Public Comment Workshop Agenda Item #15B

From: John Murphy
To: Board Coordination
Subject: Kratom Ban Hearing Public Comment
Date: Wednesday, April 15, 2026 12:53:12 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Hi I use natural Kratom on a daily basis For pain regulation, it helped me get off opiates. I understand the necessary use for it. The natural stuff is completely fine. I have never had any problems, but the synthetic version is where the problem lies that should be banned fully. I know plenty of people that are taking Kratom and none have ever had any problems synthetic is where the problem lies 100% if this gets banned, do you expect me to go back to Opia pain medication because I don't want to. I was worse off on opiate pain medication than I am on natural Kratom please take an account of the people that use this product safely and responsibly. It's just like Marijuana and you have people that abuse marijuana marijuana to the Core Alcohol is worse off than Kratom
Thank you for the Time reading my email sincerely John Murphy

From: kelley forgottennotgone.org
To: Board Coordination
Subject: Kratom testimony- Air Force Veteran Kelley Guidry
Date: Monday, April 13, 2026 4:57:20 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

My name is Kelley Guidry and I've lived in Las Vegas since 1999, getting stationed at Nellis Air Force Base from Aviano Italy. I was a Security Forces member, guarding nuclear weapons, planes, personnel and more. My job was extremely physical and I suffered physical and mentally performing my job but I did it honorably.

For the past eight years, I have responsibly used Kratom—specifically the natural leaf, without additives or enhancements—to help manage the severe pain associated with fibroids. I first learned about Kratom through a health food store, not a gas station or unregulated source, and from the beginning, my approach has been intentional, informed, and disciplined.

As a Veteran and the founder of a nonprofit dedicated to stomping out Veteran suicide for the past 13 years, I have seen firsthand the toll that chronic pain and untreated trauma take on our community. The VA often limits our options to prescription pain medications or psychiatric drugs, many of which come with heavy side effects, dependency risks, and diminished quality of life. For me, Kratom has provided a natural alternative—one that has allowed me to manage my pain without those debilitating side effects.

Because of Kratom, I've been able to continue serving my fellow Veterans—my brothers and sisters in arms—with clarity, consistency, and purpose. It has allowed me to stay engaged in my mission, lead effectively, and support others who are struggling. Without it, I truly believe my ability to show up for my community would be significantly compromised.

In 2024, I was honored to be named the first-ever Woman Veteran of the Year in Nevada by the State Department of Veterans Services. That recognition reflects years of dedication, resilience, and service—work that Kratom has quietly supported by helping me maintain my physical and mental well-being.

The idea of classifying Kratom as a Schedule I drug is deeply concerning. Such a move would not only strip away access to a tool that has helped countless individuals like myself, but it would also criminalize honorable Veterans who are simply trying to manage their pain and continue contributing to society. At a time when we are facing new conflicts and will soon welcome home a new generation of Veterans with complex physical and psychological challenges, removing access to safe alternatives is not just misguided—it's harmful.

We deserve the right to safe, regulated access to Kratom. Organizations like the American Kratom Association are doing critical work to advocate for consumers, promote education, and push for responsible regulations that ensure product safety and transparency. Many reputable companies aligned with these standards are committed to protecting users and maintaining the integrity of Kratom as a natural product.

As consumers, we welcome reasonable regulation. We want to know that what we are using is pure, safe, and properly sourced. What we do not want is prohibition that forces people into the shadows or back onto medications that may do more harm than good.

For me, Kratom has never been about escape—it's been about empowerment. It has allowed me to remain in service, to lead, and to continue fighting for the lives of others. Taking that away would not just impact me—it would ripple through the Veteran community I serve every single day.

Best Regards,
Kelley Guidry, Air Force Veteran, Founder

From: Ryan A. Heck, Ph.D.
To: Board Coordination
Subject: Public Comment – Opposition to Scheduling Mitragynine (NAC 453)
Date: Monday, April 13, 2026 5:35:19 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Hello,

I am submitting this comment in my personal capacity as a Nevada resident and wanted to provide input regarding the proposal to add mitragynine and related compounds to Schedule I.

I use kratom to manage the medical condition of restless leg syndrome. It has been effective for me in a way that other options have not been. I have tried Requip (ropinirole), which was ineffective for my symptoms and caused unpleasant side effects, including nausea.

Losing access to kratom would have a real impact on my ability to manage my condition and maintain normal sleep.

I understand the need for safety and appropriate regulation, but I would encourage the Board to consider continuing Nevada's current approach of regulating kratom products rather than moving to Schedule I classification.

I would be happy to provide additional information about my experience if that would be helpful.

Thank you for your consideration.

Ryan

Ryan A. Heck, Ph.D. | Senior Counsel
P. 503.595.5300
A. 121 SW Salmon St., Suite 1600, Portland, OR 97204 USA

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From: aadamyan56.optioncare@everyactioncustom.com on behalf of Armen Adamyan
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Monday, April 13, 2026 7:55:12 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

My Own Personal Experience with Kratom:
Never feel drowsy, altered , tired and very thankful as my excruciating back pain is managed very well and to the point that i dont even need to take any OTC painkillers or seek for heavy duty opiates which I am so against due to potential addiction .

Sincerely,
Armen Adamyan

From: allan barriga
To: Board Coordination
Subject: Keep Natural Kratom Accessible For Those Who Need It
Date: Wednesday, April 15, 2026 11:51:29 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Approximately two years ago, I sustained a back injury while working in construction. During my recovery, I attended numerous physical therapy sessions and traveled significant distances for treatment. Despite these efforts, I continue to live with chronic pain—at times so severe that changing positions offers no relief.

Kratom has provided substantial relief, allowing me to manage my condition without resorting to opioids or invasive surgical procedures, neither of which would address the underlying issue and could potentially worsen my situation.

Banning kratom would remove a critical source of relief for me and for tens of thousands of others in this state who rely on it to maintain a functional quality of life. I support reasonable regulation, particularly of synthetic 7-OH products, which should not be widely available in retail settings. However, natural kratom should remain accessible for responsible individuals who depend on it to manage chronic pain and lead productive lives.

From: [redacted]@gmail.com
To: Board Coordination
Subject: Kratom scheduling
Date: Monday, April 13, 2026 5:58:36 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

I've been using Kratom for nearly 10 years. It was what got me off of opiates and lifted my depression. It has been a complete blessing and no longer struggle with pain or depression. I will be attending the meeting In Reno Thursday, and do all I can to oppose banning Kratom, which is a lifesaver for me. Overdose is so rare that it's almost unheard of. Unlike opiates which kills people every day this is one of the only alternatives people have because opiates are so hard to get now. I am business owner. I have a high net worth and I can function perfectly as I do every day. I'll surely fight this and vote against any politician that tries to ban this

Austin Brooks

Sent from my iPhone

From: sacia fawcett
To: Board Coordination
Subject: Do not make Kratom schedule 1
Date: Thursday, April 16, 2026 10:02:51 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Making Kratom schedule 1 would be a huge mistake and would prevent it from being studied scientifically, it very clearly has medicinal value and should remain available. It's been considered safe enough that in Kansas they have begun human trials of a drug made from Kratom. This is not about public safety it's about getting rid of competition for the new drug that's being developed. It's corrupt and cruel to responsible consumers.

I am very concerned to hear there is a Kratom ban being considered and I would like to voice my opposal. I just wanted to say this plant saved my life. I am disabled and for a long time could not even leave my house for Dr. appointments or dental care due to severe agoraphobia. I spent years trapped inside of one small room. One of my prescription medications causes severe dry mouth which in turn causes damage and rapid tooth decay, not being able to get to the dentist because of uncontrolled panic attacks was horrific and I almost lost my teeth which in turn made me severely and dangerously depressed. Since I found Kratom I have been able to go outside again, I was able to get to the dentist, they were able to save most of my teeth after lots of work and many trips which I never could have tolerated without Kratom. It helps with my anxiety and it helped with the pain of having teeth pulled, being allergic to nsaids my options for pain control are either Tylenol or full blown prescription opioids which I am afraid of and was able to avoid by using Kratom. Where opioids cause respiratory depression Kratom does not. It has also helped me not become dependent on my prescribed benzodiazapines, those can kill you if you become dependent and suddenly stop taking them, Kratom does not come with that risk. No medication has worked as well and they come with scary side effects, Kratom has been gentle and I have found it to be completely safe. It has a built in ceiling effect that prevents abuse and I have never had to increase my dose. I am completely functional while using it, it doesn't impair me the way prescription anxiety medication does. I have a chance at life again, a chance to participate and contribute, I was able to visit my elderly father which is indescribably priceless to me, thinking the plant that saved me could be banned breaks my heart and scares me. This is reefer madness all over again, there is plenty of scientific evidence backing up the safety of Kratom in its natural form, it's been used safely in southeast Asia where it originates for thousands of years without issue. Kratom is not what people pushing for a ban say it is. It's the ground up leaves of a tree related to coffee, it's completely separate from that synthetic 7oh and the high potency extracts, I think people are confusing the two. The only other people I know that use it are old women who use it for chronic pain. A ban would literally just pry the tea from the arthritic hands of the elderly and make criminals of citizens who are just trying to survive, who want to be able to contribute to society. Please have mercy and don't take away the only thing that helps so many people from all walks of life. Please listen to the people who are telling you this plant saved them.

Thank you,
Ashley Davidson

From: theenduser8@everyactioncustom.com on behalf of Angela Inda
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Friday, April 10, 2026 1:17:42 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

My Own Personal Experience with Kratom: it has benefited my health and well-being greatly over the last 13 years.

Sincerely,
Angela Inda

From: Allie
To: Board Coordination
Subject: Public Comment on Proposed Scheduling of Kratom Compounds (7OH & Pseudo)
Date: Wednesday, April 15, 2026 8:27:13 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Members of the Nevada Board of Pharmacy,

I am writing to respectfully urge you to reconsider the proposal to classify 7-hydroxymitragynine (7-OH) and mitragynine pseudoindoxyl as Schedule I substances.

This issue is deeply personal to me. After years of struggling with chronic pain, severe anxiety, and major treatment-resistant depression, I found meaningful relief through kratom products, including those containing 7-OH. Before this, I was unable to function in daily life and often experienced frequent suicidal thoughts. Access to these products has given me a level of stability and normalcy that I had not experienced in years.

I also ask that the Board carefully consider the science behind these compounds. 7-OH and mitragynine pseudoindoxyl are not only naturally associated with kratom products, but they are also formed in the body after consumption. Scheduling them could therefore have broader implications for kratom access as a whole, beyond what may be intended.

Policies should be grounded in science, evidence, and consumer safety—not confusion or overly broad classification. Many responsible consumers rely on kratom as part of their daily lives, and sweeping restrictions could have unintended consequences.

Rather than prohibition, I strongly encourage the Board to consider responsible regulation and consumer protections. This approach would better support public health while ensuring safe access for those who depend on these products.

Thank you for your time and consideration.

Sincerely,
Allie Larson
(7OH Advocate)

From: Anthony Margotta Jr
To: Board Coordination
Subject: Kratom and 7-OH.
Date: Wednesday, April 15, 2026 2:12:18 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

I am emailing you to let you know that I am a 64 year old active man and I have been using kratom and 7-OH for 3 years to manage my recovery from opioid addiction. Kratom and 7-OH products have not only saved my life but they also gives me a good quality of life. Please follow the science and see how affective these products are for people in recovery. In closing I want you to know that I lost my older brother from a heroine overdose and I believe if he had these products to manage his recovery he would still be alive today. These products have the potential to save lives. Please investigate the truth above these products and you will see that the information floating around are false and misleading.

Thank you.
Anthony Margotta jr.

From: anye843@everyactioncustom.com on behalf of Andrew Nye
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Friday, April 10, 2026 1:25:25 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

My Own Personal Experience with Kratom:

I suffer from crohns disease. Natural kratom helps treat my symptoms and gives me back some autonomy over my life. Please do not schedule natural leaf. It is not 7oh.

Sincerely,
Andrew Nye

From: acprisco1@everyactioncustom.com on behalf of Aaron Prisco
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Thursday, April 16, 2026 12:00:56 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

My Own Personal Experience with Kratom. https://www.fda.gov/news-events/press-announcements/fda-takes-steps-restrict-7-oh-opioid-products-threatening-american-consumers

The second paragraph states the FDA is not concerned with pure leaf products this is from it is own site. During the meeting people wanting to ban Kratom continually lied about the FDAs stance on pure leaf kratom. It is ilegall under 18 U.S.C 1001 Making false statements to government officials, even if not under oath, can lead to charges of obstruction of justice or criminal fraud. I fully support banning 7 OH Synthetic products but not the pure leaves. Officials said there wasn't enough people representing support yet the meeting was only announced April 13 not giving anyone enough time to prepare and most supporters didn't have enough time to be notified. Furthermore loads of supporters provided physical evidence in research, articles, and solid evidence...the ones against kratom provided sad stories with no proof what so ever. Because of the false FDA information under 18 U.S.C 1001 was ilegall this meeting should legally have to be redone. I am a veteran and I have been taking kratom pure leaf for 3 to 4 years. I am not allowed to use marijuana in my industry and I respect the law. If you make kratom pure leaf ilegall you are forcing people to go to heavy drugs or harmful pharmaceutical drugs with dangerous side effects. Please reconsider this vote as it was taken after many testimonials violates laws and where made ilegally stating false information.

Sincerely,
Aaron Prisco

From: Anthony Rosa
To: Board Coordination
Subject: Agenda Item 15 - Public Comment
Date: Monday, April 13, 2026 12:11:16 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

My name is Anthony Rosa. I'm a 29-year-old California resident and six-year kratom user, and I'm writing because I'm planning to move to Reno. Nevada is the only place I've found that actually fits my needs — affordable, close to family, and away from California's fires and dysfunction — and this vote will directly determine whether that future is possible for me.

I use natural kratom leaf powder (containing mild concentrations of mitragynine) every day to manage anxiety, depression, and the relentless pressure of daily life. It is the only thing that keeps me stable, functional, and sober. Without it, I would likely return to alcoholism; something kratom helped me escape. It helped me rebuild my motivation and become a small business owner.

I am not here to defend 7-hydroxy derivatives. I've never used them and I fully support restricting them. Synthetic 7-OH can contain up to a thousand times the alkaloid concentration of natural kratom leaf. They are not the same product. Lumping them together is a scientific and moral mistake. One that even the federal Department of Health and Human Services flagged, urging California to draw that exact distinction. Texas already has, choosing a 7-OH limit over a blanket ban.

Nevada has operated under the KCPA for years. It works. The smokeshop industry is thriving. Real people are stable. Please don't undo that.

If this ban passes, I lose more than a plant. I lose the only future I've been able to picture for myself.

Please vote no.

— Anthony Rosa

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Anthony Rosa
Sonoma State University Alumni
BS in Business Administration - Management

Cell: (707) 280-4130
Work Email: rosa.anthony33@gmail.com
School Email: rosaa@sonoma.edu

From: Anthony Rosa
To: Board Coordination
Subject: Agenda Item 15 - Public Comment
Date: Monday, April 13, 2026 12:11:16 AM

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Nevada has operated under the KCPA for years. It works. The smokeshop industry is thriving. Real people are stable. Please don't undo that.

If this ban passes, I lose more than a plant. I lose the only future I've been able to picture for myself.

Please vote no.

— Anthony Rosa

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Anthony Rosa
Sonoma State University Alumni
BS in Business Administration - Management

Cell: [redacted]
Work Email: [redacted]@gmail.com
School Email: [redacted]@sonoma.edu

From: Dru Clay
To: Board Coordination
Subject: Regarding Item 15B Kratom
Date: Thursday, April 16, 2026 12:13:44 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

My name is Andrew Clay Sarrels, most commonly known as Dru. I am 37 years old. I am originally from Modesto, CA but have resided in Reno, NV since 2014.
I am writing to you today to urge you to reconsider your decision to ban/schedule the Kratom plant.
I am a 14 year Kratom advocate who has not only safely and effectively utilized Kratom in my life, but has witnessed Kratom positively impact the lives of countless individuals over the course of those 14 years. I initially found Kratom in 2012 while in search for a healthier alternative to addictive prescription pain medication. I was born with scoliosis, in my younger days my Cobb Angle was in the 30s, as I've grown older I've also grown smarter with things like stretching, breathing and exercise to help alleviate it, but in my younger days I would simply push through the pain. I've also been an athlete and martial artist my entire life, I was a multi sport athlete and martial arts competitor from age 4 to age 19. I accumulated an array of injuries in my life from being an athlete such as broken bones, arthritis, tendinitis, sprains, bumps and bruises, and have suffered several non-athletic related injuries from instances such as car accidents, one in particular my senior of high school that almost took my life. So I am no stranger to chronic pain. I was first introduced to pharmaceutical pain medication at 17 years old because of said car accident, and after high school I became heavily dependent on prescription pain medication. In the 6 years following, I dealt with things such as my parents divorce, dropping out of junior college and breaking up with my high school girlfriend, which left me with no direction in life and led me to sink further and further into dependency as it took a toll on my mental and physical health. Aside from my own story, the early 2000's was the height of the opioid epidemic and I watched it take over the lives of people around me including friends, family and loved ones. Being a natural athlete who always stressed the importance of healthy living, proper diet and fitness, I made the decision to leave the pills behind and get my life back. I began my search for healthier alternatives in 2012, that search led me to discovering Kratom for myself. Kratom helped me get my life back. Since 2012, I've not only completely stopped using pharmaceutical pain medication, but I've also quit smoking cigarettes after 13 years as a heavy smoker, as well completely stopping drinking and illicit drugs of any kind, all with the help of Kratom. I don't know about you guys, but I don't know of any Schedule 1 drugs that actually lead people to stop doing all other drugs. Over the last 14 years and counting as a Kratom and plant medicine advocate, Kratom has not only changed my life for the better, but I've witnessed first hand how Kratom has changed the life of countless others for the better, including athletes, friends, family and loved ones. I initially began my advocacy on the sports side of things, as being a lifelong athlete gave me insight to the rampant substance abuse issues involved in sports, but over time I've watched Kratom benefit all walks of life, from athletes to drug addicts to veterans to medical professionals to senior citizens and even just the average person walking down the street. As I stand before you today after 14 years of utilizing Kratom, at 37 years old I feel healthier and more capable than I did at 17 years old, I get regular checkups and blood work which have always come back perfectly normal. That's all thanks in large part to Kratom. Kratom has had zero negative effects on my health and my life, only positive.

There is immense amounts of evidence to support that Kratom is a much safer and healthier alternative to several other substances when utilized properly. I work to help spread awareness and information backed by studies and science so that other individuals can be given the same opportunity to change their lives the way I have through my discovery of Kratom.
Scheduling/Banning Kratom would not only make criminals of the many people who rely on Kratom for a better quality of life, but it would drive all of the people who have used it to help things such as chronic pain, anxiety, PTSD and sleeplessness naturally to resort to more harmful and unnatural substances, which would inevitably drive the crime and overdose rate up even further. Overdose rates over the last few decades have been as high as ever and only continuing to rise due to things such as fentanyl and illicit drugs. Scheduling/Banning Kratom would only be adding to an already overwhelming problem.
For anyone that is unfamiliar with Kratom beyond the propagated horror stories we see shown on social media and news outlets, Kratom is a tropical evergreen plant from the same plant family as the coffee plant. I'm sure that I'm not the only person that enjoyed a couple cups of coffee this morning, but it would be ridiculous to consider myself a drug addict and criminal because of those cups of coffee. That's essentially what banning or scheduling Kratom would do.
The vast majority of issues regarding Kratom stems from not the Kratom plant itself, but from extract versions of the alkaloids within the plant called Mitragynine and 7-hydroxymitragynine, more commonly known as 7-OH. These are what the poorly labeled products we see in gas stations and smoke shops consist of, and these are what the irresponsible people of the world are abusing. Not the Kratom plant itself, but the highly potent extracts. With nothing but utmost respect and condolences to anyone that has lost a loved one to a "Kratom related death," the vast majority of "Kratom related deaths" upon further review are not overdose deaths due to Kratom, but overdose deaths due to deadly concoctions of other substances while Kratom was present. 17 deaths per year in Nevada. 6 cases in 10 years involving Mitragynine alone. If an individual overdoses from mixing opioids, antidepressants, alcohol and illicit drugs but also has Kratom in their system, it is deemed a "Kratom related death," similar to how if someone ingests marijuana and then passes away in a car accident, it is deemed a "marijuana related death." The Kratom plant itself consists of around 40 different alkaloids that we know of, and all of these alkaloids combined make up anywhere from 0.5-1.5% of plant material. The most potent forms of the Kratom plant contains up to 66% of Mitragynine in this alkaloids, meaning that even the most potent forms of the Kratom plant contain 0.66% of the alkaloids in these extracts. Less than 1% of the plant is what is being deemed as "dangerous."
According to an article by kratomscience.com in 2020, a study in 2018 found the LD50 for Mitragynine in mice to be 547.7mg/kg of bodyweight, which was consistent with several other studies. (In 1972, a study administered 900mg/kg to mice with zero toxic effects.) According to the FDA draft guidelines, an equivalent dose for a 60kg human would be 44.36 mg/kg. 60kg being about 132lbs. Idk about you all but at 6ft tall and 37 years old, I haven't been 132lbs in quite some time. In order to reach 44.36mg/kg of bodyweight, a 132lb human would need to ingest 2,662 mg of Mitragynine.
Seeing as how the kratom plant contains less than 1% of the Mitragynine alkaloid, that would mean that a 132lb human would need to consume between 403.3 - 895.3 grams, or just under a kilogram of kratom leaf to reach the same LD50, which is physically impossible.
I share all this with you to show that even though the extract versions of this plant have raised concerns in our communities, it is not the plant itself that should be under scrutiny. People have utilized the kratom plant safely and effectively for centuries. Even though there are companies out there that exhibit things such as poor labeling and misinformation regarding their products, there are countless credible and reputable Kratom companies that not only

inform and direct customers on proper use and utilization, but utilize a mandatory third party lab test for all their products to ensure their purity, safety and efficacy. Avoiding negative experiences with Kratom is insanely easy, all it takes is a little bit of research, discipline, accountability and responsibility.

Banning/Scheduling the Kratom plant because there are select groups of people abusing the extracts is like banning/scheduling coffee because there are select groups of people abusing caffeine pills.

There are countless studies over the years that have proven the safety and efficacy of the Kratom plant, and there have been countless ban attempts over the years that were thrown out due to overwhelming evidence of false and misinterpreted information regarding the "dangers" of Kratom.

In fact, the entire "Kratom danger" narrative was founded by a man named Scott Gottlieb, who you all may know as the former FDA Commissioner. Via painnewsnetwork.org, Gottlieb had ties a company called Smith, Kline & French, which held patents on the alkaloids in Kratom that were issued in the 1960s. Later, the patents expired and courts ruled that one cannot patent nature, so attempts to renew the patents on the Kratom alkaloids were denied. After this is when Scott Gottleib began is "Kratom is dangerous" campaign. Since then, Gottleib has served as an advisor for several pharmaceutical companies prior to taking a position as the commissioner of the FDA in 2017. During his tenure as FDA commissioner, he repeatedly attacked Kratom and attempted to push bans across the country, which were all shot down, citing that Mr. Gottleib was unable to prove Kratom is actually dangerous. Gottleib repeatedly claimed that Kratom was fueling the opioid epidemic, which in reality was fueled by the very pharmaceutical companies that he worked with. Scott Gottleib then resigned as FDA Commissioner in 2019, does anyone know where he went after that? Gottleib left his position as FDA Commissioner on April 5, 2019, stating that he wanted to spend more time with his family, but on June 27, 2019, he would take a position on the board of directors at Pfizer. Apparently two months of spending time with his family was enough, and I don't think I need elaborate any further on what happened with Pfizer after 2019.

I share all of this with you just to give you insight as to the kind of people that are behind the "Kratom is dangerous" propaganda and their motives. We all know that those who will suffer the most from a legal, natural, effective pain relief plant is the pockets of pharmaceutical companies, and those who would suffer the most from banning said plant would be those caught in the opioid epidemic cycle.

In closing, there are plenty of studies and first hand testimonies that speak to the safety and efficacy of Kratom and directly disprove the false information regarding the "dangers of Kratom." I implore you to look into the works of people like Dr. Christopher McCurdy and Dr. Michelle Ross, and to take into the account the testimonies from people with years of experience with Kratom such as myself, Misty Brown, Bud Smith, Melody Woolf, Megan and Sean Zamorano, Madalyn Sklar, Angel Garza, Dijon Evans, and the millions of people in our country and across the world that have ultized Kratom responsibility and seen nothing but positive impacts from doing so.

I highly recommend that you consider a proper regulation of this plant as opposed to prohibition. I know that it's hard to ignore the propaganda that is spread by people who have never used Kratom and are uneducated about it, but please consider the account of someone with more than a decade's worth of experience in your decision-making process. Thank you for your time.

From: 9shallrise@everyactioncustom.com on behalf of Adam Stewart
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Friday, April 10, 2026 12:08:41 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

My Own Personal Experience with Kratom:

Without Kratom I wouldn't be alive. I have a serious and diagnosed form of general anxiety disorder, so bad it's landed me in the hospital countless times. I've been through some of the worst episodes you could ever imagine. Through the really hard times, like divorce, losing my grandpa etc, the anxiety was too much to bear. Suicide was going to be my solution. It was the only solution- pharmaceuticals make me feel WORSE and they don't work. There's chemicals in them and who knows what lasting permanent damage they will do to a person. In fact, it is my belief that pharmaceuticals may have actually caused the problems I have. One is confirmed, which was Accutane. I took it as a teenager. FDA approved but it caused many people to commit suicide. It could very well be the cause of my mental anguish, the only difference is I didn't go through with it. NATURAL MEDICINE IS GOOD MEDICINE. One day while I was at the very end of my rope, by some giant miracle, I was recommended to try Kratom. From the first try, it immediately unlocked the problem in my brain that I've never been able to cure. All of a sudden I could live a normal life, and life has been absolutely beautiful for me ever since. I can finally be a normal person! I've been taking it for over seven years, it hasn't caused any side effects whatsoever, and I'm able to live without suffering. Kratom is a miracle cure for so many people, and so many ailments, and it's 100% natural from Mother Earth. I believe it has been placed on our planet by our creator(s), specifically for our use. If Kratom goes away, I will no doubt commit suicide. I won't be able to cope. I'll be right back to the moment where it was recommended to me, where I was suffering immensely and ready to end my life. I beg of you, please stop what you're doing. Please do what is right. If you don't have mental problems then I get that you won't understand. We are all different, and we all have different needs. Please stop the ban.

Sincerely,
Adam Stewart

From: Auden Stille
To: Board Coordination
Subject: Kratom Ban Hearing Public Comment
Date: Wednesday, April 15, 2026 12:10:21 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Hello,

My name is Auden Stille, and I oppose banning natural kratom products in Nevada.

I have served as a sworn peace officer for the past seven years, and I have never once encountered or even heard of criminal behavior or medical events in connection with natural kratom products.

Unnecessarily criminalizing natural kratom products will only serve to create a new black market of unregulated products, create additional strain on law enforcement and court resources, and inflict suffering on individuals who use these products to effectively treat a myriad of health issues without the need for opioids or other pharmaceuticals.

The only groups who would benefit from a ban on natural kratom products are pharmaceutical corporations and actual dope dealers.

Please do the right thing.

From: Amy Wachtel
To: Board Coordination
Subject: Kratom/MITRAGYNA SPECIOSA
Date: Thursday, April 16, 2026 6:57:32 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

To Whom It May Concern: I am writing regarding the effort today to debate the possibility of adding Kratom to the list of Schedule 1 drugs, thus making it illegal to purchase on the free market and to use for the ordinary citizens of Nevada. I do not see that this is necessary. I understand that there have been incidents of bad reactions and deaths attributed to Kratom use, however from what I have read in the media is this is often due to extreme abuse of the product and often found to be taken with other drugs. There are many things drug abusers will over-do and get addicted to, among them: alcohol, gambling, marijuana and prostitution that are all legal in Nevada. This has more to do with the individual user than the product itself. Why single out Kratom?.
Kratom is sold in different forms. I realize that capsules can easily be abused, there is no way to know what is in them or what the potency is, and can be sold by unscrupulous vendors. I am advocating for leaving the Kratom tea leaves sold by reputable vendors out of the debate. There is no logical reason to include Kratom tea leaves in the same category as heroin. This is vast overreach. Thank you, Amy Wachtel

From: Annie
To: Board Coordination
Subject: Kratom Ban Hearing Public Comment
Date: Wednesday, April 15, 2026 2:22:53 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

I have been using the pure Kratom leaf powder for over 10 years, occasionally as needed, for pain and depression. I have many friends who also use Kratom in the pure powder leaf form. None of us are addicted and all of us have been helped greatly. We use small amounts. We should not be denied this natural remedy because irresponsible people use it incorrectly and therefore wind up in hospitals. Is alcohol banned? No. Are cigarettes banned? No. People using alcohol wind up in the hospital and cause fatal accidents and yet it is not banned. Many people who choose to smoke die of cancer and endanger the health of others and yet it is not banned. You need to do your homework about Kratom use and show some real statistical analysis about the percentage of people benefitting from Kratom compared to the percentage of people who wind up in hospitals after irresponsibly overdosing. The majority of people in Indonesia have been taking Kratom for centuries with no ill effects. Banning Kratom from the public is just wrong!
Ann Welch
Gainesville, Fl

From:	BarkerT15
To:	Board Coordination
Subject:	Do NOT Schedule Plain Leaf Kratom
Date:	Sunday, April 12, 2026 12:11:18 PM
Attachments:	Citizen Testimony 2.pdf GKC+-+Understanding+Kratom.pdf

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Hello,

I am emailing and submitting testimony in the hopes that the Nevada Pharmacy follows the national leaders and does not schedule plain leaf kratom. The truth and science show that plain leaf kratom is safe and does not deserve to be scheduled. There are states this year that faced the same issue, and they determined that plain leaf kratom is safe and does not deserve to be scheduled. There are numerous scientific studies that demonstrate kratom's safety, and kratom does not qualify to be scheduled based on the state or nation's 8-factor analysis for scheduling.

Also, the negative impact on human life would be immense. Thousands of people (mostly elderly and veterans) would be criminalized overnight, businesses would be destroyed, and a black market would be created.

Please consider my testimony and the scientific studies that I am providing. If you are a Board that follows science, you will see how this plant does not deserve to be scheduled.

Kratom Safety Studies: https://www.americankratom.org/science

Hello,

I am writing this comment to you in order to stop the banning and criminalization of kratom. I want to make it clear that I am in opposition to the scheduling of plain leaf kratom. People I know have been kratom consumers for 10+ years now. During that time, they were able to relieve the symptoms of debilitating conditions (arthritis, autoimmune diseases, work injury, etc.) Not only that, but I know several business owners whose livelihoods are based on their kratom shops. You would be ruining honest people's lives over a substance that is completely safe. Please protect this plant and allow users to consume this safe product.

Also, I want to also be clear and say plain leaf kratom is much different from 7-OH and other synthetic products. Natural plain kratom leaf has been shown to be safe in numerous scientific studies, and it should not be lumped in with these other products. One way to keep things straight and people safe is to adopt the Kratom Consumer Protection Act.The American Kratom Association has used this legislation in many states, and it has had great success. This safety-based approach would help citizens, and it would make safe kratom accessible as well. So please, listen to your fellow politicians, the American Kratom Association, and the science, and make the right choice by keeping kratom legal.

Sincerely,
Anonymous Citizen

Understanding Kratom:
A Comparative Safety and Risk Analysis

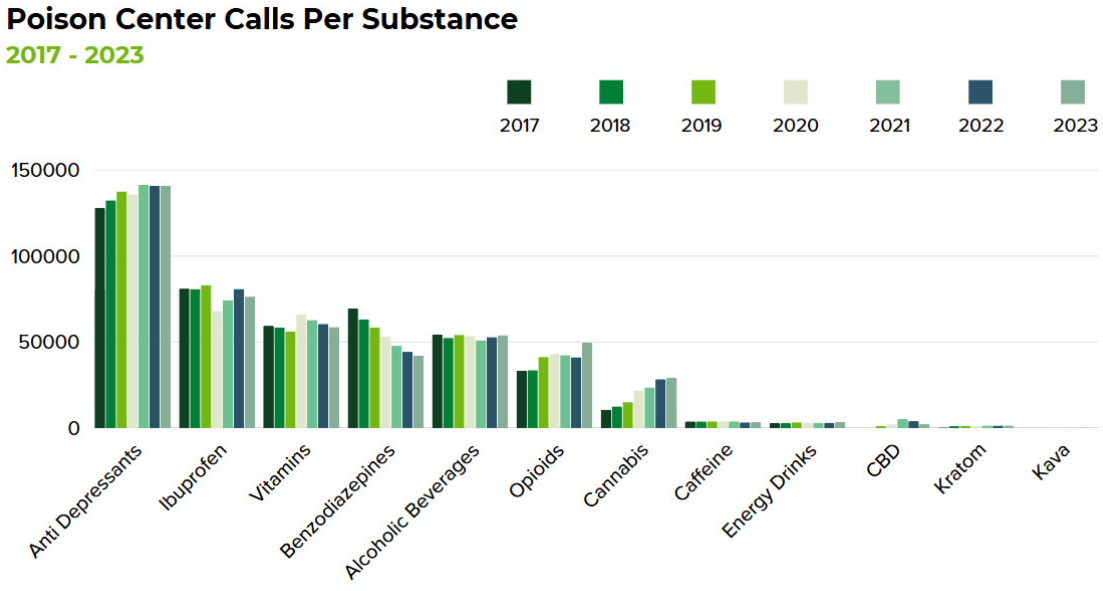
Introduction

All substances have the potential to cause consumer harm and it is important to understand the relative risks of experiencing harm when making personal decisions of products to use or formulating health policy for a population of people. By using publicly available data of adverse events reported to the Food and Drug Administration (FDA), poison control center calls, and data on prevalence, severity, and symptom endorsement of Substance Use Disorder (SUD) criteria as defined by the Diagnostic and Statistical Manual Version 5 (DSM-5), we can assess the risk profile of kratom relative to other substances. This paper will inform consumers regarding the safety and potential risks of kratom use by comparing it to a variety of legal and illicit substances.

Analyzing Reported Adverse Events:

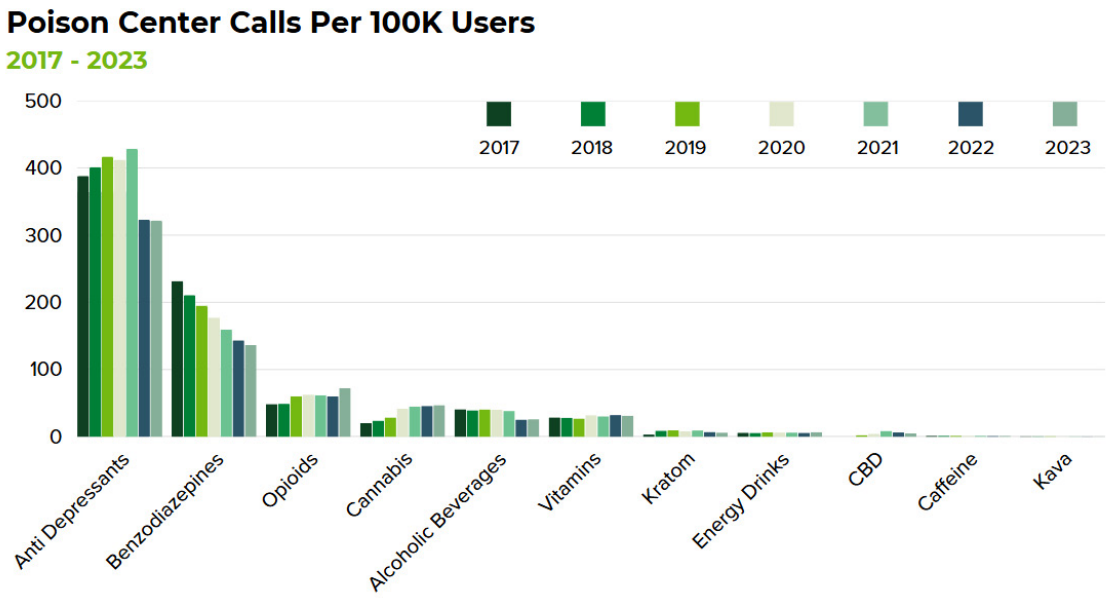
A Comparative Assessment of Kratom's Physical Impact

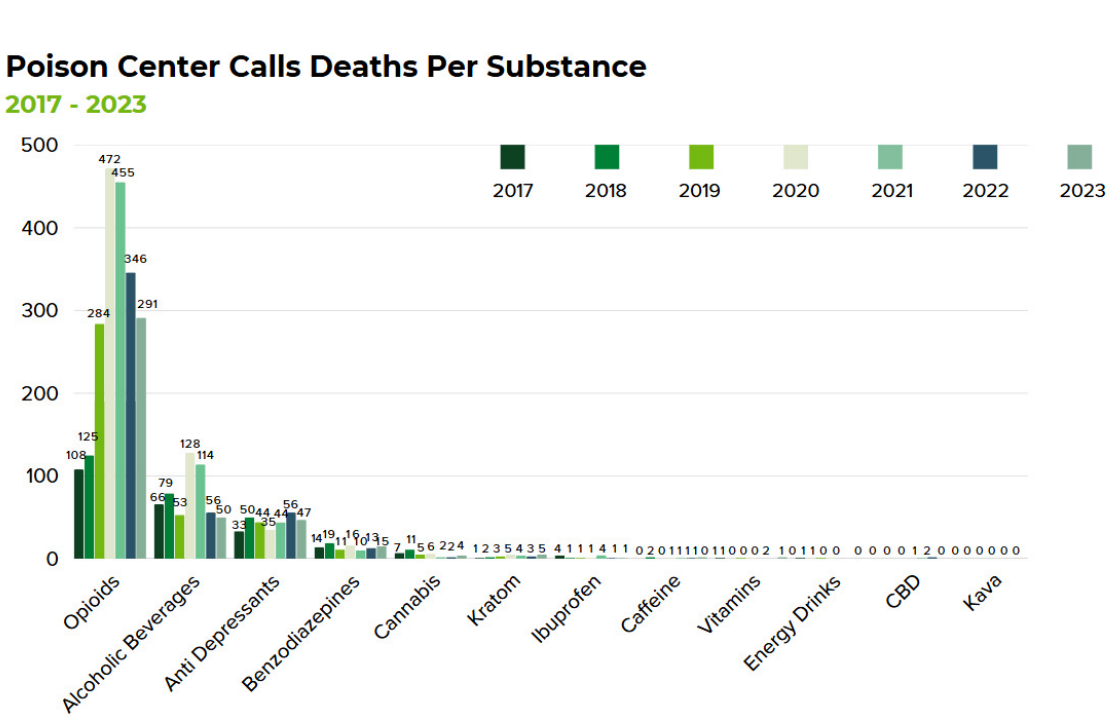
The American Association of Poison Control Centers (AAPCC) is an objective source of adverse events associated with different substances. Between 2017 and 2023, calls to Poison Control Centers regarding kratom were significantly fewer compared to other substances, such as opioids and alcohol. This shows that kratom is less likely to cause acute health emergencies.



Some substances are used more commonly than others and may have more reported adverse events but fewer events per user. As such, dividing the calls by the number of users in the United States is an important additional metric.

Analysis of poison control center calls from 2017 to 2023 reveals that kratom-related incidents are considerably lower than those for opioids and alcohol. This low incidence rate suggests that kratom is less likely to cause immediate health crises.

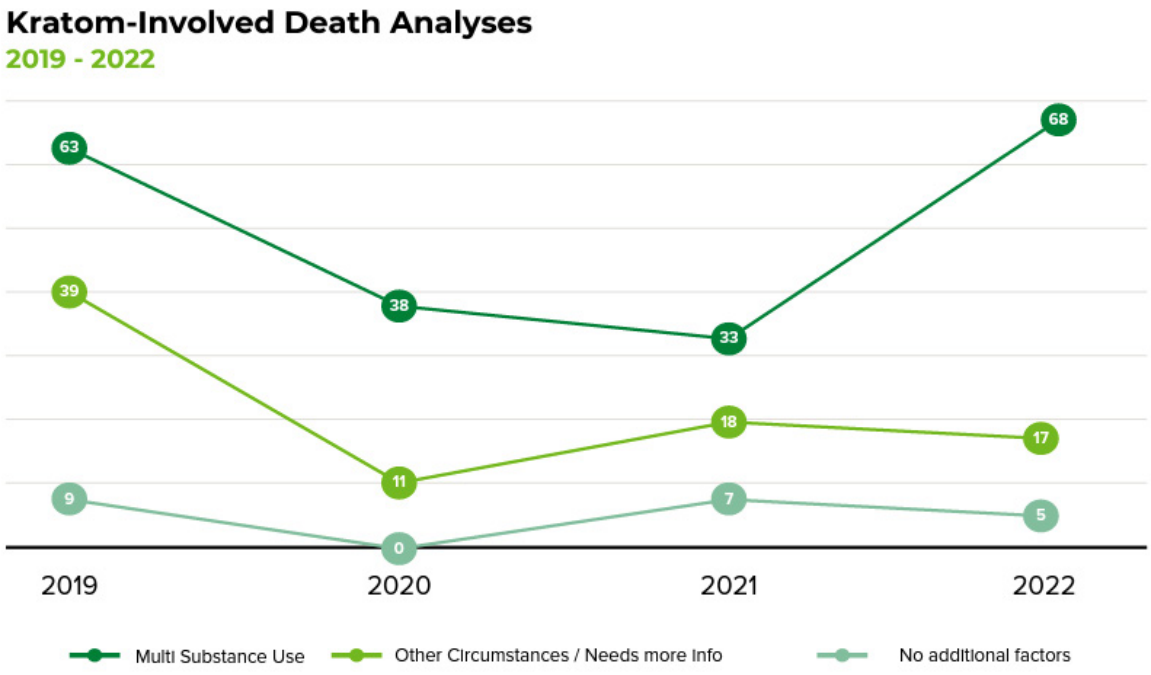




Even when kratom is associated with a death, there are frequently other substances being used in the patient at the same time. The extent to which kratom was the cause, a contributor, or an innocent bystander can often not be determined in these cases.

The data on deaths associated with substance use further supports kratom's relative safety. Upon review of the FDA Adverse Event Reporting System (FAERS) between 2019 to 2022, it is clear that most cases that involved death involved multi-substance use.

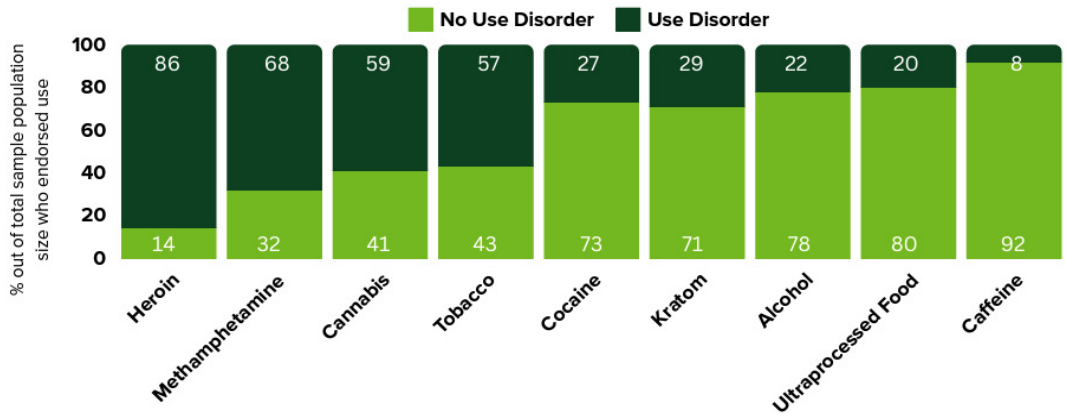
Kratom has a relatively low mortality rate, which suggests a lower level of risk, and data from the FDA Adverse Event Reporting System (FAERS) shows a decrease in deaths only involving kratom from 2019 to 2021. This evidence together highlights that kratom's risks, though present, are much smaller than those of many other substances.



Substance Use Disorder Data

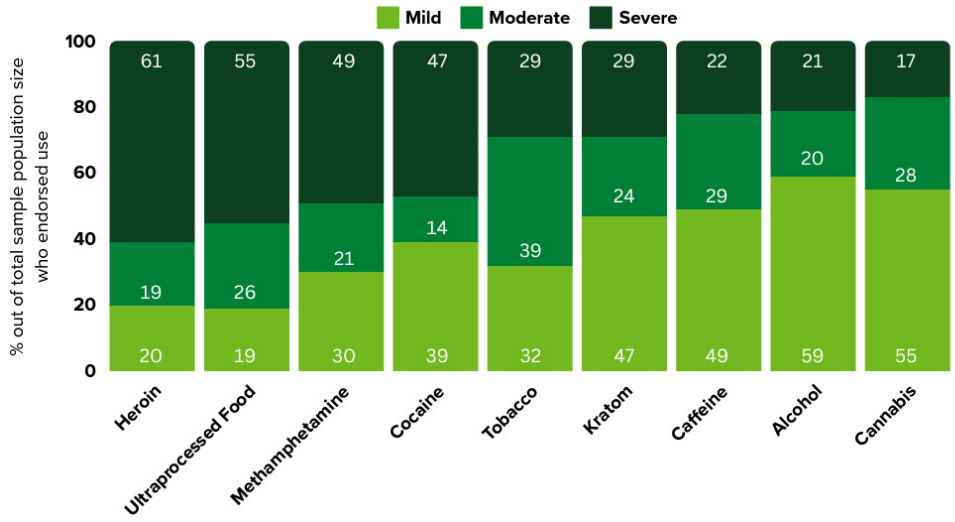
Prevalence

The DSM-5 criteria for Substance Use Disorders (SUD) provide a structured approach to understanding addiction across various substances. Heroin exhibits a high prevalence of SUD, with 85.79% of users developing addiction and 61.00% of these cases classified as severe. Similarly, methamphetamine and opioids show high prevalence rates of 67.50% and 68.59%, respectively, with substantial portions of users experiencing severe addiction.

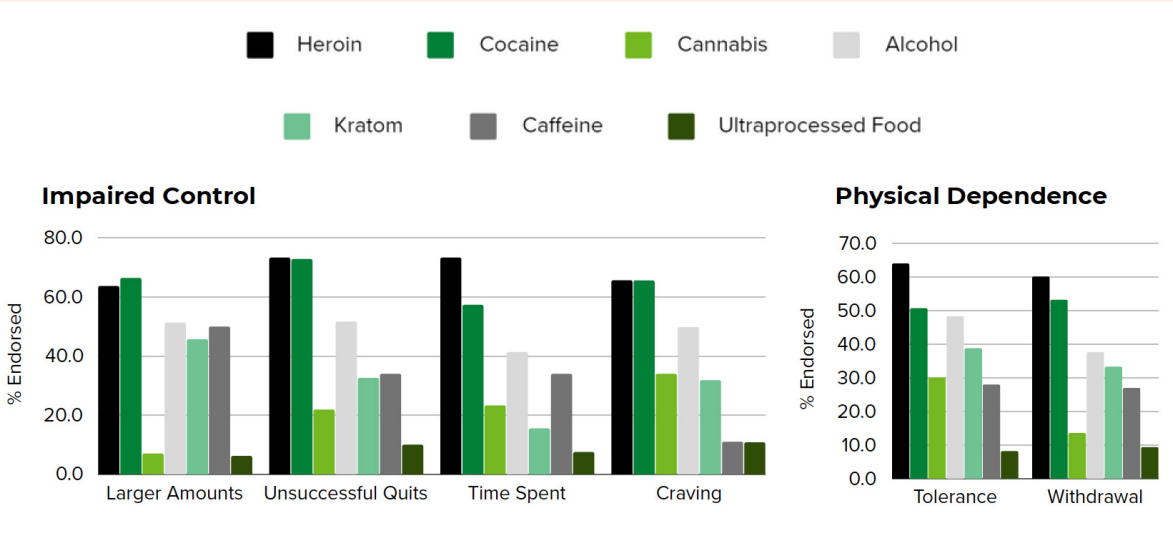


Severity of Substance Use Disorders

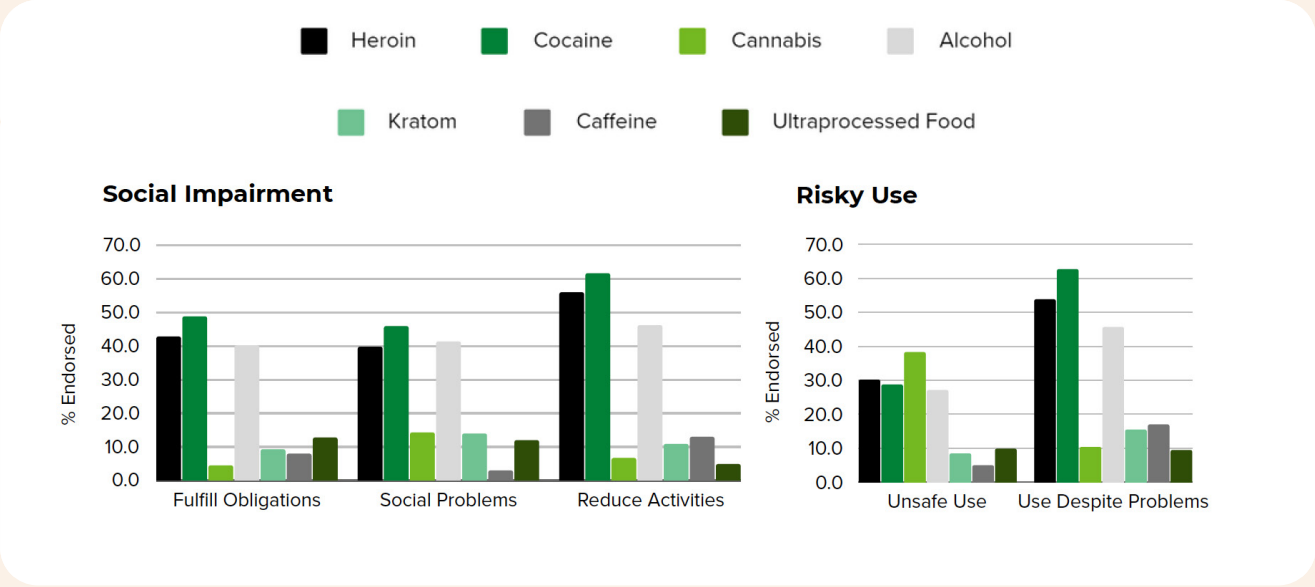
In stark contrast, kratom presents a lower SUD prevalence of 29.50%. The severity of SUD among kratom users is typically less intense. Only 28.81% of kratom users experience severe SUD, while a majority, 47.46%, fall into the mild category. This distribution shows that kratom, while potentially habit-forming, is less addictive than more dangerous substances. Its addiction profile is more akin to that of caffeine, which is legally consumed worldwide and known for its mild addiction potential.



Examining the symptom endorsement data from the DSM-5 helps provide a clearer picture of how different substances impact users. Impaired control, social impairment, risky use, and physical dependence are the key categories considered. Impaired control involves using larger amounts or for longer durations than intended, repeated unsuccessful attempts to quit, and significant time spent on substance use. Social impairment highlights the negative consequences on personal relationships and responsibilities, while risky use emphasizes the dangers of consuming substances in hazardous situations. Physical dependence, characterized by tolerance and withdrawal symptoms, underscores the physiological impacts of a use disorder.



