohio.

Sincerely,

Marion H. Little

1075947