Substance Use Disorder Data Continued



Kratom, while it can lead to SUD, tends to show symptoms more aligned with physical dependence and impaired control rather than risky use and social impairment; this contrasts with substances like heroin, cocaine, and alcohol, which exhibit high levels of social impairment and risky use. Therefore, while kratom is habit-forming, it does not represent the same level of societal risk as substances that have caused widespread social harm. Many users report that kratom, despite its habit-forming properties, is beneficial to their daily lives, which further aligns its profile closer to substances like caffeine and alcohol rather than illicit drugs.

Conclusion

As the data illustrates, kratom has some physical impacts and can be habit-forming, but its risk profile is significantly lower compared to many other substances. Kratom's safety and addiction potential are more closely aligned with commonplace substances like caffeine and alcohol rather than highly addictive drugs like heroin and methamphetamine.

Understanding these risks in the context of individual consumption patterns and risk profiles is crucial. This knowledge enables more informed decision-making regarding substance use. By considering comprehensive data on kratom, individuals and policymakers can better assess its place within the broader spectrum of substance safety and addiction potential. Ultimately, these insights can help develop balanced public health policies and promote safer consumption practices.



Sources

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From:	Bradley Bowers
To:	Board Coordination
Subject:	Oppose Mitragynine Scheduling
Date:	Friday, April 10, 2026 3:40:18 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Good afternoon,

I am writing to respectfully oppose making mitragynine a controlled substance.

This would adversely affect thounds of Nevada residents and veterans who have benefited from safe whole leaf kratom.

I have been using Kratom for several years now and I can't express enough how much it has helped me. I suffer from chronic back pain and sciatica. Kratom has been able to give me my quality of life back. I am able to lead a normal life, have a successful career, and, most importantly, be present with my friends and my loved ones.

I am happy to share more of my story with you if you would like to follow up with me.

Thank you so much for your time, and have a blessed day!

Best,

Brad

From: bradigan@everyactioncustom.com on behalf of Brad Carpenter
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Thursday, April 16, 2026 8:54:05 AM

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Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

Natural kratom leaf has a demonstrated history of safe use. It is not the same as synthetic 7-OH, which is the product usually linked to negative stories about kratom. Natural kratom has no place among Schedule I substances.

I use kratom regularly. I have used it to help with sleep issues. I have seen benefits from kratom when feeling particularly low or sad. I've used it for pain relief or anxiety. Kratom can provide diverse benefits, many of which I have seen in my life. It does not make you high.

I've found that most people who advocate for the rescheduling of kratom don't understand it and have never used it. It clearly has no place among the other Schedule I substances.

As a user of kratom, I'm concerned that I'll suddenly be considered a criminal for doing the same thing that I have been doing for years. Nevada is historically a free state; we should maintain that tradition.

Sincerely,
Brad Carpenter

From: dbirdies@everyactioncustom.com on behalf of Brooke Deal
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Friday, April 10, 2026 9:03:00 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

My Own Personal Experience with Kratom:

Sincerely,
Brooke Deal

From: Braxton Evertz
To: Board Coordination
Subject: Kratom saved my life
Date: Thursday, April 16, 2026 11:04:35 AM

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33 years old… full time worker student tax payer .. takken kratom for 10 years now multiple times a day… …..Ankylosyng spondolytis patient for 12 years… chronic pai. Every day from the time I wake up to bed… zero help from doctors … seen Rhumatologist's.
I've tried everything
Kratom gave me life back.
There is no cure for what I have, and by going to doctors seeking a cure I end up in debt and scolded because only pain relief is all I seek sense there is no cure …
My aunt had lupus, mom has AS, grandma has Parkinson's…. But yall are t worried about alchohol , SSRIs or glyphosphate ….

Well as someone who's taken kratom Ten years and still works and pays taxes ….

I think you've been mislead partially by lobbies and liberal self grandeur …

Kratom is as dangerous as alchohol…
It should have similar safe guards…
Both should have a warning label of addiction!!!! So should coffee and tea!!!

I've Taken Percocet & oxy humera & embryll and several NSAIDs …. from doctors who helped (the only 2 doctors who ever truely helped me retired) most these new doctors are pushing anti depressants & SSRIs and gabapentine for pain, , they don't work ..

I'd much rather have kratom for the rest of my life then have to rely of heroin, fentynal , OR EVEN doctors prescribed opiates!!! Which I've already taken they are stronger then kratom more addictive then kratom ….

Though I take an actual opiate only during break through pain! When pain is 10/10

I take kratom daily for the pain I'm in 24/7 normally :..

The kratom does no effect my brain like opiates do…
I've never felt even close to an over dose, infact raw leaf kratom makes you throw it all up before you even get to overdose…. A person would literally HaVE TO TRY and overdose like one would with say alchohol or water!

I really hope you take the words of actual patients….

Not lobbyists , not politicians , not executives , not out of touch public servants….

If you make kratom illegal then make alchohol illegal …

The only true solution will be a vast goverment funded rehabilitation… will take a lot of tax dollars from the rich and wealthy… maybe cut funding of goverment programs… by true rehabilitation isn't criminalization!!!!

From: Brian Jay
To: Board Coordination
Subject: Kratom Hearing
Date: Thursday, April 16, 2026 8:45:13 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

I would like to urge the Board to leave Kratom Leaf out of the ban. 7-OH is the real problem. Kratom has helped many people stay away form hard narcotics. It can be abused but it is most definitely safer than alcohol in its raw form. So please, focus on the concentration of the plant and keep the raw leaf off schedule but with regulation similar to alcohol.

From:	Becky Lentz
To:	Board Coordination
Subject:	AB322: Supporting a full comprehensive ban on ALL Kratom products
Date:	Sunday, April 12, 2026 4:02:22 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada Board of Pharmacy,

I am a parent of an only child who passed away from Mitragynine (Kratom) Toxicity on December 21, 2024. My son Josh began taking something called Kratom—readily available at gas stations, vape shops, and Kava bars. Marketed as a natural or wellness product and promoted as an energy booster, mood enhancer, and pain reliever, it sounds harmless. Josh thought so too when he purchased it at a Sunoco station.

But Kratom is far from harmless. It can cause serious side effects, is highly addictive, and has led to numerous deaths. A simple online search for “Kratom deaths” reveals a disturbing truth. While it is banned in several U.S. states and many countries worldwide—including parts of Southeast Asia, where it originates and is classified as an opioid—it remains widely sold and unregulated here.

You will hear that Kratom leaf is natural and only “synthetic” Kratom is harmful. You will hear that it helps with pain or opioid withdrawal. But a substance does not stop acting like an opioid simply because it grows on a tree. If it binds to opioid receptors, causes dependence, produces respiratory depression, and results in deaths consistent with opioid overdoes, it deserves serious public health scrutiny.

Josh died of “natural leaf” Kratom. No other illegal drugs were found in the Toxicology Report. A bag of O.P.M.S Silver powder which has the labeling on the bag as organic, natural powder and a bag of Remarkable Herb Red Vein Maeng Da, this variety is typically used for relaxation, stress relief, and, in some case mild pain relief.

Josh suffered his first seizure on a Saturday night. He saw his doctor days later, but even his physician was unaware of Kratom’s dangers. The following Saturday morning, my only child was found deceased by his father from Acute Mitragynine Toxicity.

My heart is forever shattered. No parent should have to experience this kind of loss over an herbal “organic, natural” supplement—one sold without clear labeling, dosage instructions, or warnings of its opioid-like properties and risk of dependence.

Joshua Lentz was deeply loved for his kindness, empathy, wit, love of philosophy, and affection for every dog he met. His beautiful soul lives on, and I know he would want his story shared to help others.

The FDA has warned that Kratom carries risk of addiction, abuse, and dependence. While some argue for “guardrails,” I believe the only way to truly protect individuals is a complete ban.

I respectfully ask that you support legislation to ban the retail sale of unapproved psychoactive substances, including a comprehensive ban on ALL Kratom products, including natural leaf. These products are being sold freely despite their serious and often fatal risks. I speak not only on behalf of my son but for countless families who have endured similar heartbreak.

Please take action to prevent more unnecessary deaths and protect our communities from the dangers of these unapproved substances.

Thank you for your attention and your commitment to public safety. Please take a moment to read the comments left on the petition below of those negatively impacted by Kratom.

https://www.change.org/BanKratomforJoshLentz

Respectfully,
Josh's mom - Becky Lentz
[redacted]

In Loving Memory



Joshua Lentz
May 15, 1997 - December 21, 2024

From: bret parker
To: Board Coordination
Subject: Kratom schedule change to schedule 1
Date: Saturday, April 18, 2026 7:47:16 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

I am opposed to this. I am a disabled USMC veteran and senior citizen, in 2011 I had back surgery and was put on opiate pain killers that became less and less effective and became addicted to this evil drug pushed by the pharmaceutical industry. After 5 years I stopped taking them. I have been using Kratom successively for 10 years with no side effects, this safe and effective product allows me to function normally with daily activities. If this moves to a schedule 1 drug it will make me a criminal, I served my county Honorably and I would like to see Kratom remain legal here in Nevada. Thank you for your time. Bret.

From: Bruce Reed
To: Board Coordination
Subject: Nevada State Board of Pharmacy Meeting
Date: Monday, April 13, 2026 10:49:02 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

My wife and I have been in Nevada for over 12 years and receiving high quality 'functional - homeopathic - integrative medical care' from local practitioners.

We value our value access to the current variety of treatment options available to us.

Changes to prescribing rights and options would significantly impact our ability to continue quality care with our providers.

Sincerely, Bruce & Nancy Reed

From:	Christopher Deaney
To:	Board Coordination
Subject:	Please do not ban natural kratom tea
Date:	Thursday, April 16, 2026 10:18:37 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Good morning,

I wanted to share science and facts with you about kratom. There seems to be confusion about what kratom truly is to begin with. Kratom is a tree leaf with over 50 alkaloids found in Southeast Asia that is related to coffee.

My Story and Do Not Ban Natural Kratom

My name is Christopher Deaney. I am a lifelong American, a small business owner, and someone who has lived with chronic pain since childhood after being struck by a car at the age of eight.

I am a resident of New Jersey, but I have friends all over the country who utilize natural kratom tea for their own well-being.

For many years, I followed the traditional medical path and was prescribed opioid pain medications long-term. While legal and doctor-prescribed, those medications came with escalating risks. Over time, I experienced tolerance, dependence, mental fog, and a reduced quality of life.

In 2015, after careful research and consideration, I transitioned away from that path and began using plain, natural kratom leaf prepared as a traditional tea. That decision was deliberate. I was looking for stability and functionality, not intoxication.

I reached out to the farmers and the people who have used this plant for hundreds of years. I was so curious about this plant. I was amazed how much a cup of tea helped me, so in 2015 I dedicated my life to studying and understanding this wonderful leaf.

I started a company in 2016 that is dedicated to education and the sales of natural kratom leaf tea. I have numerous binders of analytical testing dating back to 2018, which show the natural balance of alkaloids in kratom.

7-oh is NOT found in the raw kratom leaf and only appears once dried. The dried leaf contains roughly 0.00500% 7-oh, which would equate to about 20-30 pounds of kratom powder for one commercially sold package of 200 mg 7-oh tablets.

There aren't enough 7-oh in the natural leaf, or enough trees on Earth to make commercial 7-oh products.

Some of these 7-oh products are being made from synthetic Mitragynine from China and not natural kratom leaf from Indonesia. Please don't confuse the two.

https://chinarawpowders.com/mitragynine-powder/

I've worked with scientists, including Christopher McCurdy, who has studied kratom since 2005. Kratom is currently under investigation as a treatment for opioid withdrawal syndrome and alcohol cessation.

I want to be very clear about what I am speaking about.

I am not here to defend synthetic products, isolated alkaloids, or highly concentrated substances being sold under the name “kratom.” I share concerns about those products and believe they should be addressed directly through regulation or by removing them.

What I am asking you not to ban is the natural kratom leaf, or its tinctures.

Please check out the following link for all available scientific studies on kratom.

Please listen to the Congressional Briefing on Kratom Science

This distinction is supported by the American Herbal Products Association (AHPA), the national trade organization representing the herbal products industry.

• The AHPA published a new entry in its online Botanical Safety Handbook recognizing *Mitragyna speciosa* leaf as a traditional herbal material and clearly distinguishing it from concentrated extracts and synthetic alkaloids. You can view that handbook entry here:
AHPA publishes new entry for kratom in the Botanical Safety Handbook (AHPA blog, Jul 18, 2024) (ahpa.org)

• AHPA has also issued guidance warning against labeling or marketing synthesized kratom alkaloids — like concentrated 7-hydroxymitragynine (7-OH) as kratom, because those products are not representative of the botanical leaf and raise distinct safety concerns. See that guidance here:
FDA recommends scheduling of 7 OH, distinguishes kratom leaf from illicit products (AHPA blog, Jul 29, 2025) (ahpa.org)

This regulatory distinction is not theoretical. Even the FDA’s current focus is not on traditional dried leaf kratom, but on concentrated 7-hydroxymitragynine (7-OH) products that are being marketed in high-potency formats.

For additional perspective on this distinction, including discussion of FDA concerns and how 7-OH differs from natural leaf kratom, please see:

https://youtu.be/8-0Ok_rj2sQ?si=Aqhhspm4v8fGMwiL

The core scientific issue is chemical differentiation.

Mitragyna speciosa is a botanical in the coffee family, related to Coffea arabica. The primary naturally occurring alkaloid in the leaf is Mitragynine. 7-hydroxymitragynine exists in raw leaf only in trace amounts. It becomes a regulatory concern when concentrated, isolated, or synthesized into high-potency products.

There aren’t enough kratom trees in the world to produce 7-oh the way it is being sold.

This is where the Controlled Substances Act's 8-factor analysis becomes critical.

Two separate 8-factor analyses help clarify the difference:

• Henningfield / Fant — 8-factor review of Kratom (Mitragyna speciosa / Mitragynine)
This analysis evaluated kratom and Mitragynine under the eight statutory factors required by the Controlled Substances Act. The conclusion was that Mitragynine and natural kratom leaf do not meet the criteria for federal scheduling based on abuse potential, dependence liability, public health impact, and pharmacological profile.

• The Abuse Potential of 7-Hydroxymitragynine (7-OH) According to the 8 Factors of the Controlled Substances Act
In contrast, the 8-factor analysis of concentrated 7-OH indicates that it does meet scheduling criteria due to its significantly higher potency at opioid receptors and greater abuse liability when isolated and marketed in concentrated forms.

In simple terms:

The mitragynine in natural leaf and extracts does not fit the scheduling criteria. Concentrated 7-OH does.

Treating them as the same substance ignores pharmacology, chemistry, and federal statutory standards.

Policy works best when it is evidence-based and proportional. If the FDA or DEA determines that concentrated 7-OH meets scheduling criteria under the 8 factors, that is a targeted and scientifically defensible action. But extending that classification to unaltered plant material would be a category error.

There is also ongoing clinical research into kratom's pharmacology. A registered U.S. clinical trial titled "Single Ascending Doses of Kratom in Healthy Subjects" is listed on ClinicalTrials.gov, which evaluates the safety and pharmacokinetics of kratom leaf preparations:

Single Ascending Doses of Kratom in Healthy Subjects (ClinicalTrials.gov NCT06072170)

Full study record:
https://clinicaltrials.gov/study/NCT06072170

This type of structured clinical research should inform regulation, not be preempted by broad prohibitions.

History consistently shows that blanket bans do not eliminate demand. They shift it into unregulated channels. That increases consumer risk rather than reducing it.

If the goal is public safety, the path forward is targeted regulation:

• Distinguish natural leaf from synthetic or concentrated alkaloids
• Regulate or remove high-potency 7-OH products if warranted
• Require labeling and third-party testing
• Enforce age restrictions
• Hold bad actors accountable

I am also a father. I support responsible regulations. I do not support conflating a traditional botanical leaf with a laboratory-concentrated derivative.

Natural kratom leaves are not the problem.

Please listen to the Congressional Briefing on Kratom Science and Policy

Failure to distinguish between the Mitragynine-containing leaf and the concentrated 7-OH is.

Public policy should reflect chemistry, statutory criteria, and clinical evidence, not headlines.

Please know that I lost my son in 2023 to a fentanyl and xylazine overdose. He tried kratom in 2017 and told me it didn't get him high, so he wasn't interested. That was his demon he dealt with.

We have had issues with Elevated 7-Hydroxymitragynine Levels Found in Products Misbranded as Kratom.

Mislabeled products masquerading as kratom are the real issues, not the kratom itself. In 2009, a product called Krypton was sold in Sweden. People thought this was kratom, but it was not. This product had very high levels of O-Desmethyltramadol.

It was the O-Desmethyltramadol that was the culprit, not kratom.

If kratom inherently produced a "High" effect, there would be no reason for companies to spike it. Natural kratom does not produce a high at all. Kratom gives a sense of calm and a bit of energy, like coffee.

Natural kratom isn't the problem, but these other substances masquerading as kratom products are the issue.

Natural kratom is saving millions of lives, and it saved mine.

Thank you for your time and consideration. I would love to speak to you further and share analytical data that shows 7-oh is only found in trace amounts in the natural kratom leaf.

Respectfully,
Christopher Deaney
[redacted]

Salem County, New Jersey

From: history1962@everyactioncustom.com on behalf of Cray Foley
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Monday, April 13, 2026 6:22:42 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

My Own Personal Experience with Kratom:

Sincerely,
Cray Foley

From:	Ecstatically Extreme
To:	Board Coordination
Subject:	Please do not ban kratom!
Date:	Thursday, April 16, 2026 9:06:46 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Hi there,

I was writing in regards to the kratom ban meeting today.
I wanted to say that plant is part of the coffee family, is not an opioid, despite popular belief and this plant REALLY saved my life!! I do not go to doctors so I was stuck on the toilet for up to 12 hours every single day with probably Crohn's disease. I wish I had known about kratom back then. I have safely been taking it everyday since I learned about it back in 2015. It has allowed me to get back to work and to live a normal life outside of the bathroom. I don't deserve to go back to a small room all day long over political agendas! Please do the right thing and protect our loving kratom plant.

Thank you from hearing me out. The plant has completely stopped my diarrhea. I would say to ban the synthetic stuff, not the kratom..I believe kratom is even safer than marijuana. And look at all the toxic stuff they put in the weed and that is still being sold in stores. Please do not do this! A lot of lives could be ruined.

Thank you again!

Sincerely,

Christopher Gianguzzo

From:	Corinna Grassi
To:	Board Coordination
Subject:	Opposition to Proposed Scheduling of Kratom Alkaloids in Nevada
Date:	Monday, April 13, 2026 8:20:58 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada Board of Pharmacy,

I am writing to express my opposition to the proposed scheduling of the naturally occurring alkaloids in the kratom plant as Schedule I substances in the state of Nevada. As a Nevada resident and kratom vendor, I have firsthand knowledge of how natural kratom products have helped thousands of individuals.

Many people—including my business partner—have used kratom as a tool to move away from opioid dependence, manage anxiety, or simply as a mild alternative to coffee. These real-world outcomes should be carefully considered when evaluating policy decisions that could significantly impact access.

Natural kratom powder and leaf products should not be made illegal due to the irresponsible marketing of highly concentrated or synthetic 7-hydroxymitragynine (7-OH) products that have entered the market in recent years. Responsible kratom vendors do not sell these products and are actively working to remove them from the marketplace.

I understand that you will be presented with scientific data regarding mitragynine, the primary alkaloid in kratom, which has been increasingly studied. This growing body of research supports a strong case for its safety profile when used responsibly, and it does not meet the criteria for classification as a Schedule I substance.

At the same time, I recognize the concerns surrounding 7-OH. However, because small amounts of 7-OH occur naturally in dried kratom leaf, an outright ban on this compound would effectively result in a ban on natural kratom itself. A more balanced approach would be to establish limits on 7-OH levels so they remain consistent with those naturally found in kratom leaf. I also fully support reasonable age restrictions on the purchase of kratom products.

A full prohibition of kratom's naturally occurring alkaloids would not only restrict access for Nevada residents but could also hinder ongoing research into its potential benefits. I respectfully urge the Board to consider a regulatory framework that preserves access to natural kratom while addressing legitimate safety concerns.

Sincerely,
Corinna Grassi

From: Calvin Green
To: Board Coordination
Subject: Kratom Ban Proposal
Date: Wednesday, April 15, 2026 3:52:52 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Hello,

I am writing on behalf of a close friend who uses the herbal supplement, kratom. She suffers from frequent pain issues from an accident she was in years ago. For a long time she was on pain medication but it did not help and she had terrible side effects.

Once she found kratom she turned her life around. She is able to work and function again, simply by drinking 5 grams of kratom powder in a tea. I have not witnessed her impaired in any way when she uses this product, it simply allows her to help relieve symptoms related to her injuries.

I do believe kratom should be limited to those who are 21 years of age and older. I also think regulation should be put in place to ensure it is packaged and labeled properly, tested for adulterants and contamination, etc. Plain leaf kratom is safe and has been used for hundreds of years in the parts of the world where it is native to.

I understand there is a proposal that would ban kratom by making it a scheduled drug. This would be disastrous to people like my friend, who rely on this supplement. Please do not criminalize people who are simply trying to better themselves. Please keep kratom legal and accessible.

Thank you for all your hard work.

From: Cassandra Hays
To: Board Coordination
Subject: Kratom - Please Regulate it - Not Ban It
Date: Tuesday, April 14, 2026 12:30:46 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Hello:
Please regulate kratom, not ban it.

People from all over the world fly to your state. However, if you ban this natural leaf kratom, many, many people will not come to your state and this will be a problem for tourism.

The natural leaf kratom is not dangerous. It's like drinking a cup of coffee and it is related to the coffee plant. Please contact the American Kratom Association. They have so much information and can tell you all of the states who have protected people's rights.

Please consider regulating the synthetic items (not natural kratom leaf) that are harmful to people.

Thank you for your consideration.

Sincerely,
Cassandra Hays

Sent from my iPhone

From: chris@everyactioncustom.com on behalf of Chris Jepson
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Thursday, April 16, 2026 2:03:51 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

I discovered kratom back in 2012. I've been to the Kratom jungles over 19 times. And even met with the Indonesian DEA and their version of the fda. And their minister of Health. Also met with the Thai version of the fda. They do not oppose regular kratom. Because it's been used for hundreds of years with no adverse effects. All of a sudden within the last year and a half. Kratom fatalities, overdoses, and adverse effects all of a sudden skyrocketed like it's a new epidemic drug. Only thing that's different. Is that kratom did not have all these horrible effects. Just when the synthetic drugs that came out and decided to call themselves kratom in their packaging. But they were purely synthetic. They called it 7oh. The strongest Kratom extract in the world. Problem is though these are made by chemists. Using oxidizers like pool shock and other ingredients that create a synthetic opioid that you cannot consume in nature. If you remember the spice epidemic. All these adverse effects exploded when that came out to the market. This is the same thing. It's either Kratom all of a sudden evolved in this last year and a half to a deadly drug? Or did Americans only are biologically different than the rest of the world starting the last year and a half? Or these new synthetic chemical drugs we're introduced in the usa. Common sense says it is the latter. We need to get rid of these synthetic drugs. And the drug dealers that manufacture these. Making Kratom illegal will not change what is out in the streets. If anything it will eliminate the life vest that millions of America have used safely for years. It will then be packaged and named something else. Like cat's claw. Which is really a benign plant. These pressed tablets will throw an inert ingredient. And deceive the public to think in there taking a natural plant. Where in fact they are putting the next synthesize drug out into the public. And playing whack a mole with the government agencies. Changing a small molecule. Which bypasses the existing law. Then they make 6 months worth of millions of dollars while waiting for a legislature to come up with some new regulations to ban that next alkaloid. While they have three more versions in their back pocket ready to go. I suggest that they take a similar approach to what they did with spice. And create an analog act. Banning the synthesized alkaloids or drugs. And throwing it out into the market to make the next round of drug addicts. While leaving American citizens that have found a natural plant that as the FDA stated in their most recent Public Announcement last year. That Kratom is not their concern. It is the synthesized opioid called seven hydroxy. I beg you please to don't take away this life preserver that millions of Americans have relied on. Safely. Taking this away will even magnify the opioid epidemic that we've had in the recent year-and-a-half. Keep Kratom illegal in its natural form. Then ban the synthetic drugs. And prosecute those who are making and selling them. I recommend you go to the Champs Trade Show held in Las Vegas twice a year. And walk through those hallways and visit the booths of all these synthetic drug dealers. Go undercover. Ask questions. It's likely 7oh and Kratom will not be there this year. It will be the next round of drugs parading as a natural plant. I hope you consider that there is an alternative. Keep the natural plant. Regulate it. Regulate those who are Manufacturing it. And prosecute those who do not comply with these regulations thank you for your consideration. Chris Jepson president of NuWave Botanicals

Sincerely,
Chris Jepson

From: chlogirl2@everyactioncustom.com on behalf of Chloe Kyle
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Monday, April 13, 2026 6:00:37 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

My Own Personal Experience with Kratom: After having a back injury and having the doctors get me hooked on prescription drugs and not wanting to be a prisoner to the pharmacy and doctors. I was informed about Kratom and how it saved someone else's life and tried for myself. It healed me and I now work a full time job and actually considered a decent human again in societies eyes. There is Gas station Kratom that is unregulated and people add bad things to it, giving Kratom a bad name when it should be praised as a healer. Kratom itself is not bad ,its when they mix and add things to it. The pharmacy doesn't like it because they dont make as much money, because people are getting off there opiates. So what better way to give Kratom a bad name. I buy from a online retailer that is tested for purity and that's the difference. Get rid of the gas station 7oh Kratom but Kratom itself has healed me and many. If you make it illegal, people won't get better and will resort to heroin and fentanyl. But I kinda think that's what this country likes and wants is sick people to make money off of....all I can say is it did cure me and I think you guys should really do your research. And no one has oded from Kratom, just those few that are reckless and mixed 7oh with other prescription drugs. But I would think twice because you guys are going to hurt the good people. I think its just the pharmacy losing out on money honestly. Sincerely,
Chloe Kyle

Sincerely,
Chloe Kyle

From:	Creighton McCain
To:	Board Coordination
Subject:	Kratom Ban Hearing Public Comment
Date:	Thursday, April 16, 2026 4:52:54 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

To the Members of the Nevada State Board of Pharmacy,

I am writing as a law-abiding Nevada resident & this is an official public comment to go on the record please, to formally and strongly oppose the proposed scheduling of kratom alkaloids under **LCB File No. R107-25**.

I am deeply concerned that this Board is attempting to use administrative rulemaking to effectively repeal the **Nevada Kratom Consumer Protection Act (NRS 597.998)**.

The Nevada Legislature has already debated this issue and chose to **regulate** kratom products to ensure safety, rather than ban them. By attempting to schedule these alkaloids now, the Board is bypassing the clear will of our elected representatives and overstepping its administrative authority.

Natural kratom leaf has a demonstrated history of safe use and is not comparable to Schedule I substances. Regulate dangerous synthetic 7-OH products — not natural kratom.

My Personal Testimony:

For over 10 years, I have relied on the natural kratom plant to manage my personal well-being. It has been a literal lifesaver for me. Access to regulated, natural kratom has allowed me to maintain a productive quality of life and be a functioning, contributing member of my community.

I am not a person who buys "gas station" products; I am a responsible consumer who only purchases from GMP-compliant vendors that strictly adhere to safety and lab-testing standards. Banning this natural plant would not protect me—it would actively harm me by removing a safe, vital tool I use to manage my daily life.

I urge the Board to respect the existing state law and the thousands of Nevadans like me who depend on it. Please reject this scheduling proposal and uphold the KCPA.

Respectfully,
Creighton McCain
Las Vegas, NV

From: Christopher
To: Board Coordination
Subject: Please Oppose Scheduling Kratom in Nevada
Date: Wednesday, April 15, 2026 12:08:45 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Members of the Nevada Board of Pharmacy,

Please oppose any effort to classify kratom alkaloids as Schedule I in Nevada.

I am writing as someone whose life was changed by kratom after a serious injury and years of failed treatments. Chronic pain made normal daily life extremely difficult. Kratom gave me back the ability to function, work, and live productively when other options had failed. For many responsible adults, it is not a recreational substance. It is a practical tool that helps them maintain a normal life.

Placing kratom into Schedule I would wrongly treat it as if it has no accepted value and only high abuse potential. That does not reflect the real-world experiences of countless responsible consumers. It would also make chronic pain patients criminals overnight.

It is critical to distinguish between natural kratom leaf products and newer highly concentrated or synthetic products, especially enhanced 7-hydroxymitragynine products. If there are legitimate concerns, those products should be specifically addressed. They should not be used as an excuse to ban the natural plant itself.

Nevada already has a smarter path available through regulation. Age limits, product testing, labeling requirements, contamination controls, and enforcement against adulterated products protect consumers far better than prohibition. Nevada previously adopted consumer protection measures for kratom, and expanding sensible regulation would make far more sense than criminalizing responsible adults.

I also urge the Board to carefully examine claims about so-called kratom-only deaths. In widely cited cases, multiple substances are often present. Public policy should be based on verified toxicology, complete evidence, and scientific standards, not fear-driven headlines or emotional narratives.

When people lose access to safer alternatives, many are pushed back toward more dangerous substances or left to suffer unnecessarily. That is the real human cost of prohibition.

Please reject Schedule I classification for kratom and pursue evidence-based regulation instead.

Thank you for your time and consideration.

Christopher Penna

From: Cara Lee
To: Board Coordination
Subject: Please protect natural kratom !
Date: Friday, April 10, 2026 2:53:27 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

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.

While I might not be a resident of Nevada , I am a passionate advocate for the protection of natural kratom and stand up for it wherever it is under attack. I do believe there needs to be regulation to ensure consumer safety. Please enact the Kratom Consumer Protection Act for the residents of Nevada and hopefully one day nationwide.

Thank you for your time.

Cara M.

From:	Daryl Darko
To:	Board Coordination; Pharmacy Board
Subject:	NEVADA ADVOCATES: PLEASE ACT NOW TO PROTECT NATURAL KRATOM
Date:	Sunday, April 19, 2026 2:10:26 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

My name is Daryl William Barnett, and I am writing to share my personal experience with kratom as you consider legislation that may restrict or ban its use.

I previously submitted a testimony nearly ten years ago during earlier federal discussions. Today, I am offering an updated account based on over a decade of lived experience.

I was diagnosed with bipolar disorder at age 40, later reclassified as schizoaffective, and was prescribed multiple psychiatric medications. Over time, these treatments did not improve my condition. Instead, I developed agoraphobia, gained significant weight, and lost the ability to function in daily life.

In 2013, I was introduced to kratom. After researching it, I decided to try it. Within weeks, I began experiencing improvements in energy, mood, and overall stability. Over time, these changes became consistent and life-changing.

I was able to go outside again after years of severe sunlight sensitivity. I began walking daily, regained my health, and eventually returned to work after being told I likely never would.

Now, more than ten years later, I continue to use kratom as part of my daily routine. It supports my mental clarity, emotional balance, and ability to live a functional life. I also practice meditation and self-care, but kratom has been a foundational part of my long-term stability.

If access to kratom were removed, I would not return to psychiatric medications, as they significantly reduced my quality of life. Instead, I would face the challenge of maintaining my stability without a tool that has supported me for over a decade.

I respectfully ask that my experience be considered. I support reasonable regulation, including quality control and consumer protections, but I strongly oppose outright prohibition.

I respectfully urge you to protect access to kratom for responsible adults.

I am not alone in this experience. Many individuals, including people close to me who began using kratom at the same time, have experienced similar long-term benefits.

Thank you for your time and consideration.

Sincerely,
Daryl William Barnett

Daryl "Darko" Barnett

photo



Mobile: [redacted]
Email: [redacted]@gmail.com



Create your own email signature



From: Danielle Betz
To: Board Coordination
Subject: Regarding the Scheduling of Kratom
Date: Wednesday, April 15, 2026 12:58:02 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

To Whom it May Concern:

We strongly opposed the scheduling of the natural plant Kratom.

To Whom it May Concern:
I understand you are attempting to ban Kratom or possibly just the sale of the plant medicine, but there are a few things you are overlooking. Prohibition kills people. Many lives, families and livelyhoods will be destroyed. A great deal of them Veterans who fought for your freedom. I personally would not be alive had I not found Kratom. Most of my friends or aquaintances are now dead. I consider myself very blessed.

I believe in implementing a Kratom Consumer Protection Act and I don't understand why you aren't looking past the mania being caused by misinformation. There must be some kind of compromise we can agree to. Kratom saves lives. We would not be here fighting the bans if it weren't. I lost yet another person to this opioid crisis yesterday and it's absolutely devastating. All hope will be lost if you ban the plant that is one of the strongest weapons in the fight against Fentanyl, heroin and from what I now hear is a new, even more dangerous drug hitting the streets in our what used to be beautiful, wonderful country. I'm sick and tired of watching as 3 to 4 entire generations are ravaged and decimated by these toxic poisons flooding our streets. Please don't ban Kratom.

Most of the 7-OH products are coming out way too high in mg and aren't regulated at all and I know that is a serious problem. They are SYNTHETIC. With the rate that people are being ripped off of their medications in the medical industry, 7-OH is still better than either ending up dying from Fentanyl because they're in extremely severe pain and committing suicide at an unprecedented rate, but I know that it's a very slippery slope. Raw powder Kratom or even the extract powders are NATURAL and much safer. I have incurable medical conditions that actually qualify me for disability, but thanks to Kratom, I haven't needed to declare myself disabled. I'm able to function, without going back to being completely bed bound like I was the 2 yrs prior to finding Kratom, now almost 12 years ago. I cycle on and off and use other supplements. I'm not dead and have never overdosed on Kratom.

96% of the overdoses being reported actually showed positive for Fentanyl, so I don't understand why everyone is going after Kratom when we all know it's the fentanyl and poly drug abuse. I've read several of the toxicology reports myself. I'll include the letter my wrote several years back that helped us atain huge victories in fight to keep Kratom legal.

The deaths that a ban on Kratom will cause will be devastating.

Sincerely,

Danielle Betz
[redacted]

The following is the letter my Mother wrote after I started finding my way back. She really loathes drugs. But I've broken out of opioid addiction, which has a rate of 1%, so I'd say that's a win.

August 18, 2018

To Whom It May Concern:

Kratom saved my daughter's life. Danielle, my oldest daughter, who just turned 40, struggled with opioid addiction for well over a decade. During that time my daughter went from a responsible, caring and productive young woman to someone I no longer recognized although she was always beautiful. When it started to get bad, she initially had a well-paying job with benefits, security and chance for advancement. She lost that, in part due to her drug abuse, and from there things only got worse. She had a hard time finding and keeping jobs, she became financially irresponsible and stopped caring about basic things like family and keeping house. She was arrested several times and put on deferred adjudication so she has a criminal record. She had multiple doctors from which she was able to obtain prescriptions and also had contacts that supplied her with drugs illegally.

During that time, she often said that she 'missed me' even though we were in constant contact. I was codependent and spent an untold amount of money keeping a roof over her head, paying her bills, etc. It took me a long, long time to stop enabling her. I missed my daughter, too. She was there in her body, but her personality was gone. She wasn't my daughter, she was a stranger. While on opioids, her judgment was gone. She wasn't able to make good decisions, had memory problems and was aggressively manipulative. I dreaded answering the phone for two reasons: the first that she might be stoned and it would be an upsetting conversation with a lot of drama and the second that I would get a call that she had overdosed and died or that she was in jail again.

Eventually I ended up as legal guardian of her 12-year-old daughter and her daughter lived with me for several years. It was during that time that Danielle found Kratom and started on the road back to life. I started to see my daughter come back, started having intelligent conversations with her and saw her restored to emotional and physical health. Within a period of months, she went from opioid addiction to a 'normal' person. Her daughter continued to live with me while my daughter reestablished her life and eventually her daughter was able to return to live with her mother.

I do not know a lot about Kratom, although I read a bit about it and keep up on the news that is published by major news organizations that has to do with legislation and the FDA. I've done enough research to know that Kratom is a safe and better alternative than other methods that try address opioid addiction. Although my evidence is anecdotal, I see the results and I strongly believe that this should be available and remain a legal alternative without restrictions.

I cannot give exact statistics about the number opioid deaths per year (72,000 in 2017?) and I do not know how many people overdose every day and are saved, but I know it is extremely high. For that reason, I do not understand why Kratom is not part of the solution and, instead, is considered dangerous.

My daughter is a whole person again. Kratom saved my daughter, plain and simple.

I do not need to remain anonymous. I am not ashamed that my family went through and came out of opioid addiction. We are one of many, many families going through this agonizing hell

on earth. But we came out on the other side. Please keep Kratom legal.

Lois Betz

From:	dijonevans@everyactioncustom.com on behalf of Dijon Evans
To:	Board Coordination
Subject:	Oppose Mitragynine Scheduling
Date:	Monday, April 13, 2026 5:20:29 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

My Own Personal Experience with Kratom: Kratom has literally saved my life and given me the hope that I had lost due to the opioid epidemic and my medical history. I have full body CRPS with organ involvement, optical, occipital and trigeminal Neuralgia, multiple organ failure and more than 240 surgeries and procedures. I wasn't supposed to live to be 30, but here I am after a very difficult 30 years and several near death escapes, I just turned 61. I have had amputations, pulmonary embolisms, sepsis, gangrene, 17 bouts of osteomyelitis and now also have osteonecrosis of my jaw, sinuses and facial bones, including the left inner ear,,and soon to be the right, with it affecting the lentire inside of my skull.There is nothing that can be done for me because I am too high risk for the needed surgeries to repair my skull and inner ears. They can't do surgery because of the high risk that I will develop osteomyelitis and it will lead to the infection of my brain. If by chance that I didn't develop osteomyelitis, there's an even higher risk that the surgical bone placement would fail because of the necrosis. The only places that could put me into a medically induced coma and provide prophylaxis antibiotic, and then do the surgery while still keeping me in a comatose state, are far enough away that I would have to be flown to, which cannot be done because I don't have any bone in-between my brain and inner ear which provides protection to our brains when we experience pressure changes while in flight. So, now with everything else that I have encountered and fought to live through, I am nearing the end of the road. For over 15 years I was bedridden and unable to care for myself, everything had to be done for me, and it included in home nursing care for the PICC lines.. When opioids were removed from the picture, even though I was diagnosed as terminal, I wasn't a terminal cancer patient, so I wouldn't be able to get through the worst known pain to us is what I experience daily. It feels like I am being electrocuted from the inside out and my tissues are being seared together. That's on a good day! Unfortunately I was not able to take it anymore and I was ready to take my own life. After spending most of my younger years in college, including medical school, I am very good at research and the word kratom was introduced to me.

Please don't ban kratom! It doesn't take away all of my pain, but it makes it tolerable!

If you ban kratom, you will be sentencing many people to jail, a very dangerous black market or death!

Thank you for your time and consideration!

Sincerely,

Dijon Evans

Sincerely,
Dijon Evans

From: Kim Thomas
To: Board Coordination
Subject: Pharmacy changes
Date: Monday, April 13, 2026 10:22:41 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Good morning,

I have been under the excellent care of Dr. Michael Gerber for 10 years. Integrative/homeopathic medicine is very important to me and many others.
Changes to prescription prescribing rights would greatly effect the care I am given.

Thank you for your time,
Kim Thomas
Sent from my iPhone

From:	Dan gibbs
To:	Board Coordination
Subject:	Public Comment – April 16 Hearing on Kratom Scheduling (Supporting Evidence Attached)
Date:	Wednesday, April 15, 2026 10:22:34 PM
Attachments:	classification of mitragynine compounds as schedule i controlled substances.pdf

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Members of the Nevada Board of Pharmacy,

My name is Dan Gibbs.

I am writing in advance of your April 16, 2026 hearing regarding the proposed scheduling of kratom alkaloids, including mitragynine and 7-hydroxymitragynine.

On December 6, 2023, my 25-year-old son Austin died after consuming retail kratom products. The medical examiner determined his cause of death to be mitragynine toxicity. His toxicology report identified no opioids, no fentanyl, no heroin, no prescription drugs, and no other contributing substances. His death was consistent with opioid-type toxicity, including respiratory depression.

This was not an isolated or theoretical risk. This was natural kratom, purchased in a retail setting.

I am submitting, for your review, an official document from the Ohio Board of Pharmacy titled “Classification of Mitragynine Compounds as Schedule I Controlled Substances.” This document reflects a formal scientific and regulatory analysis conducted under Ohio’s statutory framework. That analysis was conducted using Ohio’s required eight-factor controlled substance review—the same structured legal and scientific framework used to evaluate Schedule I substances.

In that analysis, the Ohio Board of Pharmacy evaluated kratom’s primary alkaloids using established scheduling criteria, including abuse potential, accepted medical use, and safety. Based on that review, the Board determined that mitragynine meets the criteria for Schedule I classification.

Importantly, Ohio has already taken regulatory action on kratom-derived synthetics, placing compounds such as 7-hydroxymitragynine into Schedule I. The same scientific framework has been applied to natural mitragynine, which is currently advancing through Ohio’s rulemaking process.

You will hear testimony that kratom is “just a plant” or that it is inherently safe because it is natural. However, substances do not become safe based on how they are marketed or described. The pharmacology remains the same.

A substance cannot be described as strong enough to replace opioids like morphine, heroin, or fentanyl, and at the same time be considered a safe, unregulated consumer product.

This is not anecdotal advocacy alone—it is supported by both lived experience and formal scientific review conducted by a state regulatory authority.

As you consider Nevada’s approach, I respectfully encourage the Board to review the attached Ohio Board of Pharmacy analysis as part of the evidentiary record. It demonstrates that another state regulatory authority has already conducted a formal scientific review under established scheduling criteria and reached a determination.

I urge the Board to evaluate these substances based on their pharmacology, documented risks, and established regulatory standards—not on how they are marketed or described in retail settings.

Thank you for your time and consideration.

Sincerely,
Dan Gibbs

Classification of Mitragynine as a Schedule I Controlled Substance

Section 1: Summary

The Ohio Board of Pharmacy (Board), pursuant to section 3719.44 of the Ohio Revised Code, proposes the placement of mitragynine, the primary psychoactive alkaloid found in the Mitragyna speciosa plant, commonly known as kratom, into Schedule I.

Section 2: Background

Pursuant to section 3719.44 of the Ohio Revised Code, the Board may add or transfer a compound, mixture, preparation, or substance to Schedule I when it appears that there is a high potential for abuse, that it has no accepted medical use in treatment in this state, or that it lacks accepted safety for use in treatment under medical supervision.

In making a determination to add an unscheduled compound, the Board is required to consider the following 8 criteria:

(1) The actual or relative potential for abuse;
(2) The scientific evidence of the pharmacological effect of the substance;
(3) The state of current scientific knowledge regarding the substance;
(4) The history and current pattern of abuse;
(5) The scope, duration, and significance of abuse;
(6) The risk to the public health;
(7) The potential of the substance to produce psychic or physiological dependence liability; and
(8) Whether the substance is an immediate precursor.

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Section 3: Evaluating Mitragynine Under the 8-Factor Criteria

(1) The actual or relative potential for abuse.

Mitragynine is the primary psychoactive alkaloid found in the Mitragyna speciosa plant, commonly known as kratom. Mitragynine accounts for up to 66 percent of the alkaloid content in kratom.[i] Manufacturers of natural kratom products profess that minor alkaloids in natural kratom are undetectable.[ii] Kratom has a long history of traditional use in Southeast Asia with the use of its leaf or extracts typically ingested orally for the treatment of pain and to aid in the performance of agricultural labor.[iii] These effects have been attributed to mitragynine, which acts as a partial agonist at the human μ-opioid receptor.[iv] The effects of kratom in humans are dose-dependent, with small doses producing a 'cocaine-like' stimulation while larger amounts cause 'morphine-like' sedative-narcotic effects.[v]

Although mitragynine is the most abundant alkaloid in kratom and credited for its effects, the plant contains over 40 naturally occurring known alkaloids. One study examined the likely effects of 25 of those compounds. The study concluded that all the compounds share the most structural similarities with controlled opioid analgesics, such as morphine derivatives. Further analysis determined that 22 (including mitragynine) of the 25 compounds in kratom bind to μ-opioid receptors. The authors further noted:

> *The data from the PHASE model shows us that kratom compounds are predicted to affect the body just like opioids. Based on the scientific information in the literature and further supported by our computational modeling and the reports of its adverse effects in humans, we feel confident in calling compounds found in kratom, opioids.*[vi]

The FDA confirms that no marketer has sought to develop a drug that includes kratom in the US.[vii] Further, the World Health Organization verifies that kratom and its alkaloids have never been licensed for therapeutic use.[viii] Mitragynine has not been approved for medical use as a drug, nor is it generally recognized as safe by the FDA.[ix]

Kratom is illegal in 33 countries, including Malaysia where it is found naturally.[x] It is also banned in several states, including Alabama, Arkansas, Indiana, Vermont, Rhode Island, Louisiana, and Wisconsin.[xi] [xii] A new law in Connecticut, effective October 1, 2025, requires the state's Department of Consumer Protection (DCP) to designate kratom and 7-hydroxymitragynie as Schedule I controlled substances.[xiii] On December 10, 2025, Connecticut's DCP issued a notice of decision to move forward with the scheduling action.[xiv]

Kratom has also been identified as a Drug of Concern by the US Drug Enforcement Administration (DEA).[xv]

Despite its lack of approved use, kratom and its primary alkaloid, mitragynine, have been used to self-treat conditions such as chronic pain, fatigue, and psychiatric disorders (including substance use disorder and attention deficit hyperactivity disorder). For example, the Ohio Substance Abuse Monitoring Network reported about the availability of kratom in Ohio and its marketing towards individuals who are experiencing opioid use disorder. One respondent noted: "Advertisement for kratom [are] on Facebook…advertised as a way to get off of opiates, certain kinds of opiates; [Kratom] has similar withdrawal [symptoms as heroin]; Kratom mimics the effects of heroin…but the POs (parole officers) are aware of it now." A treatment provider also reported that people are using kratom for its purported health benefits such as the treatment of pain, noting, "you can go to the store and buy [kratom] now…because people look up positive things about it (health benefits). It's a pain reliever…it does give the effect of opiates or heroin…If someone has a little pain and they think it's healthy and natural [then they may try it]…."[xvi]

Still others begin using kratom for relaxation, euphoria, or to enhance performance.[xvii] The end result for many consumers of these products has been an inability to control their use—actual abuse. Below are comments submitted to the Ohio Board of Pharmacy by consumers of products whose manufacturers profess are natural, herbal, or kratom.

- *Good morning. I understand the Ohio Board of Pharmacy is considering a ban on Kratom. I am in support of this ban. I have a family member that has become addicted to Feel Free made by Botanic Tonics. It was originally marketed as a kava drink and alcohol alternative. Come to find out the company is facing many lawsuits due to its false marketing. While they now say it includes kratom, it's too late for my family. The drink is extremely addictive and very strong. I don't believe that it is pure leaf kratom, there has to be more in this drink. It has created many issues for my family and severely negatively impacted my family's life. Please consider this ban. This drink is legal opioid and available at most gas stations. This drink is very addictive and dangerous. Please seriously consider the ban on kratom and more specifically Feel Free. Also, please reference the Reddit thread quitting feelfree, you will see all the people suffering from the dangerous and addictive qualities of this drink.*[xviii]

- *Hello, I am a married wife of a kratom addict. I married my husband 7 years ago after he was clean off drugs (pills, cocaine, weed) for 8 years. He relapsed after 4 years into our marriage and has been addicted to kratom since. He was offered a sample by a gas station attendant … stated "are you looking for energy, try this". Since then he takes up to 60 capsules a day lost 25 pounds and is in a constant state of irritability, speedy, highs, and super lows withdrawling ect. He tried detox once and relapse 2 days later. He says it's so hard to quit bc it's so easy to get and cheap. This garbage is horrible and I cannot believe kids can get a hold of this junk. I am pleading for your office to understand the severity of this "supplement". My soon to be ex-husband has now transitioned to the "7oh tabs" that are more potent and also easy to get apparently sold at smoke shops and cbd stores. I know it is the choice of the individual to pick up a substance and it's their responsibility to quit, but I worry about my kids (16 and 5) in their future if they stumble upon this gas station heroine. To whatever it's worth I just wanted to share my story.*[xix]

- *My husband is a recovering opioid addict. Recently, he was introduced to kratom tablets and began taking them without telling me. When I first noticed the physical changes—his pupils shrinking and his energy levels spiking—I honestly believed he had relapsed on opioids. It was terrifying and brought back painful memories of our past struggles. He has now been taking kratom daily for months. He repeatedly tells me he plans to stop, but I can see that he cannot. He is worried about withdrawal and continues to use it despite the harm it is causing to his health and to our family. To me, this feels like we are back at square one, only with a substance that is currently unregulated and readily available. This is not the first time we have faced this danger. About a year ago, my husband was using the "blue bottle Feel Free" drinks (also containing kratom). After months of daily use, he ended up hospitalized with dangerously high liver enzyme levels and signs of serious liver damage. It took a long recovery, and now we are living through a repeat situation with kratom tablets. I know kratom is sometimes marketed as a "safe alternative" or a supplement, but my family's experience shows otherwise. For people in recovery, it is not a harmless plant—it is another addictive drug that threatens to undo years of hard work and healing.*[xx]

- *Someone very close to me began using kratom thinking it was a safe, natural way to manage stress and pain with out opiates. Over time, I watched it take over their life. They became anxious, detached, angry, and sick when they tried to stop. It broke my*

heart to see how something so easy to buy could cause such deep harm — not only to them, but to everyone who loves them. He would pass out while alone with our 22month old, he has been hospitalized with heart problems from use. We both have missed work, it has damaged our relationship, careers, children, and every aspect of our lives.[xxi]

According to a recent news report, "many people who descended into kratom addiction say gas station products sucked them in. The 'Quitting Kratom' subreddit has 52,000 members and several posts a day from people documenting their journeys trying to quit kratom and 7-OH."[xxii] Medications approved by the FDA to treat opioid-use disorder have been used to treat individuals experiencing substance-use disorder associated with kratom. For example, a case report of a male in his 40s with a history of kratom use was successfully treated with buprenorphine/naloxone, which helped alleviate his withdrawal symptoms and allowed him to abstain from kratom.[xxiii] Other case examples have been cited throughout medical literature to support the use of buprenorphine/naloxone to treat kratom-use disorder.[xxiv] [xxv]

Another study conducted interviews with 395 kratom users and classified users into four distinct categories. Two classes included people using kratom for the self-treatment of chronic pain or substance use disorder and comprised approximately 52 percent of respondents. The other two classes, about 48 percent of respondents, reported using kratom to "get high." The study also notes that individuals who reported using kratom to "get high" and who had the highest probability of kratom-use disorder were more likely to characterize kratom as "habit-forming, addictive, problematic, and inconsistent in its effects."[xxvi]

(2) The scientific evidence of the pharmacological effect of the substance.

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) notes that kratom and its related compounds are selective and full agonists of the μ-opioid receptor. The effects of kratom in humans are dose-dependent, with small doses producing a 'cocaine-like' stimulation while larger amounts cause 'morphine-like' sedative-narcotic effects.[xxvii]

A review published in 2024 notes that "mitragynine intake may be beneficial according to previous scientific data that presents its characteristics in antinociception, anti-inflammation, antidepressant, stimulant activity, sedative activity, anxiolytic activity, cognitive effects, and management of opioid withdrawal, which might be used as natural

remedies for various illnesses." However, the authors noted that uncontrolled use of mitragynine may promote tolerance development and produce withdrawal symptoms upon abstinence."[xxviii]

One study conducted of kratom users in Malaysia found high rates of severe kratom dependence among regular users. More than half of regular users (those using for more than 6 months) reported severe kratom dependence, while 45% showed moderate kratom dependence. Physical withdrawal symptoms commonly experienced include muscle spasms and pain, sleeping difficulty, watery eyes/nose, hot flashes, fever, decreased appetite, and diarrhea. Psychological withdrawal symptoms commonly reported were restlessness, tension, anger, sadness, and nervousness. The study authors also noted that regular users who consumed 3 or more glasses of kratom per day had "higher odds of developing severe Kratom dependence, withdrawal symptoms, and inability to control Kratom craving."[xxix]

Medications approved by the FDA to treat opioid-use disorder have been used to treat individuals experiencing kratom-use disorder. Case examples have been cited throughout medical literature to support the use of buprenorphine/naloxone to treat kratom-use disorder.[xxx] [xxxi] There are also examples of treating kratom withdrawal symptoms with medications such as clonidine and hydroxyzine that are often used off-label to manage opioid withdrawal.[xxxii] [xxxiii] [xxxiv]

A case report of a male in his 40s with a history of kratom use was successfully treated with buprenorphine/naloxone, which helped alleviate his withdrawal symptoms and allowed him to abstain from kratom:

> *The patient was introduced to kratom 12 years ago by his brother for relaxation, stress relief, and as a substitute for oxycodone. He gradually increased his dose up to 40g of powder per day from an initial 6g/daily. He purchased kratom online and at a local gas station, and his weekly expenditure on the substance ranged from $100 to $600. Over time, he spent less time with family and friends, engaged in fewer recreational activities, and spent more time using kratom to relax at home. He realized that he was dependent on the substance when he experienced withdrawal symptoms such as diarrhea and anxiety when he skipped or reduced his use of the substance. He attempted to self-treat his addiction by decreasing his dose but experienced severe withdrawal symptoms, including stress, headaches, diarrhea, nausea, and dizziness. His inability to quit kratom*

prompted him to seek medical help from his primary care physician. This was his first time seeking help from a physician. The patient was provided with the opportunity to connect with substance abuse clinics and other self-help groups, but he preferred pharmacological treatment.[xxxv]

(3) The state of current scientific knowledge regarding the substance.

Little clinical dosing research exists for kratom and its primary alkaloid, mitragynine. Neither kratom nor mitragynine have progressed past Phase 1 clinical trials.[xxxvi] [xxxvii] "Despite the increasing availability of human in vitro and in vivo animal data, rigorous fundamental information about the pharmacokinetics of kratom alkaloids in humans remains limited."[xxxviii]

Of the sparse pharmacokinetic research available, one study of twelve enrolled subjects monitored plasma levels of mitragynine and one of its metabolites, 7-hydroxymitragynine (7-OH), at various doses. The study found that 7-OH in plasma increased in a dose proportional manner after subjects consumed mitragynine contained in botanical kratom. The study also concluded that 7-OH steady state is reached after seven days of continuous dosing.[xxxix]

An increasing amount of 7-OH in plasma that is proportional with an individual's dose of mitragynine is important for two reasons. First, as discussed under Factor 4 below, mitragynine found in consumer products today is often several times more potent than traditional leaf products. Second, 7-OH is approximately 10 times more potent than mitragynine.[xl] At just 10 times the potency of mitragynine, the effects and actual abuse of 7-OH prompted Food and Drug Administration (FDA) Commissioner Dr. Martin Makary to warn that it could be the next wave of the opioid crisis.[xli]

Mitragynine has not undergone randomized, placebo-controlled studies necessary to demonstrate efficacy for any condition while minimizing the significant risks associated with it.[xlii] "FDA has warned consumers not to use kratom because of the risk of serious adverse events, including liver toxicity, seizures, and substance use disorder (SUD). In rare cases, deaths have been associated with kratom use, as confirmed by a medical examiner or toxicology reports."

Significantly, Phase I clinical studies explore the safety and tolerability of substances on 100 or fewer healthy adults.[xliv] Most drugs—nearly 70 percent—that undergo Phase 1 clinical trials succeed to Phase 2 clinical trials. It is not until Phase 2 that research on a substance's ability to treat a condition and its side effects are studied. This usually occurs with several hundred subjects who have the disease or condition in question. Approximately 33 percent of substances proceed to Phase 3 where efficacy is continued to be studied, and adverse effects are monitored on somewhere between several hundred to several thousand individuals with the disease or condition in question.[xlv]

(4) The history and current pattern of abuse.

Kratom has been used for centuries in Southeast Asia by laborers for its stimulant and analgesic effects.[xlvi] As previously discussed, kratom and its primary alkaloid, mitragynine, have been used to self-treat conditions such as chronic pain, fatigue, and psychiatric disorders (including substance use disorder and attention deficit hyperactivity disorder). Still others begin using kratom for relaxation, euphoria, or to enhance performance. [xlvii]

Despite a long history of use originating from Southeast Asia, the widespread commercialization of kratom and its primary alkaloid, mitragynine, is a recent development. Both products sold as vegetation and those labeled as ground vegetation have been found to contain several times the amount of mitragynine than actual kratom leaf material. [xlviii] Indeed, manufacturers of products marketed as "all-

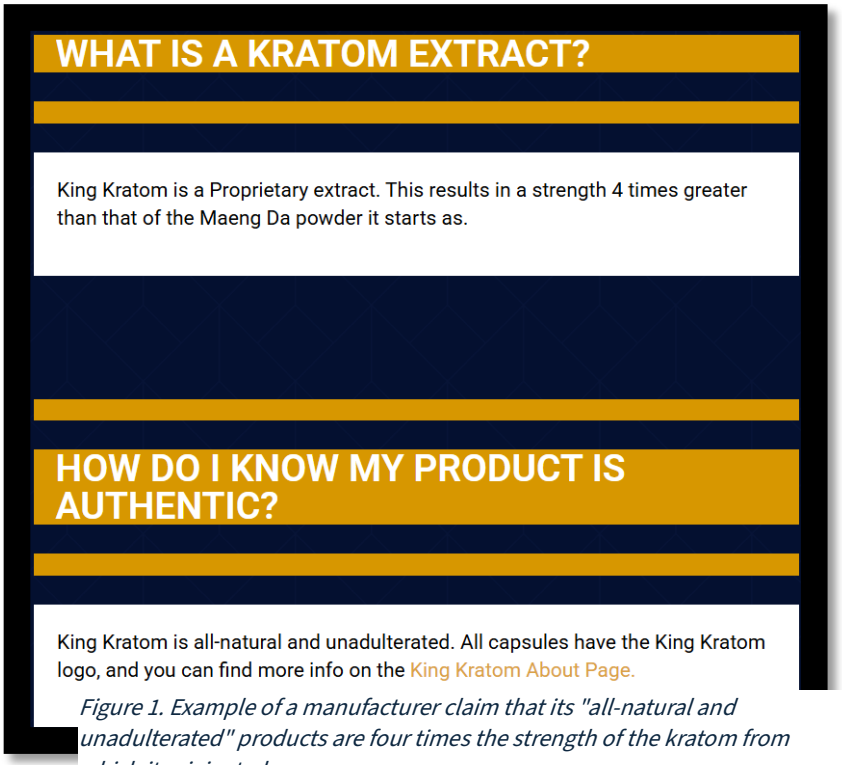


Figure 1. Example of a manufacturer claim that its "all-natural and unadulterated" products are four times the strength of the kratom from which it originated.

natural and unadulterated" acknowledge that extracts are several times greater than the plant from which they start (see Figure 1).[xlix] Postmortem toxicology findings from patients who used kratom had concentrations "higher than those reported in Thai individuals consuming traditional kratom tea without adverse effects."[l]

As kratom commercialization has grown, so too have the number of adverse events reported to poison control centers. From January 1 to July 31, 2025, poison control centers in the United States (US) received 1,690 reports of exposure cases involving kratom, a number that already surpasses the total for all of 2024.[li] Notably, adverse events associated with items that can be categorized as supplements are underreported. At least one source estimates the reporting rate for adverse events related to supplements to be approximately 2 percent.[lii] Reports of kratom exposure have been associated with opioid toxicities including seizures, agitation, and death.[liii]

The Ohio Substance Abuse Monitoring (OSAM) Network report from January 2025 found kratom use associated with opioid use, as the substance reportedly has similar effects, and kratom is reportedly advertised to help mitigate opioid withdrawal symptoms and stop opioid use. While its notoriety appears to be causing drug screening to expand, there is evidence that some individuals consumed kratom because it would not appear on drug screens. One testimonial provided, *"[a]dvertisements for kratom* [are] *on Facebook … advertised as a way to get off of opiates, certain kinds of opiates;* [Kratom] *has similar withdrawal* [symptoms as heroin]*; Kratom mimics the effects of heroin … but the POs (parole officers) are aware of it now."*[liv]

Access to mitragynine can be further abused when it is isolated from kratom leaves. It can then be synthetically transformed into 7-OH and other semi-synthetic opioids—some with significantly enhanced μ-opioid receptor activity. One such compound, MGM-15 (dihydro-7-hydroxy mitragynine), first described in 2014, is a highly potent semi-synthetic opioid that can be synthesized from 7-hydroxymitragynine in a single step. In September 2025, the presence of MGM-15 was confirmed in commercially available tablets.[lv] These compounds were legally available in Ohio until rule 4729:9-1-01.1 of the Ohio Administrative Code became effective on December 12, 2025.[lvi]

(5) The scope, duration, and significance of abuse.

Although there is apparent consensus that the number of Americans who use kratom is in the millions, the precise number of those who use it is more nebulous. The Substance Abuse and Mental Health Services Administration estimated that in 2021, 1.7 million Americans aged 12 and older used kratom.[lvii] More recently, Harvard Medical School estimated that between 2 and 15 million Americans may be using kratom.[lviii]

The Ohio Substance Abuse Monitoring (OSAM) Network report from January 2025 found kratom use associated with opioid use, as the substance reportedly has similar effects, and kratom is reportedly advertised to help mitigate opioid withdrawal symptoms and stop opioid use. They stated: *"[a]dvertisements for kratom* [are] *on Facebook … advertised as a way to get off of opiates, certain kinds of opiates;* [Kratom] *has similar withdrawal* [symptoms as heroin]*; Kratom mimics the effects of heroin … but the POs (parole officers) are aware of it now."*[lix]

One research group prioritized its study in part because, "[t]eas and powders made from the kratom . . . plant are gaining in popularity due to their opioid-like effects."[lx] A treatment provider in the Cleveland region spoke about the promoted health benefits of kratom, saying, *"[y]ou can go to the store and buy* [kratom] *now … because people look up positive things about it (health benefits). It's a pain reliever … it does give the effect of opiates or heroin…. If someone has a little pain and they think it's healthy and natural* [then they may try it]*…"*[lxi]

Reportedly, kratom is desirable to some because it is not always included on drug screens. Treatment providers observed, *"Kratom is still one of those things that's out there that's being abused, that's not being caught* [through drug screening]*; I spoke to our nurse practitioner, and in small doses* [kratom] *doesn't show up on the* [drug] *screen. It's because people are taking way high doses that are detectable* [on drug screens] *that are not good for you, you know, addiction wise; A lot of places don't test for it* [on drug screens]*. So, until we started testing for it, I didn't hear that much about it, but now our lab tests routinely include kratom."*[lxii]

Public comments serve as further evidence of the significance of kratom abuse in Ohio. As discussed in the analysis of Factor 1, the Board of Pharmacy received comments from several individuals regarding the impact of kratom use. Reported impacts include relapses by those

in recovery, significant weight loss, inability to cease use despite adverse impacts on personal relationships and finances, liver damage, and heart issues.

Finally, a reality of modern drug misuse is that an increasing number of individuals engage in polydrug use with little to no knowledge of contraindications. This is true of both illicit drugs and prescription medication. From 2019 to 2023, the amount of unintentional drug overdose deaths in Ohio that involved multiple drugs ranged from 58 to 69 percent.[lxiii] Given this context, it would be irresponsible to discount the risk of polydrug use.

Kratom is no different. "In parallel with the increase in popularity of kratom is an increase in kratom-associated overdose deaths when concomitantly used with other drugs."[lxiv] The impact of consuming kratom with other substances is described in two Reddit posts from those impacted by kratom misuse found in Appendix A. These posts warn that kratom consumption with common medications can cause heart issues and even death.

(6) The risk to the public health.

"FDA has warned consumers not to use kratom because of the risk of serious adverse events, including liver toxicity, seizures, and substance use disorder (SUD). In rare cases, deaths have been associated with kratom use, as confirmed by a medical examiner or toxicology reports."[lxv]

In Ohio, a growing number of deaths associated with kratom have been reported, indicating that it is a risk to public health. From 2019 to 2024, the Ohio Department of Health reported at least 202 deaths in which kratom is listed as a cause of death (see Table 1).

Table 1. Number of Unintentional Drug Overdose Deaths Involving Kratom (Mitragynine), 2019 - 2024[lxvi]							
Year	Total No. of Overdose Deaths	No. of Deaths with Kratom Detected in Postmortem Toxicology	% of Total Overdose Deaths with Kratom Detected in Postmortem Toxicology	No. of Deaths with Kratom Listed as a Cause of Death	% of Deaths with Kratom Detected in Postmortem Toxicology where Kratom Was Listed as a Cause of Death	No. of Deaths with Kratom Detected in Postmortem Toxicology That Were Also Positive for Other Substances	% of Deaths with Kratom Detected in Postmortem Toxicology That Were Also Positive for Other Substances
2019	3,962	19	0.5%	15	78.9%	17	89.5%
2020	4,943	34	0.7%	29	85.3%	29	85.3%
2021	5,174	49	0.9%	37	75.5%	41	83.7%
2022	4,916	47	1.0%	40	85.1%	44	93.6%
2023	4,461	52	1.2%	37	71.2%	43	82.7%
2024*	3,015	54	1.8%	44	81.5%	43	79.6%
Total	**26,471**	**255**	**0.9%**	**202**	**79.2%**	**217**	**85.1%**

**Data for 2024 is not yet complete.*

Several forensic cases of opioid-like deaths with lung congestion and high postmortem mitragynine blood concentrations with no obvious alternative causes of death have now been reported.[lxvii] [lxviii] There is also a report of naloxone being successfully used to reverse kratom intoxication.[lxix] This evidence suggests that high enough doses of kratom alkaloids may cause opioid toxicity via the usual opioid-receptor pathways implicated in conventional opioid overdoses.[lxx]

In 2019, Utah developed a regulatory scheme that allowed continued access to kratom over-the-counter. Despite age restrictions and limited alkaloid access, overdose deaths related to kratom and treatment for kratom use disorder persisted. One emergency room physician reported patients sharing that they "had no idea it was just like a narcotic," and that his patients experience the same withdrawal symptoms as those withdrawing from narcotics.[lxxi] The Utah State Medical Examiner reported nearly 160 kratom-related deaths over a five-year period. While most of those overdoses involved polysubstance use, the state saw almost 50% as many kratom-only deaths in the most recent 12-month reporting period as Utah had seen since 2014.[lxxii] Consequently, the Utah legislature proposed to add all alkaloids from kratom and their analogs to the state's list of controlled substances in November 2025. The bill sponsor originally voted to regulate kratom in 2019 but now "sees kratom in all forms as a dangerous opioid masquerading as a supplement."[lxxiii]

There are also documented cases of kratom use by expecting mothers resulting in neonatal abstinence syndrome for newborns.[lxxiv] [lxxv] [lxxvi] [lxxvii] These cases are particularly concerning given that the promotion of kratom products as safe alternatives to opioids may well persuade expecting mothers to consume kratom products to avoid the adverse impacts of opioids on their unborn child. The concern is compounded by the tendency of consumers to believe that the legal status of a substance means that it is a safe alternative to a controlled substance.[lxxviii]

At least one manufacturer reinforces this notion with misleading statements like, "[f]eel better with the only kratom products studied in clinical trials," and "US Made in our FDA-registered space in Florida" (see Figure 2).[lxxix] The FDA is unequivocal in its warning against kratom use due to its adverse effects.[lxxx] "There are no FDA-approved drugs containing kratom."[lxxxi] According to the FDA, kratom and mitragynine are also unlawful "when added to conventional foods, as dietary supplements, [and] as ingredients in any FDA-approved drug."[lxxxii]



Figure 2. Claims made by a manufacturer of self-proclaimed "pure, unadulterated" kratom.

Evidence supports the position that the ingredients in kratom available to consumers are void of robust quality control. In 2019, FDA conducted laboratory testing on 30 different kratom products from a variety of sources. The analysis found "significant levels of lead and nickel at concentrations that exceed safe exposure for oral daily drug intake."[lxxxiii] A third-party analysis of kratom products also found samples that exceeded daily exposure limits for lead. The authors noted that "non-extract products (powders, capsules, tablets) generally contain greater concentrations of elemental impurities than extract products or the soda preparation."[lxxxiv]

In 2018, the CDC investigated a multistate outbreak of *Salmonella* infections linked to kratom. The agency reported that a total of 199 people were infected with outbreak strains of *Salmonella* across 41 states, including 7 individuals in Ohio. Of those 199, thirty-eight percent of those individuals were hospitalized. CDC investigators stated that "epidemiologic and laboratory evidence indicated that kratom was the likely source of this multistate outbreak."[lxxxv]

The presence of lead and other heavy metals may increase the risk of adverse health outcomes for regular kratom users.[lxxxvi] For example, a case report from Iowa found a patient with suspected Fanconi syndrome from cadmium toxicity due to heavy kratom use. The report found high levels of cadmium in both the patient's blood stream and kratom the patient consumed.[lxxxvii]

According to the World Health Organization, chronic kratom use has been associated with at least 92 cases of liver toxicity. They note that common presenting signs and symptoms include abdominal discomfort, jaundice, pruritus, and dark-colored urine. These typically start about 3 weeks after initiation of kratom use and resolve within one month of stopping kratom use.[lxxxviii]

Additionally, there are no age verification requirements to prevent the sale of kratom products to children. This raises serious concerns about the impact of these compounds on the developing brain. The 2021 National Survey on Drug Use estimates that at least 45,000 adolescents in the US (ages 12-17) used kratom in the past year. This presents public health risks to adolescents given studies showing "adolescent kratom exposure particularly mitragynine and LKD [lyophilised kratom decoction] may cause selective cognitive and behavioural deficits. The brain metabolite profiles further suggest that the altered metabolic pathway (i.e., arachidonic acid, pantothenate and CoA, and tryptophan) may underlie the kratom-induced cognitive and behavioural deficits. Together, these findings demonstrate that adolescents' brain is sensitive to the impact of early kratom exposure during this critical development period."[lxxxix]

(7) The potential of the substance to produce psychic or physiological dependence liability.

Cases of dependence to kratom have been documented for the last several decades.[xc] Mitragynine has agonist activity at μ-opioid receptors and may lead to dependence and addiction.[xci] Further, the European Union Drug Agency, FDA, DEA, Mayo Clinic, and others agree that individuals can develop a dependence to kratom.[xcii] According to the FDA, "[c]ases of kratom-related SUD have also been observed. In these cases, individuals met certain criteria for SUD, including using kratom for longer than intended, using more kratom than intended, having cravings for kratom, continuing to use kratom despite adverse consequences (either physically or in their personal life), increasing the amount of kratom used to produce the same effect (tolerance), and experiencing withdrawal symptoms when kratom use was stopped (physical dependence)."[xciii]

In-person interviews with convenience samples of long-term daily oral kratom users in Southeast Asia find up to three-quarters reporting withdrawal symptoms after cessation of use. Typical withdrawal symptoms include irritability, anxiety, depression, sleep disturbance, lacrimation, rhinorrhea, muscle and bone pain, muscle spasm, diarrhea, and decreased appetite. The likelihood and severity of withdrawal are positively associated with duration, frequency, and intensity of kratom use.[xciv]

Recent news reports also highlight the psychic or physiological dependence of kratom. For example, an Akron woman reported developing "a debilitating kratom addiction" after consuming a product containing the substance thinking it was a safe, "plant-based" drink. She ended up losing her house, marriage, and half of her body weight because of her exposure and subsequent addiction to this compound. The woman reports "her addiction would have taken her life too, had she not gone to rehab in 2024."[xcv]

Another news report demonstrates the danger of having these products readily accessible. An individual using a popular kratom-based drink available at local gas stations reported spending about $2,000 per month (consuming about 10 to 12 bottles per day). According to the report, he "…soon found that after the immediate euphoria from the shot, he would be hit with a cycle of unpleasant symptoms, including a runny nose and achy body." The individual closed down their business and had to seek in-patient treatment.[xcvi]

Finally, it is not unusual for kratom manufacturers themselves to acknowledge the risk of developing a dependence to kratom. One such acknowledgement provides, "[s]ensing the need to up your serving size or not feeling the expected results? A tolerance break might do the trick. Take 2–3 days off from kratom, then restart at a lower serving size" (see Figure 3).[xcvii]

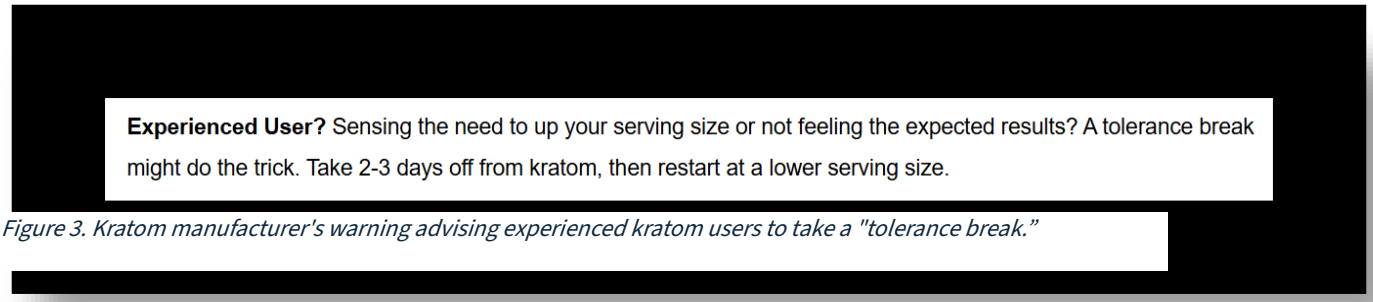


Figure 3. Kratom manufacturer's warning advising experienced kratom users to take a "tolerance break."

Despite warnings that kratom may be habit forming and should not be consumed every day, testimonials posted by kratom manufacturers encourage daily use for relief of discomfort, stating, "this is my favorite kind of kratom. . . It is the best for relieving daily discomfort in your mind or your body."[xcviii] Additional examples from a variety of manufacturers warning of the risk of addiction can be found in Appendix B.

(8) Whether the substance is an immediate precursor.

Mitragynine is a known precursor to mitragynine-related compounds, which are schedule I controlled substances in Ohio. According to the European Union Drug Agency, "[t]he chemical total syntheses reported for several kratom alkaloids are too complex to be used for economic production of any [of] these compounds. However, mitragynine can serve as a chemical precursor to the more potent 7-hydroxymitragynine."[xcix]

Mitragynine is highly likely to follow the same pattern seen with other drug classes like bath salts. Bath salts were created by modifying cathinones, a primary active ingredient found in a plant called khat.[c] As soon as one of those modifications was identified and scheduled, a new cathinone-like compound was developed to evade the law.

Looking to past illicit drug patterns, unexpected ways to synthesize mitragynine-related compounds will be established. At least one pathway would use mitragynine to make 7-OH and then MGM-15, the previously discussed potent opioid already identified in commercially

available tablets.[ci] Should unfettered access to mitragynine remain, we can anticipate the creation of additional potent novel compounds that are marketed to the general public, including children.

Section 4: Finding of the Board

Pursuant to section 3719.44 of the Ohio Revised Code, the Board may add or transfer a compound, mixture, preparation, or substance to Schedule I when it appears that there is a high potential for abuse, that it has no accepted medical use in treatment in this state, or that it lacks accepted safety for use in treatment under medical supervision.

After a review of all available data, the Board finds mitragynine has a high potential for abuse, has no accepted medical use in treatment in this state, and that it lacks accepted safety for use in treatment under medical supervision.

Section 5: Resolution of the Board

Based on these findings, the Board hereby authorizes the filing of rule 4729:9-1-01.2 of the Administrative Code with the Common Sense Initiative and the Joint Committee on Agency Rule Review to classify as a schedule I opiate or opiate derivative any material, compound, mixture, or preparation that contains mitragynine.

Section 6: Proposed Rule

4729:9-1-01.2 – Mitragynine (NEW)

Notwithstanding any other provision of the Administrative Code, the following is classified as a schedule I controlled substance opiate or opiate derivative:

(A) Mitragynine ((αE,2S,3S,12bS)-3-ethyl-1,2,3,4,6,7,12,12b-octahydro-8-methoxy-α-(methoxymethylene)-indolo[2,3-a]quinolizine-2-acetic acid, methyl ester) and / or synthetic substances, derivatives, prodrugs, isomers, esters, ethers, salts, and salts of isomers with similar chemical structure.

Appendix A - Reddit Comments

Kratom had a toxic effect with the antidepressant and antipsychotic meds and killed my daughter

My 24 yo daughter died from mixing her regular prescribed psych meds with kratom. Her full autopsy listed the cause as poly drug toxicity and her prescribed meds were all in therapeutic levels.

The toxicology and full autopsy report confirmed what was in her system:

- Aripiprazole (antipsychotic)
- Lamotrigine (mood stabilizer)
- Venlafaxine (antidepressant)
- Mitragynine (the active compound in kratom)

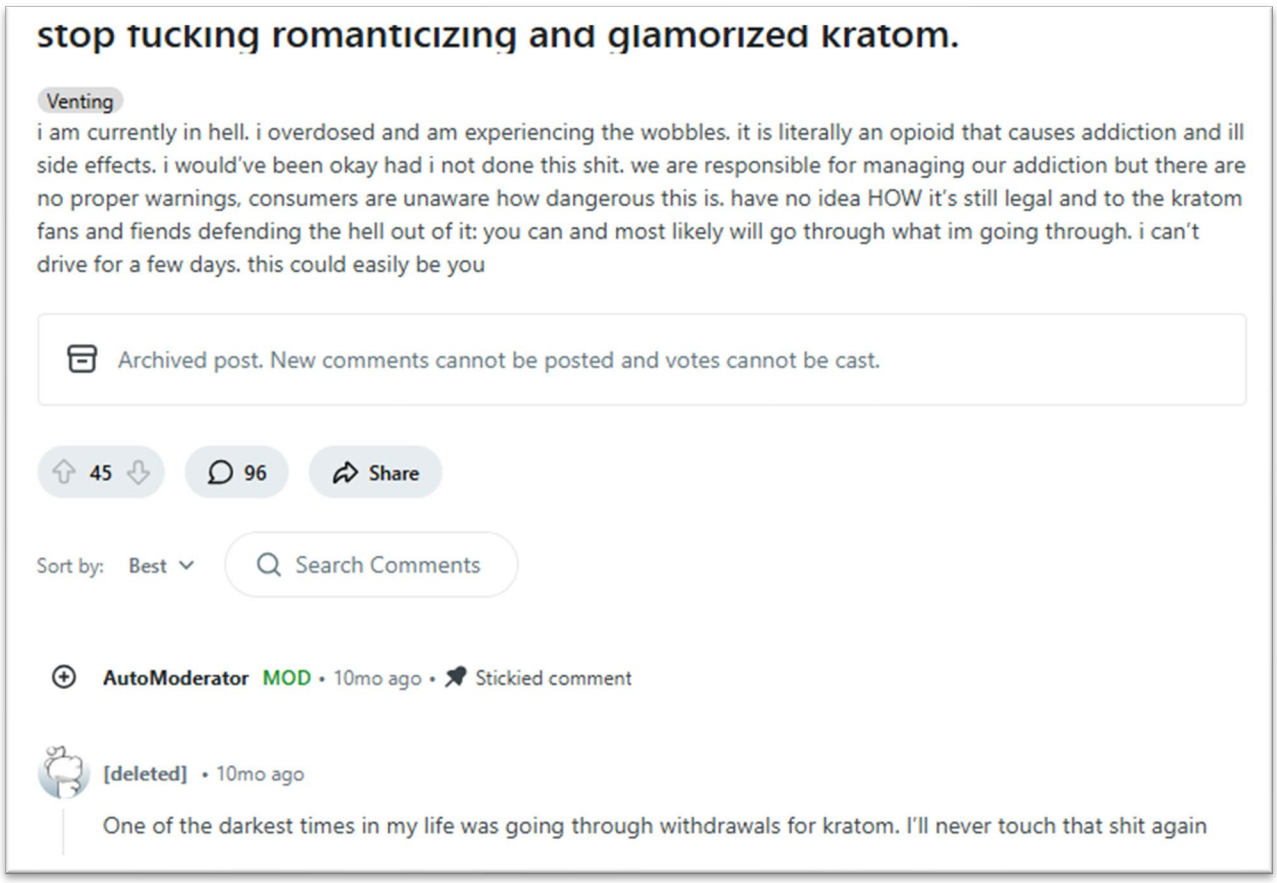
There was no warning on the kratom for interactions with other meds or the dangers. This stuff is sold in smoke shops and gas stations, over the counter and marketed as "natural" and "safe".

I was with her when she died. She was scared. She said she didn't want to die. She felt that something was wrong and her chest hurt. Her heart was beating so fast, then she had cardiac arrest and died right in front of me. CPR could not bring her back. The EMTs gave her narcan, it didn't help.

I've since learned that Kratom AMPLIFIES the toxicity of certain meds (psych meds specifically) and overwhelms the nervous system.

My daughter took what was prescribed to her, and she bought and took something she thought was safe, a supplement.

Kratom is NOT SAFE if you are taking other medications. Please share this information. I know she is not the only one this has happened to and if only there were warnings, it could have saved her life


stop fucking romanticizing and glamorized kratom.
Venting
i am currently in hell. i overdosed and am experiencing the wobbles. it is literally an opioid that causes addiction and ill side effects. i would've been okay had i not done this shit. we are responsible for managing our addiction but there are no proper warnings, consumers are unaware how dangerous this is. have no idea HOW it's still legal and to the kratom fans and fiends defending the hell out of it: you can and most likely will go through what im going through. i can't drive for a few days. this could easily be you
Archived post. New comments cannot be posted and votes cannot be cast.
45
96
Share
Sort by: Best
Search Comments
AutoModerator MOD • 10mo ago • Stickied comment
[deleted] • 10mo ago
One of the darkest times in my life was going through withdrawals for kratom. I'll never touch that shit again

KRATOM WARNING: Do not mix with these medications (heart problems)

Let me preface this by saying I've mixed kratom with tramadol myself and had no problems, but that doesn't mean it's safe. Always air on the side of caution.

I recently found out that kratom is something called a QTc interval prolonger. QTc intervals are an EKG reading. If you mix QTc proloingers, it can potentially cause a heart arrhythmia reaction called torsades de pointes arrythmia. Many common medications and drugs including psych meds and tramadol are QTc interval prolongers.

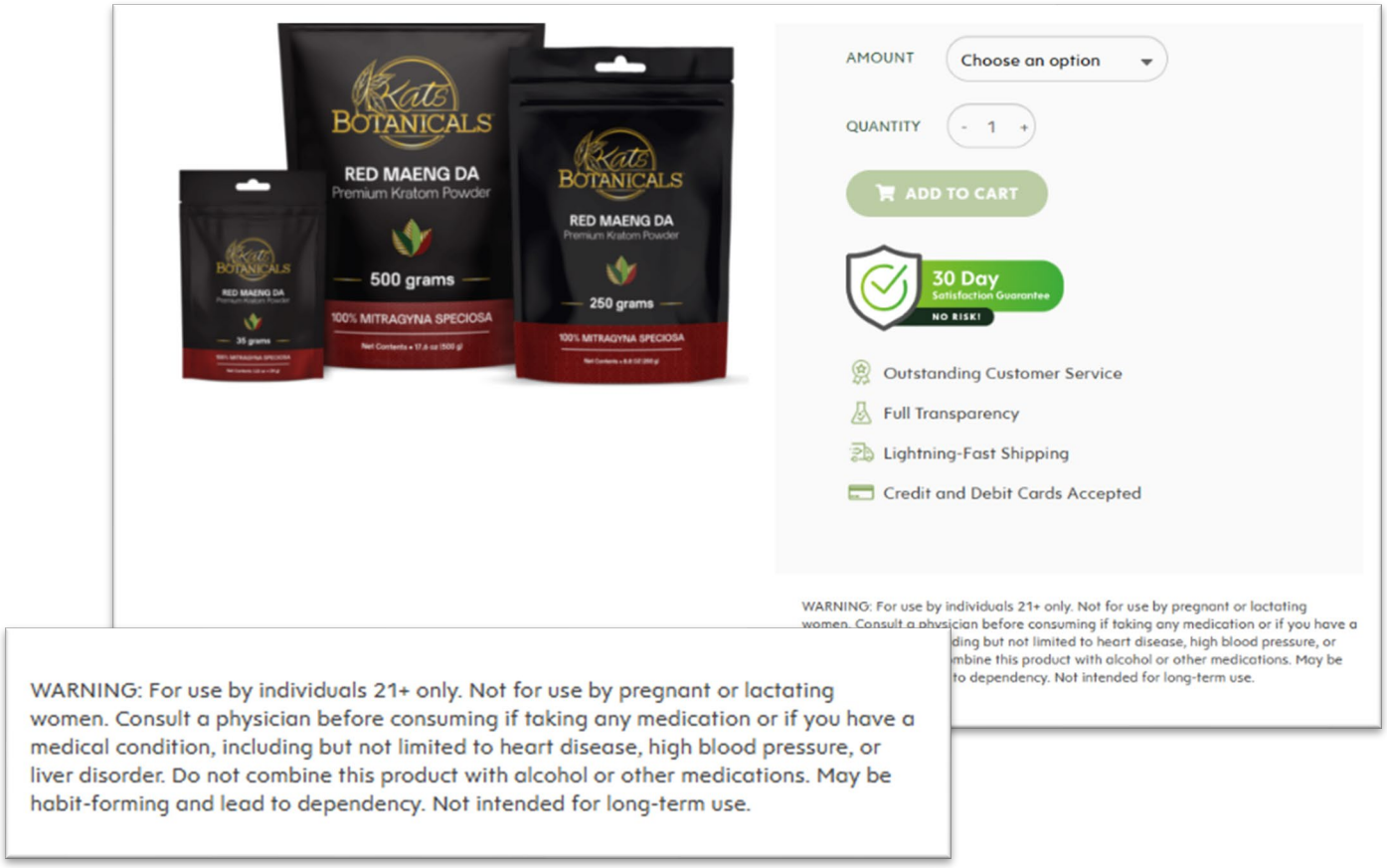
I never heard any warnings about mixing kratom with these medications. This information is important and very very unknown.

If you want to know what medications can cause a torsades de pointes arrythmia, this is a good place to start (although they require registration which is free) https://crediblemeds.org/index.php/login/dlcheck

Click all the AVAILABLE TDP RISK CATEGORIES, set show entries to all,and sort by name or category. There are also usually pubmed articles if you look for them, that will tell you whether a medication is or isn't one.

here is my source for kratom causing this reaction https://www.ncbi.nlm.nih.gov/pubmed/25535742

Appendix B – Product Labels & Examples



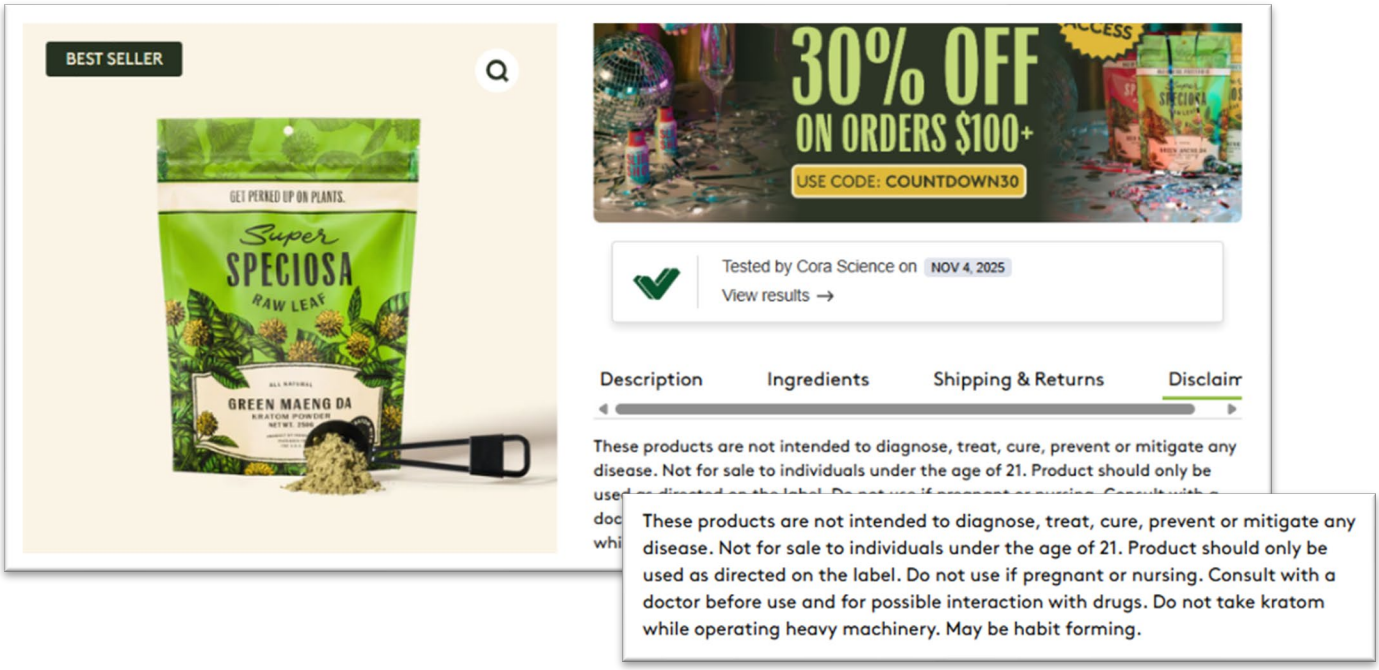
Source: ***https://katsbotanicals.com/product/red-maeng-da-kratom-powder*** ***(Last Accessed Jan 3, 2026)***



Source: ***https://amazingbotanicals.net/product/platinum-kratom-extract-tablets-80-ultra-purified-alkaloids/?srsltid=AfmBOopW-Igl9MBHQuhAoFJ_bvVLkeKiIgZoygOXYMvQH8N02PF3ZbAZ (Last Accessed Jan 3, 2026)***



Source: *https://botanictonics.com/products/feel-free-classic-tonic* ***(Last Accessed Jan 3, 2026)***



Source: https://superspeciosa.com/products/green-maeng-da-kratom-powder?_ab=0&_fd=0&_sc=1&selling_plan=5215191261 ***(Last Accessed Jan 3, 2026)***

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From: Jessica Ingersoll
To: Board Coordination
Subject: Public Opinion/ Kratom Scheduling
Date: Monday, April 13, 2026 7:44:58 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Pharmacy Board Members,

I am writing to urge you to oppose any measures that would restrict access to Kratom. This herbal supplement has been a lifesaver for many individuals dealing with chronic illness and pain.

While regulating synthetic mitragynine may be appropriate, classifying the natural leaf and powder forms as illegal substances would be a mistake. Such a decision would have a significant negative impact on many residents throughout Nevada.

Please feel free to contact me if I can provide further testimony or support regarding this matter.

Sincerely,

Jessica Ingersoll
[redacted]

Darlene Nases

From: Deborah Hicks [redacted]@gmail.com>
Sent: Monday, April 13, 2026 8:33 PM
To: Board Coordination
Subject: Death of granddaughter from "NATURAL KRATOM"

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Members of the Nevada Board of Pharmacy,

My name is Debbie Hicks, and I live in Mesquite, Nevada. I am writing as a grandmother who lost her granddaughter to what was officially determined to be acute mitragynine intoxication.

This was not a mixed drug case. It was not a guessing game. The autopsy and investigation confirmed very high levels of mitragynine, the primary active alkaloid in kratom. She had multiple bags of partially used natural kratom in her home. She used what is commonly sold and marketed as natural kratom. There were no synthetic substances involved.

The findings were clear. Her cause of death was attributed to mitragynine toxicity alone. The medical findings also documented green staining within her stomach and organs, consistent with ingestion of kratom plant material. This was a young life lost to a product widely promoted as safe and natural.

My granddaughter believed what many are being told, that because it is a plant, it is safer. That belief cost her her life.

As you consider whether to classify kratom alkaloids as Schedule I, I ask that you focus on the documented evidence. This substance has no FDA approved medical use, yet it has demonstrated the ability to cause fatal toxicity. The products being sold are unregulated, inconsistent in potency, and accessible without true safeguards.

No family should have to learn the truth this way.

Please put public health and safety first. I urge you to move forward with scheduling kratom alkaloids as Schedule I to prevent further loss of life.

Respectfully,
Debbie Hicks
Mesquite, Nevada

Yahoo Mail: Search, Organize, Conquer

From: DeNae Jones
To: Board Coordination
Subject: Please move forward with Schedule I classification
Date: Monday, April 13, 2026 6:10:56 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Board Members,
I am writing to you as a family member of someone who lost her life to natural kratom.
My niece, died after using natural kratom powder. The coroner confirmed acute mitragynine was the cause of death . This was not speculation. It was not a combination of substances. It was natural kratom.
The autopsy findings showed green staining in her stomach and on some of her organs consistent with kratom tea powder. As well as bags of natural kratom powder bat the scene. This was physically present and directly tied to what she consumed.
What families are experiencing does not reflect a substance that can be safely managed through regulation. Addiction, escalation, and harm are increasing.
Your effort to classify these alkaloids as Schedule I is the kind of action that can prevent further loss.
Please move forward with classification and do not delay action that could save lives.
The outcome of this decision will directly impact whether more families experience this kind of loss.
Sincerely,
DeNae Jones

Yahoo Mail: Search, Organize, Conquer

From:	Di Lucas
To:	Board Coordination
Subject:	Nevada Board of Pharmacy Testimony for Public Workshop #15B 4/16/26 9:00 am
Date:	Friday, April 10, 2026 3:08:56 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Good morning,

Thank you for giving me this chance to let you know what Kratom and 7-OH have done to completely change my life. This story is probably a bit different the some of the other ones you will hear, but I feel it is important to let you know the dangers of Kratom and 7-OH.

My daughter Tana Ray Lam (Lucas) was the apple of my eye, not to say that she was perfect. She had had trouble in her youth and as a young adult with substances, she had worked hard to overcome that part of her life, was happily married to a wonderful man and looking forward to all the wonderful things this life holds. Until she was introduced to Kratom by a co-worker who told her it was a natural substitute for energy drinks and would be better for her, she bought Kratom at her local gas station. That is where everything turned bad, she started doing Kratom 9 years ago, then she heard that Kratom could have lead or other heavy metals and that the "concentrates" were clean and safe. She switched to the "cleaner concentrates" not knowing that the 7-OH in the concentrates were 5 to 50 times more potent than the Kratom powder she had been using. She was able to purchase the 7-OH at her local gas station, smoke shop or online because it is legal and unregulated.

In January 2026 Tana and her husband decided to have a baby so she decided to quit Kratom and 7-OH. She did not know that she should have never tried to go cold turkey but wean off or go through a medical detox. The withdrawals from 7-OH are worse than withdrawals from Morphine, Heroin or Alcohol.

She suffered with the agony and torturous withdrawals of this evil, insidious drug until she could no longer take it. On January 21, 2026, my funny, strong, amazing Tana took her own life to escape the pain of the withdrawals that came from her doing 7-OH. One of the last things she said to her husband was "when I get through this, I will become an advocate to inform people of the dangers of Kratom and 7-OH". She will not see that wish come to realization on this side, so I have picked up where she left off to let people know the snares of Kratom and 7-OH. This easy to get, legal, unregulated danger should be taken off the market ASAP before it costs us more lives.

Thank you again for giving me this chance to tell Tana's story,

Di Lucas
Kingman AZ

From:	Dennis Shove
To:	Board Coordination
Subject:	Kratom Ban Hearing Public Comment
Date:	Thursday, April 16, 2026 1:58:25 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Hi I received an email from IDK saying theres a potential ban trying to be put in effect in NV. I see it has something to do with pharmaceutical companies. I see the email ends with pharmacy.nv. I was told to contact and say no to the Kratom ban.

The main reason is loss of potential prescription patients yes? That's the only reason in my opinion for any kind of ban wanting to be put in effect. There are absolutely no dangers at all and any video testimony is completely staged BS. Ive used Kratom for 10 years before finding and using 7oh for the last 5, another medication pharmaceutical companies are upset with. Calling it addictive and dangerous also. Who is leading this anti everything that makes a person feel better protest? There is absolutely no proof other than more made up phoney testimony. And what product that makes any person feel good not addictive Why woukd anyone stop if it makes them feel better? This isn't coke or meth. That's what its being compared to. And why isn't McDonald's or ice cream being banned? how many billions are addicted to those? How many have died from being overweight and unhealthy from eating "bad" food? That's different though right???? yeah no its not. What's the total number of deaths associated with Kratom or 7oh? hmmmm..Zero. What's the total of deaths associated with prescription medication Oxycodone, percocet, Vicodin, Norco. Millions or so its been said. Crack heads have caused everyrhing to be regulated or banned. Theres weirdos sniffing Muscle relaxers.
I cannot get my achy self out of bed or even get anything done without taking 1 20mg 7oh pill. about 4 a day. My father in law has a tray filled with 30 pills he takes every morning. He's not doing well at all and is in the hospital every other week. Is he addicted? yes. so why arent his bills being banned? I can guarantee 1 7OH will be more effective than all his 30 pills. But damn that's a lot of money the pharmaceutical company won't be making. And that's the only reason for the ban attempt.

The person that emailed me telling me to call in for a meeting about kratom this evening is also a clown. Who put this goofball in charge of defending Kratom?
Telling people what to say if they call using zoom. Telling us to say leave Kdatom alone and ban the "dangerous" 7 oh. I told them where they could go with their idiotic statement. This is my reply back to them.
Dennis Shove
Henderson. NV

I was all for this until I read your ignorant statement about 7 OH. Your wrong about 7OH. Why would u even say it dangerous. How the hell is it dangerous? If you support Kratom u should support 7oh. Thousands of kratom users have switched to it because it works quicker and doesn't taste disgusting. You know nothing of it if u say its dangerous. Ill call and ill let them know what kind of goofball is scripting people what to say. I used Kratom for 10 years until I found 7OH to be much better helping me with pain and giving me a positive attitude and good feeling. If an inexperienced person takes too much they will feel sleepy or as the same with Kratom feel nauseous. No danger. So stop with your no experience accusations. Its people with your mentality that are trying to shut down everything including Kratom.

From:	emileealexander27@everyactioncustom.com on behalf of Emily Alexander
To:	Board Coordination
Subject:	Oppose Mitragynine Scheduling
Date:	Thursday, April 16, 2026 5:57:14 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

To the Nevada Board of Pharmacy,

I am writing to you as a Nevada resident to respectfully ask that you do not move forward with any decision to ban kratom.
Kratom has played such an essential role in my ability to manage daily pain, maintain a functional and productive life..
Before I found kratom, my pain made it difficult to work consistently and meet basic responsibilities.
Since incorporating kratom into my routine, I have been able to stay working, support myself and maintain a sense of stability that would otherwise be out of reach for myself.

For me kratom is not recreational, it is a practical, plant based tool that allows me to live with dignity.
Removing access to kratom would have serious and immediate consequences for my quality of life.
It would make it significantly harder if not impossible to manage my pain effectively and continue working to provide for myself and my family.

I understand the importance of public safety and thoughtful regulation, however, a outright ban would harm responsible individuals like myself who rely on this plant as a safer alternative to other options.

I ask that you consider the real life impact this decision would have on the people in our community who are quietly using kratom to stay functional, independent and engaged in daily life.

Thank you for your time and consideration

Sincerely
Emily Alexander

Sincerely,
Emily Alexander

From: Eric
To: Board Coordination
Subject: Strongly Oppose Scheduling Kratom Alkaloids as Schedule I – Nevada Resident
Date: Wednesday, April 15, 2026 3:35:50 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada State Board of Pharmacy Members,

I am writing as a concerned Nevada resident to strongly oppose the proposed scheduling of mitragynine and 7-hydroxymitragynine as Schedule I controlled substances.

Natural kratom leaf has a long, demonstrated history of safe traditional use and is not comparable to any Schedule I substances, which are defined by having no accepted medical use and a high potential for abuse. I believe the right approach is to regulate dangerous synthetic or concentrated 7-OH products that may pose risks, rather than banning natural kratom leaf that millions of responsible adults use safely.

A Schedule I classification would criminalize law-abiding consumers like myself who rely on this currently legal product under Nevada's existing Kratom Consumer Protection Act. It would remove access to a helpful wellness tool without addressing the actual concerns around adulterated or high-potency extracts.

Kratom has helped my health immensely. It has significantly improved my daily pain management, energy levels, and overall well-being, allowing me to function better without needing stronger prescription options. Real stories from constituents like me show how responsible use of natural kratom supports wellness for many Nevadans.

I respectfully urge the Board to reject this scheduling proposal and instead focus on targeted enforcement and stronger consumer protections that distinguish between safe natural leaf products and potentially harmful synthetics.

Thank you for considering my comments and for the opportunity to provide public input before the April 16, 2026 hearing.

Sincerely,

Eric William

Las Vegas Resident

From: FrG TheMachine
To: Board Coordination
Subject: Kratom Ban Hearing Public Comment
Date: Wednesday, April 15, 2026 12:16:38 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Good afternoon,

Please oppose scheduling kratom alkaloids as Schedule I. Natural kratom leaf has a demonstrated history of safe use and is not comparable to Schedule I substances. Regulate dangerous synthetic 7-OH products — not natural kratom."
Natural Kratom leaf helped me get off a 3yr addiction to prescription pain pills. I tried every other doctor approved method prior to get my addiction cleaned up & nothing they prescribed worked for me. Kratom is nothing like an opioid, the synthetic 7-OH is what needs to be scheduled. All these synthetics are what is actually hurting people. Any normal Kratom user is not taking 7-OH pills, gummies & however else they market it. There are thousands of other out there with similar stories that natural Kratom has saved. So keep natural Kratom regulations that are already in effect in place & ban the synthetics!!

From: colfergavin@everyactioncustom.com on behalf of Gavin Colfer
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Tuesday, April 14, 2026 7:51:16 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

Hello,

My name is Gavin and I am an advocate for natural kratom leaf. My experience with kratom has been very positive. Kratom is a natural plant that has wonderful medicinal properties such as pain relief, anxiety relief, and overall can greatly benefit persons in all walks of life.

To take away this valuable plant medicine who those who need it for a variety of different reasons is unfair and will do more harm than good. People have been using this plant to stay off of both prescribed and synthetic street opioids which contribute to the epidemic our country has been facing in the last decade. Furthermore, making Kratom illegal can have the unintended effect of creating a black market for those who need this plant for their quality of life. This could be incredibly dangerous if people seek out black market products. Education and research is a much better route in terms of handling kratom legislation. I ask on behalf of myself and all of those who use kratom in a safe and responsible manner to please reconsider the criminalization of this natural plant medicine.

Thank you for your time and I hope you take my testimony as well as many others into consideration.

Sincerely,
Gavin Colfer

Sincerely,
Gavin Colfer

From: Hannah Mckinnish
To: Board Coordination
Subject: Kratom ban
Date: Thursday, April 16, 2026 3:18:13 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Hello,
I am a two time small business owner in Nevada who relies on the use of kratom to survive because of the midevil age laws you have created against opiates for sick people. The medical board has made it impossible for chronic pain patients to get the medicine they need to survive. I am a chronic pain patient with 5 diagnosed diseases. 2 of which are some of the most painful diseases known. Last year I was ripped off my pain meds because I was “too young” to feel pain according to my doctor, the same doctor who has never felt the pain I live in in a daily basis. Kratom is the only thing I have to keep my pain even somewhat subdued so I can go to work and pay pmy bills. If you also ban this, you will be responsible for the deaths of many people. None of us asked for the pain were In. We didn’t ask doctors to over prescribe and cause a mass epidemic. That was the multi millionaires and corporations, yet we are the ones getting punished.
Maybe before banning this substance, you can lighten your restrictions on other meds so people in real pain, like me, can get the meds they need to have any sort of quality of life.

From: radiostarhn@everyactioncustom.com on behalf of Heather Morgan
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Wednesday, April 15, 2026 9:55:36 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

Hello, my name is Heather, and I am writing to ask you to oppose any Kratom ban bill, and to please support regulation in Nevada instead. Kratom has helped me with my anxiety and chronic back pain and due to it my life has improved significantly. Kratom is not dangerous, it's natural and healing. I would not be able to live my life fully, and I believe in a person's indivdual freedoms to help choose the right solution for the problems they experience. Thank you for your time today!

Sincerely,
Heather Morgan

From: Hunter Shaw
To: Board Coordination
Date: Monday, April 20, 2026 10:53:12 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Members of the Nevada Board of Pharmacy,

I am writing to formally express my opposition to the proposed ban on 7-hydroxymitragynine (7-OH).

This substance is a critical component of my daily health regimen, enabling me to effectively manage chronic pain and avoid the use of illicit opioids. It has been essential to my personal recovery and has significantly improved my quality of life while managing long-term health challenges.

Furthermore, I would like to highlight the current lack of scientific evidence suggesting that 7-OH is dangerous or life-threatening. I urge the Board to consider the positive impact this substance has on individuals who rely on it as a safer alternative for pain management before making a final determination.

Thank you for your time and for considering my testimony on this important matter.

Best regards,

Hunter Shaw

From:	Hilary Tesluck
To:	Board Coordination
Subject:	Re: Attendance for 4/16 at 9am
Date:	Wednesday, April 15, 2026 10:28:29 AM
Attachments:	Di Lucas Written Statement.pdf Lexi Written Statement.pdf Bob Peters Written Statement.docx Info - NV Board of Pharmacy Kratom Hearing.pdf

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Good evening,

Thank you for the information. I have attached an infographic along with written and video testimonials for the upcoming hearing.

Submission Summary:

- **Written:** 3 Testimonials
- **Video:** 4 Testimonials (approx. 1 min each)
- **Total Impact:** 6 unique constituents represented (Ms. Lucas provided both formats).

Video Testimonials:

GA Christina Galindo KratomTestimony
GA Kelly Rinaldi Kratom Testimony
TN Jimmy Price Kratom Testimony
AZ Di Lucas Kratom Testimony

Thank you again for helping to coordinate this important hearing. Please let me know if anything provided requires a different format.

Kindly,
--
Hilary Tesluck
Executive Director
End Kratom Addiction
P: (810) 887-8753 | E: hilary@endkratomaddiction.org
www.endkratomaddiction.org

EndKratom
ADDICTION ADVOCACY

PROTECT NEVADA
CLASSIFY KRATOM AND 7-OH AS SCHEDULE I

THE PROBLEM:
Kratom and its alkaloids work as potent opioids in the body, creating a high risk for addiction and physical dependence. Despite acting on mu-opioid receptors, these products are sold without restriction in gas stations and vape shops throughout Reno, often marketed as "wellness tonics" or "herbal supplements.

THE RECOMMENDATION:
The Nevada Board of Pharmacy is at a critical juncture in evaluating the placement of mitragynine and 7-hydroxymitragynine (7-OH) within the state's controlled substance schedules. Given the substance's immediate accessibility and the sometimes fatal documented adverse events, Schedule I classification is the only designation that aligns with the statutory criteria for public safety.

THE INDUSTRY'S OWN WARNINGS:

O.P.M.S. Optimized Plant Mediated Solutions

Using Mitragyna Speciosa can be dangerous. There have been reports of adverse health effects associated with using kratom products. Some publications have suggested kratom may be associated with serious potential side effects, including seizures, liver damage, withdrawal, addiction, abuse, and death. Please review the FDA's advisories and commentary for concerns about kratom products, available at the FDA's website.

Happy Hippo

Kratom may have addictive properties that can cause dependency issues. Please speak to a physician before using Kratom or any botanical compound. The U.S. Drug Enforcement Administration (DEA) lists Kratom as a 'Drug and Chemical of Concern.' The U.S. Food and Drug Administration (FDA) has not approved Kratom as a dietary supplement or for any medical use. The FDA is actively evaluating Kratom and currently recommends against consumption of Kratom due to concerns about the risks of addiction, abuse, and dependence.

feel free.

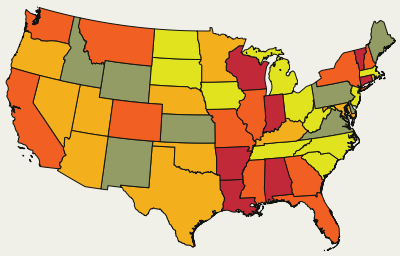
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MILITARY BANS:
Kratom was recently banned by the Marine Corps and Navy Reserve.

For more info on kratom visit EndKratomAddiction.org

THE REASONS:
The following evidence supports the immediate necessity of Schedule I classification to address a documented public health crisis in Nevada and nationwide:

1. **1,200% Surge in Poisonings:** Recent CDC analysis of the National Poison Data System found that kratom-related exposures increased from **258** in **2015** to **3,434** in **2025**, a record high.
2. **Confirmed Mortality:** In Nevada alone, **118 kratom-related deaths** were reported by the CDC for the years 2020-2024. In one case, mitragynine was the sole cause of death.
3. **Unpredictable Liver Failure:** Case reports show that regular use of raw leaf powder is associated with severe hepatotoxicity (liver injury), including jaundice and acute hepatitis, occurring unpredictably **even in low-dose users.** (NIDA, 2026)
4. **Documented Withdrawal Crisis:** A 2026 audit of emergency department visits revealed that 30.4% of kratom-related hospitalizations were **specifically for managing severe withdrawal symptoms** from **kratom leaf** products (Tennessee Department of Health, 2026).
5. **Morphine Substitution:** Studies show **both** mitragynine (leaf) and 7-OH fully substitute for morphine in the central nervous system, making them functionally identical to classic addictive opioids (Johns Hopkins University, 2026).



ADDICTION STORY: HERBAL ENERGY DRINK



As a college athlete, our son, Cameron (Midlothian), was led to believe traditional kratom was a safe, plant-based, herbal supplement to boost focus, mood, and energy. In time, his life took a downward spiral, but we didn't associate it with the green kratom powder he mixed like tea—until a terrifying trip to the ER late one night. It eventually took a five day outpatient detox process—similar to heroin—to get him through the withdrawal. His road to recovery was hell. I wouldn't wish it on anyone, and he's still not whole.

– Dean Francis (Dad)

Kratom was introduced to me by a friend who was seeking a non-alcoholic alternative for her husband and herself. She introduced and recommended a Kava bar which I have never heard of before. The Kava bar itself sold Kratom leaf teas, kava, and other botanicals. These said drinks were not mentioned as having any health impacts nor were there any warnings or labels within the shop that would have concluded me to believe that Kratom would cause harm. After spending many months in the kava bar scene, I found Feel Free to be another alternative to Kratom related product that was stronger and easier to purchase due to it being at gas stations and vape shops. Feel Free became my larger addiction due to the ease of access and it being easier to transport than Kratom tea. During this time, I had noticed that the Kratom tea leaf product had made me more dependent on consuming thus leading to heavier consumption of Feel Free Products. If I did not take Feel Free shots, I did not feel well and started to experience withdrawal symptoms, but I have never had previous problems with an opioid substance. I just spiraled and eventually kept increasing my consumption of Feel Free bottle till I peeked between 8-10 bottles a day along with kratom tea and sometimes various powders as well. After about two years of using Kratom products such as tea, powder, and Feel Free, I had lost almost 40 pounds and was very lethargic, malnourished, and not in a good state of health. I decided to consult an addiction doctor after reading Reddit testimonials. I suffered through two weeks of acute withdrawal symptoms which sent me to the emergency room on day two of my quitting process. It took weeks to regain a regular sleep schedule and to gain good weight back. During this time, I found a few support groups to work through the recovery process but also heard of products such as 7-OH, synthetic kratoms, and various other Kratom related products that have also impacted thousands of other people. These products are not safe and there is an abundance of false information and marketing tactics used against consumers. These products and all Kratom related

products need to be banned. They are not safe for consumer consumption, and we have all heard the stories that the Kratom companies will tell you are false and lie constantly about. It is time for our local, state, and federal officials to look at this seriously. These products cause a lot of harm to others, and I have seen that firsthand myself. Please do your research and understand that these products need to be removed from stores and online retailers before this becomes a larger issue.

Thank you for your time and consideration.

Bob Peters

Cleveland, OH

Good morning,

Thank you for giving me this chance to let you know what Kratom and 7-OH have done to completely change my life. This story is probably a bit different from some of the other ones you will hear, but I feel it is important to let you know the dangers of Kratom and 7-OH.

My daughter Tana Ray Lam (Lucas) was the apple of my eye, not to say that she was perfect. She had had trouble in her youth and as a young adult with substances, she had worked hard to overcome that part of her life, was happily married to a wonderful man and looking forward to all the wonderful things this life holds. Until she was introduced to Kratom by a co-worker who told her it was a natural substitute for energy drinks and would be better for her, she bought Kratom at her local gas station. That is where everything turned bad. She started doing Kratom 9 years ago, then she heard that Kratom could have lead or other heavy metals and that the "concentrates" were clean and safe. She switched to the "cleaner concentrates" not knowing that the 7-OH in the concentrates were 5 to 50 times more potent than the Kratom powder she had been using. She was able to purchase the 7-OH at her local gas station, smoke shop or online because it is legal and unregulated.

In January 2026 Tana and her husband decided to have a baby so she decided to quit Kratom and 7-OH. She did not know that she should have never tried to go cold turkey but wean off or go through a medical detox. The withdrawals from 7-OH are worse than withdrawals from Morphine, Heroin or Alcohol.

She suffered with the agony and torturous withdrawals of this evil, insidious drug until she could no longer take it. On January 21, 2026, my funny, strong, amazing Tana took her own life to escape the pain of the withdrawals that came from her doing 7-OH. One of the last things she said to her husband was "when I get through this, I will become an advocate to inform people of the dangers of Kratom and 7-OH". She will not see that wish come to realization on this side, so I have picked up where she left off to let people know the snares of Kratom and 7-OH. This easy to get, legal, unregulated danger should be taken off the market ASAP before it costs us more lives.

Thank you again for giving me this chance to tell Tana's story,

Di Lucas
Kingman AZ

To Whom It May Concern,

My name is Lexi Rose, and I am writing to share my personal experience with 7-hydroxymitragynine (7-OH) that is currently being sold in vape and smoke stores, many of which do not ask for ID upon selling substances

I initially tried 7-OH out of curiosity after hearing it could make me feel good. Within only a few days it became something I felt I needed to take regularly. What began as experimentation quickly turned into a habit that I could not stop. I got addicted for almost the entirety of 2026.

During the three months I used 7-OH, I experienced two overdoses. One episode involved severe hallucinations where I heard voices, saw things that I knew were not there but still terrified me to see them, and felt like people were in my apartment when they were not. It was horrifying and made me feel as though I was on the verge of a psychiatric crisis. In another incident, I woke up violently vomiting, with blurred vision and temporary hearing loss. Paramedics responded and told me I likely had to wait for the drug to leave my system. From both situations, I ended up okay, but makes me fearful for others who could be doing this. I am particularly fearful of this being sold to kids under 21 because most shops don't ask for ID (I am 31 but look young and should be carded). Children could get addicted and be afraid to tell their parents and experience an overdose or a crisis like I did. Same with adults; this substance can harm anyone

My addiction escalated quickly. There were multiple stores selling 7-OH within a mile or two of my home, which made it extremely easy to continue purchasing it. Over those months I drained my bank account and eventually lost my job. I lost all of my money due to this substance and had to detox at home, and then at a treatment center because I could not handle the pain alone.

When I finally stopped using 7-OH, the withdrawal was severe. For roughly two weeks I experienced extreme body pain, sweating, hot and cold flashes, vomiting, muscle spasms, insomnia, and hallucinations. Even now, nearly three weeks after stopping, I continue to have pain that starts in my feet and radiates up my legs and back. I now require multiple medications daily just to manage the pain and muscle spasms. These medications have me absolutely exhausted all day but I have to take them anyway because the pain is unbearable. I can't work under these conditions that the medicine has contributed to.

This substance completely changed my behavior and mental health while I was using it. I became irritable, obsessive about obtaining more, and experienced worsening ADHD symptoms and manic behavior.

I am sharing my experience because these products are widely available in retail stores, and many people likely assume they are safe. My experience shows how quickly this substance can cause serious harm. I don't want others to go through what I went through when I simply thought it would just be a fun pain relieving substance while it truly is an addictive and evil product

I urge policymakers to closely examine the availability and regulation of both mitragynine and 7-hydroxymitragynine products so others do not experience the same harm I did. Please consider banning this completely.

Thank you for your time,

Lexi Rose

From: Holly Trouville
To: Board Coordination
Subject: Kratom death
Date: Monday, April 13, 2026 5:56:04 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada Board of Pharmacy,

I am writing tin favor of scheduling all Kratom, natural and synthetic

My name is Holly Trouville and I lost my only child, my 25-year-old son Tyrell to Mitragynine toxicity on Feb. 6th, 2024. It was his sole cause of death. He had no opioids in his system and nothing else contributed to his death (see attached death certificate). He died from drinking a Kratom seltzer marketed as alcohol free, caffeine free, sugar free, and had less than 2 % 7OH that Kratom advocated claim is safe.

I am not making money, I am not a lobbyist in the billion-dollar Kratom industry, and I am not a user. My only goal is to prevent another parent to have to feel the complete and utter devastation that I feel on a daily basis.

You will hear and see a lot of Kratom advocates, people like Mac Haddow, and others trying to push through a KCPA law they claim is safe. To determine the safety of Kratom, the AKA Is entrusted to determine which vendors pass GMP standards. However, The AKA GMP (Good Manufacturing Standards) program focuses on **ONLY** validating that the manufacturing process ensures consistency and safety, rather than inspecting each individual item produced. The people determining dosage are the vendors and the consumers themselves.

What this means, and is of utmost importance, is that the AKA cannot determine the alkaloid profile and concentration of Kratom plants. It is because the geographical origin of Kratom matters significantly as it is directly influencing the alkaloid profile and concentrations. This is turn determines the plants potency and its effects which is due to changes in soil composition, climate, environmental stress, harvesting production, etc.

Most of the Thailand Kratom leaves have 66 percent Mitragynine in them while others may have 22 percent. This is quite important and concerning and; further proves why the alkaloid content makes a difference.

You will hear advocates say that 7OH is unsafe and to ban it. What they will not say though is to make 7OH, you extract pure mitragynine and mix it with other chemicals in a lab. Mitragynine breaks some of itself down into 7OH, naturally in the system with liver enzyme CYP34A. How then can any person argue that mitragynine is safe? Pharmacology does not change. Just because you turn 21 does not make it safe. You cannot fight science.

In SE Asian countries, ingesting Kratom was by chewing fresh leaves or boiling them. But, in the U.S., Kratom is marketed primarily through online vendors, convenience stores, and specialty shops. Its products now include powders, capsules, tablets, concentrated extracts, gummies, and energy drinks. These formulations contrast sharply with traditional Southeast Asian use and enable higher, more concentrated, and more frequent dosing. That is the current problem.

Even though the AKA says these SE Asian countries have been using it safely for years, I have attached an article from Bangkok Thailand, written 4 weeks ago, about the dangers of Kratom. It is being called a narcotic there.

Also, There are a growing number of Kratom deaths where Mitragynine is the sole cause of death.

However, many Kratom deaths do have more than one substance in the body at the time of death.

That should be even more concerning as there is not enough scientific evidence to know mixing what substances with Kratom will cause adverse effects.

A polysubstance does not mean a mixture of drugs like fentanyl. It could be Benadryl, prescription drugs, alcohol, etc. The people determining dosages are the vendors and customers themselves.

I am attaching a picture of a AKA certified, GMP stamped natural powdered Kratom currently sold in stores. Notice the back says only for use as a botanical specimen. That means not for human consumption. There should be no debate about the dangers of Kratom after reading that.

I implore you to ban all Kratom. There is no oversight, no regulation, and it should not be able to be controlled by the vendor and consumer.

Just last week the CDC came out with the numbers for Kratom poison control calls between 2010-2015. It jumped 1200 percent for single substance and 1300 for polysubstance. That should be concerning.

Thank you and with much respect,

Holly

I have also attached a series done by the Tampa Bay Times on Kratom. I hope you read it as it is very eye opening.
https://www.bangkokpost.com/thailand/general/3210399/thai-youth-drug-use-reaches-crisis-stage

https://project.tampabay.com/investigations/deadly-dose/kratom-overdose-deaths-florida-mitragynine-testing/

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3 attachments Download all



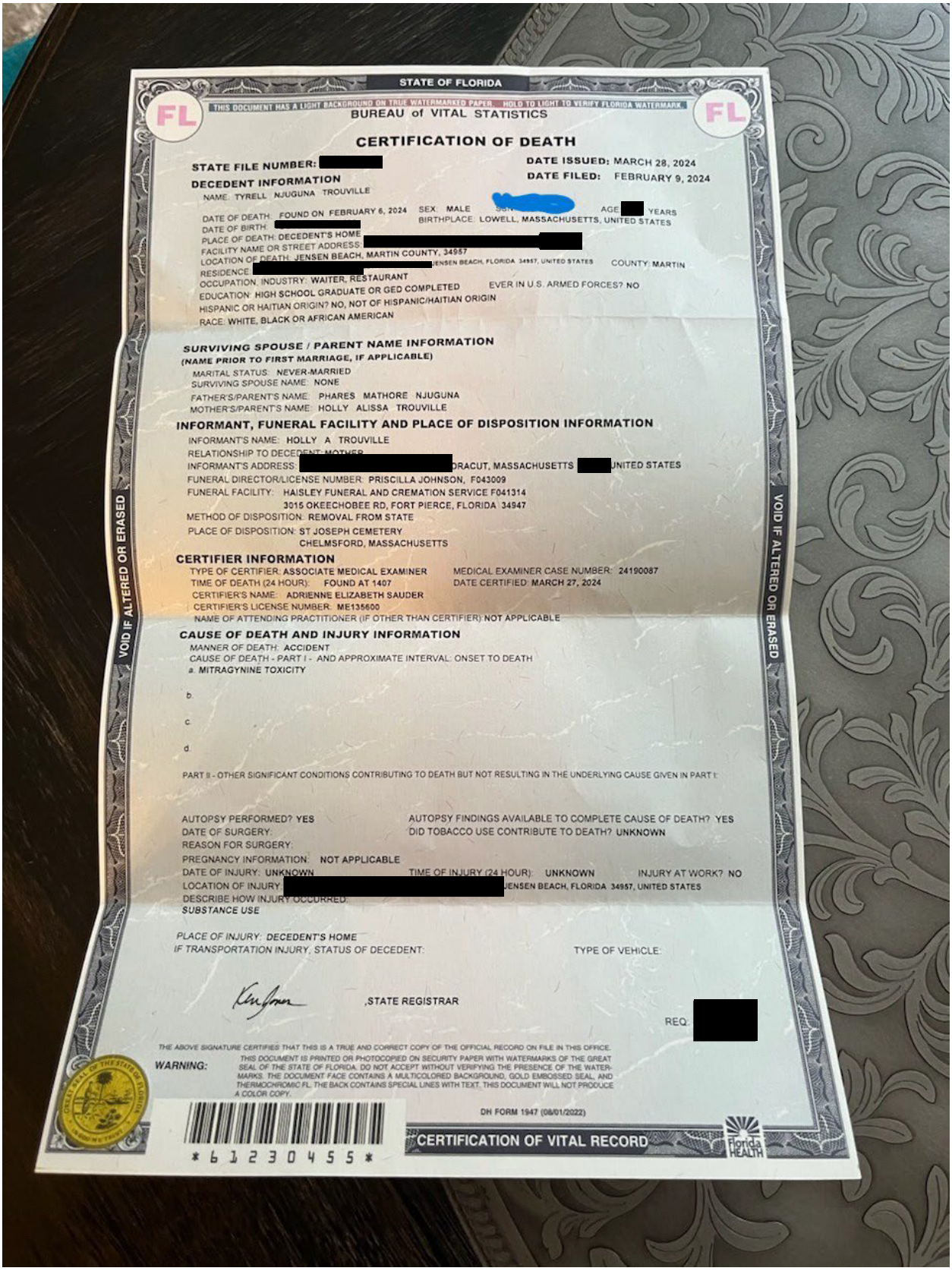
- natural.jpg

  JPG · 243 KB



- American Kratom Association.jpg

  JPG · 188.2 KB



STATE OF FLORIDA

THIS DOCUMENT HAS A LIGHT BACKGROUND ON TRUE WATERMARKED PAPER – HOLD TO LIGHT TO VERIFY FLORIDA WATERMARK

BUREAU of VITAL STATISTICS

CERTIFICATION OF DEATH

STATE FILE NUMBER: [redacted]

DATE ISSUED: MARCH 28, 2024
DATE FILED: FEBRUARY 9, 2024

DECEDENT INFORMATION

NAME: TYRELL NJUGUNA TROUVILLE
DATE OF DEATH: FOUND ON FEBRUARY 6, 2024 SEX: MALE [redacted] AGE [redacted] YEARS
DATE OF BIRTH: [redacted] BIRTHPLACE: LOWELL, MASSACHUSETTS, UNITED STATES
PLACE OF DEATH: DECEDENT'S HOME
FACILITY NAME OR STREET ADDRESS: [redacted]
LOCATION OF DEATH: JENSEN BEACH, MARTIN COUNTY, 34957
RESIDENCE: [redacted] JENSEN BEACH, FLORIDA 34957, UNITED STATES COUNTY: MARTIN
OCCUPATION, INDUSTRY: WAITER, RESTAURANT
EDUCATION: HIGH SCHOOL GRADUATE OR GED COMPLETED EVER IN U.S. ARMED FORCES? NO
HISPANIC OR HAITIAN ORIGIN? NO, NOT OF HISPANIC/HAITIAN ORIGIN
RACE: WHITE, BLACK OR AFRICAN AMERICAN

SURVIVING SPOUSE / PARENT NAME INFORMATION

(NAME PRIOR TO FIRST MARRIAGE, IF APPLICABLE)

MARITAL STATUS: NEVER-MARRIED
SURVIVING SPOUSE NAME: NONE
FATHER'S/PARENT'S NAME: PHARES MATHORE NJUGUNA
MOTHER'S/PARENT'S NAME: HOLLY ALISSA TROUVILLE

INFORMANT, FUNERAL FACILITY AND PLACE OF DISPOSITION INFORMATION

INFORMANT'S NAME: HOLLY A TROUVILLE
RELATIONSHIP TO DECEDENT: MOTHER
INFORMANT'S ADDRESS: [redacted] DRACUT, MASSACHUSETTS [redacted] UNITED STATES
FUNERAL DIRECTOR/LICENSE NUMBER: PRISCILLA JOHNSON, F043009
FUNERAL FACILITY: HAISLEY FUNERAL AND CREMATION SERVICE F041314
3015 OKEECHOBEE RD, FORT PIERCE, FLORIDA 34947
METHOD OF DISPOSITION: REMOVAL FROM STATE
PLACE OF DISPOSITION: ST JOSEPH CEMETERY
CHELMSFORD, MASSACHUSETTS

CERTIFIER INFORMATION

TYPE OF CERTIFIER: ASSOCIATE MEDICAL EXAMINER MEDICAL EXAMINER CASE NUMBER: 24190087
TIME OF DEATH (24 HOUR): FOUND AT 1407 DATE CERTIFIED: MARCH 27, 2024
CERTIFIER'S NAME: ADRIENNE ELIZABETH SAUDER
CERTIFIER'S LICENSE NUMBER: ME135600
NAME OF ATTENDING PRACTITIONER (IF OTHER THAN CERTIFIER): NOT APPLICABLE

CAUSE OF DEATH AND INJURY INFORMATION

MANNER OF DEATH: ACCIDENT
CAUSE OF DEATH - PART I - AND APPROXIMATE INTERVAL: ONSET TO DEATH
a. MITRAGYNINE TOXICITY
b.
c.
d.

PART II - OTHER SIGNIFICANT CONDITIONS CONTRIBUTING TO DEATH BUT NOT RESULTING IN THE UNDERLYING CAUSE GIVEN IN PART I:

AUTOPSY PERFORMED? YES AUTOPSY FINDINGS AVAILABLE TO COMPLETE CAUSE OF DEATH? YES
DATE OF SURGERY: DID TOBACCO USE CONTRIBUTE TO DEATH? UNKNOWN
REASON FOR SURGERY:
PREGNANCY INFORMATION: NOT APPLICABLE
DATE OF INJURY: UNKNOWN TIME OF INJURY (24 HOUR): UNKNOWN INJURY AT WORK? NO
LOCATION OF INJURY: [redacted] JENSEN BEACH, FLORIDA 34957, UNITED STATES
DESCRIBE HOW INJURY OCCURRED:
SUBSTANCE USE

PLACE OF INJURY: DECEDENT'S HOME
IF TRANSPORTATION INJURY, STATUS OF DECEDENT: TYPE OF VEHICLE:

[signature] ,STATE REGISTRAR

REQ: [redacted]

THE ABOVE SIGNATURE CERTIFIES THAT THIS IS A TRUE AND CORRECT COPY OF THE OFFICIAL RECORD ON FILE IN THIS OFFICE.

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DH FORM 1947 (08/01/2022)

CERTIFICATION OF VITAL RECORD

Florida HEALTH

VOID IF ALTERED OR ERASED

VOID IF ALTERED OR ERASED

From: romanyukivan@everyactioncustom.com on behalf of Ivan Romanyuk
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Tuesday, April 14, 2026 5:40:51 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

I would like kratom to remain available to public it's helped me to give me boost when I need it so I can work without pain. I helped few people that was using drugs to stop using drugs now they are good workers people helping our economy. And great people of community.

Sincerely,
Ivan Romanyuk

From: Pharmacy Board
To: Board Coordination
Subject: Fw: Access to homeopathic and integrative medical care
Date: Tuesday, April 14, 2026 8:09:46 AM
Attachments: Outlook-xzhud50k.png

Thank you.

Nevada State
Board of Pharmacy
985 Damonte Ranch Pkwy Suite 206
Reno, NV 89521
Office: 775-850-1440
Fax: 775-850-1444
Web Page: https://bop.nv.gov/

This information is provided as a courtesy on behalf of the Nevada State Board of Pharmacy. This information does not constitute legal advice and does not override the specific provisions of Nevada law as applied to a particular set of facts.

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From: Janet Blackburn [redacted]@hotmail.com>
Sent: Tuesday, April 14, 2026 8:01 AM
To: Pharmacy Board <pharmacy@pharmacy.nv.gov>
Subject: Access to homeopathic and integrative medical care

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada State Board of Pharmacy,

I am a patient receiving homeopathic/integrative care and value access to my current treatment options. Changes to prescribing rights would impact my ability to continue care with my provider and negatively impact my health and well-being. I am a spry 70 year old woman and want to stay that way!

Sincerely yours,
Janet Blackburn
Mariposa, California

From: jl.bodenbender@everyactioncustom.com on behalf of Jenilee Bodenbender
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Monday, April 13, 2026 7:02:38 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

Please don't criminalize a safe plant that helps people.

Sincerely,
Jenilee Bodenbender

From: crystallil@everyactioncustom.com on behalf of Jennifer Bradpiece
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Wednesday, April 15, 2026 11:51:34 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

My Own Personal Experience with Kratom:I'm a chronic pain & illness sufferer for nearly 30 years. Careful use of small amounts of Kratom have given me back some of my life.
Kratom can turn the low & medium grade sick/ pain days into productive or creative mornings.
It turns mornings of tears, excruciating pain, feelings of uselessness into a few hours you can breathe through. Something that is possible & not torture. It's the only thing I've found that actually lifts brain fog for a time. It also helps me gently exercise my body so I can move better. Some days it helps me wash & dress my body when I otherwise could not. Many of those I know with chronic illness & pain are sensitive or intolerant to many stronger pharmaceuticals. Those that aren't & need them are no longer able to access them. My doctors have seen the difference in me & test my liver & kidneys regularly. Careful use of this plant as medicine are possible & necessary to many of us. As less medicinal options are available to the chronic pain communities, depression, isolation, & suicide will rise. Please consider those of us who intentionally use this medicine to claim what we can of our lives back. The thought of returning to daily hell levels of pain is horrifying. Thank you.

Sincerely,
Jennifer Bradpiece

From: jared_cats02@everyactioncustom.com on behalf of Jared Crawford
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Friday, April 10, 2026 11:24:18 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

Please allow me to share a testimony on how natural, whole leaf kratom has impacted a dear friend.

Following a routine knee surgery in 2012, my friend developed chronic pain and was starting to become dependent on prescribed opioid pain medication. Despite physical therapy and ongoing treatment, the pain persisted and in fact was becoming more intense. Over time, both their physical and mental health declined. They withdrew socially, isolated themselves away from family friends, struggled with depression and severe anxiety, and faced the constant urge and fear that they would have to rely on stronger medication just to get by.

In 2017, after careful consideration, including identifying reputable vendors through the American Kratom Association, they began using powdered kratom (natural crushed leaf, not extracts). Within weeks, their pain became manageable, sleep improved, and their motivation and engagement with family started to return. The change was significant; in fact I cannot properly describe the difference. It was nothing short of a miracle. To be fair, their problems did not magically disappear, but they did start to ease and improve. And if you have ever personally dealt with a chronic illness, or seen a loved one go through one then you know that any improvement can have HUGE implications for quality of life. Over time, they became more and more alive with life!

That was nine years ago. Since then, kratom has remained a positive part of their life. They have not developed dependency, experienced illness from its use, nor turned to any other illicit substances. They never became a statistic in the ongoing war with opiate abuse.

I support regulation of whole leaf, natural kratom because increased demand for kratom has brought inconsistent and potentially adulterated products into the marketplace. Sensible regulation—such as product testing, labeling standards, and age restrictions—protects consumers while preserving access for responsible adults who have benefited from kratom for many, many years.

A Bill that safeguards the public without removing access for individuals who benefit from kratom I feel critical. Banning or scheduling it as a Schedule I substance would eliminate a valuable option for many people striving to live productive, healthy lives; to have options in addition to other forms of therapy.

Thank you for your time.

Sincerely,
Jared Crawford

From:	Joseph Harrington
To:	Board Coordination
Subject:	Formal testimony for the public record in opposition to the prohibition of pure-leaf kratom
Date:	Friday, April 17, 2026 8:45:45 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Please Don’t Take Away My Second Chance: Support the Kratom Consumer Protection Act

Formal testimony for the public record in opposition to the prohibition of pure-leaf kratom

Dear Honorable Jade Jacobo and Krystal Freitas,

For years, I was a ghost in my own home. I suffered from Myalgic Encephalomyelitis (M.E.), a debilitating neuro-immune condition characterized by a profound, pathological disruption in cellular energy. This silent prison of pain stripped me of everything. I spent my days in a darkened room, unable to tolerate light or sound, my body failing to produce the basic energy required for a simple conversation. Traditional pharmaceuticals offered no relief, instead bringing a carousel of severe side effects that only deepened my isolation.

There were months when my entire world was reduced to the four walls of a bedroom with the curtains taped shut. It wasn't just exhaustion; it was a physical inability to exist in a world with light or sound. The hum of the refrigerator two rooms away felt like a jackhammer against my skull, and even the weight of a bedsheet on my skin was sometimes more than I could bear. I spent years essentially buried alive, watching the clock move but unable to even lift my head to speak. I became a bystander in my own home, listening to the muffled sounds of life happening in the kitchen while I lay in the dark, wondering if I would ever again have the strength to do something as simple as sit at a table and eat a meal with my family.

That cycle of total isolation only ended when I finally found a botanical that did what years of prescriptions could not. For the first time in my life, the brain fog lifted, and the systemic neuroinflammation receded enough for me to rejoin the world. The emotional impact of this shift cannot be overstated. It allowed me to return to being a present, active husband to my wife and a functional member of society. Today, I am proud to hold a full-time supervisory position at my company, working a rigorous schedule. Without the biochemical support of unadulterated, pure-leaf kratom, this level of sustained professional output would be physically impossible.

However, this hard-won independence is currently under threat. I share your deep concerns about the unregulated marketplace. We are facing a crisis where bad actors sell unsafe, adulterated products that jeopardize the health of law-abiding citizens. Recently, the market has seen the rise of highly concentrated 7-hydroxymitragynine (7-OH) extracts. These isolated extracts pose a severe risk and do not represent the natural, leaf-form kratom that I and millions of others rely upon. Whereas natural kratom leaf contains only negligible, trace amounts of 7-OH (not exceeding 0.1%), these hazardous retail concentrates represent a massive escalation in potency, reaching levels 500% higher than the unadulterated botanical.

Banning kratom outright will not stop illicit markets; it will only punish constituents like me, forcing us back into a prison of darkness and endless suffering. For me, a ban is not a mere inconvenience; it is a forced return to a bedbound existence where I can no longer support my family or maintain my employment. We need a law-and-order approach that cracks down on fraudulent manufacturers while protecting consumers' access to safe, natural botanicals.

I respectfully urge you to support the Kratom Consumer Protection Act. This legislation will:

1. Strictly prohibit the sale of any kratom products to individuals under 21.

2. Cap the allowable concentration of 7-OH to a fraction of a percent to eliminate dangerous, opioid-like retail extracts.

3. Mandate third-party laboratory testing to ban synthetic adulterants, heavy metals, and microbial contamination.

Please do not allow the one therapeutic tool that gave me my life back to be regulated out of existence. By supporting the KCPA, you are establishing safety boundaries that penalize dangerous manufacturers while protecting the medical autonomy and lives of your constituents.

Sincerely,
Joseph Harrington
[redacted]@gmail.com
South Abington Township, PA
A sufferer of M.E. given a second chance

Further Reading

Research into the pharmacological and chemical properties of kratom distinguishes between the safety profile of the natural botanical and the risks posed by concentrated extracts or adulterated products. Studies suggest that many adverse health events are not caused by the plant itself, but by synthetic contaminants like O-desmethyltramadol found in unregulated mixtures. Furthermore, the medicinal chemistry of the primary alkaloids in pure leaf is being explored for its potential to provide therapeutic relief with a different safety profile than traditional opioids.

1. Dresen, S., Ferreirós, N., Pütz, M., Westphal, F., Zimmermann, R., & Weinmann, W. (2010). Kratom alkaloids and O-desmethyltramadol in urine of a "Krypton" herbal mixture consumer. Forensic Science International, 202(1-3).

2. U.S. Food and Drug Administration (FDA) & Clinical Investigators. (2025). Safety and tolerability of single and multiple daily oral doses of dried kratom leaf powder in a randomized trial in healthy volunteers. (As reported in Therapeutic Drug Monitoring and PubMed).

3. Kruegel, A. C., & Grundmann, O. (2018). The medicinal chemistry and neuropharmacology of kratom: A preliminary review. Psychopharmacology, 235(6).

4. McGill University. (2017). Kratom- Potential Opioid Saviour? Office for Science and Society (OSS).

5. Takayama, H., Ishikawa, H., Kurihara, M., Kitajima, M., Aimi, N., Ponglux, D., Koyama, F., Matsumoto, K., Moriyama, T., & Horie, S. (2002). Studies on the synthesis and opioid agonistic activities of mitragynine-related alkaloids. Chemical and Pharmaceutical Bulletin, 50(8), 1141-1143.

6. Garcia-Romeu, A., Cox, D. J., Smith, K. E., Dunn, K. E., & Griffiths, R. R. (2020). Natural herb kratom may have therapeutic effects and relatively low potential for abuse or harm, according to a user survey. Drug and Alcohol Dependence, 210, 107955. https://doi.org/10.1016/j.drugalcdep.2020.107955

7. Singh, D., Narayanan, S., Müller, C. P., Swogger, M. T., Chear, N. J., &

Grundmann, O. (2021). Motives, effects and benefits of kratom use: A cross-sectional survey among kratom users in Malaysia. Journal of Ethnopharmacology, 272, 113940.

8. Smith, K. E., Rogers, J. M., Schriefer, D., & Grundmann, O. (2024). Kratom safety and toxicology in the public health context: Research needs to better inform regulation. Frontiers in Pharmacology, 15. https://doi.org/10.3389/fphar.2024.11180979

9. Todd, D. A., Kellogg, J. J., Wallace, E. D., Khin, M., Flores-Bocanegra, L., Tanna, R. S., ... & Cech, N. B. (2020). Chemical composition and biological effects of kratom (Mitragyna speciosa) tea. Planta Medica, 86(18), 1278-1285.

From: Jessica Ingersoll
To: Board Coordination
Subject: Public Opinion/ Kratom Scheduling
Date: Monday, April 13, 2026 7:44:58 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Pharmacy Board Members,

I am writing to urge you to oppose any measures that would restrict access to Kratom. This herbal supplement has been a lifesaver for many individuals dealing with chronic illness and pain.

While regulating synthetic mitragynine may be appropriate, classifying the natural leaf and powder forms as illegal substances would be a mistake. Such a decision would have a significant negative impact on many residents throughout Nevada.

Please feel free to contact me if I can provide further testimony or support regarding this matter.

Sincerely,

Jessica Ingersoll
[redacted]

From: John Montagano
To: Board Coordination
Subject: Kratom Hearing
Date: Tuesday, April 14, 2026 11:37:26 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Hello

My name is John Montagano and I live in Mound House NV. I am writing to tell you to please oppose scheduling kratom alkaloids as Schedule I. Natural kratom leaf has a demonstrated history of safe use and is not comparable to Schedule I substances. Regulate dangerous synthetic 7-OH products — not natural kratom

From: James Da Giant Peach
To: Board Coordination
Subject: Kratom Ban
Date: Wednesday, April 15, 2026 1:23:55 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

If you ban kratom, or make access to kratom more difficult, you will see an increase in actual hard drug use, and overdoses. Kratom is a miracle plant that helped my brothers and I get off hard drugs, and it would have saved my father, who was overprescribed pharmaceuticals by doctors who had been swayed by big pharmaceutical companies.

Please I urge you to reconsider this scheduling, as 7-hydroxymitragynine is found naturally in the plain leaf kratom, as high as 2%, and both alkaloids are found in the body after ingesting plain leaf kratom, as they are a byproduct of the main alkaloid Mitragynine.

From: 2nd Account
To: Board Coordination
Subject: Please Reject the Proposal to Schedule Kratom in Nevada
Date: Wednesday, April 15, 2026 4:44:20 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Members of the Nevada Board of Pharmacy,

I am writing to express my deep concern and intense dismay over the recent proposal to classify kratom as a Schedule I substance in Nevada.

Nevada has long recognized the importance of personal freedom and practical policymaking. This is a state known for allowing adults to make their own choices in many areas of life. Nevada moved beyond past mistakes such as cannabis prohibition, and it would be deeply disappointing to see the state repeat that same kind of error by banning kratom.

Kratom has been legally used in the United States for decades and has grown in popularity over the last twenty years because many adults have found it helpful for pain management, mood support, and as an alternative to far more dangerous substances. Despite repeated claims made by opponents, so-called kratom deaths consistently involve multiple other substances in the person's system. These cases cannot honestly be presented as kratom alone.

Much of the current push for bans is being driven by a national advocacy group known as the KDA, which has been traveling from state to state urging prohibition. Many involved are grieving parents who believe kratom was responsible for the loss of their children. While that grief deserves compassion, public policy must still be based on facts and evidence. A widely cited case is Matthew Davenport in Tennessee. Publicly discussed toxicology findings indicate multiple substances were present, including reportedly lethal levels of diphenhydramine. Presenting such a case as a simple kratom-only death is misleading and should not be the basis for criminal law.

No parent should ever have to endure the loss of a child. At the same time, these emotional campaigns are affecting the lives of chronic pain patients and responsible adults who rely on kratom to function and live normal lives.

If kratom is scheduled, Nevada would not only be creating criminals out of law-abiding citizens, but also pushing many people back toward far more dangerous opioids and illicit drugs that kratom helped them leave behind.

There is also an important distinction that must be made regarding 7-hydroxymitragynine products, often called 7-OH. These concentrated or lab-altered products are not the same as traditional natural kratom leaf. Their effects, potency, and risk profile are different. If Nevada has concerns, those products should be examined separately rather than using them as justification to ban natural kratom.

On a personal note, kratom has helped me turn my life around over the last ten years. After serious pain issues and failed options, it gave me a path back to a functional and productive life. If it is banned, you would be condemning me and thousands of others to renewed pain

and hardship.

Regulation is the responsible path. Nevada has already taken steps in that direction before, and strengthening sensible safeguards such as testing, labeling, age limits, and contamination standards would protect consumers far better than prohibition ever could.

Please make the right decision. My life, and the lives of many others, truly depend on it.

Thank you for your time and consideration.

John Penna

From:	liamjefreagan@everyactioncustom.com on behalf of Jef Reagan
To:	Board Coordination
Subject:	Oppose Mitragynine Scheduling
Date:	Saturday, April 11, 2026 7:32:02 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

My Own Personal Experience with Kratom:

My father served as a USAF fighter pilot and drinking was part of a pilot's persona, and was an acceptable activity for most in the 1960s and 70s. I followed in my parent's footsteps, but after decades of drinking, it accelerated into full blown (albeit semi-functioning) alcoholism.

I served my country building nuclear submarines in an outside machinist capacity, but after decades of wear and tear on my body, my back broke down very painfully (degenerative disc disease, osteoarthritis, spinal stenosis and sciatica.) I was eventually forcefully retired at full disability. I needed a walker to get to the bathroom and could not help my wonderful dutiful wife do household activities.

I say all of that to tell you that by just taking two or three teaspoons of lab tested unadulterated kratom leaf powder per day, I was able to stop the cravings of alcohol (six years sober) and relieve my pain enough to drive, do household chores and not use my walker. I can help my wife once again. I cannot tell you how glad that makes me feel.

I am only one of millions of people to whom kratom has returned some semblance of normalcy; many have much worse ailments than I have, and their stories are desperate and heartbreaking.

You likely have enough life experience and know what addiction can do to an individual and/or a family. Kratom brought me back to my Lord, my wife and family, and continues to help me live a life I thought was behind me.

I don't get drunk or high. Only synthetic or concentrated unnatural substances in this arena, such as 7OH (7-Hydroxy Mitragynine) or MGM-15 & 16 (semi-synthetic derivatives known for their higher potencies as agonists of opioid receptors) make people high, and not natural leaf kratom. Many folks with an addictive personality and people experiencing chronic pain take kratom responsibly to live normal lives.

It doesn't cure life's ills, but it sure helps the multitudes of folks like me; some estimates ranging into the tens of millions. I humbly ask that you allow people to make the choice to buy natural kratom unadulterated, properly examined and labeled, kept away from those under 21, and available to good people who don't want to get high, and only want to live without excruciating pain or addiction.

W. Jef Reagan
Gloucester, VA

You are wondering why a person from out-of-state is concerned with this legislation. Let me tell you why I advocate for natural leaf kratom users out-of-state:

When I first started drinking kratom, I had no idea that it was under attack. I relied on other people who were aware of the actions taking place in non-local governments standing up for me to keep kratom legal. Work and family kept me from following how kratom was under attack, even in my state. We do have professional lobbyists to represent us also, but there are many caring volunteers.

I have since retired and have become aware of people throughout the country who are even worse off than I was in regards to chronic pain and addiction. There are groups of us volunteer kratom advocates who try to keep an eye out for our fellow kratom users in need throughout the country, many of whom don't realize the leaf that they rely on is becoming endangered.

We don't get paid, and try to keep fellow advocates apprised of hurtful legislation. We then, with as much tact as we can muster, try to educate good people in government, such as yourself, about the pros and cons of kratom; many of whom are glad they became more aware, as they were previously unsuspecting of what some of us pain or addiction victims endure.

I am not a professional anything at the moment, but I hope that in my clumsy way I have cleared up why we volunteers do what we do for folks in other areas of the country.

I wish you well. Thank you so much for your time.

Sincerely,
Jef Reagan

From: jordanroy284@everyactioncustom.com on behalf of Jordan Roy
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Thursday, April 16, 2026 12:26:55 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

My Own Personal Experience with Kratom:

I respectfully urge you to oppose any efforts to ban Kratom. This natural plant has played a meaningful role in the lives of many responsible, law-abiding individuals across the country. For many, it has become a valuable tool for maintaining balance, supporting wellness, and staying productive in their daily lives.

Speaking from personal experience, Kratom has had a positive impact on my own well-being. It has helped me stay focused, motivated, and able to manage the demands of everyday life in a healthier way. I know I am not alone—many others, including hardworking parents, professionals, and community members, have found similar benefits.

Rather than banning Kratom, I encourage thoughtful regulation that ensures safety, quality, and responsible use while preserving access for those who rely on it. Taking away this option could negatively affect countless people who are simply trying to live healthier, more productive lives.

Thank you for your time and consideration.

Sincerely,
Jordan Roy

From: Jon Russe
To: Board Coordination
Subject: Kratom
Date: Monday, April 13, 2026 6:02:36 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Hello,

Anyone actually moving to make Kratom schedule 1 isn't targeting the right Kratom. The regular natural stuff will not supress respirations and is only a partial agonist, and is pretty mild stuff unless someone overdoses (this could happen with anything even Tylenol) and with this drug, you would just throw up and go about you day. The synthetic versions should be banned, but this drug has been a miracle for me. I was on Tramadol for years and when I discovered Kratom it got me off it. I am a combat veteran and it is a mild pain reliever and big help for focus and motivation. Do not ban Kratom in Nevada....there is no reason to do this. No one overdoses on just Kratom unless they take an insane amount, and making it schedule 1 is the most absurd thing I've ever heard in my life. Tramadol is what schedule 4? This isn't as nearly as strong!

Real opioids - people overdose they die, this isn't a real opioid by a long shot. In fact at lose doses it's a mild stimulant. If you ban Kratom you will just hurt people...because natural Kratom is helping. This is especially absurd when marijuana which if you ask me is serially strong and psychoactive is legal in this state. Focus on something that does real harm.

Very Respectfully,
Jon Russe

From: Matt Scott
To: Board Coordination
Subject: Kratom meeting
Date: Tuesday, April 14, 2026 6:01:15 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Hello, I would like to express my concerns in making Kratom a schedule one substance. I agree the synthetic Kratom product on the market is damaging and harmful, especially towards young people, but the natural flower form has been a huge benefit in my life by allowing me not to use other substances and even alcohol. I personally believe that most people that use the natural substance do not have an issue. The problem comes in when they are making it as synthetic substance and selling it in gas stations in liquid form that I believe needs to be regulated or banned, but the traditional form of the plant has many healing properties and has helped me in my journey to avoid substance abuse. Thank you for your time and allowing me to comment.

James

Sent from iPhone

7 HOPE Alliance
7-Hydroxymitragynine Outreach for Public Education

April 16, 2026

Northern Office Nevada State Board of Pharmacy
Via email: teambc@pharmacy.nv.gov

Re: Opposition to Kratom and 7-OH Scheduling

Good morning

My name is Jackie Subeck. I am the Executive Director of 7 Hope Alliance, the leading consumer protection and public education non-profit in the country on 7-OH and kratom. I am respectfully submitting written comment in opposition as public comment was cut off at today's hearing before I was called.

I have 4 main points to share with you today.

1. Prohibition never works, but regulation does. We have decades of data to prove that bans drive consumers back to the illicit market. When the State of Florida banned 7-OH in 2025, overdoses rose by 300% in the first month alone. We do not want Nevada to inadvertently send people back to the streets for fentanyl or heroin, potentially leading to their deaths, by over-correcting on a substance that carries far less risk.

2. Kratom and all its alkaloids are the same plant used by the same consumers – this includes mitragynine, 7-OH and mitragynine-pseudoindoxyl. All these alkaloids are naturally occurring in the kratom plant. This is simple science backed up by peer-reviewed paper after peer-reviewed paper.

   Any mention of "natural or whole leaf" being the only safe substance as well as any reference to "pool shock chemicals" should not be taken seriously. This is part of a coordinated misinformation campaign designed to purposely distract you from the reality. Organizations who are trying to protect their own and ban the rest of the plant are attempting to pull the wool over your eyes. There is real and factual data out there that you can refer to for verification. Those comments are simply a scare tactic – there is no truth to them.

3. 7 Hope Alliance is firmly anti-prohibition and believes that regulating the entire plant and all its alkaloids is the safest path forward. Kratom and 7-OH are extremely helpful to millions of people across the country including the estimated 200,000 Nevadans currently using these products. We call for the State of NV to conduct a fair and balanced study to analyze all the data available and have an opportunity to hear from more than a few consumers before jumping back to prohibition.

4. Finally, and it is unfortunate that I must bring this up, but I want to put this on the record. Dr. Jack Henningfield, who presented testimony at this morning's hearing:

   a) Bypassed all available factual science and attempted to share with you that "natural leaf" is just fine and that "7-OH, mitragynine-pseudoindoxyl and other alkaloids" are the dangerous drugs;
   b) Did not disclose that he is financially consulting the American Kratom Association under Mac Haddow's guidance and;
   c) Is the same Dr. Jack Henningfield who testified in front of Congress in 2004* on behalf of Purdue Pharma and the Sackler family saying that OxyContin was safe. I encourage you to take a moment and consider that. Nearly one million people died from the drug Dr. Henningfield testified was safe. Why should you believe him when he says that "mitragynine" is safe, but "7-OH and the other alkaloids" are dangerous? This would be like saying cannabis is safe, but cannabis gummies are not. Real-world data supports the safety of the entire kratom plant when regulated.

      *Jack Henningfield 2004 testimony obo Purdue Pharma:
      https://www.govinfo.gov/content/pkg/CHRG-108hhrg95555/html/CHRG-108hhrg95555.htm

Thank you for your time. 7 Hope Alliance formally opposes any move to put kratom or any of its alkaloids on the Nevada controlled substance schedule. We are available anytime you would like additional information.

Sincerely,

Jackie Subeck
7 Hope Alliance, Executive Director
310.849.4403
jackie@7hopealliance.org
www.7hopealliance.org

From: jon.trust@everyactioncustom.com on behalf of Jonathan Trustman
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Sunday, April 12, 2026 10:23:45 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

I work as an Emergency Physician in Flagstaff, AZ. We are not seeing plain leaf, natural kratom as an issue on the ground in the ER. I have met many people helped by this plant. In my personal and professional experience, I believe kratom leaf, and ancient herbal remedy, is a safe and effective supplement.

In my review of the literature, the preponderance of the so-called overdose cases, involved multiple substances, with these other substances already being known to be dangerous in overdose. In these instances, correlation is not causation.

In addition, there has, unfortunately, been an increase in adulterated projects, synthetic concentrates (i.e. 7-hydroxymitragynine), and mis-labeled products. I do believe that many of these projects are, in fact, dangerous and some nuanced legislation in this vein could be appropriate.

In closing, as a regulatory body of medical professionals, I would ask that you please review the data and listen to the anecdotes of the millions of people who responsibly take plain leaf natural kratom. I believe some commonsense regulation halting the sale of synthetic kratom adjacent products, creating a kratom consumer protection act, and not creating criminals out of good citizens who responsibly use kratom leaf is a morally and scientifically-based path forward .

Thank you for time and consideration.
-Jonathan Trustman, DO

Sincerely,
Jonathan Trustman

From: mywar1932@everyactioncustom.com on behalf of JASON VILLANUEVA
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Saturday, April 11, 2026 10:01:49 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

U.S. ARMY veteran. I served 4 tours in iraq and kratom has helped me with ptsd and anxiety as well as my physical injuries. Thank you and God bless

Sincerely,
JASON VILLANUEVA

From: Jay W
To: Board Coordination
Subject: Vote Against Possible Kratom Ban and Scheduling
Date: Wednesday, April 15, 2026 3:23:05 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Good morning

I am writing this email to urge you to not support any bans against Kratom and its alkaloids.

For people like me and countless others, this is a crucial life line to living a pain free life. We are tax payers, community members, and active contributors to the region. To do something as extreme as making this compound schedule one, we would all instantly become criminals, affecting our livelihood, families and freedom overnight.

It is an absolute shame that the people who responsibly use this amazing plant and compound will be the ones who get their lives turned upside down the most.

There are many other ways to limit access to this compound without making it completely illegal. I can speak for many Kratom advocates when I say that we don't want this being in every single gas station either.

We, the responsible Kratom user, aren't profiting from this and we had nothing to do with the influx or availability of this compound yet we are going to be the ones most hurt by this. I know I have reiterated this point already; however, I need you to realize how crucial and important this is to so many people.

Personally, I have been utilizing this plant for a decade and it has had no negative effect on my health. My yearly physicals and repeated blood tests always come back normal. This story is one that the vast majority of people in the kratom community share.

There have to be better ways to limit access other than doing something as extreme as scheduling the compound.

To turn these people into criminals overnight by passing this bill would be such a gut punch to someone like myself who has never been in trouble with the law and never even have had a speeding ticket! Prohibition is not the right answer to this question of how to deal with this plant as history dictates that has failed over and over again.

Please realize the huge ramifications and impact that so many US citizens will face if this goes through and let my voice and the voices of the tens of thousands of responsible users of this incredible plant be heard.

There *has* to be a better way to do this than total prohibition.

I would love the opportunity to talk to you further about this as soon as possible as it is an extremely important subject to myself and so many others.

Thank you for taking the time to hear my concerns.

Sincerely,

Jordan Weir

From:	James Wilson
To:	Board Coordination
Subject:	Public Comment on Kratom Ban
Date:	Wednesday, April 15, 2026 4:38:58 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Please oppose scheduling kratom alkaloids as Schedule I. Natural kratom leaf has a demonstrated history of safe use and is not comparable to Schedule I substances. Regulate dangerous synthetic 7-OH products - not natural kratom.

I have been using natural kratom for years and have benefitted from it with no problems or side effects. I know of several other people who have as well. Lumping natural kratom in with the synthetic versions is not fair to the people who benefit from natural kratom.

--
Ride Strong,

James Wilson



Facebook I Twitter I Blog

From: J W
To: Board Coordination
Subject: Kratom Ban Hearing Public Comment
Date: Thursday, April 16, 2026 9:08:31 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

I am a resident of Laughlin, NV. Please do not make Keaton a schedule 1 substance. It is not remotely close to that type of drug. I have been taking Keaton for a few years and scheduling Keaton would have a significant negative impact on my life. I have had several injuries and surgeries and kratom has helped me significantly and kept me from needing prescription opioids. If it is banned I will be forced to pay for a doctor appointment every month and use opioid pain medication. That situation will certainly have a very negative impact on my health. Please keep kratom legal and accessible thank you for your time.

Sent from my iPhone

From: [redacted]@gmail.com
To: Board Coordination
Subject: Please ban kratom
Date: Monday, April 13, 2026 5:38:31 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

My husband has been addicted since 2019. The money and the stress has been detrimental. The withdraw is terrible and can't be managed with detox medications. Its disgusting.
Kaitlyn Banford

From: Kristi Berg
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Monday, April 13, 2026 1:04:58 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

To whom it may concern -

I am reaching out to provide my comments for the upcoming hearing regarding the classification of kratom as a schedule I substance.
There are many people who use kratom responsibly for energy and pain relief. I am one of those people. I was paralyzed in a car accident 20 years ago and I'm on my own without much help. I use kratom to help control my pain levels and get a little more energy to clean the house.
Without this natural tea I would be back in the arms of Big Pharma.
Please take into account regular people like me. I am a business owner, a board certified professional and an occasional kratom user.
There are already age restrictions and SO much less harm coming from this plant than alcohol. These are the types of comparisons that will put safety of substances into perspective. I am respectfully asking that you use logic vs fear when you make decisions that will impact people in big ways.
Thanks so much for your time,
Kristi Berg

From: Kenan Davidson
To: Board Coordination
Subject: Opposing Kratom Schedulization
Date: Wednesday, April 15, 2026 3:33:02 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

This is just my story

I'll keep this brief but I am betting you will probably get thousands of stories just like my own. I was a drug addict in my teens and twenties. I managed to get clean and have stayed that way for close to 13 years now. When I had a back injury 2 years ago, I was so fearful of being put on opiates, I knew I couldn't handle it and that it would destroy the life I have built. I was introduced to Kratom by another person in recovery who also uses it for their back. They were very wise to explain the difference between natural plain leaf kratom and the synthetics that are being derived from it. The synthetic versions are exponentially more powerful and are not even in the same ball park. I have stayed away from these and have only used raw leaf kratom for the past 2 years and believe it or not my life has actually improved quite a bit. I never thought that could be possible. I hold down a leadership position within the insurance field, I own my own home, I run a car club in my local city, love offroading and being out in nature. I've been able to still do all these things even with the occasional back problems. Even my health has improved, verified by labs done from 2 years ago to now. I've lost weight that I was hoping to lose, I am eating better, my sleep has drastically been improved. I am a fully functioning actively contributing member of society and it pains me to see how Kratom is being lumped into the narcotic category and treated as if it is heroin. This is so far beyond factual; please listen to others who can tell you more scientifically how this is just wrong and unfair. Limiting people's access to this plant will affect millions of Nevadans. I am right next door in AZ and we have chosen regulation many times over prohibition and NV should do the same. This will instantly criminalizing a huge portion of our population and cancel out billions of dollars for businesses in your state. It would be nothing short of a tragedy for many many residents and visitors to NV. Think of the people this will affect and what that might do to society.

From: Kayemille Goss
To: Board Coordination
Subject: Kratom ban
Date: Tuesday, April 14, 2026 3:45:38 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

To Whom it may concern:
Thank you for considering a ban on all Kratom related products.
I am not a resident of Nevada however, Kratom took our son's life on June 5th, 2025. We live in Fort Worth, Texas. This was our 22year old son's first and only time taking this supplement. Both Kratom and 7OH were found in his system. He and his 3 friends stumbled upon the supplement when they went out for burgers & beer after they had just completed their Junior year of college. They stopped at a vape shop and thought they would all try it. They all took the same amount , 3 tablets. Our sons 3 friends were fine. Our son, Kaden did not awaken the following morning. The Kratom suppressed his respiratory system to the point that he stopped breathing.
It has devastated our family and community beyond words. We barely breath through each day.
Our son was NOT out looking for cocaine, heroin or something dangerous. All the boys were just having fun and under the false impression that this was a safe all natural product that would give them a sense of relaxation as they went back to one of their college homes to hang out.
We had never even heard of Kratom or 7-OH until that day. Now we will never forget it or forgive it.
We know now that it is an opioid receptor, more addictive than heroin and 13x stronger than morphine, NO ONE needs this product under any circumstances.! There are other safe alternatives for those with anxiety or pain. Those that do not want the ban are either addicted or are making money from the sale of this poison. No level of pain or anxiety is more important than human life. And No pain supercedes losing a child. There is nothing in comparison and there is no recovery for us.
Please ban all forms of Kratom to save innocent lives and to protect families from going through what we are enduring.
Respectfully,
Kayemille Goss
Fort Worth, Texas
[redacted]
Sent from my iPhone

From: kathmag1990@everyactioncustom.com on behalf of Kathy Magliaro
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Friday, April 10, 2026 12:28:21 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

My Own Personal Experience with Kratom:I am 56 yrs old. I have been married for 36 yrs,and i am a mom to 2 adult children.
My story starts in 2007, when I was diagnosed with Trigeminal Neuralgia. If you Google Trigeminal neuralgia you will find that Neurology medical literature labels it as one of the worst pains known in all of medicine. And it also carries the moniker of being the suicide disease. Why ? Because the pain is so severe that many opt to end their life, as a pain management treatment, since they have failed all other efforts. This is what I went through. My kids, and my husband watched me through the year's, fail treatments year after year, and I became bed bound, stuck in my prison of a bedroom.
In 2018 my Drs finally said there was nothing more they could try for treating my Trigeminal Neuralgia. The hopelessness you feel when you get that news, is indescribable. But I fought and I prayed. Finally in 2019 I found out about this leaf, natural kratom leaf. It completely changed my world, and it saved my life. Let me repeat that..... this natural leaf Kratom saved my life. And it gave me back a quality of life that is productive, and my family now has me back fully functioning daily.
Have you considered what will happen to the millions..of people who use natural leaf Kratom to treat their pain, if you ban natural leaf Kratom alongside more potent synthetic versions? Are you aware of the suicide statistics for chronic pain patients? That statistic will likely increase. And if you research what happened to chronic pain patients when New prescription guidelines came out that cut them off from their successful treatment using opioid medication, you will also find there was a drastic increase in suicide, and also illicit street drug use as they were desperate to treat their pain. We are talking about pain levels that various diseases and conditions cause that the pain is so severe you cannot move, you cannot dress, shower, you cannot eat, or even think.
That is the level of suffering a ban decision will put us all back into. And basically leave us with the absolute worst choice of ending our life. Because there still has not been a change to treating chronic pain in mainstream medicine. We found this natural leaf Kratom because mainstream medicine refused to help.
Please do not ban Natural leaf Kratom that has been shown in studies by The University of Florida, and the agency NIDA studies, to not be harmful at any level.
Read the science data that is clearly available. And all the conclusions state, Natural kratom leaf is not harmful.
We need regulations that still make natural kratom leaf accessible to those who need it. Age restrictions, clear labeling, and 3rd party testing.
Regulations historically work. Outright banning, and criminalization on top, does not ever work. Look at the statistics of drug use today even with bans on certain substances in place. Has those statistics reversed or gone down ? No. Absolute the opposite. But everything creating the increase is street substances. It is not natural leaf Kratom.

I implore you all , to do due diligence in seeking out the research on Natural kratom leaf.
The director of NIDA, the University of Florida, the FDA themselves have also conducted an ascending dose study....each and every study shows natural kratom leaf is not harmful at any level, and ....it is not addictive. NIDA themselves conducted that study.

Please regulate, and oppose any ban. As have many other States, and locations have done. Allow responsible adults to have access to Natural kratom leaf.

Thank you for your time,
Kathy Magliaro

Sincerely,
Kathy Magliaro

From: Pharmacy Board
To: Board Coordination
Subject: Fw: In Support of classifying Kratom as a Schedule 1 drug
Date: Monday, April 13, 2026 2:14:56 PM
Attachments: Outlook-tg4lt3jp.png

Thank you.

Nevada State
Board of Pharmacy
985 Damonte Ranch Pkwy Suite 206
Reno, NV 89521
Office: 775-850-1440
Fax: 775-850-1444
Web Page: https://bop.nv.gov/

This information is provided as a courtesy on behalf of the Nevada State Board of Pharmacy. This information does not constitute legal advice and does not override the specific provisions of Nevada law as applied to a particular set of facts.

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From: Kelli McCann <[redacted] gmail.com>
Sent: Sunday, April 12, 2026 12:53 PM
To: Pharmacy Board <pharmacy@pharmacy.nv.gov>
Subject: In Support of classifying Kratom as a Schedule 1 drug

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Members of the Board,

My name is Kelli McCann. I am writing in strong support of classifying kratom as a schedule 1 drug in Nevada. My oldest child and only son, Benjamin, died from acute mitragynine intoxication on 09/12/2024. His autopsy revealed nothing unusual. Benjamin used kratom to manage pain from psoriatic arthritis, believing it was a safe, natural alternative to prescription medications — as harmless as coffee. This misconception cost him his life and has left our family with indescribable heartbreak.

Although I reside in Montana, my advocacy for banning kratom extends nationally because this is not just a state issue; it is a matter of humanity. Kratom is sold and shipped across the United States, and my son received his supply from an out-of-state vendor.

Benjamin and I discussed kratom once. He described it in a way that made me think it was like green tea; kratom is often referred to as “tea.” I had no concerns. I was shocked to learn the truth about kratom when I began researching it after Benjamin’s death. It was upsetting to discover that many states did not act when the DEA attempted to classify

kratom as a controlled substance in 2016. Since then, the situation has escalated, with more dangerous derivatives, rising deaths, addiction, and adverse health effects. I have connected with many families who have suffered the same devastation of losing a loved one to kratom.

Regulation alone will not protect the public and may even foster a false sense of safety and the misconception that kratom-related issues have been resolved. Kratom includes mitragynine,7-hydroxymitragynine and 40+ additional alkaloids. If it is not banned its entirety, access to all the alkaloids remains as well as the ability to continue creating more dangerous derivatives.

I am including links with further information regarding kratom and its industry. The first one includes a letter signed by eleven state senators to the Commissioner of the Food and Drugs encouraging consideration for kratom to be banned in its entirety. The second one is from a site created by a pharmacist who advocates for kratom to be banned. The fourth and fifth links include statements regarding kratom from Dr. Christopher McCurdy – a researcher in Florida. He is believed to be aligned with the kratom industry but his comments in the following links support that there is much not known about kratom. The seventh link is a brief podcast by Jermaine Galloway (Tall Cop Says Stop) that puts the kratom issue into perspective so well. The last one is an article I interviewed for to bring awareness in my own state.

- Ricketts' Letter Calls on FDA to Address Kratom Scheduling Loophole - Senator Pete Ricketts
- Kratom Briefing for Lawmakers | Mothers Against Herbal Abuse
- The law and the profits: Inside kratom's political underbelly | Courthouse News Service
- Examining kratom's growing controversy, use in U.S.
- nccih.nih.gov/training/videolectures/22/3
- Deadly Dose - A Tampa Bay Times investigation into the kratom industry
- The Tides Are Shifting on Krat… - Tall Cop Says Stop™ - Boots On The Ground - Apple Podcasts
- Parent warns of the dangers of kratom after son's death

The American Kratom Association is defending the kratom industry without regard for those who have died because of this substance. One of their lobbyists often discredits coroners and medical examiners, claiming our loved ones did not die from kratom. The Association played a significant role in stopping the 2016 DEAs ban effort. This decision cost many families, including mine, beyond measure. The DEA continues to list kratom as a "drug of concern".

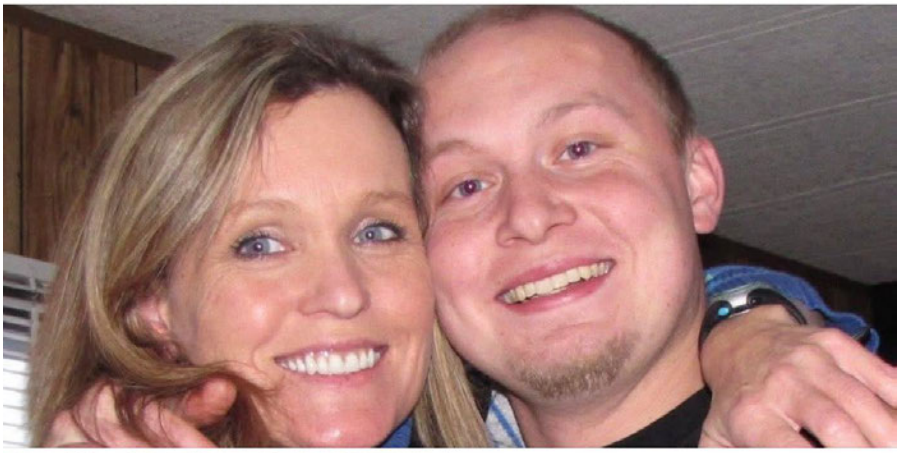
Please support scheduling/banning kratom in its entirety and protect Nevada citizens from the devastation kratom has caused many individuals and families.

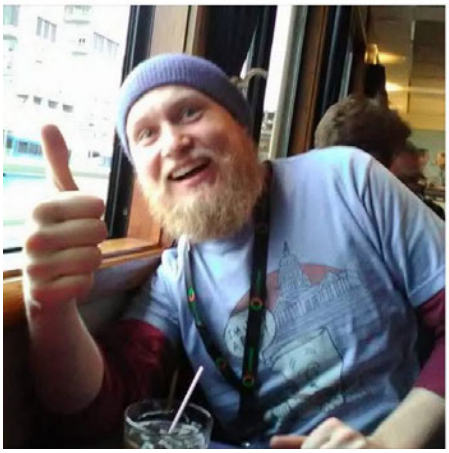
Thank you for your time and consideration.

Respectfully,

Kelli McCann (Benjamin's mom)


Drug Epidemic Memorial
Benjamin Wilcock
Forever 40
Acute mitragynine (kratom) intoxication
Montana







From:	karinsnoble@everyactioncustom.com on behalf of Karin Noble
To:	Board Coordination
Subject:	Oppose Mitragynine Scheduling
Date:	Tuesday, April 14, 2026 11:24:15 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

My Own Personal Experience with Kratom:
I am a 63-year-old woman who has been using Kratom since 2010. Please don't take the plant that is successfully giving me a life without the constant cycle of pain. The pain medications my doctors prescribed did not work and left me in more pain while struggling with dependence. A horrible existence. One of the most fortunate days of my life is when a friend introduced me to kratom, as they were alarmed by my constant misery. I was not living just existing. My life is improved and my lifestyle is healthy. Kratom is not a drug. It has been used safely in Asia for over two centuries. Your bill to ban synthetics will also include natural Kratom. This is in grave error. So many people depend on natural kratom to have healthy, happy existence. IT IS NOT A DRUG. Restricting synthetic analogues is the right thing to do. Nobody knows what the long-term affects are as it does not have a 200 plus year safety profile. It is not Kratom and it is offensive to be spoken of in the same context. I agree restrictions for age and accessibility for natural kratom products is correct. As is an outright ban on synthetics that are marketed as safe natural kratom. It is misleading and extremely dangerous.
Thank you ,
Karin Noble

Sincerely,
Karin Noble

From: MrEternityroad
To: Board Coordination
Subject: Kratom Issue
Date: Wednesday, April 15, 2026 1:18:18 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Hi,
I have been informed of a meeting tomorrow where the subject of Kratom use will come up. I am not at all certain I can make that meeting due to another appointment so I am writing to implore you to NOT make Kratom a Schedule 1 substance. I am a long-time sufferer of Restless Leg Syndrome and Kratom alleviates my symptoms very well. In fact I have been using Kratom for Restless Legs Syndrome for nearly nine years with no adverse effects. I have tried other medications including Gabapentin and they do not help. Without Kratom I would have to rely exclusively on the opioid Hydrocodone which would not only be more expensive, but possibly harmful in greater quantities. I am 78 years of age and I am on a fixed income. I could not afford the Hydrocodone in the quantity it would take to relieve my symptoms so I am asking that you consider persons who use Kratom for medicinal purposes.

Respectfully,
Kenneth Wanamaker

From:	cabpark@everyactioncustom.com on behalf of Kyle C
To:	Board Coordination
Subject:	Oppose Mitragynine Scheduling
Date:	Wednesday, April 15, 2026 2:20:04 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

I understand the fears in the media (especially with so many outlets confusing plain leaf kratom with the semi-synthetic 7-OH products), but banning kratom is a huge mistake.

I know countless people who use it in Nevada, and countless more who come to both Reno and Las Vegas multiple times a year that use it. These aren't people in the streets creating issues. They're people who travel for a living.

I also know quite a few people who quit either drinking or hard opioids with plain leaf kratom. Suboxone and Methadone don't work for everyone, or cause other issues for opioid users. There's a reason that overdoses are down, and it's not just narcan.

(And just as an aside: Mitragynine isolate as a prescription will not do the same thing that regular kratom does. There's a myriad of reasons for that. If that is the goal, it just flat out will not work. I seriously hope that's not the goal, so I'm going to optimistically believe it isn't.)

I would heavily implore the board to look into a system more in line with other states. A KCPA approach is more sensible. Banning 7-OH products makes sense to me (it's just a bit too much, personally), but regular kratom has been in the US for decades now. It just wasn't a big news story.

Please take this into consideration. I don't want people pulling out business from the state, and I don't want to see people traveling to the state being criminalized over something so incredibly trivial. Regulate kratom like so many other states have. Do not ban it. People's lives are at stake. Thank you for your time.

Sincerely,
Kyle C

From: Leon Dura
To: Board Coordination
Subject: Thursday April 16 Workshop Agenda Item 15: B
Date: Wednesday, April 15, 2026 5:10:12 PM

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I hope that unrefined Mitragyna speciosa leaf, i.e. kratom leaf, would not be considered for Schedule I listing.

Respectfully,
Leon J Dura M.D.

From: llpar6@everyactioncustom.com on behalf of Lauren Parish
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Friday, April 10, 2026 11:25:45 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

Many people rely on natural kratom as a critical tool for managing chronic pain, mitigating symptoms of anxiety and depression, and as a safe alternative to more dangerous substances.

Sincerely,
Lauren Parish

From:	Melissa Broadwater
To:	Board Coordination
Subject:	Public Comment Opposing Scheduling of Kratom Alkaloids as Schedule I
Date:	Wednesday, April 15, 2026 6:50:54 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

To the Nevada State Board of Pharmacy,

My name is Melissa Broadwater and I am submitting this public comment regarding the proposed scheduling of kratom and its alkaloids such as 7-hydroxymitragynine and mitragynine pseudoindoxyl as Schedule I substances.

I respectfully urge the Board to reconsider this approach. Classifying these compounds as Schedule I could have a much broader impact on kratom products as a whole. These alkaloids are naturally associated with kratom and are also formed in the body when kratom is consumed, so this proposal would effectively extend far beyond isolated compounds.

From my own experience, kratom and its alkaloids have been life changing. I have lived with a severe gastrointestinal condition for over 20 years that causes constant and sometimes debilitating pain. On severe pain days, I rely on 7-hydroxymitragynine for relief when kratom is not enough or when I am not able to consume kratom due to the amount of plant material it requires. Kratom has also helped me regain stability and live a more normal life again.

I also view kratom as an important harm reduction tool. Many responsible adults use it to manage pain or to avoid returning to dangerous substances that kratom and 7oh helped them quit and stay off of. Removing or severely restricting access without strong scientific justification risks causing real harm to people who rely on it.

I respectfully ask the Board to base any decisions on science, evidence, and real world use, and to consider responsible regulation rather than broad prohibition that could unintentionally restrict access to kratom and its alkaloids such as 7-hydroxymitragynine (7oh).

Thank you for your time and consideration,

Melissa Broadwater

From: Melanie Shamblin
To: Board Coordination
Subject: STOP KRATOM BAN IN NEVADA
Date: Sunday, April 19, 2026 3:48:11 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

I am opposing the scheduling of Kratom alkaloids as Schedule 1

2. Natural Kratom leaf has a demonstrated history of safe use and is not comparable to schedule 1 substance

3. Schedule 1 classification would criminalize responsible consumers who rely on a safe legal product

Kratom has supported my wellness by relieving my pain to a tolerable level when doctors refused to help me and refused to prescribe me pain medication. I have fibromyalgia and many bulging discs as well as my cervical fusion C3-C7 due to being hit by a drunk driver many years ago. I cannot get injections due to my fibromyalgia as it causes a flare and unbearable pain throughout my body. My daughter and I both suffer from chronic pain and i don't know how we would get through the day if we cannot obtain Kratom as needed. Please do not make Kratom a schedule 1 classification as it would change my life for the worse.
Sent from my iPad

From: megandonofrio@everyactioncustom.com on behalf of Megan Donofrio
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Friday, April 10, 2026 10:44:38 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

My Own Personal Experience with Kratom:

Sincerely,
Megan Donofrio

From: ellettmakayla@everyactioncustom.com on behalf of Makayla Ellett
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Friday, April 10, 2026 11:34:52 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

My Own Personal Experience with Kratom:
Kratom has helped me with pain and restless leg syndrome. Kratom has enabled me to function and it is way less harmful than pharmaceuticals. Thank you for your time on this matter.

Sincerely,
Makayla Ellett

From:	newauthor57@everyactioncustom.com on behalf of Mary Fish
To:	Board Coordination
Subject:	Oppose Mitragynine Scheduling
Date:	Friday, April 10, 2026 1:42:47 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

My Own Personal Experience with Kratom: I have had chronic pain from degenerative arthritis for 30+ years. I have been prescribed all types of pain relievers from OTC to prescribed controlled medications. At this point those of us must suffer as we are treated as if we all are addicts if we request tougher pain cont. It's shameful and offensive.

Kratom has given me pain free days 60% of the day. I have been consuming kratom for almost 9 years and have been comfortable during the day. This organic plant helps immensely and would be missed if taken away. I understand this plant has caused issues with addiction, although those individuals will find something else to overdose on.

Please do not remove another pain reliever from us. We are not children and many of us are on fixed income.

Thank you for your attention.

Mary Fish

Sincerely,
Mary Fish

From:	Michael Garrison
To:	Board Coordination
Subject:	Kratom scheduling
Date:	Wednesday, April 15, 2026 1:11:43 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Good afternoon,

My life has changed dramatically for the better since finding kratom and 7-hydroxymitragynine extracts. I have an actual life now. I am married, I have a beautiful baby boy who turns 2 on April 20th. I have a career and a house and a great life. All of these things are because kratom allowed me to free myself from street drugs like heroin, fentanyl, and prescription pain medication. I have been sober from drugs and alcohol since 2016 all because of this miracle plant.

If you schedule 7-hydroxymitragynine or mitragynine pseudoindoxyl then you are effectively scheduling plain leaf kratom. Both of these alkaloids are found naturally in the body after ingesting plain leaf kratom, as mitragynine is oxidized in the body into those two alkaloids, as well as 7-hydroxymitragynine being found naturally in plain leaf kratom in amounts as high as 2% of plant matter. If you schedule these alkaloids you are effectively removing my free will and my ability to stay sober and off alcohol and unsafe, polluted street drugs.

Please I urge you to reconsider this scheduling of naturally occurring alkaloids that has a higher safety profile than acetaminophen, ibuprofen, alcohol, tobacco, and most pharmaceutical medications. I have found peace and equilibrium with this plant.

From: chefmichct@everyactioncustom.com on behalf of MICHELE GAY
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Friday, April 10, 2026 11:05:22 AM

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Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

My Own Personal Experience with Kratom:

My own state took away kratom as my medicine. That's what it is. There's many of us that have bad side effects with most traditional medications.

Please don't do that. Please do age restrictions or a protection act.

I'm one step closer to having to claim disability cause I have no other choice. Do your want that for your residences?

Sincerely,
MICHELE GAY

From: feldispie@everyactioncustom.com on behalf of Mika Gillispie
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Friday, April 10, 2026 2:58:09 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

I respectfully urge you to reconsider any proposed ban on natural kratom leaf, and to ask that any legislation targeting 7-hydroxymitragynine (7-OH) be carefully written to distinguish it from plain kratom leaf, because even the FDA draws that distinction.

The FDA itself has separated 7-OH from natural kratom leaf. On July 29, 2025, the FDA announced steps to restrict 7-OH products, explicitly stating that their action targets "a concentrated byproduct of the kratom plant" and is "not focused on natural kratom leaf products." The FDA Commissioner described 7-OH as a synthetic concentrate that "can be more potent than morphine", a description that does not apply to the plain botanical leaf. Natural kratom leaf contains only approximately 0.02% 7-OH by composition. The concentrated 7-OH products being sold in vape shops and gas stations are a fundamentally different substance. Banning kratom leaf in response to 7-OH concerns would be like banning poppy seed bread because of fentanyl.

For millions of Americans, natural kratom leaf is a lifeline. Kratom is a botanical in the coffee family that has been used safely for centuries in Southeast Asia. In the United States, it has become an important tool for people managing chronic pain, anxiety, depression, and opioid withdrawal - often when conventional medicine has failed them. I am one of those people. I have tried every FDA-approved antidepressant available, and none have provided relief for my depression. Natural kratom leaf has. It has allowed me to function, to care for my family, and to remain a contributing member of my community.

A ban on natural kratom would cause serious harm. The people who rely on kratom leaf are not seeking a dangerous high. They are teachers, parents, veterans, and taxpayers who have found a natural option that works. If this leaf is banned, many will face a desperate choice: return to opioids and alcohol, go without any relief at all, or be criminalized for using a tea leaf. That is not a public health solution. It is a public health crisis in the making.

What I am asking for is precision, not inaction. I support protecting consumers from dangerous concentrated 7-OH products. Restrict those. Regulate them. But please do not sweep natural kratom leaf into that same category when the FDA's own scientists have said it does not belong there. Legislation should be targeted and evidence-based.

I urge you to stand with the thousands of constituents who depend on natural kratom leaf for their health and wellbeing. We are not criminals. Please do not make us into ones.

Sincerely,
Mika Gillispie

From:	David Wuest
To:	Board Coordination
Cc:	Yenh Long
Subject:	FW: Documents for Nevada Board of Pharmacy
Date:	Wednesday, April 15, 2026 9:12:59 AM
Attachments:	FDA Pilot Dose Finding Study.pdf The Abuse Potential of 7-Hydroxymitragyine (7-OH) According to the 8 Factors of the Controlled Substances Act FOR SUBMISSION Final.pdf Henningfield 8-Factor on Kratom Abuse Potential.pdf Kratom Science Update 2024.pdf Kratom_as_a_potential_substance_use_diso.pdf fphar-15-1403140.pdf Johns Hopkins Study on Adult Kratom Consumers 2020.pdf

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Darlene,

Move public comment sent to me. Please add it to the others.

Thanks

Dave

From: Mac Haddow <mhaddow1@verizon.net>
Sent: Tuesday, April 14, 2026 7:24 PM
To: David Wuest <dwuest@pharmacy.nv.gov>
Subject: Documents for Nevada Board of Pharmacy

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David:

Here are a set of documents for submission to the Board Members for Thursday's meeting:

FDA Single Ascending Dose Study:

Henningfield, et al., 8-Factor on 7-Hydroxymitragynine:

Kratom Abuse Potential 2021:

Kratom Science Update - December 2023:

Kratom as a Potential Harm Reduction Agent:

Kratom Safety and Toxicology in Public Health Context:

User Demographics, use patterns, and implications for the opioid epidemic:

Thanks for assisting with these materials being available to the Board.

Mac

A Pilot, Dose-Finding, Pharmacodynamic and Pharmacokinetic Study of Orally Administered Botanical Kratom

Chad J. Reissig, PhD,[1] Ling Chen, PhD,[1] Srikanth C. Nallani, PhD,[1] E. Gregory Hawkins, PhD,[1] Steven Galati, MD,[1] Katherine Bonson, PhD,[1] Siva Rama Raju Kanumuri, PhD,[2,3] Christopher R. McCurdy, PhD,[2,3,4] Abhisheak Sharma, PhD,[2,3] Beatrice Setnik, PhD,[5,6] Denise Milovan, PhD,[5] Debra Kelsh, MD,[5] and Dominic Chiapperino, PhD[1]

Background: Kratom (*Mitragyna speciosa*) is a plant indigenous to Southeast Asia. This pilot study evaluated the pharmacodynamic (PD) effects, safety, and pharmacokinetics (PK) of kratom and several of its alkaloids.

Methods: Recreational polydrug users (8 participants/cohort; 6 active: 2 placebo, N = 40) completed the study. Participants had experience with opioids but were otherwise healthy. This study utilized a double-blind, between-subjects design where participants randomly received a single dose of placebo or kratom. The kratom used in the study had alkaloid levels representative of botanical kratom products (i.e., leaf) previously characterized in the literature and contained trace levels of 7-hydroxymitragynine (7-OH). The starting dose was 1 g and doses of 3, 8, 10, and 12 g were administered after safety reviews after each dose. After dosing, pupillometry and assessments of subjective effects were performed, and blood samples were collected. Safety assessments included adverse events (AE) monitoring, laboratory tests, vital signs, ECG assessments, physical examination findings, and assessment of suicidality.

Results: No deaths or serious adverse events (SAEs) occurred. Somnolence, vomiting, and nausea were the most common AEs reported. Kratom alkaloid concentrations showed generally orderly, dose-related effects. At doses ≥3 g, kratom produced pupillary constriction. Few dose-related effects were observed, although the 12 g dose of kratom produced increases on several subjective measures including ratings of "drug liking."

Conclusions: This study investigated the safety of single-sourced botanical kratom; the results may not be representative of other kratom-containing products. Kratom produced some opioid-like effects including pupillary constriction, and the 12 g dose produced effects commonly associated with drugs of abuse such as visual analog scale (VAS) ratings of drug liking, good effects, and high.

Key Words: kratom, abuse, pharmacokinetcs, pharmacodynamics

(*J Clin Psychopharmacol* 2026;00:000–000)

Kratom (*Mitragyna speciosa*) is a wetlands tree native to Southeast Asia including Thailand, Indonesia, and Malaysia.[1] Kratom has been used for centuries in a variety of sociocultural contexts including the treatment of opioid withdrawal, pain relief, and for mood-enhancing effects.[1–3] In the United States, kratom began increasing in popularity in the 1990s. According to the National Survey on Drug Use and Health, an estimated 1.7 million Americans aged 12 and older used kratom in 2021.[4] Characterizing kratom use is complicated by a heterogeneous product landscape that includes teas, tablets, extracts, and whole leaf products with varying routes of administration and alkaloid content. Much of the data regarding the use patterns of kratom in the United States is derived from survey-based studies. For example, Garcia-Romeu et al. found that most regular kratom users reported using 1 to 3 g (49%) or 4 to 6 g (33.4%) per consumption.[5] In other survey studies, the self-reported average consumption of kratom powder was 4 to 5 g per serving with a range of 2.6 to 7.5 g.[6,7] When quantifying mitragynine levels consumed through the use of kratom products, individuals self-reported consuming an average of 31.3 mg of mitragynine/serving, corresponding to 78.3 to 134.6 mg of mitragynine per day.[8]

As of November 2025, no drug products containing kratom or its components have been approved by the US Food and Drug Administration (FDA) and FDA has concluded that:

> *"…kratom is a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury and, therefore, dietary supplements that are or contain kratom are adulterated under section 402(f)(1)(B) of the FD&C Act. Further, FDA has determined that kratom, when added to food, is an unsafe food additive within the meaning of section 409; food containing an unsafe food additive, such as kratom, is adulterated under section 402(a)(2)(C)(i). On the basis of these determinations by FDA, kratom is not lawfully marketed as a dietary supplement and cannot be lawfully added to conventional foods."*[9]

Received for publication September 29, 2025; accepted December 28, 2025.

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US Food and Drug Administration under contract 75F40121C00199.

Address correspondence to: Chad J. Reissig, PhD, United States Food and Drug Administration, 10903 New Hampshire Ave. Building 51, Silver Spring, MD 20903 (e-mail: Chad.reissig@fda.hhs.gov).

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.psychopharmacology.com.

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ISSN: 0271-0749
DOI: 10.1097/JCP.0000000000002158

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Despite the lack of regulatory oversight of kratom and kratom-related products, there has been substantial scientific interest in the pharmacology of kratom and its alkaloids. More than 40 alkaloids have been identified in kratom, the most abundant of which is mitragynine. Mitragynine accounts for ~66% of the total alkaloid content, and 4 additional alkaloids (speciociliatine, speciogynine, paynantheine, and corynantheidine) make up roughly 20% of the alkaloid content.[1,10] The minor alkaloids make up the remaining ~14% of alkaloid content of the leaf material and there are few data describing the pharmacological effects of these minor alkaloids.

Research efforts investigating kratom have focused primarily on its alkaloid constituents and mitragynine has been the subject of most of these studies given its abundance in the kratom in the tree. Mitragynine has affinity for, and binds to mu-opioid receptors.[11] Mitragynine also has affinity for a variety of receptor subtypes including adrenergic (α_{1a}, α_{1b}, α_{1d}, α_{2a}, α_{2b}, and α_{2c}), adenosine A_{2A}, dopamine D_2, and serotonin (5-HT_{1A}, 5-HT_{2B}, 5-HT_{2C}, and 5-HT_7) receptors.[12–14] The effects of mitragynine on mu-opioid receptors vary by the assay system utilized. For example, in vitro functional assays have characterized mitragynine as a full agonist,[15] partial agonist,[11,16] and as an antagonist.[17] In vivo assessments of antinociception using the hot plate test have shown that mitragynine functions as an agonist, producing a degree of antinociception similar to classic opioids such as morphine and oxycodone.[18,19] In contrast, mitragynine did not produce significant antinociception in hot plate tests utilizing rats.[17] Drug discrimination procedures have been used to examine the stimulus effects of mitragynine and model its subjective effects. In a drug discrimination study that trained rodents to discriminate mitragynine from vehicle, administration of morphine produced full substitution for the mitragynine cue.[20] In a second group of animals trained to discriminate morphine from vehicle, administration of mitragynine produced full substitution for the morphine stimulus cue (i.e., symmetrical generalization). Of note, the substitution of mitragynine for the morphine cue was dose-dependent: where the middle dose of mitragynine produced full generalization to the morphine cue but the low and highest doses examined did not.[20] Although the drug discrimination results from Harun and colleagues seem to be in keeping with mitragynine's mu-opioid receptor binding profile, disparate drug discrimination results have been reported. For example, in separate groups of rats trained to discriminate either mitragynine or morphine from saline, mitragynine failed to produce full substitution for the morphine stimulus cue, and morphine did not substitute for the stimulus effects of mitragynine.[17] Interestingly, a variety of other opioids did substitute for the mitragynine stimulus cue including fentanyl, nalbuphine, and buprenorphine.[17] The authors hypothesized that the incomplete substitution of mitragynine for morphine (and vice versa) may be due to rate-limiting effects, and that the stimulus effects of mitragynine are dose-related and may be mediated by more than mu-opioid agonist effects alone.

The rewarding properties of mitragynine have also been examined using conditioned place preference (CPP). In CPP studies with isolated mitragynine, rats demonstrated a place preference for mitragynine that was similar to stimulants and morphine, suggesting its rewarding properties.[21,22] A follow-up study using naloxone suggested that although opioid receptors mediated the acquisition of CPP, they were less involved in CPP expression after it was acquired.[23] In contrast, when the reinforcing effects of mitragynine were examined directly using self-administration procedures, mitragynine was not self-administered in rats previously trained to self-administer morphine.[24]

Although data characterizing the pharmacology of the minor alkaloids are sparse, 7-hydroxymitragynine (7-OH) has been the subject of numerous research efforts. 7-OH is typically reported to account for $< 0.05\%$ of dried kratom leaf mass, a substantially lower proportion than mitragynine.[25] 7-OH has been postulated to be a post-harvest artifact of kratom and is also formed as a metabolite of mitragynine in humans.[26] 7-OH has received considerable attention due to its greater affinity and activity at mu-opioid receptors relative to mitragynine and the other kratom alkaloids.[11,27] Importantly, 7-OH is self-administered in preclinical models, demonstrating its reinforcing effects and potential for abuse.[24]

Despite the extensive literature on kratom and its alkaloids using in vitro, in vivo, and epidemiological data to characterize its pharmacology and use patterns, prospective and properly controlled clinical studies are sparse. For example, Trakulsrichai and colleagues conducted a prospective study of the pharmacokinetics (PK) of kratom by administering kratom tea to regular kratom tea users. However, there was no placebo or positive control comparator, and subjective effects (i.e., abuse-related measures) were not assessed. In addition, the dose range of kratom was relatively limited and only 3 mitragynine equivalent doses were examined: 6.25, 9.96, and 11.5 mg.[28] Vicknasingam and colleagues examined the effects of kratom tea on pain tolerance using the cold pressor test. The authors found an increase in analgesia, though only a single dose of kratom tea was administered and mitragynine (1.6 mg/kg) was the only alkaloid measured in the tea.[29] Tanna et al.[30] also assessed the PK profile of a 2 g tea, whereas Huestis et al.[31] performed a double-blind, dose-escalation study of 0.5 to 4 g encapsulated dried leaf kratom powder administered orally to assess its PK profile. Other clinical assessments of kratom have allowed participants to self-administer their own kratom products in uncontrolled, outpatient settings without active or placebo comparators.[32–34] Given the dearth of rigorously controlled clinical studies of kratom, along with an absence of abuse-related outcome measures, the objective of this single ascending-dose study of botanical kratom was to generate pilot data on its behavioral effects and safety profile and to inform the design of a future human abuse potential (HAP) study.

MATERIALS AND METHODS

Study Design

This single-center, single-dose, randomized, adaptive, double-blind, placebo-controlled study consisted of 5 single ascending-dose cohorts. Dose levels could be adjusted to higher or lower doses following a review of the safety, tolerability, and pharmacodynamic (PD) data from previous cohorts by a Safety Review Committee (SRC). The SRC consisted of the principal investigator at the investigational site, the study manager, and personnel from FDA's scientific team. The study was conducted at Altasciences

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company in Overland Park, Kansas. The study received ethical approval from an Institutional Review Board and was performed under an Investigational New Drug Application (IND).

Kratom

The kratom used in the study was obtained from Sun Distribution, Super Organics. The kratom was powdered, raw leaf, and administered in 500 mg, size 00 capsules. To meet the chemistry, manufacturing, and controls (CMC) requirements for the IND, repeated stability testing was performed and the kratom met USP guidelines for heavy metals, microbial load, pesticides, mycotoxin, residual solvents, and moisture content. The kratom product was analyzed for alkaloidal content using a validated method UPLC-MS/MS as reported earlier,[35] and stability studies were performed at room temperature in a stability chamber (25°C and 60% RH) for 13 months. Kratom product was found stable (acceptable limit, 90% of initial content) and the alkaloid content seemed to be consistent with that reported in the published literature (Table 1).[8,36] For each cohort, matching placebo capsules containing 500 mg of microcrystalline cellulose were administered.

Quantitative Analysis Using UPLC-MS/MS

Two separate bioanalytical methods were developed and validated for quantitative analysis of mitragynine and 7-hydroxymitragynine and speciogynine, speciociliatine, and paynantheine at Alta Sciences and University of Florida, respectively. In brief, mitragynine and 7-hydroxymitragynine were quantified using AB Sciex API5500 triple quadrupole mass spectrometer coupled with Shimadzu Nexera X2 ultra high-performance liquid chromatography system (UPLC-MS/MS) for a linearity range of 0.5 to 500 and 0.2 to 100 ng/mL, respectively. Analysis was conducted in multiple reaction monitoring (MRM) mode using precursor to product ion mass transitions of *m/z* 415.22 > 397.30, 399.23 > 238.10, 418.24 > 400.20, and 402.25 > 238.10, respectively, for 7-hydroxymitragynine, mitragynine, 7-hydroxymitragynine *d3*, and mitragynine *d3*, respectively. 7-hydroxymitragynine *d3* and mitragynine *d3* were used as an internal standard for 7-hydroxymitragynine and mitragynine, respectively. Chromatographic separation was achieved using a gradient flow (0.6 mL/min) of mobile phase consisting of methanol and water containing 0.5% formic acid and a Raptor biphenyl (100 ×2.1 mm, 2.7 μm) column. UPLC-MS/MS analysis of speciogynine, speciociliatine, and paynantheine was carried out using Waters Acquity Class I Plus UPLC coupled with a Waters Xevo TQ-S Micro triple quadrupole mass spectrometer for a linearity range of 1-250 ng/mL in human plasma. The chromatographic separation was achieved using Waters Acquity Premier CSH C18 (1.7 μm, 2.1×10 mm) with Vanguard fit guard column using the mobile phase consisting of aqueous ammonium acetate buffer, (2.5 mM, pH-3.5 ± 0.1) (A) – acetonitrile (B) with a gradient elution. The column and autosampler temperatures were kept at 55 and 4 °C, respectively. The mobile phase was delivered at a flow rate of 0.5 mL/min, and the injection volume was set to 2 μL. The source temperature was 150°C, Ion spray voltage was set at 500 V, desolvation temperature was 500 °C, desolvation gas flow was 900 L/h, and the cone gas flow was 50 L/h. The mass spectrometer was operated in positive ion mode and detection of the ions was performed in MRM mode, monitoring the transition of *m/z* 399.25 precursor ion $[M+H]^+$ to the *m/z* 174.16 product ion for speciogynine and speciociliatine (collision energy 32 V and cone voltage 60V), *m/z* 397.16 precursor ion $[M+H]^+$ to the *m/z* 174.16 product ion for paynantheine (collision energy 30 V and cone voltage 58 V), *m/z* 402.21 precursor ion $[M+H]^+$ to the *m/z* 177.06 product ion for internal standard (collision energy 30 V and cone voltage 26V) (mitragynine-*d3*). Both bioanalytical methods were validated for selectivity, specificity, accuracy, precision, calibration and range, carryover, matrix effect, dilution integrity, and stability following FDA/ICH M10 guidelines for bioanalytical method validation.

Participants

A total of 40 healthy male and female, nondependent, recreational polydrug users with prior opioid experience were included in the study (8 subjects in each of the 5 cohorts). Recreational drug users were defined as those who had used opioid drugs for recreational purposes (i.e., for psychoactive effects) at least 10 times in the subject's lifetime and at least once in the last 12 weeks from screening. Inclusion criteria included a history of recreational use of 2 or more perception-altering (eg, lysergic acid diethylamide (LSD), kratom, cannabis, dronabinol, ketamine, phencyclidine, dextromethorphan, 3,4 methylenedioxymethamphetamine (MDMA), mescaline, psilocybin, tryptamine derivatives or ring-substituted amphetamines with perception-altering effects) or stimulant drugs (eg,

TABLE 1. Alkaloid Composition and Stability of Kratom Capsules (25°C/60% RH)

	Timepoint (mo)					
Alkaloid*	**0**	**1**	**2**	**3**	**6**	**13**
Mitragynine	5.22 ± 0.65	5.08 ± 0.35	4.90 ± 0.51	5.22 ± 0.46	5.07 ± 0.71	5.38 ± 0.32
Speciogynine	0.99 ± 0.12	0.96 ± 0.07	0.90 ± 0.10	0.97 ± 0.08	0.92 ± 0.13	0.94 ± 0.07
Speciociliatine	2.02 ± 0.24	1.98 ± 0.14	1.98 ± 0.21	1.94 ± 0.17	1.98 ± 0.26	1.82 ± 0.12
Mitraciliatine	0.29 ± 0.03	0.28 ± 0.02	0.29 ± 0.03	0.31 ± 0.02	0.29 ± 0.04	0.25 ± 0.02
7-hydroxymitragynine	0.06 ± 0.01	0.06 ± 0.01	0.03 ± 0.01	0.03 ± 0.00	BLLOQ	0.04 ± 0.01
Paynantheine	1.34 ± 0.16	1.32 ± 0.09	1.26 ± 0.13	1.33 ± 0.12	1.28 ± 0.18	1.19 ± 0.08
Corynantheidine	0.14 ± 0.02	0.13 ± 0.01	0.13 ± 0.01	0.13 ± 0.01	0.13 ± 0.02	0.14 ± 0.01
Corynoxine A	0.05 ± 0.01	0.05 ± 0.01	0.05 ± 0.00	0.04 ± 0.00	0.04 ± 0.01	0.04 ± 0.00
Corynoxine B	BLLOQ	BLLOQ	BLLOQ	BLLOQ	BLLOQ	0.03 ± 0.00
Mitraphylline	BLLOQ	BLLOQ	BLLOQ	BLLOQ	BLLOQ	BLLOQ

*Alkaloids content(s) are expressed as the milligram (mg) amount per 500 mg capsule.
BLLOQ indicates below the lower limit of quantitation (1 ng/mL equivalent to 32 ng/capsule); RH, relative humidity.

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cocaine, amphetamine, methamphetamine, methylphenidate, methcathinone, and other synthetic cathinones) on at least 5 occasions in the participant's lifetime. Polydrug recreational users with prior opioid experience were selected to ensure familiarity with a broad range of psychoactive drug effects. This population is considered appropriate and face-valid for evaluating the pharmacodynamic profile of escalating kratom doses, given its reported spectrum of activity ranging from stimulant-like effects at low doses to opioid-like sedation and dissociative/hallucinogenic effects at higher doses.[37–39] Experienced recreational polydrug users also represent the typical participant population enrolled in HAP studies, which this SAD study was designed to inform.[40] All participants provided written informed consent form (ICF) and agreed to use appropriate contraception methods (eg, abstinence, systemic contraceptives, intrauterine device, double-barrier method, etc.).

Exclusion criteria included: (1) Difficulty swallowing capsules; (2) females who were lactating or pregnant; (3) self-reported sensitivities to kratom; (4) significant history of disease including gastrointestinal, liver or kidney disease, cardiovascular, pulmonary, hematologic, neurological, psychiatric, gastrointestinal, endocrine, immunologic, ophthalmologic, or dermatologic disease; (5) smoking or a history of heavy smoking; (6) excessive caffeine intake; (7) other physiological diseases or abnormalities identified at screening, including ECG abnormalities and QT prolongation; and (8) additional criteria, including a history of substance use disorder and intake of kratom in the 14 days before study participation.

Procedures

After successful screening, participants were confined to the clinical site from the day before drug administration until 48 hours after drug administration. Subjects were randomized 6:2 (active: placebo) to kratom or placebo in each cohort.

Kratom or placebo was administered under double-blind conditions. Study treatments were administered in the morning, 30 minutes after a standardized high-fat breakfast (fed state) after an overnight fast of at least 10 hours. This approach was chosen to increase tolerability, facilitate dose escalation, and mitigate nausea and vomiting previously reported under fasted conditions.[30] Capsules were administered with ~240 mL of water at room temperature. Given the large number and size of capsules required for certain cohorts (range of 2 to 24 size 00 capsules), an additional 240 mL of water was allowed if required. Time of dosing was set equal to the time when the first capsule was administered to the subject. The dosing procedure had to be completed within 5 minutes. Dosing procedures completed up to 2 minutes outside the allowed time window were not considered protocol deviations but were documented. Start and end times of dosing and the volume of water consumed were recorded. All capsules were swallowed whole and not chewed or broken.

Safety

Safety assessments included adverse event (AE) monitoring, clinical laboratory tests, vital signs (blood pressure, pulse, respiratory rate, oxygen saturation, and body temperature), ECG assessments, physical examination findings, and assessment of suicidality using the Columbia-Suicide Severity Rating Scale. At the investigator's discretion, additional safety assessments could be performed as needed to ensure subject safety.

Pharmacokinetic Assessments

Blood samples for PK measurements were collected predose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, and 48 hours, post-dose. Samples were collected from an intravenous catheter or direct venipuncture, if necessary. The time of PK blood sample collection was calculated relative to the time of treatment administration. PK measurements of the study included plasma concentrations of mitragynine, 7-hydroxymitragynine, speciogynine, speciociliatine, and paynantheine using validated bioanalytical methods (see Supplemental Digital Content 1, http://links.lww.com/JCP/B19 and 2, http://links.lww.com/JCP/B24).

Pharmacodynamic Assessments

Before completing computerized PD measures, all participants underwent a standardized training and practice session. Participants who seemed to have difficulty differentiating between bipolar and unipolar VAS (eg, making errors such as selecting a score of 50 to indicate the absence of a drug effect on a unipolar scale) or difficulty distinguishing between "at this moment" and "overall" measures received additional training focused on these distinctions.

Participants were monitored to ensure that PD assessments were completed appropriately. Reasonable attempts were made to rouse participants who fell asleep during testing. If a participant was unable to complete PD assessments in a timely manner before the next required procedure or timepoint due to an AE or other clinical concern, the PD assessment at that timepoint was aborted.

Pupillometry

Data from a series of frames were used in the calculation of pupil size. Measurements were collected using a handheld electronic pupillometer (NeurOptics VIP-300 Pupillometer System, CA) under mesopic lighting conditions. For each participant, the same eye was used for all assessments when feasible. The pupillometry assessment was completed immediately before the administration of other PD measures at each prespecified timepoint.

Visual Analog Scales (VAS)

All VAS were scored on a 0 to 100 scale and measured at predetermined time points. The VAS were structured as either bipolar or unipolar scales, depending on the subjective effect being measured. Bipolar scales asked about the neutrality, direction, and intensity of a subjective opinion, whereas unipolar scales only asked about the extremity or intensity of a subjective effect. When VAS were administered as bipolar scales, a neutral point equal to 50 was included in the scale [eg, drug liking, overall drug liking (ODL), take drug again (TDA), drowsiness/alertness VAS]. The neutral point reflected a state whereby a subject was experiencing neither negative nor positive effects (eg, neither dislike nor like the effects of the drug) and was labeled with an anchor, such as "neither like nor dislike." When VAS were administered as unipolar scales, anchors were presented using text such as "not at all" (score = 0) to "extremely" (score = 100; eg, good, bad, high, and any drug effects VAS). Unipolar scales did not include a neutral point but rather, a rating of "0" reflected the complete absence of a subjective effect, whereas a rating of "100"

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reflected the maximum presence of a subjective effect (eg, no good effects = 0, extremely good effects = 100). Scales that referred specifically to drug (eg, drug liking, good drug effects, bad drug effects, and any drug effects VAS) were not administered at predose.

Bowdle Visual Analog Scale

An adapted computerized version of the Bowdle VAS, consisting of 13 unipolar items, was administered to assess perceptual changes. Each item was scored from 0 ("not at all") to 100 ("extremely") with lower scores indicating fewer perceptual and psychedelic effects.

The individual items were:

1. My body or body parts seemed to change their shape or position (BODY)
2. My surroundings seemed to change in size, depth, or shape (SURROUNDINGS)
3. The passing of time was altered (TIME)
4. I had feelings of unreality (REALITY)
5. It was difficult to control my thoughts (THOUGHTS)
6. The intensity of colors changed (COLORS)
7. The intensity of sound changed (SOUND)
8. I heard voices or sounds that were not real (VOICES)
9. I had the idea that events, objects, or other people had particular meaning that was specific for me (MEANING)
10. I had suspicious ideas or the belief that others were against me (SUSPICIOUS)
11. I felt anxious (ANXIOUS)
12. I felt high (HIGH)
13. I felt drowsy (DROWSY)

Responses to items 1, 2, 3, 5, 6, and 7 were summed to produce a "subjective external perceptions" composite score. Response to items 4, 8, 9, 10, and 11 were summed to produce a "subjective internal perceptions" composite score. Items 12 and 13 were not included as they were administered as part of the individual VAS items. If a response to one of the items was missing, the associated composite score was not calculated.

Drug Similarity VAS

Drug Similarity VAS items provided an estimate of how similar the test drug was to drug classes with which participants were familiar. On a unipolar scale ranging from "not at all similar" to "very similar," participants were asked to compare a drug they had taken previously to the test drug. A drug use history was completed during screening and used to create a subject-specific drug similarity measure. Drugs that a subject had not used often (< 2 lifetime uses of a given drug), were not included in their questionnaire.

Addiction Research Center Inventory (ARCI)

The Addiction Research Center Inventory (ARCI)[41–43] Morphine-Benzedrine Group (MBG), Amphetamine (A), Benzedrine Group (BG), Pentobarbital-Chlorpromazine-Alcohol Group (PCAG), and lysergic acid diethylamide (LSD) scales were administered alongside the basic VAS measures.

The 49-item ARCI was a shortened version (49 true-false items) compiled by Martin and colleagues from the original 550-item ARCI.[41–43] This version contained 5 scales, which measured the following effects: Euphoria—MBG scale; Stimulant effects—Amphetamine scale and BG scale; Dysphoria—LSD scale; and Sedation—PCAG scale. Subjects indicated their responses by selecting "false" or "true." One point was given for each response that agreed with the scoring direction on the scale (i.e., true items received a score of 1 if the answer was "true;" a score of 0 was given when the answer was opposite to the scoring direction).

The following scales were administered:

- Euphoria: Morphine-Benzedrine Group (MBG) scale
- Stimulant effects: Amphetamine (A) scale, Benzedrine Group (BG) scale
- Dysphoria: Lysergic acid diethylamide (LSD) scale
- Sedation: Pentobarbital-Chlorpromazine-Alcohol Group (PCAG) scale

Statistical Analyses

For measures collected within 24 hours, the peak responses [maximum (E_{max}) or minimum (E_{min}), as appropriate] were the endpoints. The primary pharmacodynamic endpoint was E_{max} of drug liking VAS. Key secondary endpoints included Emax scores of high VAS, overall drug liking VAS, and take drug again VAS. Inferential statistics using the aforementioned peak responses were performed on the primary and key secondary endpoints. Because of the large number of endpoints and the large number of comparisons in the study, for controlling overall type I error rate only descriptive statistics were calculated for other endpoints.

ANOVA model was prespecified for the statistical analyses for the primary and key secondary endpoints. The 1-sided Dunnett test at 5% significance level was used for the comparisons between each dose of kratom and pooled placebo.[44] For the sensitivity analysis, Hodges-Lehmann estimator was used to estimate the difference between each dose of kratom and pooled placebo.[45,46] The 1-sided Mann-Whitney *U* test (or called Wilcoxon rank sum test)[47,48] at 5% significance level was used to test the null hypothesis that: "the observations produced by kratom and pooled placebo have the same distribution" versus the alternative hypothesis: "the distribution of observations produced by kratom is shifted to the right of that of pooled placebo." The Benjamin-Hochberg procedure[49] was used to adjust multiplicity for the comparisons between each dose of kratom and pooled placebo for each endpoint. As the dosing escalating study is exploratory in nature, the type I error rate adjustment was not performed for the multiplicity among endpoints.

RESULTS

Safety Analyses and Adverse Events

All 40 enrolled participants in the study were included in the safety analysis population. Overall, 18 of the 40 participants (45.0%) that received kratom or placebo experienced a total of 38 treatment-emergent adverse events (TEAEs) and 33 of the TEAEs (86.8%) were considered related to study drug (Table 2). The most commonly reported TEAEs were somnolence, vomiting, and nausea. Somnolence occurred in 1 of 6 participants (16.7%) receiving kratom 8 g, 3 of 6 (50.0%) receiving kratom 10 g, and 2 of 10 (20.0%) receiving placebo. Vomiting occurred in 2 of 6 participants (33.3%) in each of the kratom 8 g and 12 g cohorts, and in 1 of 6 (16.7%) in the kratom 10 g cohort. Nausea occurred in 2 of 6 participants (33.3%) receiving kratom 8 g, and in 1 of 6 (16.7%) in each of the kratom 10 g and 12 g cohorts. Nausea and vomiting

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TABLE 2. Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term and System Organ Class

System Organ Class and MedDRA Preferred Term	Kratom 1 g (N = 6) 2 Capsules	Kratom 3 g (N = 6) 6 Capsules	Kratom 8 g (N = 6) 16 Capsules	Kratom 10 g (N = 6) 20 Capsules	Kratom 12 g (N = 6) 24 Capsules	Pooled Placebo (N = 10)	Overall (N = 40)
Subjects with at least one TEAE *	1 (16.7)	1 (16.7)	5 (83.3)	4 (66.7)	3 (50.0)	4 (40.0)	18 (45.0)
Ear and labyrinth disorders	0	0	0	1 (16.7)	0	0	1 (2.5)
Tinnitus	0	0	0	1 (16.7)	0	0	1 (2.5)
Gastrointestinal disorders	0	0	3 (50.0)	2 (33.3)	2 (33.3)	0	7 (17.5)
Dry mouth	0	0	0	1 (16.7)	0	0	1 (2.5)
Nausea	0	0	2 (33.3)	1 (16.7)	1 (16.7)	0	4 (10.0)
Vomiting	0	0	2 (33.3)	1 (16.7)	2 (33.3)	0	5 (12.5)
General disorders and administration site conditions	0	0	0	1 (16.7)	1 (16.7)	0	2 (5.0)
Chills	0	0	0	1 (16.7)	0	0	1 (2.5)
Feeling hot	0	0	0	0	1 (16.7)	0	1 (2.5)
Infections and infestations	0	1 (16.7)	0	0	0	0	1 (2.5)
Viral upper respiratory tract infection	0	1 (16.7)	0	0	0	0	1 (2.5)
Investigations	0	0	0	0	0	1 (10.0)	1 (2.5)
Blood pressure systolic increased	0	0	0	0	0	1 (10.0)	1 (2.5)
Musculoskeletal and connective tissue disorders	0	1 (16.7)	0	0	0	0	1 (2.5)
Neck pain	0	1 (16.7)	0	0	0	0	1 (2.5)
Nervous system disorders	1 (16.7)	0	2 (33.3)	4 (66.7)	1 (16.7)	3 (30.0)	11 (27.5)
Dizziness	0	0	0	2 (33.3)	0	0	2 (5.0)
Headache	0	0	1 (16.7)	0	1 (16.7)	1 (10.0)	3 (7.5)
Paresthesia	1 (16.7)	0	0	0	0	0	1 (2.5)
Presyncope	0	0	1 (16.7)	0	0	0	1 (2.5)
Somnolence	0	0	1 (16.7)	3 (50.0)	0	2 (20.0)	6 (15.0)
Psychiatric disorders	0	0	2 (33.3)	2 (33.3)	0	0	4 (10.0)
Anxiety	0	0	0	1 (16.7)	0	0	1 (2.5)
Euphoric mood	0	0	1 (16.7)	1 (16.7)	0	0	2 (5.0)
Irritability	0	0	1 (16.7)	0	0	0	1 (2.5)
Renal and urinary disorders	0	0	1 (16.7)	0	0	0	1 (2.5)
Leukocyturia	0	0	1 (16.7)	0	0	0	1 (2.5)
Skin and subcutaneous tissue disorders	0	0	0	0	1 (16.7)	1 (10.0)	2 (5.0)
Hyperhidrosis	0	0	0	0	1 (16.7)	0	1 (2.5)
Pruritus	0	0	0	0	0	1 (10.0)	1 (2.5)

Data are reported as n (%).

*Each TEAE was counted only once for each subject within each MedDRA SOC and PT.

MedDRA indicates Medical Dictionary for Regulatory Activities; N, number of subjects who received the specified treatment; n, number of subjects in a category; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

were not observed in the pooled placebo group. No serious adverse events or deaths were reported, and no participants discontinued the study due to TEAEs.

Pupillometry

Mean (SE) pupil diameter over time at each dose level of kratom and placebo is illustrated in Figure S1 (Supplemental Digital Content 3, http://links.lww.com/JCP/B20). Minimal fluctuations in pupil diameter were observed for placebo and kratom 1 g. In contrast, kratom doses of 3, 8, 10, and 12 g produced decreases in pupil diameter (i.e., constriction), with an apparent dose-related effect. Mean maximum pupil constriction over time was 0.9 mm for kratom 1 and 3 g, 2.2 mm for kratom 8 g, 1.9 mm for kratom 10 g, and 2.4 mm for kratom 12 g compared with 1.1 mm for placebo. Summary statistics for maximum pupil constriction are presented in Table 3.

Dunnett test[44] was used to test the difference in means between each dose of kratom and pooled placebo for maximum pupil constriction. The results showed that the means of maximum pupil constrictions produced by 8 and 12 g of kratom were significantly smaller (i.e., produced more pupil constriction) than that in the pooled placebo group ($P < 0.05$).

Pharmacokinetic Results

All doses of kratom produced a measurable plasma concentrations of the targeted alkaloids.

Mitragynine

Plasma concentration-time profiles for mitragynine are shown in Figure 1, and PK parameters are summarized in Table 4. After a single oral administration of kratom under fed conditions, mitragynine was absorbed into the systemic

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TABLE 3. Summary Statistics for Maximum Pupil Constriction (mm)

Parameter	Kratom 1 g (N = 6)	Kratom 3 g (N = 6)	Kratom 8 g (N = 6)	Kratom 10 g (N = 6)	Kratom 12 g (N = 6)	Pooled Placebo (N = 10)
Mean (SE)	−0.9 (0.2)	−0.9 (0.2)	−2.2 (0.3)	−1.9 (0.3)	−2.4 (0.4)	−1.1 (0.3)
Median	−0.7	−0.8	−2.2	−1.7	−2.3	−0.8
Min, max	−1.9, 0.3	−1.5, −0.5	−3.0, −1.2	−3.1, −1.3	−3.9, −1.1	−2.6, 0

circulation with a median time to reach peak plasma concentration (T_{max}) ranging from 3.0 to 5.0 hours across cohorts 1 to 5. Mean observed peak plasma concentration (C_{max}) ranged from 41.7 to 378.5 ng/mL with increasing kratom doses from 1 to 12 g. The mean estimated area under concentration-time curve up to the last timepoint ($AUC_{0\text{-}T}$) ranged from 305.4 to 3271.2 h·ng/mL. An increase in mitragynine C_{max}, and $AUC_{0\text{-}T}$ was noted with an increased dose of kratom; however, dose-proportionality could not be concluded because of the limited number of subjects in parallel dosing cohorts.

7-Hydroxymitragynine

Concentration-time profiles for 7-hydroxymitragynine (7-OH) are shown in Figure 2, with PK parameters provided in Table 4. After a single oral administration of kratom under fed conditions, 7-OH produced a median T_{max} ranging from 2.8 to 6.0 hours for cohorts 1 to 5. The mean observed C_{max} ranged from 6.7 to 58.4 ng/mL with increasing kratom doses from 1 to 12 g. The mean estimated $AUC_{0\text{-}T}$ ranged from 53.5 to 574.3 h·ng/mL. An increase in 7-OH C_{max}, and $AUC_{0\text{-}T}$ was noted with an increased dose of kratom; however, dose-proportionality could not be concluded because of the limited number of subjects in parallel dose cohorts.

Paynantheine

Plasma concentration-time profiles for paynantheine are shown in Figure S2 (Supplemental Digital Content 3, http://links.lww.com/JCP/B20), with PK parameters provided in Table 4. Paynantheine produced a median T_{max} ranging from 2.99 to 5.04 hours for cohorts 1 to 5. The mean observed C_{max} ranged from 7.7 to 66.7 ng/mL with increasing kratom doses from 1 to 12 g. The mean $AUC_{0\text{-}T}$ estimate ranged from 47.0 to 727.6 h·ng/mL. An increase in paynantheine C_{max}, and $AUC_{0\text{-}T}$ was noted with increased dose of kratom; however, dose-proportionality could not be concluded because of the limited number of subjects in parallel dose cohorts.

Speciogynine

Plasma concentration-time profiles for speciogynine are shown in Figure S3 (Supplemental Digital Content 3, http://links.lww.com/JCP/B20), with PK parameters provided in Table 4. Speciogynine had a median T_{max} ranging from 2.54 to 5.04 hours for cohorts 1 to 5. The mean observed C_{max} ranged from 6.3 to 58.9 ng/mL after administration of kratom doses from 1 to 12 g. The mean estimated $AUC_{0\text{-}T}$ ranged from 53.4 to 819.2 h·ng/mL. An increase in speciogynine C_{max}, and $AUC_{0\text{-}T}$ was noted with increased doses of kratom; however, dose-proportionality

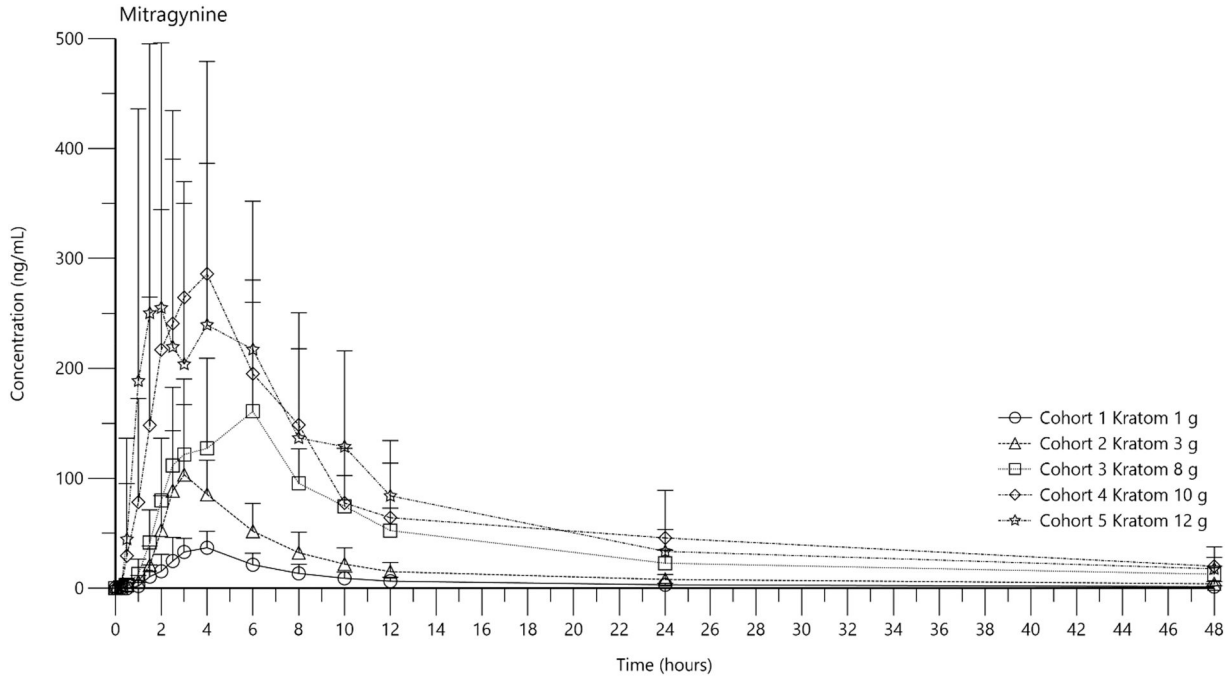


FIGURE 1. Plasma concentration-time profiles of mitragynine (Mean ± SD) by cohort in healthy participants (N = 6, each). The inset displays the 0 to 2 hours profile.

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TABLE 4. Pharmacokinetic Parameters of Mitragynine and 5 Additional Alkaloids After a Single-Dose Oral Administration of Kratom to Healthy Participants

Parameter* (Unit)	Cohort 1 (1 g) N = 6	Cohort 2 (3 g) N = 6	Cohort 3 (8 g) N = 6	Cohort 4 (10 g) N = 6	Cohort 5 (12 g) N = 6
Mitragynine (mg)	9.8-10.7	29.4-32.3	78.4-86.1	98.0-107.6	117.6-129.1
C_{max} (ng/mL)	41.7 (35.4)	118 (39.7)	197.5 (44.7)	318.1 (51.4)	378.5 (48.9)
T_{max} (h)	4.0 (2.5-6.2)	3.0 (2.5-4.0)	5.0 (2.5-6.1)	3.5 (2.5-4.0)	2.0 (1.0-6.0)
$AUC_{0\text{-}T}$ (h·ng/mL)	305.4 (37.9)	784.8 (48.5)	1942 (38.0)	3254 (68.0)	3271 (48.2)
λ_Z (1/h)	0.042 (21.5)	0.038 (14.6)	0.04 (24.5)	0.034 (29.5)	0.045 (22.1)
T_{half} (h)	17.28 (21.3)	18.64 (15.2)	17.47 (32.4)	22.07 (30.2)	15.9 (17.6)
7-hydroxymitragynine (mg)†	0-0.12	0-0.36	0-0.96	0-1.2	0-1.4
C_{max} (ng/mL)	6.7 (32.4)	17.8 (48.9)	34.0 (32.9)	48.4 (41.3)	58.4 (38.9)
T_{max} (h)	4.0 (2.5-6.2)	3.5 (3.0-4.0)	6.0 (3.0-10.0)	4.0 (3.0-4.0)	2.8 (1.5-6.0)
$AUC_{0\text{-}T}$ (h·ng/mL)	53.5 (40.4)	132.9 (64.5)	412.6 (37.2)	459.1 (49.3)	574.3 (33.9)
Metabolite:parent ratio (%)	17.5	16.9	21.2	14.1	17.6
Paynantheine (mg)	2.38-2.68	7.14-8.04	19.04-21.44	23.8-26.8	28.56-32.16
C_{max} (ng/mL)	7.7 (34.3)	19.0 (26.5)	29.7 (49.0)	66.7 (54.8)	65.8 (52.0)
T_{max} (h)	4.02 (2.5-6.18)	2.99 (2.5-4.0)	5.04 (3.0-6.14)	3.0 (2.5-4.0)	3.29 (1.5-6.01)
$AUC_{0\text{-}T}$ (h·ng/mL)	47.0 (40.3)	132.9 (33.1)	320.2 (41.8)	725.2 (62.4)	727.6 (54.7)
λ_Z (1/h)	0.13 (44.4)	0.077 (100.3)	0.043 (26.2)	0.041 (41.9)	0.049 (21.1)
T_{half} (h)	6.33 (50.2)	15.26 (60.2)	16.86 (23.8)	19.07 (35.0)	14.7 (20.5)
Speciogynine (mg)	1.8-1.98	5.4-5.94	14.4-15.84	18-19.8	21.6-23.76
C_{max} (ng/mL)	6.3 (30.4)	15.8 (27.2)	23.2 (43.5)	58.9 (60.3)	55.5 (55.9)
T_{max} (h)	4.02 (2.5-6.18)	3.0 (2.99-4.0)	5.04 (3.0-10.02)	4.0 (3.0-6.0)	2.54 (1.5-6.01)
$AUC_{0\text{-}T}$ (h·ng/mL)	53.4 (36.0)	154 (28.6)	341 (43.3)	819.2 (63.7)	790 (57.4)
λ_Z (1/h)	0.086 (69.6)	0.052 (45.7)	0.039 (16.9)	0.038 (37.6)	0.047 (19.4)
T_{half} (h)	11.06 (50.3)	15.91 (42.8)	18.09 (17.0)	20.26 (34.9)	15.20 (19.3)
Speciociliatine (mg)	3.64-4.04	10.92-12.12	29.12-32.32	36.4-40.4	43.68-48.48
C_{max} (ng/mL)	39.1 (30.0)	106.6 (22.4)	168.9 (40.3)	388.1 (56.0)	409.7 (47.3)
T_{max} (h)	4.02 (3.0-8.04)	5.0 (3.0-9.99)	8.07 (3.0-12.0)	5.0 (4.0-8.0)	5.06 (2.0-10.01)
$AUC_{0\text{-}T}$ (h·ng/mL)	573.9 (49.7)	1910.9 (24.9)	3359.2 (37.4)	7904.8 (60.6)	7449.8 (49.6)
λ_Z (1/h)	0.072 (33.3)	0.059 (24.8)	0.056 (41.1)	0.043 (18.7)	0.062 (16.6)
T_{half} (h)	11.17 (52.6)	12.55 (30.5)	14.04 (35.1)	16.39 (18.0)	11.41 (14.8)

*Doses are approximate based on measured alkaloid levels in capsules (Table 1).
†Some capsules were verified to have levels of 7-hydroxymitragynine below the limit of quantitation.
λ_Z indicates elimination rate constant; $AUC_{0\text{-}T}$, area under concentration-time curve up to last timepoint; C_{max}, peak plasma concentration; T_{half}, elimination half-life; T_{max}, time to reach C_{max}.

could not be concluded because of the limited number of subjects in parallel dose cohorts.

Speciociliatine

Plasma concentration-time profiles for speciociliatine are shown in Figure S4 (Supplemental Digital Content 3, http://links.lww.com/JCP/B20), with PK parameters provided in Table 4. Median T_{max} ranged from 4.02 to 8.07 hours for cohorts 1 to 5. Mean C_{max} ranged from 39.1 to 409.7 ng/mL with increasing kratom doses from 1 to 12 g. The mean estimated $AUC_{0\text{-}T}$ ranged from 573.9 to 7904.8 h·ng/mL. An increase in speciociliatine C_{max}, and $AUC_{0\text{-}T}$ was noted with increased doses of kratom; however, dose-proportionality could not be concluded because of the limited number of subjects in parallel dose cohorts.

Pharmacodynamic VAS Results

Statistical Analysis on the Primary and Key Secondary Endpoints

In the tables and figures, K1, K3, K8, K10, K12, and P denote 1, 3, 8, 10, and 12 g doses of kratom, and pooled placebo, respectively. Table 5 summarizes the mean, SD, minimum (Min), the first quartile (Q1), median (Med), the third quartile (Q3), and maximum (Max) rating for the primary and key secondary endpoints for all 6 treatments.

As shown in Table S1 (Supplemental Digital Content 3, http://links.lww.com/JCP/B20), mean E_{max} values produced by 8 and 12 g kratom had at least 10 points difference from the placebo group for the primary and all key secondary endpoints. A noticeable difference in median values between each dose of kratom and pooled placebo was found for the comparison between kratom 12 g and pooled placebo for all primary and key secondary measures except E_{max} of Take Drug Again VAS. The median TE_{max} for the primary endpoint was calculated and occurred ~1 hour post-dose for 12 g kratom. Figure S5 (Supplemental Digital Content 3, http://links.lww.com/JCP/B20) shows the mean dose-response curves for these 4 endpoints. The mean dose responses produced by kratom 10 g for the primary and key secondary endpoints were all smaller than those produced by kratom 8 g. We plotted the heat maps for the individual time-course response profiles for 8, 10, and 12 g doses of kratom for the primary measure of drug liking VAS in Figure S6 (Supplemental Digital Content 3, http://links.lww.com/JCP/B20).

Among the 6 participants who received kratom 8 g, one participant (ID 35) reported a drug liking VAS score of 100 at every timepoint, including the first assessment (i.e., 15 min after administration). Without including this subject, kratom 8 g would not show any meaningful effect on assessments of drug liking. Thus, it is possible the 12 g dose was the only dose to produce meaningful changes on subjective measures of drug effects. Figures S7A and S7B

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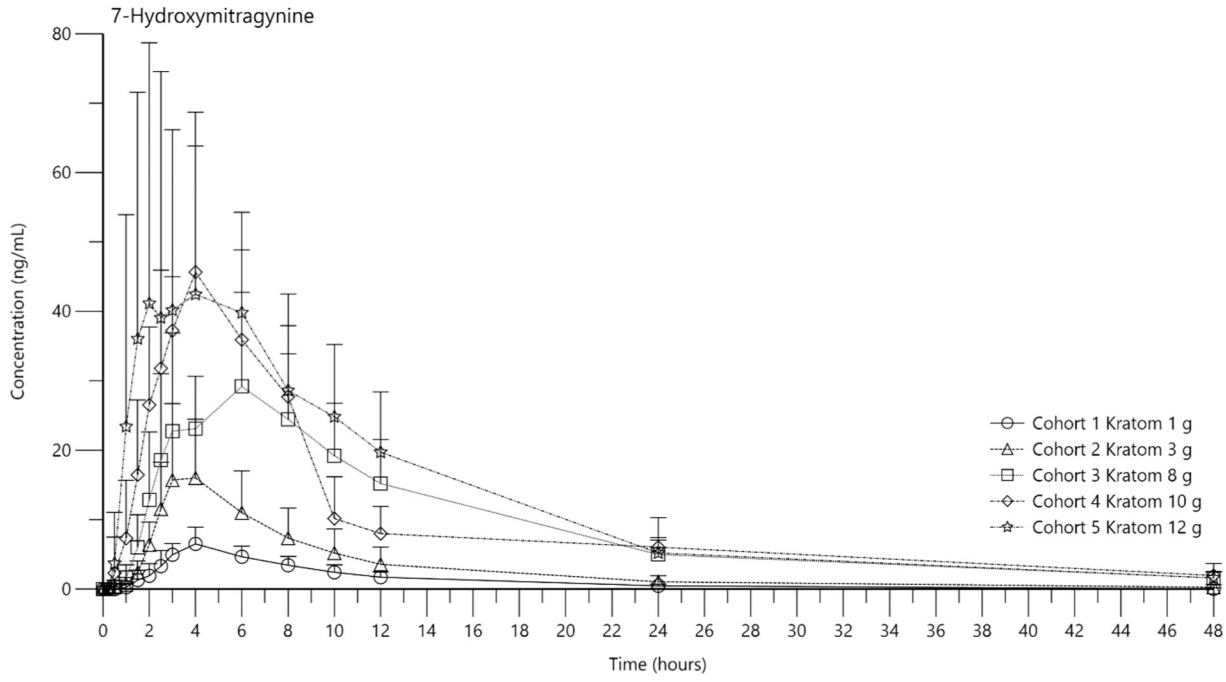


FIGURE 2. Plasma concentration-time profiles of 7-hydroxymitragynine (mean ± SD) by cohort in healthy participants (N = 6, each). The inset displays the 0-2 hours profile.

(Supplemental Digital Content 3, http://links.lww.com/JCP/B20) display the mean time-course profiles for drug liking VAS and High VAS.

In human abuse potential studies, the placebo range is typically considered to be between 40 and 60 for drug liking VAS. Figure S7A and S7B (Supplemental Digital Content 3, http://links.lww.com/JCP/B20) shows that the mean time-course profiles are bounded between 40 and 60 except the mean liking score of kratom 10 g that is below 40 eight hours post dose. For High VAS, the mean time-course profile for kratom 12 g is > 20 from 1.5 to 6 hours post dose. The peak mean response to kratom 12 g (33.7) occurred 6 hours post dose. As no data were collected between hours 6 and 8, it is possible, albeit unlikely, that the time to peak mean response occurs at hour 7.

Figure S8 (Supplemental Digital Content 3, http://links.lww.com/JCP/B20) shows mean values with SDs for overall drug liking VAS and take drug again VAS 12 and 24 hours post dose for each treatment. Even though the means produced by pooled placebo were below 50, the means produced by kratom for these 2 endpoints were below, or close to 60.

Inferential Statistics

An ANOVA model was used to test treatment differences for the primary and key secondary endpoints. To control for multiplicity, Dunnett's test was used to compare the means of kratom groups to pooled placebo. Significant treatment differences were demonstrated only for drug liking Emax and High Emax. The analysis results are presented in Table S1 (Supplemental Digital Content 3, http://links.lww.com/JCP/B20).

The mean differences between kratom 12 g and pooled placebo were 18.5 and 45.9 for drug liking E_{max} and High E_{max}, respectively. The analysis results show that the mean of kratom 12 g is significantly larger than that of pooled placebo at the significance level of 5% for these endpoints. The limitation of this inferential analysis is that the sample size for each treatment was very small. The assumptions of the ANOVA model were not met.

As a sensitivity analysis, Hodges-Lehmann estimator was used to estimate the difference between each dose of kratom and pooled placebo, the Wilcoxon Rank Sum test was conducted for each comparison, and Benjamini-Hochberg procedure was used for multiplicity adjustment. In the sensitivity analysis a significant result was only demonstrated in the comparison between kratom 12 g and pooled placebo for High Emax. However, clearly the difference in distributions between 8, 10, and 12 g doses of kratom and pooled placebo does not differ only in location. Therefore, the results from both the Dunnett test and Wilcoxon Rank Sum test should be interpreted with caution.

Descriptive Statistics for other Endpoints

Descriptive statistics are provided for 8 VAS endpoints: Emax scores of any effects, bad effects, good effects, feeling drunk, bowdle external perceptions composite, bowdle internal perceptions composite, and E_{min} scores of drowsiness/alertness, and relaxation/agitation, and 5 ARCI Emax endpoints: A, BG, LSD, MBG and PCAG, as well as Drug Similarity VAS. Table S2 (Supplemental Digital Content 3, http://links.lww.com/JCP/B20) summarizes mean and SE for these endpoints produced by 8, 10, and 12 g doses of kratom and pooled placebo.

For kratom 12 g, VAS assessments of any effects, good effects, psychedelic effects (as measured through the Bowdle VAS), and bad effects were larger than those produced by 8 and 10 g doses of kratom and pooled placebo. Sedative effects (including PCAG) and LSD

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TABLE 5. Summary Statistics for Primary and Key Secondary Pharmacodynamic Endpoints

Endpoint: E_{max}	TRT	N	Mean (SD)	Min	Q1	Med	Q3	Max
Drug liking VAS	P	10	50.2 (0.4)	50.0	50.0	50.0	50.3	51.0
	K1	6	50.7 (1.6)	50.0	50.0	50.0	51.0	54.0
	K3	6	51.7 (4.1)	50.0	50.0	50.0	52.5	60.0
	K8	6	60.2 (20.0)	50.0	50.0	50.0	70.8	100.0
	K10	6	52.2 (2.4)	50.0	50.0	51.5	54.5	56.0
	K12	6	68.7 (22.6)	50.0	50.0	60.0	95.0	98.0
High VAS	P	10	0.4 (1.0)	0.0	0.0	0.0	0.3	3.0
	K1	6	0.5 (1.2)	0.0	0.0	0.0	0.8	3.0
	K3	6	1.2 (2.9)	0.0	0.0	0.0	1.8	7.0
	K8	6	10.8 (12.1)	0.0	0.0	9.0	21.3	28.0
	K10	6	8.5 (13.0)	0.0	0.0	3.5	16.0	34.0
	K12	6	46.3 (34.6)	0.0	22.5	37.0	83.5	94.0
Overall drug liking VAS	P	10	45.1 (15.5)	1.0	50.0	50.0	50.0	50.0
	K1	6	50.2 (0.4)	50.0	50.0	50.0	50.3	51.0
	K3	6	50.0 (0.0)	50.0	50.0	50.0	50.0	50.0
	K8	6	61.8 (20.5)	50.0	50.0	50.0	78.3	100
	K10	6	55.7 (32.4)	2.0	37.3	55.0	79.8	100
	K12	6	67.0 (19.5)	50.0	50.0	63.0	85.0	94.0
Take drug again VAS	P	10	45.9 (16.4)	0.0	49.8	50.0	50.0	60.0
	K1	6	53.3 (7.7)	50.0	50.0	50.0	55.5	69.0
	K3	6	50.0 (0.0)	50.0	50.0	50.0	50.0	50.0
	K8	6	65.2 (19.7)	50.0	50.0	59.0	79.8	100
	K10	6	49.8 (42.0)	0.0	0.8	56.0	89.5	100
	K12	6	61.0 (21.0)	42.0	48.0	50.0	83.0	95.0

E_{max} indicates peak response expressed as the maximum response; K, kratom dose; Max, maximum; Med, median; Min, minimum; *P*, placebo; Q1, first quartile; Q3, third quartile; (1 = 1 g, 3 = 3 g, 8 = 8 g, 10 = 10 g, 12 = 12 g); TRT, treatment; VAS, visual analog scale.

(dysphoria) were also larger for kratom 12 g than those produced by other doses of kratom and pooled placebo.

The drug similarity unipolar VAS items provide an estimate of how similar the drug classes with which drug users have familiarity with are compared with the test drug. On a 100 mm scale ranging from "Not at all similar" to "Very similar," participants are asked to compare the drug they received that day to a drug they previously declared having familiarity/experience with taking.

Drugs that a participant has not personally experienced often enough to use as a standard of comparison (< 2 lifetime uses of a given drug), are not included in the questionnaire. Most subjects had experience with benzodiazepines, nicotine, opioids, and THC. One subject in the kratom 10 g group and 3 subjects in the placebo group did not have experience with nicotine. One participant in the kratom 8 g group did not have experience with benzodiazepines.

From the summary statistics of Drug Similarity scores for benzos, caffeine, cocaine, ketamine, LSD, MDMA, methadone, nicotine, opioids, PCP, placebo, speed, Sudafed, and THC, Table 3 (Supplemental Digital Content 3, http://links.lww.com/JCP/B20) displays summary statistics for participants choosing benzodiazepines, opioids, and THC which produced larger means compared with other choice of drugs by participants in 8, 10 and 12 g doses of kratom groups. Placebo ratings are also included. Although all participants in the pooled placebo group correctly recognized that placebo was not a benzodiazepine or opioid, ~75% of these participants assigned a Drug Similarity score of 100 to THC.

DISCUSSION

This study was designed to evaluate the safety and tolerability, PK, and PD of single ascending oral doses of kratom in healthy, nondependent recreational polydrug users with opioid experience and to inform dose selection for a future human abuse potential study of kratom. Overall, using the specific botanical kratom sourced for the study and in a controlled clinical setting, kratom was generally well-tolerated in healthy subjects after oral doses of 1, 3, 8, 10, and 12 g. No serious adverse events (SAEs) or deaths occurred and no participants discontinued due to adverse events (AEs). The most frequently observed AEs were somnolence, nausea, and vomiting, which were observed at doses ≥ 8 g. The tolerability findings were likely attributable to kratom exposure rather than capsule burden, as placebo-treated participants who received an equivalent number of matched capsules did not exhibit similar AEs. However, the small sample size (n = 6 per dose) was insufficient to thoroughly characterize the safety profile of the kratom used in the study, and the study was not powered to capture rare or infrequent AEs.

Kratom doses of 8, 10, and 12 g produced measurable pupillary constriction relative to placebo. These data seem consistent with the reported agonist and partial agonist effects of kratom alkaloids (eg, mitragynine, speciociliatine, and 7-OH) on mu-opioid receptors. The magnitude of pupillary constriction produced by kratom was relatively mild, with a mean maximum constriction of −2.4 (0.38) mm at the 12 g dose. Although limited by cross-study comparisons, other investigations have reported larger reductions in pupil diameter after administration of classic opioids (eg, ≥ 3.0 mm after 40 mg oxycodone).[50,51] Although pupillary constriction may be considered a sign of mu-opioid receptor activation, many of the kratom alkaloids also exhibit affinity for mu-opioid receptors, as well as adrenergic, serotonergic, dopamine, and adenosine receptors, and their intrinsic efficacy at these receptor subtypes varies.[12–14,52,53] Moreover, the efficacy and activity of the alkaloids at these receptor subtypes can

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vary, giving rise to the complex pharmacology of kratom that has led some authors to describe kratom as an "atypical opioid."[54]

Generally, kratom doses of 1 and 3 g were similar to placebo across subjective measures and did not show effects on VAS assessments of drug effects. Compared with placebo, increased at-the-moment drug liking and high, and overall drug liking, as well as a desire to take the drug again were observed for kratom 12 g. Kratom doses of 8 and 12 g showed increases in endorsements of positive subjective effects with 12 g showing the highest responses compared with placebo for most measures. However, across the primary and key secondary endpoints, only the 12 g dose showed a statistically and clinically significant difference compared with placebo for drug liking and High E_{max}. The 12 g dose was also associated with increased ratings of feeling drunk, and good drug effects compared with placebo. These ratings were generally ≥10 points above placebo, suggesting they were clinically significant and may be indicative of an abuse potential. Of interest, the 10 g dose did not show a similar degree of increase, despite being the intermediate dose of 8 and 12 g. Consistent with these findings, the 10 g dose showed a trend of pupillary constriction that was not as pronounced as the 8 or 12 g doses. Bad drug effects were highest for the 12 g dose compared with placebo. The mean E_{max} of bad drug Effects produced by the 12 g dose was 25.5. Compared with placebo, the 8 and 12 g doses were associated with increased drowsiness and 8, 10, and 12 g doses were associated with increased relaxation. When examining psychedelic effects, only the 12 g dose showed elevated Bowdle VAS scores (mean External Perceptions 80.8; Internal Perceptions 67.3). Taken together with the AE profile (which did not show notable increases in the 10 g dose compared with 8 and 12 g), these data do not support the hypothesis that negative effects suppressed subjective responses at the 10 g dose. Rather, the apparent elevation in effects at 8 g seems to have been driven by a single participant (ID 001-035). This subject produced maximum ratings of drug liking at every timepoint, including the 15-minute post-dose time period where absorption of kratom is expected to have been minimal. This underscores the need for caution when interpreting data from small cohorts and highlights the potential value of qualification phases to identify and manage atypical response patterns in future studies.

The ARCI responses showed that the 12 g dose produced higher ratings of PCAG (sedatives) and LSD (dysphoria) compared with placebo. When assessed for similarity with known drugs of abuse, all doses of kratom were rated as being similar to THC (minimum similarity score = 82, maximum similarity score = 100). Kratom doses of 8, 10, and 12 g were also reported to produce effects similar to benzodiazepines and opioids. Irrespective of dose, kratom was not found to produce effects similar to drugs with stimulant or psychedelic-like properties including caffeine, cocaine, LSD, ecstasy, phencyclidine, or amphetamines.

Despite the limitations in the study due to few subjects in each dose cohort, plasma mitragynine, 7-hydroxymitragynine, paynantheine, speciogynine, and speciociliatine were measurable at every dose, and increased with dose as assessed by the extent of absorption after single doses of kratom from 1 to 12 g. Notable increases in the coefficient of variation were also observed with the administration of 10 g kratom for all compounds, with a general increase with increasing dose. Future studies may incorporate a larger sample size to decrease the variation observed in the PK data.

Peak plasma concentrations (C_{max}) of speciociliatine increased with dose as assessed by peak concentrations across the 1 to 12 g range. Plasma mitragynine, 7-hydroxmitragynine, paynantheine, and speciogynine increased in a slightly less than dose-proportional manner as assessed by peak concentration (C_{max}) after single doses of kratom from 1 to 12 g. The lack of dose-related increases in (C_{max} and AUC) was seen in doses above 8 g, and continued with subsequent doses of 10 and 12 g under fed conditions. These data suggest there is saturation in absorption of these compounds. It is important to note that the number of capsules also increased with increasing doses. Given the large number of capsules necessary to administer the higher doses (eg, 20 and 24 size 00 capsules for the 10 and 12 g doses), it is possible the large volume of botanical plant matter inhibited or slowed absorption.

Median times to peak concentration for mitragynine, 7-hydroxymitragynine, paynantheine, speciogynine, and speciociliatine were all similar, with median T_{max} values ranging from 2.00 to 8.07 hours. We note that the T_{max} values generally did not occur before the 2-hour timepoint and did not coincide with peak effects on subjective measures. The interaction of PK and PD effects is complex. Although reviews have found that maximum ratings of dug liking generally occur no later than peak plasma concentrations T_{max} or C_{max} alone may not be predictive of abuse potential.[55] The average range of elimination for mitragynine and speciociliatine was similar between cohorts 1 to 5, with values ranging from 11.17 to 22.07 hours. There were only 2 additional blood sample measurements after 12 hours at 24 hours and the last sample at 48 hours. This sampling schedule is limited in accurately determining the elimination rates for all kratom alkaloids in this study. With these limitations considered the average range of elimination half-life values for 7-hydroxymitragynine, paynantheine and speciogynine were not similar between cohorts 1 to 5, with values ranging from 6.69 to 19.07 hours. Increases in average range of elimination generally correlated with increased dose. Notably, other studies of encapsulated dried kratom powder found differences in T_{max} values, producing peak mitragynine concentrations 1 to 1.3 hours after administration and 7-OH T_{max} values 1.2 to 1.8 hours after administration.[31] However, the dose range was lower (0.5 to 4 g) and participants received kratom under fasting conditions. The present study administered kratom in the fed state, after a high-fat meal and preclinical data have demonstrated food effects in the bioavailability of mitragynine.[56] Interestingly, when examining the C_{max} values at identical (1 g) doses, broadly similar values were obtained, although there was substantial variability in our study due to the small sample size.[31]

An additional consideration when interpreting findings is the composition of kratom and the method of administration. Botanical formulations can vary greatly in the composition of the alkaloids that contribute to their pharmacological effects. Although mitragynine is the most abundant alkaloid isolated from kratom, minor alkaloids such as 7-hydroxymitragynine (which exhibits greater opioid potency than mitragynine and morphine)[37,38] and speciociliatine (which also has greater opioid activity than mitragynine)[13] may exert disproportionate influence on abuse-related and safety outcomes. The specific composition of the kratom used in this study contained ~5 mg of mitragynine per capsule (1% by weight) and low levels of 7-hydroxymitragynine (ranging from undetectable amounts to 0.07 mg/capsule). The kratom used in our study had alkaloid values similar to what has been reported in the literature;[8,10,36] however, it may be anticipated that different kratom

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formulations with different alkaloid compositions or amounts may have variable pharmacological effects. The kratom sold in the United States is commonly in the form of dry plant material filled into capsules. In contrast, kratom use in Asian countries is commonly consumed as an herbal tea or chewed. Variability in composition, preparation, and administration may all affect bioavailability and exposure. In this study, dry plant material was filled into oral capsules, as would be commonly available in the United States. Future studies may examine various strains or the effects of isolated alkaloids in characterizing the safety, PK, and PD effects of kratom.

In summary, in the current study, orally administered botanical kratom was well-tolerated with the most commonly reported AEs observed at the highest doses (eg, 8-12 g) and classified as mild in severity (i.e., grade 2 or lower). Doses ≥ 8 g produced modest pharmacodynamic effects, including pupillary constriction, and all doses produced measurable plasma concentrations of key kratom alkaloids. Kratom alkaloid exposure was generally dose proportional and the time to maximum plasma concentrations ranged from 2 to 4 hours. The highest dose of kratom (12 g) was associated with increases in a variety of subjective effects measures associated with abuse potential, including statistically significant increases in drug liking and also on a positive measure of drug effects "high" relative to placebo. When subjects completed drug similarity measures, kratom effects were reported as resembling those of THC, and being somewhat similar to opioids and benzodiazepines.

The small sample size, between-subjects design, and absence of a qualification phase to reduce variability in response measures (eg, inappropriate responding on VAS measures) limit conclusions regarding the subjective effects and abuse potential of kratom. Appropriately powered studies are required to further characterize kratom's PD profile, safety, and its relative potential for abuse. Finally, although the botanical kratom used in the study was well-characterized, it is unknown how the kratom used in our study compares to the variety of kratom-related products available in the commercial marketplace. Although the kratom used in this study had an alkaloid profile consistent with botanical products reported in the literature, it seems to have a substantially different alkaloid composition relative to newly emergent "spiked" or enhanced kratom-related products in the commercial marketplace.[57–59] Further studies are necessary to more thoroughly characterize the abuse potential of botanical kratom and determine the effects of the various alkaloids on its pharmacological effects.

AUTHOR DISCLOSURE INFORMATION

C.M. has served as an expert witness in several kratom lawsuits. B.S. and D.K. are full-time employees of Altasciences. D.M. is a part-time consultant of Altasciences. The remaining authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Funding Source: This study was funded by the US Food and Drug Administration under contract 75F40121C00199. Ethics Statement: Clinical studies with Kratom were conducted by Altasciences Inc. following approval of an institutional review board and written informed consent from participating subjects. Study procedures were carried out in accordance with the Declaration of Helsinki. Disclaimer: The opinions expressed in this article are those of the authors and should not be interpreted as the position of the US Food and Drug Administration.

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frontiers | Frontiers in Pharmacology

TYPE Review
PUBLISHED 03 June 2024
DOI 10.3389/fphar.2024.1403140

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RECEIVED 18 March 2024
ACCEPTED 30 April 2024
PUBLISHED 03 June 2024

CITATION
Henningfield JE, Grundmann O, Huestis MA and Smith KE (2024), Kratom safety and toxicology in the public health context: research needs to better inform regulation.
Front. Pharmacol. 15:1403140.
doi: 10.3389/fphar.2024.1403140

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Kratom safety and toxicology in the public health context: research needs to better inform regulation

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Although kratom use has been part of life for centuries in Southeast Asia, the availability and use of kratom in the United States (US) increased substantially since the early 2000s when there was little information on kratom pharmacology, use patterns, and effects, all critical to guiding regulation and policy. Here we provide a synthesis of research with several hundred English-language papers published in the past 5 years drawing from basic research, epidemiological and surveillance data, and recent clinical research. This review of available literature aims to provide an integrated update regarding our current understanding of kratom's benefits, risks, pharmacology, and epidemiology, which may inform United States-based kratom regulation. Recent surveillance indicates there are likely several million past-year kratom consumers, though estimates vary widely. Even without precise prevalence data, kratom use is no longer a niche, with millions of United States adults using it for myriad reasons. Despite its botanical origins in the coffee tree family and its polypharmacy, kratom is popularly characterized as an opioid with presumed opioid-system-based risks for addiction or overdose. Neuropharmacology, toxicology, and epidemiology studies show that kratom is more accurately characterized as a substance with diverse and complex pharmacology. Taken together the work reviewed here provides a foundation for future scientific studies, as well as a guide for ongoing efforts to regulate kratom. This work also informs much-needed federal oversight, including by the United States Food and Drug Administration. We conclude with recommendations for kratom regulation and research priorities needed to address current policy and knowledge gaps around this increasingly used botanical product.

KEYWORDS

mitragynine, abuse potential, dependence, toxicology, epidemiology, surveillance, therapeutic effects, neuropharmacology

1 Introduction

Kratom (*Mitragyna speciosa* Korth.) refers to herbal products derived from the leaves of a tropical tree in the Rubiaceae family that grow throughout Southeast Asia and regions of Africa, China, and India (Brown et al., 2017). Domestic cultivation in Florida and Hawaii was also reported. Kratom products marketed in the United States (US) and globally are diverse. These include dried leaf powder that is used in tea-like decoctions, pressed into pellets or encapsulated, as well as more concentrated extracts that range widely in their content of kratom's major alkaloid, mitragynine (MG), and other minor alkaloids or metabolites, including 7-hydroxymitragynine (7OHMG) (Prozialeck et al., 2020; Todd et al., 2020; Manwill et al., 2022; Sengnon et al., 2023; Grundmann et al., 2024).

In the United States, kratom products are marketed as dietary ingredients and meet criteria under the Food, Drug and Cosmetic Act for regulation by the United States Food and Drug Administration's (FDA's) Office of Dietary Supplements but have yet to be accepted for regulation or provided with any regulatory standards for product purity, ingredients, labeling or warnings (FDA, 2024a). At least six kratom products were submitted to FDA by kratom product manufacturers as new dietary ingredient notifications; all were rejected by FDA (Johnson, 2022).[1] At this writing, we are not aware of any submissions to FDA of new drug applications containing kratom or kratom derivatives. The FDA regulatory position on kratom evolved over the past decade and as of 22 February 2024, it included the following statement on its kratom website: "kratom is not lawfully marketed as a dietary supplement and cannot be lawfully added to conventional foods" (FDA, 2024).

The safety of kratom products from consumer and public health perspectives is a controversial and dynamic topic, as evidenced by differences in United States Federal agencies' communications on kratom (FDA, 2017b; FDA, 2018; NIDA, 2022; DEA, 2023; FDA, 2024a). Similarly, leading medical institutions including Johns Hopkins University and Mayo Clinic also differ in their characterization of kratom and its place in public health (Johns Hopkins Medicine, 2020; Mayo Clinic, 2022). Recent research on kratom's alkaloids, *in vivo* and *in vitro* pharmacology, as well as toxicology and epidemiology research, provides new evidence to help address the aforementioned United States regulatory gaps and unreconciled opinions about kratom and public health. Specifically, more than 200 relevant manuscripts published since 2018--many supported by National Institute on Drug Abuse (NIDA) and Southeast Asia organizations, such as the Centre for Drug Research, Universiti Sains Malaysia, Malaysia (Henningfield et al., 2022d)--address some of the controversies and points of confusion, and are included in this review (Henningfield et al., 2022d).[2]

The present review focuses on key areas of debate related to kratom's safety, abuse potential, use motivations, and risk/benefit ratio at the United States consumer and public health levels. Areas of research to address important gaps in knowledge and to support the development and implementation of federal regulation of kratom products are identified, as are potential regulatory actions based on available evidence.

2 Epidemiology

2.1 Prevalence

In the United States, anecdotal reports suggest that kratom commerce and use began in the last quarter of the 20th century but was largely limited to Southeast Asia immigrants and returning United States veterans with no published estimates of kratom use prevalence until the 21st century. In 2015, the Botanical Education Alliance (BEA) survey of kratom vendors estimated three to five million kratom consumers in the United States (BEA, 2016). The major United States surveillance systems tracking trends in recreational substance use and treatment-seeking for "addiction" or substance use disorder (SUD) did not include kratom on their annual reports until 2020[3]. The National Survey on Drug Use and Health (NSDUH) prevalence data suggested approximately 1.7–1.8 million past-year kratom consumers from 2019–2021 (Palamar, 2021; SAMHSA, 2022; 2023a; b;c), while the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) system estimated 2.03 million, with lifetime prevalence at 3.4 million based on 2018–2019 data (Schimmel and Dart, 2020). Covvey et al. estimated lifetime prevalence of kratom use at 6.1% based on a 2019 survey (Covvey et al., 2020). Other approaches to estimating kratom use prevalence based on kratom import volume and market data projected more than 10 million current users in 2019 (American Kratom Association, 2019). Together, evidence

1 New Dietary Ingredient Notifications (NDINs) can be accepted by FDA or rejected, but not approved. Acceptance is based primarily on the basis of whether the specific product as submitted, including its packaging, level or concentration of ingredients per specified serving size "will be reasonably expected to be safe under the conditions of use recommended or suggested in the labeling" (FDA, 2023b). The NDIN process is distinct from the drug approval process in which new drug applications are subject to review for approval based on therapeutic claims considering the benefit to risk determination supported by clinical studies (FDA, 2022a).

2 NIDA is the lead kratom research supporting agency in the United States. See NIDA's overview of research and key kratom facts (NIDA, 2022). NIDA's research funding is also encouraged by legislation from the United States Congress that included language and funding in 2022 and 2023: 116th Congress Report, second Session House of Representatives, Appropriations Bill 2021; 117th Congress Report, first Session, House of Representatives, Appropriations Bill 2022; 117th Congress Report, second Session, House of Representatives Appropriations Bill 2023 all from the Departments of Labor, Health and Human Services, and Education, and Related Agencies.

3 Such surveys discussed in this review include the NIDA supported Monitoring the Future Survey (MTFS); three systems from the Substance Abuse and Mental Health Services (SAMHSA): Drug Abuse Warning Network (DAWN), National Survey on Drug Use and Health (NSDUH), Treatment Episode Data Set (TEDS); and the Denver Health Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System.

suggests that the NSDUH and RADARS systems likely underestimate kratom use prevalence, indicating that better methods for estimation of novel product use are needed (Henningfield et al., 2022b; Palamar, 2022).

2.2 Frequency of use per day

Frequency of kratom use varies considerably and is influenced by reasons for use. Several online surveys suggest that many people use occasionally for relief of acute pain, whereas others use daily in place of or in addition to caffeinated products for mental acuity, for chronic pain, to self-manage mood disorders and opioid and other drug withdrawal symptoms, and to abstain from drugs (Grundmann et al., 2022; Tobacyk et al., 2022). Among people who use regularly, dosing appears to be 1–3 times per day based on proximal needs or goals, such as pain management or increasing energy, focus, alertness, and to enhance productivity (Garcia-Romeu et al., 2020; Smith et al., 2022d; Smith et al., 2024). Using ecological momentary assessment (EMA), Smith et al. (Smith et al., 2022a; Smith et al., 2022b; Smith et al., 2024) obtained13,401 unique kratom use events reported in real-time across 357 participants during a 15-day assessment period, finding that most use occurs more often within the first half of people's waking hours, with no evidence of weekend binge use or trends of late-night use (Smith et al., 2024).

2.3 Reasons for kratom use

The most commonly reported reasons for use in the United States are generally similar to those reported in Southeast Asia field studies and surveys (Singh et al., 2019b), although these studies do not provide nationally representative estimates of the reasons for use. For example, surveys with a targeted focus on people with opioid use histories (e.g., Coe et al., 2019; Garcia-Romeu et al., 2020), or male sexual health issues (Deebel et al., 2023) may overestimate reasons for use related to such issues, compared to surveys based on convenience sampling of current, active kratom consumers, irrespective of use motivation (Grundmann, 2017; Grundmann et al., 2023). Overall, survey and social media self-report are consonant with the approximately 20,000 consumer comments made to Drug Enforcement Administration (DEA) after its proposal to schedule kratom in the Controlled Substances Act (CSA) in 2016, where myriad reasons for use were described, such as sleep improvement, or symptom management for posttraumatic stress disorder (PTSD), fibromyalgia, depression, insomnia, substance use disorders (SUDs), and pain (DEA, 2016; Smith et al., 2021; Smith et al., 2022c; Smith et al., 2024).

A recent EMA study characterizing patterns of kratom use among long-term and regular (using at least 3 days per week) United States kratom consumers found that most participants took kratom to relieve pain, increase energy, productivity, and focus, and for mood improvement (Smith et al., 2024). Among these long-term consumers who used regularly, a motivation of use for some was to avoid kratom-related withdrawal. Taken together, these findings suggest that most use kratom to feel good generally, and not to get "high" (Smith et al., 2024). Such momentary data suggests that many are using kratom for multiple and diverse reasons to address dynamic needs or desires and which may or may not align with broader use motivations. For instance, while some in this EMA study broadly reported using kratom as a long-term substitute for other substances, discrete kratom use events were driven more by quality-of-life needs. This was evidenced by the fact that nearly one-third of the sample had a broad motivation for using kratom as a long-term drug substitute, but few reported a use event to reduce an acute craving for a substance other than kratom which implies that for some, long-term kratom use successfully attenuated drug craving (Smith et al., 2023a; Smith et al., 2024). Surveys investigating reasons for use also suggest that motivations for trying kratom may be evolving within and across consumers with multiple factors driving use, such as increased energy, recreation, aside from self-management of mood or pain (e.g., Smith et al., 2022b).

Indeed, many consumers initiate kratom use for specific health and wellness indications, but continue to use for broader perceived benefits, such as increasing daily productivity (Smith et al., 2022c; Smith et al., 2023a). An evaluation of social media data with independent raters coding 1,274 Reddit posts showed that some believe kratom to be "life-saving" and helpful, whereas others believed that some products may, over time, become "ruinous" (Smith et al., 2021). This is similar to recent findings that among some long-term consumers, those taking more kratom servings with greater frequency and regularity were more likely than others with more varied use patterns to perceive kratom as "life-saving" but also as "habit-forming," indicating a complex relationship (Smith et al., 2024). However, many consumers, irrespective of use motivations, have reported perceiving kratom as more effective, tolerable, and with less severe side-effects or risks than FDA-approved medicines; kratom consumers also noted that products are accessible and affordable, and are preferred as "natural" and "dietary" approaches over conventional medicines for their lifestyle needs (DEA, 2016; Grundmann, 2017; Smith et al., 2022c; Grundmann et al., 2023; Smith et al., 2024).

2.4 Comment on therapeutic and beneficial use

Reasons for kratom use as documented by self-report surveys and field studies of kratom users (e.g., Singh et al., 2015; Grundmann, 2017) are often taken as proxies for therapeutic usefulness (e.g., Grundmann et al., 2018; Prozialeck et al., 2019). However, it is important to note that the FDA generally reserves the terms "therapeutic" "beneficial," and "medical" use for FDA-approved drugs, not for dietary ingredients or supplements for which only limited health-related (but not "therapeutic") claims can be made (FDA, 2005). Neither kratom nor any of its naturally occurring alkaloids were submitted for approval nor approved as medicines by the FDA or other major medicine regulatory agencies worldwide. However, evidence of therapeutic potential and beneficial use of kratom are recognized by the US Department of Health and Human Services (DHHS) and World Health Organization (WHO) (Giroir, 2018; United Nations Commission on Narcotic Drug, 2021). Moreover, FDA approval of a substance or

product is not the only basis for determining therapeutic or medical use, as most recently demonstrated by the United States DHHS evaluation of marijuana for therapeutic use and rescheduling (U.S. Department of Health and Human Services, 2023a; U.S. Department of Health and Human Services, 2023b).

In 2024, the United States DHHS demonstrated another approach in its determination that marijuana met criteria for "commonly accepted medical use" (CAMU), with the caveat that this was not a determination of efficacy and safety under the Federal Food, Drug, and Cosmetic Act drug approval standard (US DHHS, 2023a; US DHHS, 2023b). By this analysis, marijuana was found to meet criteria for "CAMU in the United States" thus supporting its recommendation that marijuana should be removed from Schedule I of the United States CSA, which is reserved exclusively for substances that are not deemed CAMU (US DHHS, 2023a; US DHHS, 2023b).

The standard required and achieved for marijuana with this approach by DHHS, which involved FDA, was considerable. It included widespread documentation of clinician-recommended use for a variety of medical conditions in 38 states, the District of Columbia and four United States territories, as well as many randomized clinical trials. Presently, kratom would not meet this standard. Nonetheless, it is important to recognize that for centuries in Southeast Asia, kratom was used as a traditional medicine for its beneficial or therapeutic effects (Singh et al., 2015; Singh et al., 2019a). Analogously, but not meeting the level of evidence documented for marijuana by the United States DHHS, therapeutic and beneficial use of kratom were extensively documented in self-report data from United States consumers as discussed in this review (e.g., Swogger and Walsh, 2018; Prozialeck et al., 2019; Smith et al., 2023a; Grundmann et al., 2023). US DHHS review of FDA's recommendation to place kratom in Schedule I of the CSA included consideration of the fact that many people use kratom to manage pain and opioid use and that banning kratom could lead to "intractable pain, psychological distress, suicide; transition to proven deadly opioids. transition to other potent or harmful drugs." (Giroir, 2018). Similarly, in its prereview of kratom for potential international drug control and scheduling, the WHO Expert Committee on Drug Dependence determined that scheduling was not warranted, taking into consideration that evidence for kratom abuse liability in animals and humans was "mixed" and "limited," and that kratom is "used as a part of traditional medicine in some countries" (United Nations Commission on Narcotic Drugs, 2021).

With the caveat that none of the above should be interpreted as supporting the conclusion that kratom should be considered a therapeutic drug by FDA's drug approval process standard, the findings do support the conclusion that many kratom consumers in the United States and globally report improved health, wellbeing, and quality-of-life from taking kratom (Grundmann et al., 2019; Sharma and McCurdy, 2021). Such human use patterns, and the preponderance of consumer self-report of efficacy, are consistent with nonhuman animal studies investigating kratom alkaloids to attenuate pain, opioid withdrawal, and other conditions (Harun et al., 2021b; Henningfield et al., 2022d; Grundmann et al., 2023). Such convergence of evidence is unsurprising given the known pharmacology of kratom alkaloids (Smith et al., 2023d).

2.5 Recreational use

Although self-report data cited above suggest that much kratom use relates to health and wellbeing, what is often referred to as "recreational use" also occurs (Henningfield et al., 2018; Swogger and Walsh, 2018; Smith et al., 2021; Pont-Fernandez et al., 2023; Smith et al., 2024). This is not diagnostically defined and generally refers to people who occasionally use a substance for nonmedical reasons but who do not meet criteria for dependence or use disorder or withdrawal as used by FDA in recommendations for participants for human abuse potential studies (FDA, 2017a). In practice, distinguishing use to self-manage medical problems (e.g., mood disorders, pain, withdrawal), from use to improve productivity, exercise regimens, cognitive performance and focus, pleasurable mood states and sexual pleasure is not always clear in consumer self-reports of reasons for use (e.g., Swogger and Walsh, 2018; Veltri and Grundmann, 2019; Singh et al., 2020; Adzrago et al., 2022; Deebel et al., 2023).

An additional complication is that some use kratom to manage medical problems and in the same time frame or after the medical problem resolves, continue to use for recreation and general wellbeing reasons (Adzrago et al., 2022; Smith et al., 2022c; Deebel et al., 2023; Smith et al., 2024). The many reasons for kratom use are rarely mutually exclusive and are wide-ranging, in keeping with kratom's complex pharmacology. Importantly, recreational use is not linked to a distinct altered mental state often regarded as a "high" or to development of use disorders, abuse, or addiction to other substances, even though some (not all) who initiate kratom use may have a polysubstance use history (Smith et al., 2024). Contrarily, kratom was clearly linked with the substitution of CSA-listed stimulants, opioids, and alcohol as a harm-reduction agent (Smith and Lawson, 2017). To date there is no evidence that kratom use serves as a gateway to the initiation or use of potent and reinforcing substances, such as stimulants or opioids.

3 Kratom use disorder, withdrawal and addiction

3.1 Definitions

In this review and the following discussion, we use the terms "use disorder," "withdrawal," and "addiction," similarly as presented in the American Psychiatric Association' Diagnostic and Statistical Manual of Mental Disorders, fifth Edition (APA, DSM-5, 2013). Note that the World Health Organization's 11th edition of its International Classification of Diseases (WHO ICD-11, 2019) is in general harmony but not identical to APA's DSM-5.

The term "substance use disorder" generally replaces what was referred to as dependence in earlier editions of the DSM and ICD. Typically, an SUD assessment includes substance/substance class specifiers (e.g., alcohol, opioids, and stimulants as in alcohol use disorder, opioid use disorder (OUD), and stimulant use disorder, respectively) to form a substance-specific SUD diagnosis. As discussed in DSM-5: "The essential feature of a SUD is a cluster of cognitive, behavioral, and physiological symptoms indicating that the person continues using the substance despite significant substance-related problems" and includes specific criteria and

examples (APA, 2013, *p*. 483). SUDs are not all-or-none but range, based on the number of 11 total symptoms, from mild (two to three symptoms), moderate (four to five symptoms), to severe (>6 symptoms). However, not all symptoms are equal, and patients must be evaluated on a case-by-case basis based on which criteria are endorsed. For instance, craving is a pervasive symptom irrespective of substance, but by itself does not necessarily signal serious harm. Conversely, continued use despite a desire to quit or use in physically hazardous situations provides a clearer signal of clinical severity.

"Addiction" is the more general term used to communicate to the public about SUDs and the risk that a substance may produce potent rewarding and reinforcing effects that may contribute to the development of a harmful SUD, as is the case for fentanyl, cocaine and methamphetamine. Thus, although addiction is not a formal diagnostic term in use by either the APA or WHO, as acknowledged in the DSM-5, addiction may sometimes be used interchangeably by some clinicians in reference to patients with severe SUD. Further complicating interpretation of what addiction means to lay persons, the term is widely used to describe a broad range of behaviors that do not necessarily include substances of abuse (regardless of whether there is associated personal or societal harm). For example, "addiction" to caffeinated beverages may be the most prevalent "addiction" among all psychoactive substances self-reported worldwide, but caffeine use is generally considered relatively benign and overall more beneficial than harmful (Goldstein, 2001; Sweeney et al., 2020), supporting the rationale for caffeine use disorder not being listed as a DSM-5 SUD.

Withdrawal refers to the constellation of "substance-specific problematic behavior change, with physiological and cognitive concomitants, that is due to the cessation of or reduction in heavy and prolonged (i.e., chronic) substance use." (APA, 2013, *p*. 486). Pharmacologically, withdrawal is presumed to reflect neuroadaptation, tolerance, and a state of physiological dependence caused by substance exposure for a sufficiently long time and level of intake that may be specific to the drug (Brunton et al., 2011). Withdrawal symptoms differ widely across drug classes and the DSM-5 lists the symptoms specific to each. Withdrawal is neither necessary nor sufficient for a SUD diagnosis. For example, fetal exposure and chronic use of medicines with a risk of SUD may produce physical dependence, including withdrawal, without evidence of an SUD. Similarly, as noted by the FDA, "The presence of physical dependence or tolerance (as indicated by a withdrawal syndrome) does not determine whether a drug has abuse potential" (FDA, 2017a, *p*. 4). However, withdrawal is included among potential SUD diagnostic symptoms in the DSM-5 and hence *in the presence of an SUD*, the co-occurrence of withdrawal generally implies a more severe SUD (see also FDA, 2017a).

The foregoing is not to imply that withdrawal in the absence of an SUD is not of concern from a health and wellbeing perspective. Withdrawal (and use to avoid withdrawal, i.e., negative reinforcement) can contribute to perpetuation of use in people who do develop SUDs and can be important to manage, particularly in cases where withdrawal can be seriously debilitating such as with alcohol, sedatives, and opioids (Volkow et al., 2016; Szalavitz et al., 2021). In contrast, most people self-manage their caffeine withdrawal, and although withdrawal can occur following discontinuation of stimulants, benzodiazepines, and many antidepressants, the syndromes were not widely recognized by experts or in drug labeling until the 1990s. This was because most patients did not display debilitating symptoms or syndromes requiring medical assistance when they discontinued their medication use that had been at prescribed levels of intake. As implied by the forgoing, self-reported "addiction" with or without withdrawal is not of equal concern across all substances.

3.2 Clinical and nonclinical evidence related to kratom use disorders, withdrawal and addiction

Neither DSM-5 nor ICD-11 defined or listed kratom use disorder or withdrawal. However, "kratom use disorder" (KUD), is increasingly used when a kratom consumer meets several of the same criteria as applied to SUDs more broadly. This is evident in NIDA's conclusion (with the caveat that more research is needed) that "preliminary data suggest that a minority of people report experiencing kratom-related withdrawal symptoms and a smaller minority report experiencing SUD symptoms related to kratom use" and that withdrawal is generally mild to moderate when it does occur (NIDA, 2022).

Research on KUD and withdrawal advanced considerably in the past 5 years and was reviewed in detail elsewhere in an evaluation of kratom's abuse and withdrawal potential (United Nations Commission on Narcotic Drugs, 2021; Henningfield et al., 2022d). More recently, the findings of a global forum that included at least one representative of most of the research centers that conducted kratom withdrawal and abuse potential studies since 2018 were published (Henningfield et al., 2023). They concurred that KUD and withdrawal profiles are not identical to opioid or other substance disorders in animal or human studies and were overall of lower severity when they did occur (Henningfield et al., 2023; see also Smith et al., 2023b; Smith et al., 2024). As concluded by Henningfield et al. (2023), more research is needed to better inform potential diagnostic listings in the DSM and ICD. Several studies published since that forum also add to the following summary of the state of the science at this writing (see Smith et al., 2023b).

Animal model data suggest low reinforcing and abuse-related effects of kratom's major alkaloid, MG, which is sometimes the sole kratom-derived ingredient in marketed kratom products. These animal models are relied upon by FDA, NIDA, and WHO for abuse potential evaluations. Specifically, reinforcing effects were weak in two intravenous MG self-administration studies compared to morphine, heroin, and methamphetamine (Yue et al., 2018; Hemby et al., 2019). Specifically, MG pretreatment of animals that had the opportunity to self-administer morphine or heroin intravenously, resulted in reduced opioid self-administration (Yue et al., 2018; Hemby et al., 2019). Another approach to assessing MG reward, conditioned place preference, suggests that MG is not reliable in producing conditioned placement across studies (Yusoff et al., 2018; Wilson et al., 2020).

Drug discrimination studies indicated that MG can weakly or partially generalize to morphine (Hiranita et al., 2020; Obeng et al., 2021). However it most robustly generalized to a nonscheduled alpha-adrenergic drug, lofexidine, which was approved by the FDA

for treating opioid withdrawal, and the over-the-counter cold medicine, phenylephrine (Reeve et al., 2020). These findings are consistent with the characterization of MG's diverse pharmacology that includes effects at several opioid receptors in addition to agonism at adrenergic, serotonergic, D2-dopaminergic and adenosine receptors as discussed in Section 4.3 and other reviews and studies (Kruegel et al., 2016; Kruegel et al., 2019; Henningfield et al., 2022c; Qu et al., 2023; McCurdy et al., 2024).

7-hydroxymitragynine (7OHMG), a MG metabolite not reliably detected in fresh kratom leaves but results from hepatic metabolism is, at high doses, self-administered intravenously by animals, indicating its reinforcing effects (Hemby et al., 2019). More research is needed on other kratom alkaloids and metabolites, such as speciociliatine, to determine if they contribute to the rewarding or reinforcing effects of kratom, or to the self-reported reasons for use and beneficial effects from human kratom use (e.g., Flores-Bocanegra et al., 2020; Henningfield et al., 2022d; Kamble et al., 2022; Huisman et al., 2023).

At high dosages, relative to typical human consumption, discontinuation of chronic MG administration in rodents can produce withdrawal signs that are generally weaker and not identical to those produced by abrupt discontinuation of chronic opioid administration. In animals which were made physically dependent on opioids by daily opioid administration, pretreatment MG can prevent opioid withdrawal when chronic opioid administration was discontinued. Conversely, opioids that are approved by FDA for treating opioid withdrawal can treat MG withdrawal when chronic administration of MG is abruptly discontinued (Harun et al., 2020; Hassan et al., 2020; Wilson et al., 2020; Harun et al., 2021a; Hassan et al., 2021; Johari et al., 2021; See summary of earlier studies and additional discussion in Henningfield et al., 2022d; Henningfield et al., 2023).

3.3 Prevalence of KUD, physical dependence and withdrawal

It is important to understand the prevalence of KUD and kratom withdrawal at the population-level. Although US surveys which evaluated KUD suggest that many kratom consumers do not meet criteria for KUD, or if they do it is of mild severity, and do not seek assistance for KUD or withdrawal, some reported "addiction" or withdrawal and seek medical assistance to manage withdrawal, or to aid cessation of kratom use (e.g., Singh et al., 2016; Grundmann, 2017; Singh et al., 2018; Swogger and Walsh, 2018; Coe et al., 2019; Garcia-Romeu et al., 2020; Smith et al., 2021; Smith et al., 2023b; Smith et al., 2024). A recently conducted EMA study of kratom consumers found that greater frequency of use was modestly associated with a greater number of KUD symptoms and taking kratom to avoid kratom-related withdrawal, but that irrespective of frequency, the mean number of KUD symptoms was less than four across the sample (Smith et al., 2024). In that study, 66.7% of participants who were experienced kratom consumers (93.0% had used for >1 year or more) met KUD diagnostic criteria that was predominantly mild (2 or three out of 11 DSM-5 symptoms) in severity, and most reflective of physical dependence (e.g., tolerance, withdrawal), followed by symptoms of craving and using more than intended (Smith et al., 2024). The foregoing findings were recently extended by an anonymous cross-sectional online survey of kratom consumers which found that 25.5% of respondents met KUD criteria; of these, 61.1% were of mild severity (20.0% moderate, 13.9% severe), with the odds of meeting KUD diagnostic criteria 2.83 times higher in those with SUD or psychiatric health histories (Hill et al., 2024). Similar to Smith et al., 2024, the most frequent symptoms were related to tolerance, withdrawal (Hill et al., 2024).

These are useful snapshots of active kratom consumers, but there is no reliable basis for estimating the actual prevalence of kratom use, or KUD and withdrawal in the United States, or the risk for these to develop among consumers. However, some existing evidence provides a basis for designing studies needed to make more precise estimates. Ideally, future surveys would include alternate approaches to represent the population at large. Additionally, it would be important to obtain nationally representative data addressing recency and frequency of use within and across days, and perhaps proxy data estimating KUD and withdrawal. Overall, the animal research is generally consistent with earlier discussed kratom surveys and clinical studies that did not observe kratom withdrawal-related symptoms following various doses of kratom products (Henningfield et al., 2023; Henningfield et al., 2022d) but more study of KUD and withdrawal is clearly needed.

Consumers who report "addiction" and seek help should be offered treatment following addiction treatment strategies in general (Smith et al., 2022a; Swogger et al., 2022). However, treatment with opioids such as buprenorphine and methadone should be judicious and possibly limited to kratom users with histories of opioid use so as not to establish opioid tolerance, physical dependence, and possibly a new use disorder in people who do not have a current or past OUD (Smith et al., 2022c).

3.4 Kratom use and abuse-related risks to users and public health

Proxy data indicative of a current or emerging national drug threat is sometimes inferred from estimates of treatment-seeking for use disorder, addiction, or withdrawal. Such data were used by the DEA to support temporary or "emergency" placement (scheduling) in the CSA. Treatment-seeking estimates for kratom were never reported in the SAMHSA Legacy Drug Abuse Warning Network (DAWN) that collected treatment-seeking and other data suggestive of an emerging drug threat from 1992 through 2011, nor the 2019 reestablished DAWN system that includes data from 53 sentinel hospitals (SAMHSA, 2021; 2022). The Treatment Episode Data Set (TEDS), also conducted by SAMHSA since 1992 (SAMHSA, 2023c) collects data including types of substances and demographics on people seeking treatment for SUD. TEDS did not report kratom treatment-seeking as an emerging problem in any of its reports.

The absence of evidence of abuse-related public health problems and treatment-seeking from these federal surveillance systems should not be interpreted as suggesting there are no problems related to KUD or withdrawal and that treatment-seeking does not occur. Published case report data indicate that such events do occur (e.g., Grundmann, 2017; Garcia-Romeu et al., 2020). However, the apparent low rates of KUD or kratom withdrawal treatment seeking in the United States or globally suggest that

kratom's "addiction" related risks are lower than those associated with many controlled substances such as amphetamine, cocaine, and morphine-like opioids (Smith et al., 2023b). Taken together, (e.g., Grundmann, 2017; Garcia-Romeu et al., 2020), these findings and those from a recent EMA study indicate that some users with KUD may experience withdrawal (Smith et al., 2024). However, as summarized by Smith et al. (2024), even among kratom consumers who had indicators of KUD or withdrawal, it was not accompanied by social or functional impairment, hazardous use, or use despite adverse consequences (Smith et al., 2024). The Smith et al. (2024) data are generally consistent with the conclusions of earlier surveys (e.g., Grundmann, 2017; Coe et al., 2019; Garcia-Romeu et al., 2020; Smith et al., 2023b; Henningfield et al., 2023) and the results of two clinical trials that did not observe withdrawal upon discontinuation of kratom administration (Vicknasingam et al., 2020; Huestis, 2022). Still, systematic study of KUD and withdrawal is clearly needed to address the many ambiguities in diagnostic assessment and guide the development of valid clinical assessment instruments (Henningfield et Smith et al., 2022a; 2023b).

4 Epidemiology: safety, risks, associated deaths and public health threat

The most commonly reported adverse effects of kratom consumption are indigestion and nausea, which are generally tolerable, self-resolving, and contribute to limiting consumer intake (Swogger et al., 2022; Smith et al., 2023a). Some frequent kratom users report stronger discomfort and adverse effects (e.g., dizziness, constipation and heart palpitations) that also are generally tolerable and self-resolve (Smith et al., 2023a; Feldman et al., 2023). A smaller fraction of kratom consumers, 0.65% of 7,893 respondents in the 2017 survey, sought medical assistance (Grundmann, 2017). The most serious risks of kratom life-threatening sickness and overdose death may be co-ingested drugs, contaminants (e.g., *salmonella*), and adulterants (e.g., opioids including fentanyl and methamphetamine).

The authors are not aware of publications indicating that kratom contributes to violent behavior or serious crime related to its effects on behavior, distribution, or marketing. There are some reports of potential impairment when driving under the influence of kratom; however, whether these were kratom only or involved multiple substances is uncertain (e.g., Knoy et al., 2014; Wright, 2018; Veltri and Grundmann, 2019; Kedzierski and Mata, 2023; Papsun et al., 2023). Papsun et al. (2023) reported detectable blood MG concentrations in 127 impaired driving investigations; however, there is presently no accepted basis for determining what blood mitragynine concentrations produce impairment. Mean and median concentrations in these cases were 133 and 62 ng/mL, respectively, with a range of 8.8–1,000 ng/mL, lower than those of 541 postmortem cases that had 360 and 120 ng/mL mitragynine, respectively, with a range of 5.4–11,000 ng/mL (Wright, 2018; Veltri and Grundmann, 2019).

A recent direct-observation laboratory-based study of 10 adult kratom consumers did not detect impairment following self-administration of participants' typical kratom product dose or changes in cognitive performance from (pre-dosing) baseline assessments. Two computerized psychomotor tasks and a validated immersive driving simulator capable of detecting alcohol- and cannabis-related driving impairment did not find evidence of impairment or intoxication on all outcomes assessed (Smith et al., 2023c; Zamarripa et al., 2024). However, this exploratory study only examined the acute effects of kratom at self-selected servings among a small sample of long-term kratom consumers, not kratom-naïve individuals. As kratom consumption increases (particularly in public consumption locations such as kratom or kava bars), field sobriety tests coupled with blood plasma levels for MG and other alkaloids are needed in addition to more rigorous PK/PD lab-based assessments.

As discussed below, kratom-associated deaths almost always include the presence of toxic concentrations of other substances. Many reports do not include comprehensive toxicological testing to determine if a kratom-associated death was likely appropriately attributed to kratom (see the following for recommended types of evidence to support determinations of causality in substance related deaths: Gudin et al., 2013; Ossiander, 2014; Davis et al., 2020; Davis and Fligner, 2023). Kratom may be found onsite at an opioid fatality due to its use in managing OUD and withdrawal. Also, intake of novel psychoactive substances (NPS) including designer opioids and benzodiazepines may not be identified with routine toxicology testing, requiring additional testing at reference laboratories at additional costs to resource-restricted public forensic testing laboratories.

Papsun et al. (2023) recently reviewed hundreds of MG cases analyzed at NMS Labs, Inc. And noted MG cases involving blood concentrations up to 1,000 ng/mL in living impaired drivers. The authors highlight the co-positivity of MG with other drugs and also suggest that MG blood concentrations greater than 1,000 ng/mL may be more likely to be associated with severe adverse events (AEs) including death, however, to date there are insufficient data to define a fatal MG blood concentration. Papsun et al. also supported the need for comprehensive toxicology testing prior to assigning cause of death (Gudin et al., 2013; Ossiander, 2014; Davis et al., 2020; Davis and Fligner, 2023).

4.1 America's poison centers' national poison data system (NPDS)

Kratom exposure and injury reports to the NPDS increased over the past decade along with increases in kratom use and, possibly, related to kratom product adulteration and/or contamination (e.g., Henningfield et al., 2022d; Grundmann et al., 2023). The first reports from the NPDS occurred in 2016 in which fifteen kratom-only deaths were reported. However, it is impossible to confirm how many, if any, of these deaths were primarily caused by kratom or to determine the full extent of toxicology testing performed. For example, an emerging category of potential confounding substances that rapidly proliferated since the early 2000s, NPS, of which many carry serious risks of addiction, morbidity and mortality may be contributing to overdose deaths in which kratom was associated (Huestis et al., 2017; Hall and Miczek, 2019; Higgins et al., 2019; Baumann et al., 2020; Crulli et al., 2022). As discussed by Huestis et al. (2017), the possibility that novel psychoactive substances were consumed and may have

contributed to overdose deaths is not typically investigated due to the cost of analysis and the constantly changing predominant novel psychoactive substances available. Novel opioid and benzodiazepine novel psychoactive substances are increasingly abused and also present as adulterants in many types of products including kratom (Di Trana et al., 2022; Collins et al., 2023).

In 2021, the NPDS included 1,524 kratom case mentions. Of those, 948 were single exposure reports, of which 67 were associated with major medical outcomes and four associated deaths (Gummin et al., 2022). For comparison, there were 282,880 pharmaceutical and illegal opioid reports, of which 178,714 were single exposures, resulting in 8,324 major medical outcomes and 720 deaths. More specifically, prescription fentanyl had 4,125 case mentions with 2,151 single exposures resulting in 788 major medical outcomes and 33 deaths, and non-prescription fentanyl had 2,902 case mentions with 1,104 single exposures resulting in 276 major medical outcomes and 136 deaths. Nationwide, the Center for Disease Control and Prevention (CDC) National Center for Health Statistics (NCHS) estimated 107,622 drug overdose deaths in the United States during 2021 of which an estimated 80,816 were attributed to opioids (CDC, NCHS, 2022).

We are not aware of the NCHS ever reporting estimates of kratom-associated deaths as contributing to the national drug overdose estimates (CDC, NCHS, 2022). However, as discussed below, the number of kratom-associated deaths is substantially lower than the main reported contributors to United States overdose deaths. Most kratom-associated deaths include the presence of multiple potentially lethal drug concentrations, making the role of kratom difficult to ascertain (Henningfield et al., 2019).

4.2 Kratom-associated deaths cited by other organizations

Estimates of kratom-associated overdose deaths vary widely depending upon the assumptions, the year, and the reporting entity. For example, from its launch until July 2018, the NIDA webpage on kratom stated "Kratom by itself is not associated with fatal overdose, but commercial forms of the drug are sometimes laced with other compounds that have caused deaths." This webpage was revised in 2018, and the most recent webpage at the time of this writing stating: "A very small number of deaths have been linked to kratom products compared to deaths from other drugs. (Kronstrand et al., 2011; Eggleston et al., 2019; Henningfield et al., 2019; Post et al., 2019; United Nations Commission on Narcotic Drugs, 2021; NIDA, 2022).

In 2018, the FDA reported 44 deaths "involving the use of kratom," including the 9 Swedish Krypton deaths (FDA, 2018), acknowledging that most of these involved polydrug use. For example, the Swedish deaths followed use of a kratom containing product called Krypton that contained lethal doses of *O*-desmethyltramadol that was determined to be the cause of death by Swedish toxicologists in 2011 (Kronstrand et al., 2011).

In 2019, a Centers for Disease Control and Prevention (CDC) report concluded that 91 of 27,338 overdose deaths in 27 states identified kratom among other substances (Olsen et al., 2019). All but seven included documented polysubstance exposure. Regarding the 7 decedents where MG was the only substance positive on postmortem toxicology, the authors cautioned that other substances may have caused or contributed to death but could not be ruled out because of limited toxicology testing. Comprehensive follow-up testing of samples from reported kratom-only decedents revealed that in all cases with available blood the presence of other potentially lethal substances was revealed (Gershman et al., 2019). Thus, the possible contribution of kratom to these polysubstance deaths is unknown.

In contrast to numerical estimates of annual opioid attributable deaths that exceeded 80,000 in the US in 2021 as discussed in Section 4.1, federal agencies have not provided numerical estimates but rather emphasize the relative rarity of kratom only associated deaths, as illustrated in FDA's February 2024 update of its "FDA and Kratom" website which states as follows "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."

4.3 Potential pathophysiological basis for kratom-associated deaths

For most substances of abuse that are attributed with a causal role in the more than 107,000 United States drug overdose deaths in 2021, there is at least a general understanding of the pathophysiological basis for lethality based on animal studies and human forensic toxicology (Brunton et al., 2011; Klaasen, 2018; Rohrig, 2019; Levine and Kerrigan, 2020) For example, rapid and profound respiratory depression is a substantial risk with high doses of morphine-like opioids; alcohol poisoning deaths frequently involve coma and asphyxiation as vomit is inhaled; barbiturate-type sedatives can produce profound sedation and respiratory depression; cocaine and methamphetamine can produce tremors followed by flaccid paralysis, loss of vital support, cardiac arrest, and circulatory failure. Thus, it is often possible for medical examiners to determine the likely substance or substances that contributed to death based on toxicology results and a dose-related profile of effects of the substance(s).

Although some organizations warned of opioid-type kratom overdose risks, the main mechanism of opioid overdose, respiratory depression, does not appear to be a substantial risk from kratom due to differences in the mechanisms of action and signaling pathways of MG and 7OHMG. Evidence suggests that this may reflect their relative weak recruitment of beta-arrestin at opioid receptors (e.g., Kruegel et al., 2016; Kruegel et al., 2019; Henningfield et al., 2022c; Qu et al., 2023; McCurdy et al., 2024). As discussed, MG's relatively weak respiratory effects as compared to morphine-like opioids may also reflect the "balanced agonist effects of diverse kratom alkaloids and metabolites" (Hill et al., 2022; Qu et al., 2023).

Mitragynine has a complex pharmacology including partial agonism at the μ-opioid receptor, antagonism at the κ-opioid receptor and agonism at adrenergic, serotonergic, D2-dopaminergic and adenosine receptors. Although research on kratom alkaloids and metabolites is expanding, most kratom research has heretofore been focused on MG and 7OHMG. Additional research on MG, speciociliatine, pantetheine and the

many other kratom alkaloid's pharmacology is needed to advance our knowledge of the potential adverse effects of kratom and mechanisms of potentially lethal effects (Henningfield et al., 2022d; Annuar et al., 2024; McCurdy et al., 2024).

Presently, there are no published data describing a physiological pathway by which MG or other kratom alkaloids might produce acute lethality in animals in doses many times that of human intake (Henningfield et al., 2022c). However, such pathways by which MG or another kratom alkaloid could produce lethality in nonhuman animals warrant further research (Annuar et al., 2024). In a direct-observation study conducted at NIDA, respiratory depression was not detected after kratom product self-administration at servings of 1.1–10.9 g of whole-leaf material; all vital signs remained within normal parameters and no AEs occurred (Smith et al., 2023c). Similarly, two other recent clinical studies of MG pharmacokinetics did not observe respiratory depression or serious AEs following controlled administration of 53.2 mg mitragynine in a dried kratom leaf powder (Huestis et al., 2024) or 2 g of kratom powder in an oral solution (Tanna et al., 2022).

4.4 Lethal dose

As mentioned above, neither the lethal dose of kratom nor any of its constituents is established in humans. Nonetheless, one study led investigators to the conclusion that a greater than 1,000 ng/mL blood MG concentration was associated with an elevated risk of overdose after review of 6,860 blood positive MG cases analyzed by NMS Labs (Papsun et al., 2023). The authors also discussed the fact that most kratom-associated deaths involve polydrug use complicating determination of causation.

In addition to limitations in toxicology testing in kratom-associated overdose deaths, there are not consistent signs and symptoms for kratom-only overdose-associated deaths, and summaries of medical report findings and autopsies reveal a diverse assortment of associated conditions, frequently consistent with the individual's medical history, use of NPS, and evidence of SUDs (Domingo et al., 2017; Babin, 2018; Henningfield et al., 2019). For example, kratom-associated death in medical examiner and case reports included cardiovascular, hepatic intoxication and seizure, with most not listing a suspected pathophysiological basis for death (see also Papsun et al., 2023).

Part of the apparent difficulty in determining the lethal dose of oral kratom is related to the difficulty of achieving oral lethal doses in animals. Henningfield et al. (2022c) compared the respiratory effects of up to 400 mg/kg oral MG to up to 150 mg/kg oral oxycodone in rats with the study design published by United States FDA scientists for evaluating opioid respiratory effects. MG doses were systematically increased with the goal of achieving lethality or the highest achievable dose due to MG's limited aqueous solubility and the maximum allowable volume per gastric delivery. Oxycodone administration produced significant dose-related respiratory depressant effects in blood gases including significantly increased carbon dioxide partial pressure and significantly decreased oxygen saturation and pronounced sedation with one death each at 60 and 150 mg/kg. MG had no significant dose-related respiratory depressant or life-threatening effects. Sedative-like effects, milder than produced by oxycodone, were evident at the highest MG dose. Maximum oxycodone and MG plasma concentrations were dose-related. Consistent with MG's pharmacology that includes partial μ-opioid receptor agonism with little recruitment of the respiratory depressant activating β-arrestin pathway, MG produced no evidence of respiratory depression at doses many times higher than known to be taken by humans. Another approach to assessing respiratory safety examined MG up to 90 mg/kg in mice as compared to morphine (Hill et al., 2022). Mitragynine produced a small non-life-threatening decrease in respiratory rate at 10 mg/kg with no further effect at the higher doses, consistent with the "ceiling effect" of a partial agonist.

There are also reports of potential hepatic toxicity risks at higher kratom doses (e.g., Gurley et al., 2022); however, the contribution of the well-established hepatic toxins acetaminophen and alcohol that may have been heavily used in persons who use kratom to manage pain and SUDs needs to be disentangled. Similarly, seizures were also reported in some kratom users, and it is possible that the stimulant effects of kratom might reduce seizure threshold; however, these reports are rare. Because caffeine and a broad range of over the counter and prescription medications can also lower seizure thresholds (Hill et al., 2015; van Koert et al., 2018; Epilepsy Foundation, 2023) it is not clear at present whether kratom itself carries such risks. These are examples of potential adverse effects that will benefit from FDA review to determine if the evidence supports mandated kratom product warnings and if so, how the warnings should be worded to meet FDA comprehension standards for product labeling.

None of the foregoing should be taken to imply that kratom or MG is without potential as a primary or contributing cause of death, 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., 2019; NIDA, 2022). We agree with Papsun et al. (2023) that "Current interpretation of MG 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 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.

5 Kratom safety across product types in the United States

A perennial topic of discussion is whether United States kratom products carry more risks than those in SEA, because reports of kratom-associated deaths and other adverse effects are more frequent in the United States than in SEA. In fact, kratom-related fatalities were reported in SEA, though the role of co-ingested substances, and the failure to quantify MG, as in United States cases, makes discerning causality practically impossible (Davidson et al., 2021; Weiss and Brent, 2023). An overlapping array of kratom

product types, extracts, decoctions of varying concentrations, encapsulated powders, and other product forms are marketed in the United States and SEA; however, fresh leaf made decoctions and leaf chewing are common in Southeast Asia but not the United States. It was reported that some marketed and home brewed products in the United States and elsewhere contain substantially higher concentrations of MG and 7OHMG than achievable by typical tea-making like protocols as well as preparations that included, caffeine, cold medications, opioids and other substances (EMCDDA, 2012; Cinosi et al., 2015; Singh et al., 2016; Prozialeck et al., 2020).

In both the United States and SEA, users report adjusting their preparation and or product selection and pattern and frequency of use to achieve their desired effect and apparently self-regulating intake to minimize undesired effects (e.g., nausea). It is not clear that product type is a determinant of total alkaloid intake at any one time or over the course of a day in multiple times per day consumers (Smith et al., 2023d). Whether product or leaf contamination (e.g., with *salmonella*) and adulteration (e.g., with fentanyl and methamphetamine) is more common in the US as opposed to Southeast Asia is not known.

To date, consumers who use mostly leaf powder products (e.g., in capsules or loose) appear to be self-selecting into research studies (Smith et al., 2022d; Smith et al., 2024). Regular routines based on leaf powder may be due to preference, lower cost as compared to formulated products and extracts, or situation-specific needs where the extracts may be less desired during work or school routines, but more desired for episodic pain or recreation (Smith et al., 2023a; Smith et al., 2024). Research on kratom extract product consumption is needed because extracts vary widely in concentrations and relative ratios of alkaloids and other substances and their pharmacokinetics and effects may differ from dry leaf powder preparations (Todd et al., 2020; Manwill et al., 2022; Sengnon et al., 2023; Grundmann et al., 2024).

Whether the difference in reported kratom-associated adverse effects and deaths in the US compared to Southeast Asia is due to product types or reflects actual real-world differences in rates and types of events is unclear because the United States has an extensive umbrella of reporting systems[4] that is not matched by any Southeast Asia country in which kratom use is common. Thus, it is possible, if not plausible, that there were kratom-associated deaths in Southeast Asia that would be detected by United States type surveillance systems. It is also apparent that within the US, despite the extensive surveillance, many if not most kratom associated adverse effects and deaths involve other substances.

It is possible that there are product categories (e.g., highly concentrated extracts versus powdered leaf filled capsules, versus low concentration extract and home-brewed decoction) differences in the risk of adverse events and kratom-associated deaths (Grundmann et al., 2023). However, none of the United States surveillance systems reported differences in rates of events or deaths across kratom product types, primarily because the type of product was not mentioned or further scrutinized. This does not mean there are no differences in risk, however, the "signal" that there may be such differences may be below the threshold for reliable detection by these surveillance systems. A national regulatory framework, as could be implemented by FDA, could also ensure that surveillance provided product category specific information and this might provide more sensitive and reliable data to inform regulatory evolution if certain product categories were found to be of higher risk and warrant differential labeling or restrictions on marketing and access.

6 Public health and response by regulatory agencies at the state and United States national level

In the United States, kratom was primarily marketed as a dietary supplement without regulatory oversight at the state or federal level. As summarized in a report by the Congressional Research Service, from 2014–2015, six states listed MG and 7OHMG as Schedule I substances, and a seventh state listed synthetic MG and 7OHMG as Schedule I substances. As of this writing four of those states are deliberating replacing their Schedule I bans with regulations to ensure consumer access to kratom that meets regulatory standards with variations on the Kratom Consumer Protection Act (KCPA) first established in Utah in 2018. At the time of this writing, 13 states implemented KCPA versions and five other states provide some regulatory oversight, such as minimum age requirements for purchasing (Heflin, 2023).

In August of 2016, the DEA proposed placing MG and 7OHMG in Schedule I of the CSA by its temporary scheduling authority.[5] In

4 Major United States reporting systems that provide AE and overdose death data: America's Poison Centers National Poison Data System (APC -NPDS), FDA Adverse Events Reporting System (FAERS), and several systems by the Centers for Disease Control and Prevention (CDC): National Vital Statistics System (NVSS), Web-based Injury Statistics Query and Reporting System (WISQARSW), and the Wide-ranging Online Data for Epidemiologic Research (WONDER).

5 Note that Schedule I is the only option in the United States for substances with "high" abuse and risk potential but which are not approved for therapeutic use by the FDA. Temporary CSA Schedule I placement (i.e., "emergency scheduling") by the DEA requires determination that use is substantially due to abuse-related effects and poses a known or imminent threat to public health based on the three public health factors of the CSA, i.e., Factors 4, five and 6. The evidence base for these factors typically rest substantially on major national surveillance systems listed in Footnote 4, and documentation of serious risks such as confirmed overdose deaths, and frequently crime and violence. Permanent Scheduling by the DEA requires evaluation of all eight factors of the CSA to support that recommendation to (e.g., by FDA or a citizen petition) or by the DEA. For drug products that are approved by the FDA, if they pose substantial abuse related risks and warrant CSA control, then the level of control and scheduling based on evaluation of the eight factors of the CSA to guide appropriate placement in one of the four schedules reserved for approved drugs, i.e., Schedules II, III, IV or V (see discussion as pertains to kratom in Henningfield et al., 2022; and more generally in FDA, 2017; DEA, 2023; or Henningfield, Coe, Griffiths et al., 2022a).

September 2016, the DEA withdrew its proposal out of concerns about the health risks of a kratom ban expressed by consumers, scientists, and policymakers, and its own reconsideration of the evidence (DEA, 2016; Heflin, 2023).

In November 2017, the FDA proposed permanent Schedule I placement of MG and 7OHMG to the DEA. In an unusual departure from DEA's general responsiveness to such FDA requests, as of August 2018, the DEA had not acted on FDA's proposal and the proposal was formally rescinded by the United States DHHS following its review of the scientific evidence and public health implications. In its rescission letter, the Department concluded that kratom did not meet statutory criteria for CSA scheduling and noted that FDA failed to consider the foreseeable public health consequences if kratom was banned and possession criminalized, including risk of "thousands of people" overdosing on opioids if kratom was banned (Giroir, 2018; Heflin, 2023).

NIDA-supported kratom research increased dramatically over the past decade exploring the potential risks and benefits of kratom, including the development of potentially safer new medicines for treating pain, addiction and other disorders with kratom, kratom constituents, and new chemical entities either derived from or similar to kratom constituents (NIDA, 2022). In light of the diverse reasons for kratom use that were summarized in Section 2.3, it is the authors understanding that funding for kratom use may be emerging from other NIH institutes including the National Center for Complementary and Integrative Health, National Institute on Alcohol Abuse and Alcoholism, and National Institute of Mental Health.

DEA continues to monitor kratom, evaluating samples found in drug enforcement operations; however, DEA's last listing of kratom/MG in its annual National Forensic Laboratory Information System (NFLIS) reports was in 2016 because detection in such cases remained low and relatively stable at about 0.02%–0.03% of all annual substance reports (approximately 1.5–1.9 million) from 2016–2022 (DEA, 2023). DEA never listed kratom or its constituents as a public safety threat in its annual National Drug Threat Assessments, though DEA continues to routinely monitor kratom as a "chemical of concern."

In part, the absence of crime associated with kratom distribution and marketing is due to the fact that most kratom sold in the United States is marketed by commercial companies and sold in retail stores and over the internet. Approximately 95% of the United States kratom supply is grown, ground, and exported from Indonesia (Pain News Network, 2019). Thailand is beginning to develop its own global kratom export potential since it rescinded its prior Schedule I substance designation for kratom in 2021 (The Nation, 2021), and the University of Florida is researching the development of kratom as a potential domestic agricultural crop (University of Florida, 2023).

7 Discussion

Kratom availability and use in the United States increased considerably since its apparently more regional and possibly culture-specific use that occurred during the last quarter of the 20th century. Most use appears motivated by health reasons, wellbeing, and for increasing daily productivity and energy (Smith et al., 2024). Considering the absence of regulatory oversight and absence of standardized labeling (e.g., guidance for use, serving sizes and dosing), rates of serious adverse events and deaths associated with kratom use are low compared to many substances that are used largely for recreational reasons (Henningfield et al., 2019; Prozialeck et al., 2019; Prozialeck et al., 2021; Papsun et al., 2023).

7.1 Need for regulation at the state and national level

None of the foregoing is to imply that kratom does not carry risks or should not be monitored or regulated. To the contrary, the DHHS scheduling rescission letter (Giroir, 2018) was explicit that kratom was not without risks and that further research was needed to guide appropriate regulation. Similarly, the WHO ECDD called for continuing surveillance. Many United States states also considered these issues and, as of the writing of this manuscript, 16 states passed KCPA laws that vary across states, with 11 providing multifaceted approaches that include standards to prevent the sale of contaminated and adulterated products, to prevent unsubstantiated claims and sale to minors, to require registration of marketers and products, and to mandate some stipulations for product labeling and warnings (Heflin, 2023).

The emerging interest and passage of laws at the state level highlights the importance of a national regulatory framework by FDA which has considerable expertise in all aspects of dietary supplement regulation from product performance standards to labeling and warnings as are summarized in Table 1.

In the absence of FDA-guided labeling, articles and guidance that address safety and potential beneficial use emerged in the medical literature and on the internet from clinician/researchers and health organizations (e.g., WebMD, 2020; NIDA, 2022; NIH NCCIH, 2022; Swogger et al., 2022; University of Florida, 2024).

Cautions as recommended by Swogger et al. (2022), and which include not using concurrently with other substances, using no more than is needed to achieve the intended benefit, and talking to one's healthcare provider about use, all seem in order and prudent until the FDA develops standardized warnings and labeling for all kratom products marketed in the United States by retail stores and online.

7.2 FDA regulatory science needs to guide the implementation of kratom product regulation and evolution over time

Research that is relevant to FDA regulatory science needs is vital to ensure that kratom regulation is evidence-based and evolves to address and minimize risks. The advancement of public health related to kratom hinges on FDA guidance. With respect to kratom itself, research has advanced the understanding of kratom chemistry, pharmacology, epidemiology, benefits, and risks considerably over the past 5–10 years. Although most of this research was not designed and conducted for the purpose of guiding FDA kratom product regulation, much of it is relevant as FDA generally takes a comprehensive approach to product

TABLE 1 Research Priorities to guide evolving regulation, labeling and general consumer information.

• Expanded chemistry and pharmacology research to better understand the contributions of kratom's diverse constituents and metabolites on positive and adverse effects to inform regulatory performance standards for product constituent levels.
• Expanded animal toxicology and pharmacology research to better understand potential harmful consequences related to acute and daily dosing and drug interactions.
• Expanded clinical research to better understand the pharmacokinetics and pharmacodynamics of kratom's major alkaloids and metabolites, beyond MG and 7OHMG, which have heretofore been the major foci of kratom pharmacology research in general. This should include behavioral research to provide appropriate warnings about potential adverse behavioral effects.
• Expanded clinical research to establish serving size recommendations and maximum daily exposure to kratom and its alkaloids that is considered safe.
• Expanded surveillance and epidemiology research to better understand patterns of use and their association with potential benefits and harms and factors that might increase the risks of use such as drug and other dietary substance intake and preexisting health conditions.

TABLE 2 Regulatory priorities to protect public health.

• Product performance standards including:
• Maximum allowable concentrations of physiologically active constituents and/or content per serving and possibly per container in the case of manufactured extracts
• Standards for testing for maximum allowable levels of potential contaminants to define and assure purity.
• National labeling requirements and format that includes the ingredient listings consistent with requirements for other dietary supplements, and with the levels by percentage and/or the weight per serving size.
• Prohibition of adulteration by any psychoactive substance or drug product, allowing only accepted flavorings and other substances allowed for food products with labeling consistent with manufactured food products such as coffee, tea, and dietary supplements.
• Potential evidence-based and consumer-tested product warning and precautions, for example, the absence of studies of kratom safety during pregnancy and lactation where FDA needs to consider the evidence and develop labeled warnings.
• Prohibition of unauthorized health claims and examples of what types of descriptive marketing statements are allowable.
• Minimum age of procurement of 21 years.
• Identification of manufacturer or marketer with contact information for consumer comments and AE reporting.

regulation and strives to ensure that its actions are evidence-based and in the interests of public health. FDA product regulation in new areas, including new product types, not only needs a sufficient basis to begin the regulatory process, but requires an ongoing pipeline of regulatory science research to guide the evolution of regulation over time as is evident in FDA's support (often in collaboration with the United States National Institutes of Health) to guide ongoing regulation of food, drug and tobacco products (e.g., FDA, 2022b; FDA, 2023a). Research priorities to address knowledge gaps as well as to support kratom product regulation and kratom-based new medicines are summarized in Table 2.

The research reviewed here clarifies that there is presently an adequate epidemiological and basic science evidence base to initiate regulation, as is already occurring in many states, and which could be expertly developed by FDA's Office of Dietary Supplements. FDA is not only monitoring kratom, but its Office of Dietary Supplements undoubtedly learned much through its review of NDINs and interactions with their sponsors. State-level efforts provide examples of consumer-, manufacturer-, and researcher-informed approaches. FDA already contracted research on the safety of single kratom doses and announced requests for research, such as its 2023 request for proposals, in collaboration with the National Institutes of Health, to study the human abuse potential of botanical kratom, presumably using doses identified during their single ascending dose safety study (FDA, 2024b).

It is important to keep in mind that the time from initiation of Phase 1 clinical drug development trial to submission of a new drug application to FDA is typically 10 years or more, at a cost of a billion dollars or more and that most such efforts do not result in approval of the new drug by FDA (DiMasi et al., 2016; Wouters et al., 2020). New drugs that are approved for therapeutic use by FDA are then for use only by prescription. We note that the FDA has recommended development of new drug applications for potential kratom-derived products, including by its botanical drug development pathway. At the time of this writing, we are aware of at least one such effort that has been made public (e.g., atai Life Sciences, 2022; Sparian Biosciences, 2023).

This process will likely be ongoing, and it is plausible that products will be approved, but for prescription use only within the next decade. Thus, that regulatory pathway will not serve the millions of consumers who presently desire regulatory oversight of the various kratom products they purchase and consume (e.g., DEA, 2016; Grundmann, 2017). Similarly, FDA encouraged development of kratom as pharmaceutical products by FDA's Botanical Drug Pathway program (FDA, 2016). However, that drug development pathway, only yielded two approved products out of the more than 800 Investigational New Drug Applications received prior to 2018, which speaks to the risks, costs, and uncertainties of this pathway as discussed by FDA officials (Wu et al., 2020). Furthermore, the product of a new drug from the botanical pathway, will also likely be a prescription pharmaceutical product that may or may not appeal to currently available botanical product kratom users.

8 Conclusion

In the near term, United States kratom consumers would seem most expeditiously served by an FDA approach to regulate all kratom products to ensure that they meet basic standards for purity, product constituent levels, and labeling and warnings to ensure access to product meeting those standards and prohibit legal sales of products that do not meet the standards. It appears that kratom regulation could be most efficiently developed for the protection of public health by the same type of rulemaking protocols that FDA uses for other dietary products (FDA, 2020). This process includes opportunities for comment and input by diverse stakeholders (including consumers, researchers, manufacturers and public health experts) to ensure that the resulting rule is guided by the latest science, is in the interests of public health, serves consumers, and is practically viable from an industry perspective. Ongoing kratom research, as is already underway with NIH support, helps ensure continuing input into the evolution of consumer and public health evidence-based kratom regulation (NIDA, 2022).

Author contributions

JH: Conceptualization, Writing–original draft, Writing–review and editing. OG: Writing–review and editing. MH: Writing–review and editing. KS: Writing–review and editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. The publication fee was paid by Pinney Associates, Inc. Pinney Associates, Inc., had no input in the conception, content, or opinions expressed in this article, nor to its review, approval or decision to submit the manuscript for publication. Pinney Associates, Inc., routinely pays publishing fees and Open Access fees for articles that are especially important to public health.

Acknowledgments

The authors are grateful for the contributions of Floe Foxen, Yolanda Green, Megan Harris and Daniel Wang for their editorial assistance including formatting for the journal and referencing.

Conflict of interest

JH and MH consult on kratom science and regulatory issues and studies paid by sponsors of potential kratom and kratom derivative-based new dietary ingredient applications and new drug applications to the United States Food and Drug Administration, and to the American Kratom Association on many of the same scientific and regulatory issues as discussed in this article through Pinney Associates. Through Pinney Associates, support of the American Kratom Association, 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. MH is a paid expert witness in legal cases related to kratom. In the past year, KS has served as a paid scientific advisor to the International Plant and Herbal Alliance and to The Kratom Coalition. KS is a paid expert witness in legal cases related to kratom. OG reported representing parties in legal disputes related to kratom use resulting in impairment or death. Neither commercial nor non-profit entities had any input into the conception, content, or opinions expressed in this article, nor to its review, approval or decision to submit the manuscript for publication.

The reviewer DS declared a past co-authorship with the authors JE, OG, and MA to the handling editor.

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

Kratom Abuse Potential 2021: An Updated Eight Factor Analysis

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

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

OPEN ACCESS

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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 l 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; Jagabalan 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; Covvey 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 Use 0.7%. 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) (U.S. Department of Health and Human Services, 2020; Schimmel et al., 2021; Covvey et al., 2020), (Botanical Education Alliance, 2016)		
Kratom Use Prevalence		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
Covvey et al. (2020) (Covvey 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.

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Conflict of Interest: Authors JH, DW, and MH were employed by the company PinneyAssociates, Inc.

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

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Survey of Adult Kratom Users in the U.S.

Provides Insight Into Potential for Harm or Abuse

2,798 kratom users

WHO:

84% at least some college
40 years old on average
61% are women

WHY:

91% pain relief
67% treat anxiety
64% treat depression
41% treat **opioid dependence**[1]

Of those treating opioid dependence:

87% reported relief from withdrawal symptoms
35% were free from opioids >1 year

SIDE EFFECTS:

19% mild
1.9% serious[2]
9.5% withdrawal

<10% met criteria for mild kratom substance use disorder
<3% met criteria for moderate or severe kratom substance use disorder



1. many people reported multiple reasons for use
2. including symptoms like anxiety, irritability, depression and insomnia

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Full length article

Kratom (*Mitragyna speciosa*): User demographics, use patterns, and implications for the opioid epidemic

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ARTICLE INFO

Keywords:
Kratom
Mitragyna speciosa
Mitragynine
Opioids
Opioid use disorder
Harm reduction

ABSTRACT

Background: Kratom, a Southeast Asian plant with opioid-receptor mediated effects, has emerged as a potential substance of abuse, with limited data on its use and effects. This study characterized kratom user demographics, use patterns, and perceived drug effects.

Methods: A cross-sectional, anonymous online survey was conducted between January and December 2017.

Results: 2,798 kratom users – mean age 40 (SD = 12); predominantly White (90 %), female (61 %), and located in the US (97 %) – completed the survey. Kratom was primarily taken orally in doses of 1 – 3 g (49 %), with daily use (59 %) being most common. Kratom was used for pain (91 %), anxiety (67 %), and depression (65 %), with high ratings of effectiveness. 1,144 (41 %) used kratom to stop or reduce prescription or illicit opioid use, citing decreased opioid withdrawal and craving related to kratom use, with 411 reporting > 1-year continuous abstinence from opioids attributed to kratom use. Roughly one-third of respondents reported adverse effects of kratom, largely rated as mild in severity and lasting ≤ 24 h. Seventeen participants (0.6 %) sought treatment for adverse effects. Fifty-six individuals (2 %) met DSM-5 criteria for a past-year moderate or severe kratom-related substance use disorder (SUD). When asked how troubled they felt regarding their kratom use, the mean (SD) rating was 3.2 (9.8) on a scale from 0 to 100.

Conclusion: Kratom is used among White, middle-aged Americans for symptoms of pain, anxiety, depression, and opioid withdrawal. Although regular use was typical, kratom-related SUD and serious adverse effects were uncommon. Additional research on kratom epidemiology and pharmacology is imperative in light of the present opioid epidemic.

1. Introduction

Kratom (*Mitragyna speciosa*) is an evergreen tree in the coffee (*Rubiaceae*) family native to Southeast Asia (SEA), where it has a long history of traditional use (Hassan et al., 2013; Singh et al., 2016). Kratom leaf or extract are typically ingested orally for treating pain and other medical conditions, and to aid in the performance of agricultural and manual labor (Hassan et al., 2013; Singh et al., 2016). Kratom and its alkaloids have been classified as atypical opioids because they are structurally and biologically distinct from classical opioids (e.g., morphine) that are derived from the poppy (*Papaveraceae*) family (Raffa et al., 2018). Kratom has emerged as a natural product available for purchase over the internet (Babu et al., 2008; Prozialeck, 2016), and has been identified as a Drug of Concern by the US Drug Enforcement Administration (DEA, 2017). Surveys and case studies suggest many Americans are using kratom to self-medicate a range of conditions including pain and opioid withdrawal (Boyer et al., 2007; Coe et al., 2019; Grundmann, 2017; Henningfield et al., 2018; Smith and Lawson, 2017; Swogger et al., 2015), although there are limited empirical data available to support a therapeutic benefit for such use.

Kratom contains more than three dozen unique indole alkaloids, including its primary alkaloid mitragynine, which makes up approximately 66 % of the total alkaloids in kratom leaves (Kruegel and Grundmann, 2018; Takayama, 2004). Preclinical studies of mitragynine suggest it may hold potential toward developing new and efficacious pain medications (Kruegel and Grundmann, 2018; Macko et al., 1972; Takayama, 2004). Mitragynine is a G-protein-biased partial agonist of the mu-opioid receptor that does not recruit the β-arrestin signaling

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https://doi.org/10.1016/j.drugalcdep.2020.107849
Received 25 July 2019; Received in revised form 4 January 2020; Accepted 8 January 2020

pathway like classical opioids (Kruegel et al., 2016; Váradi et al., 2016). It is thus hypothesized to confer analgesic effects with lower risk of respiratory depression than classical opioids (Kruegel et al., 2016; Siuda et al., 2017; Váradi et al., 2016). Mitragynine and kratom extracts have shown robust antinociceptive effects in rats, mice, and dogs, suppressing nociceptive response to both mechanical and thermal noxious stimuli with minimal respiratory depression (Hassan et al., 2013; Macko et al., 1972; Matsumoto et al., 1996; Sabetghadam et al., 2010). Furthermore, these antinociceptive effects are blocked by the opioid antagonist naloxone, suggesting an opioid-receptor mediated mechanism of action (Matsumoto et al., 1996; Sabetghadam et al., 2010). Abuse liability testing of mitragynine in rats has shown that it reduces morphine self-administration but does not substitute for morphine, and it does not engender or maintain intravenous self-administration, suggesting low abuse liability (Hemby et al., 2018). In addition, pretreating rats with mitragynine has also been shown to reduce heroin self-administration though mitragynine itself is not self-administered (Yue et al., 2018). However, 7-hydroxymitragynine, a minor alkaloid present at low levels (~2 % of alkaloids) in kratom leaves (Ponglux et al., 1994) has shown mu-opioid receptor-mediated analgesic effects (Matsumoto et al., 2004), and has been found to substitute for morphine and engender and maintain intravenous self-administration in rats in a dose-dependent manner (Hemby et al., 2018).

Survey studies indicate kratom has been used as a substitute for opioids and to alleviate opioid withdrawal both in SEA (Vicknasingam et al., 2010) and the US (Boyer et al., 2008; Coe et al., 2019; Grundmann, 2017). Internet-based studies have found that in the US, kratom is predominantly being used by White, middle-aged, middle-income, college-educated individuals for treatment of pain, opioid withdrawal, and mental health conditions, with relatively minor (e.g. stomach upset), dose-dependent adverse effects (Grundmann, 2017; Henningfield et al., 2018; Swogger et al., 2015). Among a sample of 8,049 kratom users in the US, more than a quarter of respondents reported using kratom to reduce illicit (e.g. heroin; n = 539) or prescription (e.g. opioid medication; n = 1813) drug dependence or withdrawal (Grundmann, 2017).

To date, the behavioral pharmacology and abuse liability of kratom have not been well-characterized in humans. One study conducted in Thailand that administered different doses of kratom tea to 10 chronic kratom-using males and evaluated blood and urine mitragynine levels found linear pharmacokinetics, time to maximum plasma concentration of roughly 1 h, and a terminal half-life of about one day (Trakulsrichai et al., 2015). Otherwise, no controlled laboratory research with kratom or its alkaloids has been conducted in humans. Given the lack of controlled human studies, it is important to understand more about kratom use patterns, users' motives, and outcomes following kratom exposure. This information can help inform prospective evaluations of kratom for different indications as well as regulatory decisions regarding scheduling. The present study collected demographic and self-report data from individuals who use kratom to extend the limited existing literature on contemporary kratom use.

2. Methods

2.1. Data collection

We conducted this cross-sectional, anonymous online survey to further characterize kratom user demographics, reasons for and patterns of kratom use, and perceived benefits of use. Self-reported adverse effects associated with kratom use were examined, including potential kratom withdrawal symptoms. Finally, indicators of abuse liability and problematic kratom use were assessed. All data were collected anonymously (no name or personally identifiable information recorded) using Qualtrics (Qualtrics, Provo, UT, USA). IP addresses were collected so the same person could not respond to the survey repeatedly, but were destroyed after data collection was completed. Between January 2017 and December 2017 participants were recruited using online advertisements and email announcements distributed via sites of interest to kratom users (e.g., American Kratom Association, Erowid, Reddit). Participants were required to be age 18 years or older, English language proficient, and have used kratom in the past year. Information about the purpose of the study was provided prior to beginning the survey, and by choosing to begin the survey respondents indicated their consent for voluntary participation. Participants who completed the initial pilot version of the survey through Amazon Mechanical Turk (n = 36) received $3.10 for completing the survey. Otherwise, no incentives were offered for study participation. Due to its confidential and anonymous nature, the Johns Hopkins University School of Medicine Institutional Review Board determined this did not qualify as human subjects research.

2.2. Measures

Participants provided demographic information (e.g., age, highest level of education, household income), location of residence, past-year use of licit (e.g., alcohol, nicotine), illicit (e.g., heroin, psychedelics), and prescription drugs (e.g., antidepressants, prescription opiates), and lifetime medical diagnoses. The 10-item Patient-Reported Outcomes Measurement Information System Global Health (PROMIS-GH) scale was used to assess general physical and mental health (Broderick et al., 2013). Chronic pain was assessed using the 15-item Brief Pain Inventory (BPI) (Cleeland and Ryan, 1994).

Data regarding kratom use patterns, including age of kratom use initiation, frequency of use, typical dose of kratom, and route of administration were collected. Participants were asked to endorse whether they used kratom for specific conditions (e.g., pain, depression), if they would recommend kratom as a remedy for these conditions, and to rate how effective they considered kratom for these conditions using a visual analog scale (VAS) from 0 (not at all) to 100 (extremely). Participants were asked to report whether they had ever used kratom to help reduce or stop using heroin and/or licit or illicit use of pharmaceutical pain medications (e.g., Oxycontin, Percocet). Those who reported using kratom for this purpose then provided information on the perceived effectiveness of kratom to mitigate opioid use and ways in which kratom may have been useful in this capacity.

Incidence of self-reported adverse effects or side effects attributed to kratom was queried, and information on duration, severity, and medical treatment for adverse effects was collected. Similarly, potential kratom-related withdrawal was probed, with those endorsing possible kratom withdrawal completing the 16-item Subjective Opiate Withdrawal Scale (SOWS) to evaluate symptom severity (Handelsman et al., 1987). Participants rated typical subjective effects of kratom across 13 items from the Drug Effects Questionnaire (DEQ), assessing type, strength, and desirability of kratom effects associated with abuse liability (e.g., drug liking, euphoria, desire) using VAS from 0 (not at all) to 100 (extreme) (Morean et al., 2013). Additionally, participants were asked to rate how troubled or bothered they were by their kratom use using VAS from 0 (not at all) to 100 (extreme). Participants completed a DSM-5 substance use disorder (SUD) symptom checklist to assess whether past-year kratom use met diagnostic criteria for a kratom-related SUD (American Psychiatric Association, 2013; Hudziak et al., 1993).

2.3. Data analysis

Descriptive statistics were generated to determine the prevalence, means, and proportions of relevant variables. Chi-square (categorical variables) and Mann-Whitney U (continuous variables) tests were used to examine differences between those who used kratom to reduce opioid use and those who did not. To evaluate factors related to kratom use outcomes, we conducted four independent multivariate logistic regressions using Maximum Likelihood estimates for each of the

following outcomes: negative effect of kratom use ≥1 lifetime/never lifetime); experience withdrawal from kratom use (≥1 symptom/0 symptoms); ever sought treatment for kratom use (yes/no); and lifetime use of kratom to reduce opioid use (yes/no). Several demographic and drug use variables were entered into the models as predictors, including: age, sex, race, relationship status, education, employment status, income, geographic region, past 12-month alcohol use, past 12-month opioid use, diagnosis of bipolar disorder, diagnosis of depression, age of first kratom use, kratom use frequency, number of kratom-related SUD symptoms, SOWS total, pain severity, experienced opioid withdrawal, and the total number of different types of opioids used in past 12 months. Data were analyzed using IBM Microsoft SPSS version 25 (IBM®, 2017), and Prism version 7.0 (GraphPad, La Jolla, CA, USA).

3. Results

3.1. Sample characteristics

Of the 4,302 individuals who began the survey, 2,826 (66 %) met all study inclusion criteria and completed the entire survey. Of these, 28 were removed due to inconsistent responses or technical issues, resulting in a final sample of 2,798 kratom users. Fifty-three percent of the final sample learned about the survey through the American Kratom Association and 44.2 % found it through Facebook or other social media websites.

Table 1 displays the means and proportions for demographic and substance use items. Respondents were on average 40.2 years old (SD = 11.8) and majority female (60.7 %). Most were married or in a committed relationship (66.5 %), employed (68.4 %), and had some college education (83.9 %). The median annual household income was between $50,000-$59,000. The largest geographic residential concentration for respondents was the U.S. South (41.0 %). Alcohol was the most commonly reported substance used in the past year (47.4 %), followed by tobacco (42.2 %), cannabis (37.2 %), and opioids (33.0 %). Roughly half the sample (52.9 %) reported ever experiencing opioid withdrawal symptoms or difficulty controlling opioid use.

3.2. Physical and psychological health

A majority of the sample (n = 1,924; 68.8 %) reported experiencing chronic pain over the past 3 months. Among this group, the mean (SD) BPI pain severity score was 4.1 (1.8), and the mean pain interference score was 4.9 (SD = 2.9), with possible scores ranging from 0 to 10 and greater scores indicating more pain or pain interference in daily activities. Pain was most commonly reported in the lower (53.8 %) and upper back (34.6 %), shoulders (33.1 %), and knees (31.3 %). Among this chronic pain group, 39.4 % reported currently taking a prescribed medication to treat pain, and 87.6 % reported current kratom use for pain.

Among the entire sample, the most commonly reported lifetime medical diagnoses (Table 1) included back pain (72.5 %), depression (65.0 %), muscle pain (62.9 %), neck pain (55.0 %), joint pain (54.5 %), panic attacks (48.1 %), and arthritis (43.8 %). PROMIS-GH physical health mean (SD) scores were 13.7 (3.2), and mental health scores were 12.8 (3.5), which both convert to standardized PROMIS-GH T-scores of approximately 45, slightly below the US general population mean of 50 (Hays et al., 2009).

3.3. Reasons for kratom use and use patterns

Most respondents endorsed using kratom for pain relief (91.3 %), and/or to treat mood-related issues such as anxiety (67.2 %), and depression (64.5 %). Among these, the majority said they would recommend kratom for pain relief (98.7 %), and mood-related issues (96.7 %). Mean (SD) efficacy ratings of kratom for treating pain on a scale from 0 (not at all) to 100 (extremely) were 83.3 (18.5); for anxiety

Table 1
Demographic characteristics and comparisons of respondents who did and did not report using kratom to reduce opioid use.[a]

Respondent Group				
Characteristic	Total Sample N = 2,798	Opioid reduction users N = 1,144	Other users N = 1,654	*P* value[b]
Age in years, Mean ± SD	40.2 ± 11.8	39.8 ± 10.5	40.5 ± 12.6	.449
Sex, No. (%)				
Female	1,699 (60.7)	696 (60.8)	1,003 (60.6)	.916
Race, No. (%)				
American Indian/ Native Hawaiian	40 (1.4)	25 (2.2)	15 (0.9)	.013
Asian	14 (0.5)	4 (0.3)	10 (0.6)	
Black/African American	11 (0.4)	2 (0.2)	9 (0.5)	
More than one race/ some other race	176 (6.3)	60 (5.2)	116 (7.0)	
White	2,513 (89.8)	1,035 (90.5)	1,478 (89.4)	
Prefer not to respond	44 (1.6)	18 (1.6)	26 (1.6)	
Relationship status, No. (%)				
Single, never married	530 (18.9)	206 (18.0)	324 (19.6)	.671
In committed relationship/ married	1,860 (66.5)	775 (67.8)	1,085 (65.6)	
Separated/divorced	362 (12.9)	144 (12.6)	218 (13.2)	
Widowed	46 (1.6)	19 (1.7)	27 (1.6)	
Education, No. (%)				
Did not complete High school	51 (1.8)	22 (1.9)	29 (1.8)	.006
High school graduate or equivalent	401 (14.3)	189 (16.5)	212 (12.8)	
Some college	998 (35.7)	424 (37.1)	574 (34.7)	
College degree (e.g., AA, BS)	921 (32.9)	362 (31.6)	559 (33.8)	
Some graduate school	150 (5.4)	55 (4.8)	95 (5.7)	
Advanced degree (e.g., Ph.D.)	277 (9.9)	92 (8.0)	185 (11.2)	
Employment status, No. (%)				
Employed	1,915 (68.4)	785 (68.6)	1,130 (68.3)	< .001
Unemployed	313 (11.2)	148 (12.9)	165 (10.0)	
Student	109 (3.9)	27 (2.4)	82 (5.0)	
Other (e.g., disabled, retired)	461 (16.5)	184 (16.1)	277 (16.7)	
Household income, No. (%)				
< $10,000–$29,999	716 (25.6)	305 (26.7)	411 (24.8)	.098
$30,000–$49,999	608 (21.7)	266 (23.3)	342 (20.7)	
$50,000–$62,999	459 (16.4)	192 (16.8)	267 (16.1)	
$70,000–$99,999	483 (17.3)	180 (15.7)	303 (18.3)	
≥$100,000	532 (19.0)	201 (17.6)	331 (20.0)	
Geographic region, No. (%)				
Northeast	417 (14.9)	163 (14.2)	254 (15.4)	.132
Midwest	540 (19.3)	223 (19.5)	317 (19.2)	
South	1,147 (41.0)	495 (43.3)	652 (39.4)	
West	612 (21.9)	237 (20.7)	375 (22.7)	
Outside U.S./Prefer not to say	82 (2.9)	26 (2.3)	56 (3.4)	
Past 12-month substance use, No. (%)				
Alcohol	1,327 (47.4)	489 (42.7)	838 (50.7)	< .001
Antidepressants	787 (28.1)	296 (25.9)	491 (29.7)	.028
Benzodiazepines	702 (25.1)	327 (28.6)	375 (22.7)	< .001
Cannabis	1,041 (37.2)	419 (36.6)	622 (37.6)	.278
Cocaine	103 (3.7)	57 (5.0)	46 (2.8)	.002
Hallucinogens	161 (5.8)	51 (4.5)	110 (6.7)	.014
Opioids (prescribed or illicit)	922 (33.0)	550 (48.1)	372 (22.5)	< .001
Tobacco	1,180 (42.2)	573 (50.1)	607 (36.7)	< .001
Lifetime medical diagnoses, No. (%)				
Arthritis	1,225 (43.8)	532 (46.5)	693 (41.9)	.016
Back pain	2,028 (72.5)	875 (76.5)	1,153 (69.7)	< .001
Depression	1,818 (65.0)	797 (69.7)	1,021 (61.7)	< .001
Herniated disc	792 (28.3)	413 (36.1)	379 (22.9)	< .001
Joint Pain	1,526 (54.5)	664 (58.0)	862 (52.1)	.002
Menopause	538 (19.2)	187 (16.3)	351 (21.2)	.001

(continued on next page)

Table 1 (*continued*)

Respondent Group				
Characteristic	Total Sample N = 2,798	Opioid reduction users N = 1,144	Other users N = 1,654	*P* value[b]
Migraine/serious headaches	1,140 (40.7)	509 (44.5)	631 (38.1)	< .001
Muscle pain	1,760 (62.9)	774 (67.7)	986 (59.6)	< .001
Neck pain	1,540 (55.0)	669 (58.5)	871 (52.7)	.002
Ovarian cyst	550 (19.7)	261 (22.8)	289 (17.5)	< .001
Panic attacks	1,346 (48.1)	596 (52.1)	750 (45.3)	< .001
PTSD	711 (25.4)	327 (28.6)	384 (23.2)	.001
Restless leg syndrome	799 (28.6)	408 (35.7)	391 (23.6)	< .001
PROMIS-GH				
Physical health,[c] Mean ± SD	13.7 ± 3.2	13.8 ± 3.0	13.6 ± 3.3	.203
Mental health,[c] Mean ± SD	12.8 ± 3.5	13.0 ± 3.4	12.7 ± 3.5	.014

Abbreviation: No, number; SD, standard deviation; PTSD, Post-Trumatic Stress Disorder; PROMIS-GH, Patient-Reported Outcomes Measurement Information System Global Health scale.

[a] Opioid reduction users were classified as those who responded affirmatively to the question, "Have you ever used kratom to help you cut down or stop using heroin or prescription pain medications (such as Vicodin, Percocet, Oxycontin, etc.)?".

[b] P values calculated using chi-square and 2-tailed Mann-Whitney U tests.

[c] Range = 4–20. Greater values indicate better physical / mental health.

were 76.7 (24.3); and for depression were 76.5 (25.4). Subgroups also reported using kratom for post-traumatic stress (29.6 %) or bipolar mood (24.6 %), with mean (SD) efficacy ratings of 60.2 (38.2), and 51.4 (39.9), respectively.

The mean (SD) age for kratom use initiation was 38 (12.2) years (Table 2). The majority of respondents reported using kratom ≥100 times in their lifetime (76.2 %), and most had used kratom in the 24 h before completing the survey (80.7 %). The most commonly reported typical dose range per occasion was 1 – 3 grams (49.0 %), followed by 4 – 6 g (33.4 %). Daily use was reported by the majority of respondents (59.1 %), with a mean (SD) of 2.7 (1.3) doses used per day. Ingesting kratom orally in powder form was the most common method of administration (43.6 %) followed by drinking as a prepared beverage (e.g., tea, smoothie; 37.0 %).

3.4. Kratom adverse effects

Approximately 19 % of participants reported adverse effects from kratom use (Table 2), with an additional 12.8 % reporting possible kratom-related adverse effects. Among those reporting definite or possible adverse effects, only 1 % (n = 9) indicated serious to extreme severity, and 1.9 % (n = 17) reported seeking medical treatment for adverse effects. Most adverse effects were rated mild in severity (63.2 %) and lasted ≤1 day (86.1 %). Kratom-related withdrawal symptoms were reported by 9.5 % of respondents with another 17.5 % reporting possible kratom-related withdrawal. The overall logistic regression model fit was significantly improved by including the abovementioned predictor variables (χ^2 = 580.73, p < .001). Logistic regression revealed that adverse effects of kratom use were significantly associated with younger age (aOR > 1.20 for people 65 years or younger; 95 % CI: 0.18, 13.42)[1], male sex (female aOR = 0.75; 95 % CI: 0.59, 0.95), having less education (aOR > 0.90 for people without a graduate/professional degree; 95 % CI: 0.35, 2.07), and lower income (aOR > 1.20 for people earning < $250k annually; 95 % CI: 0.44, 6.14), as well as past 12-month alcohol use (aOR = 0.61 for no alcohol in past 12 months; 95 % CI: 0.48, 0.76), past 12-month opioid use (aOR = 0.59 for no opioid use in past 12 months; 95 % CI: 0.45, 0.76), kratom-related withdrawal (i.e., SOWS total; aOR < 0.01 for SOWS total < 50; 95 % CI: 0.00, 1.21 × 10^{10}), and the number of opioids used in the past 12-months (aOR > 2.45 for people whose used 8+ different types of opioids; 95 % CI: 0.00, 1.44 × 10^{13}). Self-reported depression (aOR = 0.68 for no depression; 95 % CI: 0.54, 0.87), pain severity (χ^2 = 9240.28, p < .001), and kratom-related DSM-5 SUD symptoms (χ^2 = 149.93, p < .001) were also related to kratom adverse effects.

3.5. Symptoms of withdrawal following kratom abstinence

The mean (SD) SOWS score among these individuals was 8.8 (8.4), indicating mild opiate withdrawal symptoms (i.e., SOWS score < 11). Most respondents (87.7 %) did not meet diagnostic criteria for a past-year kratom-related substance use disorder (SUD) based on the DSM-5 symptom checklist. Less than 3 % met diagnostic criteria for moderate and severe kratom-related SUD. When asked how troubled or bothered they were by their kratom use on a scale from 0 (not at all) to 100 (extremely), the mean (SD) response across the entire study sample was 3.2 (9.8). The most highly rated subjective effects of kratom on a 0–100 VAS (Table 2) included 'good effects' (M = 86.4; SD = 23.0) and 'drug liking' (M = 85.7; SD = 23.7), followed by 'alert' (M = 49.8; SD = 30.9) and 'stimulated' (M = 41.3; SD = 28.6), with lower ratings of 'euphoric' (M = 25.1; SD = 27.1) and 'high' (M = 12.0; SD = 20.1), suggesting potential differences in subjective effects profiles of kratom from classic opioids (Walsh et al., 2008). The overall logistic regression model fit was significantly improved by including the abovementioned predictor variables (χ^2 = 4015.85, p < .001). Logistic regression analyses revealed that experiencing kratom withdrawal was significantly predicted by the number of kratom-related DSM-5 SUD symptoms (χ^2 = 3301.90, p < .001), sex (female aOR = 0.21; 95 % CI: 0.09, 0.47), total SOWS score (χ^2 = 77.25, p < .001), and having experienced opioid withdrawal (aOR = 0.14 for never experiencing opioid withdrawal; 95 % CI: 0.05, 0.36). Seeking treatment for kratom use was also significantly predicted by the number of kratom-related DSM-5 SUD symptoms (all aOR < 0.01 for < 9 DSM-5 SUD symptoms; 95 % CI: 0.00, < 0.01) and SOWS total (all aOR < 0.01 for SOWS total < 50; 95 % CI: 0.00, < 0.01).

3.6. Kratom for opioid use reduction

A subsample of 1,144 individuals (40.9 %) reported using kratom to reduce or stop opioid use, including prescription opioid medications and heroin. Kratom was endorsed by this group as effectively treating their opioid withdrawal symptoms (87.3 %; n = 999), addressing underlying pain related to opioid use (86.1 %; n = 985), reducing opioid cravings (79.6 %; n = 911), and improving mood while tapering off opioids (72.0 %; n = 824). Kratom was widely reported to reduce opioid withdrawal symptoms among this group, including anxiety (86.5 %; n = 989), body aches (86.5 %; n = 989), restlessness (86.4 %; n = 988), and insomnia (79.5 %; n = 910).

Among these respondents, Percocet (33.2 %; n = 380) and Vicodin (32.3 %; n = 369) were the most commonly used opioids in the past year, and heroin exhibited the least past-year use (5.8 %; n = 66). Among this group 122 (10.7 %) reported past-year Suboxone use, 89 (7.8 %) reported past-year methadone use, and 411 (35.9 %) reported no past-year opioid use. Most of these respondents (74.2 %; n = 849) reported achieving ≥6 months of abstinence from opioids attributed to kratom use. The large majority of these participants (99.2 %; n = 1,135) said they would recommend kratom as an opioid withdrawal treatment. The overall logistic regression model fit was significantly

[1] Adjusted odds ratios (aOR) are included where data showed a significant monotonic relationship. χ^2 values are included where the predictor variable had a significant non-linear relationship to the dependent variable. Where multiple categories exist for a variable, the 95% CI shows the range of minimum-to-maximum for all catgeories.

Table 2
Kratom use patterns and comparisons of respondents who did and did not report using kratom to reduce opioid use.[a]

Respondent Group				
Kratom Use Characteristic	Total Sample N = 2,798	Opioid reduction users N = 1,144	Other users N = 1,654	*P* value[b]
Reasons for kratom use,[c] No. (%)				
Treatment of mood-related or psychiatric symptoms	1,975 (70.6)	873 (76.3)	1,102 (66.7)	< .001
Anxiety	1,881 (67.2)	827 (72.3)	1,054 (63.7)	< .001
Depression	1,804 (64.5)	814 (71.2)	990 (59.9)	< .001
Bipolar Mood	687 (24.6)	340 (29.7)	347 (21.0)	< .001
Post-traumatic Stress Disorder (PTSD)	829 (29.6)	402 (35.1)	427 (25.8)	< .001
For treatment of pain	2,554 (91.3)	1,078 (94.2)	1,476 (89.2)	< .001
To reduce or stop using prescription or illicit opioids	1,144 (40.9)	1,144 (100.0)	0 (0)	< .001
Age of kratom use initiation, Mean ± SD	38.0 ± 12.2	37.3 ± 11.0	38.4 ± 12.9	.107
Has used kratom ≥ 100 times, No. (%)	2,133 (76.2)	939 (82.1)	1,194 (72.2)	< .001
Last time of kratom consumption, No. (%)				
Past 24 h	2,258 (80.7)	990 (86.5)	1,268 (76.7)	< .001
Past week	300 (10.7)	88 (7.7)	212 (12.8)	
Past month	129 (4.6)	33 (2.9)	96 (5.8)	
Past Year	111 (4.0)	33 (2.9)	78 (4.7)	
Typical dose in grams, No. (%)				
< 1	242 (8.6)	60 (5.2)	182 (11.0)	< .001
1–3	1,372 (49.0)	542 (47.4)	828 (50.1)	
4–6	935 (33.4)	424 (37.1)	509 (30.8)	
7 or more	249 (8.9)	118 (10.3)	135 (8.2)	
Number of doses per day, Mean ± SD	2.7 ± 1.3	3.1 ± 1.3	2.4 ± 1.3	< .001
Past-year frequency of use, No. (%)				
≤ 1 time per month	109 (3.9)	26 (2.3)	83 (5.1)	< .001
2–4 times per month	152 (5.4)	27 (2.4)	125 (7.6)	
2–3 times per week	375 (13.4)	99 (8.7)	276 (16.7)	
4–6 times per week	508 (18.2)	197 (17.2)	311 (18.8)	
Daily	1,654 (59.1)	795 (69.5)	859 (51.9)	
Route of administration, No. (%)				
Capsule/pill	530 (18.9)	214 (18.7)	316 (19.1)	< .001
Prepared as tea/beverage	1,035 (37.0)	373 (32.6)	662 (40.0)	
Ingested powder	1,221 (43.6)	550 (48.1)	671 (40.6)	
Other (e.g., smoked, IV/SC, consumed as extract)	12 (0.4)	7 (0.6)	5 (0.3)	
Experienced adverse effects from kratom, No. (%)				
Yes	540 (19.3)	198 (17.3)	342 (20.7)	.045
Maybe	357 (12.8)	140 (12.2)	217 (13.1)	
No	1,901 (67.9)	806 (70.5)	1,095 (66.2)	
Adverse effect severity, No. (%)				
Not at all	274 (9.8)	95 (8.3)	179 (10.8)	.589
Mild	567 (20.3)	219 (19.1)	348 (21.0)	
Moderate	47 (1.7)	20 (1.7)	27 (1.6)	
Serious to Extreme	9 (0.3)	4 (0.3)	5 (0.3)	
Sought medical treatment due to adverse effects	17 (0.6)	9 (0.8)	8 (0.5)	.311
Duration of adverse effects, No. (%)				
≤ 1 day	772 (27.6)	288 (25.2)	484 (29.3)	.476
2–6 days	76 (2.7)	28 (2.4)	48 (2.9)	
1–12 weeks	30 (1.1)	14 (1.2)	16 (1.0)	
4–11 months	6 (0.2)	4 (0.3)	2 (0.1)	
≥ 1 year	13 (0.5)	4 (0.3)	9 (0.5)	
Has experienced kratom-related withdrawal symptoms, No. (%)				
Yes	267 (9.5)	140 (12.2)	127 (7.7)	< .001
Maybe	491 (17.5)	251 (21.9)	240 (14.5)	
No	2,040 (72.9)	753 (65.8)	1,287 (77.8)	
SOWS Score,[d] Mean ± SD	8.8 ± 8.4	9.2 ± 8.4	8.3 ± 8.5	.017
Past-year DSM-5 kratom-related SUD criteria, No. (%)				
No criteria met	2,454 (87.7)	981 (85.8)	1,473 (89.1)	.043
Mild	276 (9.9)	131 (11.5)	145 (8.8)	
Moderate	51 (1.8)	26 (2.3)	25 (1.5)	
Severe	17 (0.6)	6 (0.5)	11 (0.7)	
How troubled or bothered by kratom use?[e] Mean ± SD	3.2 ± 9.8	3.4 ± 9.9	3.1 ± 9.8	.034
Ratings of typical kratom effects,[f] Mean ± SD				
Drug Effect	27.3 ± 29.8	25.9 ± 29.3	28.2 ± 30.1	.061
Drug Liking	85.7 ± 23.7	87.3 ± 22.5	84.6 ± 24.4	< .001
High	12.0 ± 20.1	11.1 ± 18.9	12.6 ± 20.8	.265
Good Effects	86.4 ± 23.0	86.7 ± 23.5	86.2 ± 22.6	.009
Bad Effects	11.5 ± 15.7	10.8 ± 15.5	12.0 ± 15.9	.036
Desire	30.1 ± 28.9	33.3 ± 29.3	27.9 ± 28.4	< .001
Stimulated	41.3 ± 28.6	42.5 ± 27.9	40.6 ± 29.0	.066
Euphoric	25.1 ± 27.1	24.7 ± 26.6	25.4 ± 27.4	.981
Sick	6.2 ± 12.3	5.8 ± 11.8	6.5 ± 12.6	.094

(*continued on next page*)

Table 2 (*continued*)

Respondent Group				
Kratom Use Characteristic	Total Sample N = 2,798	Opioid reduction users N = 1,144	Other users N = 1,654	*P* value[b]
Dizzy	4.8 ± 10.9	4.9 ± 11.4	4.7 ± 10.5	.703
Alert	49.8 ± 30.9	52.5 ± 30.7	47.9 ± 30.8	< .001
Anxious	3.9 ± 9.6	3.8 ± 8.6	4.0 ± 10.3	.385
Sleepy	22.3 ± 23.6	20.4 ± 22.0	23.6 ± 24.7	.009

Abbreviation: No, number; SD, standard deviation; SOWS, Subjective Opioid Withdrawal Scale; SUD, Substance Use Disorder.

[a] Opioid reduction users were classified as those who responded affirmatively to the question, "Have you ever used kratom to help you cut down or stop using heroin or prescription pain medications (such as Vicodin, Percocet, Oxycontin, etc.)?".

[b] P values calculated using chi-square and 2-tailed Mann-Whitney U tests comparing Opioid reduction users (n = 1,144) and Other users of kratom (n = 1,654).

[c] Respondents could identify multiple reasons for use.

[d] SOWS scores can range from 0 to 64, with scores 0–10 = mild, 11–20 = moderate, > 20 = severe.

[e] Possible scores range 0 (not at all) to 100 (extremely).

improved by including the abovementioned predictor variables (χ^2 = 2988.20, $p < .001$). Kratom use for opioid use reduction was significantly associated with age of first kratom use (aOR > 8.87×10^4 for starting use at age 65 or younger; 95 % CI: 0.00, 12.92×10^6), lifetime kratom use on < 100 occasions (aOR = 0.26; 95 % CI: 0.13, 0.52), frequency of current kratom use (χ^2 = 10.64, $p = .031$), never having experienced opioid withdrawal (aOR < 0.01; 95 % CI: 0.00, < 0.01), greater number of opioids used in the past 12-months (χ^2 =644.46, $p < .001$), and past 12-month opioid use (aOR = 5.89; 95 % CI: 3.35, 10.39).

3.7. Comparison of kratom users by motivation for use

Tables 1 and 2 show between-groups comparisons of individuals who reported using kratom to reduce opioid use (n = 1,144), and those who reported using kratom for other reasons such as pain or depression (n = 1,654). These groups were similar in many respects including age, sex, relationship status, and geographic location (Table 1). However, groups differed significantly in education and employment status, with those using kratom for opioid use reduction showing lower rates of college or advanced degrees, fewer current students, and greater unemployment.

Those who used kratom to reduce opioid use were less likely to have used alcohol ($p < .001$), antidepressants ($p = .028$), and hallucinogens ($p = .014$), but more likely to have used tobacco ($p < .001$), opioids ($p < .001$), benzodiazepines ($p < .001$), and cocaine ($p = .002$) in the past year (Table 1). Individuals who used kratom to reduce opioid use reported significantly greater lifetime prevalence across a variety of medical diagnoses including back pain, depression, and panic attacks, with menopause being the only diagnosis more common among those using kratom for purposes other than opioid use reduction. Respondents who used kratom to reduce their opioid use also showed significantly higher rates of endorsing kratom use for anxiety, depression, post-traumatic stress, bipolar mood, and pain.

Those who reported using kratom for opioid use reduction exhibited greater likelihood of having used kratom in the 24 h prior to completing the survey, higher dose used per occasion, more doses used per day, greater frequency of use, and higher prevalence of kratom-related withdrawal symptoms (Table 2). Between-group differences in typical subjective effects of kratom were also observed, with opioid reduction users reporting significantly greater drug liking, good effects, alertness, and desire for kratom, and significantly less sleepiness. Those who reported using kratom for opioid reduction were slightly more likely to meet DSM-5 criteria for mild or moderate kratom-related SUD in the past year.

4. Discussion

The current study collected data on kratom user demographics, use patterns, and perceived therapeutic and adverse effects. Participants in the present study were predominantly White, middle-aged, female, with some college education, in a committed relationship, and employed. Physical and psychological health in the current sample was on average slightly below US general population means (Hays et al., 2009), though lifetime pain and depression diagnoses were highly prevalent among respondents. These findings are congruent with observed comorbidity between opioid use disorder, pain, and psychiatric conditions such as depression (Conway et al., 2006; Fischer et al., 2012). Interestingly, respondents who reported using kratom for opioid use reduction had a higher life-time prevalence of depression, but were less likely to use antidepressants than other respondents. It is possible that these individuals use kratom as an alternative to antidepressant medications, though this might also be related to lack of access to medical care, which was not explicitly probed in this survey and should be examined in future studies. Consistent with other recent research (Boyer et al., 2007; Coe et al., 2019; Grundmann, 2017; Henningfield et al., 2018; Smith and Lawson, 2017; Swogger et al., 2015), these data suggest individuals in the US are using kratom to self-treat medical conditions such as pain, depression, anxiety, and opioid withdrawal symptoms, and reporting robust effectiveness for these indications.

This study supports the results of previous studies (Coe et al., 2019; Grundmann, 2017; Smith and Lawson, 2017; Swogger et al., 2015) 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. Adverse effects reported here were most commonly rated as mild and lasted ≤1 day, and less than 1 % of the total sample found the effects of kratom to be severe enough to seek medical treatment. Adverse effects of kratom use were related to a number of demographic, health, and drug use variables including age, sex, education, income, depression, pain severity, and past 12-month alcohol and opioid use. Therefore, younger individuals or people with depression or more severe pain may experience more kratom-related adverse effects, potentially related to co-use with alcohol or other opioids. However, daily kratom users among the current sample were unlikely to meet criteria for a kratom-related SUD, or report substantial problems or concerns related to their kratom use. Logistic regression models additionally found that greater kratom-related SUD symptoms predicted negative effects of kratom use, kratom withdrawal, and seeking treatment for kratom use, but not kratom use for the purposes of opioid reduction. Thus, kratom may differ in important respects from typical opioids, and may have significant therapeutic potential in light of the present opioid crisis (Henningfield et al., 2018; Raffa et al., 2018).

The major limitation of this and other internet-based surveys of kratom users is the self-selected convenience sample queried. Because data were collected online, and recruitment was conducted through websites of interest to kratom users, the sample likely exhibits selection bias towards individuals who are younger, more affluent, and more

positively inclined towards kratom. Therefore, these results may underrepresent individuals from lower socio-economic status backgrounds, older and less technologically-fluent people, and those with negative experiences using kratom (e.g., who discontinued use due to adverse effects and are no longer part of the kratom-using online community). Thus, adverse effects may be underestimated, and benefits overestimated. It was also impossible to distinguish medically prescribed from illicit use of opioid medications in the current dataset, representing another significant limitation of the present study.

Kratom is currently unscheduled in the US, although the US Drug Enforcement Administration and Food and Drug Administration have raised the possibility of Schedule I classification of kratom and its alkaloids, which would strongly deter research and pose a significant public health risk for individuals currently using kratom in place of other opioids (DEA, 2017; Henningfield et al., 2018; Prozialeck, 2016). The rationale for Schedule I classification includes 44 possible kratom-related deaths worldwide over the past decade, most of which are known to involve other substances and/or preexisting medical conditions (Henningfield et al., 2018). The current scope of kratom use in the US remains unknown, and only one controlled human laboratory study of kratom has been conducted to date (Trakulsrichai et al., 2015), highlighting a notable lack of empirical information about the epidemiology and pharmacological effects of kratom in humans. Nationally-representative epidemiological research is needed, along with controlled studies of the potential risks, benefits, medication interactions, and abuse liability of kratom in humans prior to any Scheduling action that may confer unintended, but deleterious, public health consequences. There is a high likelihood that banning kratom or its constituents would compel individuals who are presently using kratom for pain relief or opioid use reduction to return to using prescription or illicit opioids with a known risk of dependence and possible lethal overdose.

With nearly 49,000 opioid-related overdose deaths in the US in 2017, the current opioid epidemic has reached unprecedented levels (Ahmad et al., 2018). Prescription opioid use has increased more than 4-fold since 1999 (Frenk et al., 2015), comprising 245 million prescriptions for opioid medications in 2014 (Levy et al., 2015; Rudd et al., 2016), and contributing to almost half of current US opioid overdose deaths (Ahmad et al., 2018; Rudd et al., 2016). The majority of pharmaceutical opioids are prescribed for the management of acute pain. However, prescription opioid misuse, diversion, and use disorder represent rapidly growing public health concerns (Vowles et al., 2015), highlighting an urgent need for novel pain management options that are safer, and less addictive than current medications (Volkow and McLellan, 2016). If controlled research in humans finds that kratom exhibits analgesic effects with minimal abuse liability and risk of respiratory depression, this could provide a much-needed avenue towards the development of novel medications for pain management and potentially OUD. Thus, additional investigation of kratom and its alkaloids is both timely and promising, and may have critical public health ramifications in the midst of the current opioid crisis.

Contributors

Dr. Garcia-Romeu made substantial contributions to the conception and design of the study, the acquisition, analysis, and interpretation of the data, and the drafting of the manuscript. Dr. Cox made substantial contributions to the analysis of the data, and made critical revisions to the manuscript. Dr. Smith made substantial contributions to the design of the study, the analysis of the data, and made critical revisions to the manuscript. Dr. Dunn made substantial contributions to the conception and design of the study, the acquisition and interpretation of the data, and made critical revisions to the manuscript. Dr. Griffiths made substantial contributions to the conception and design of the study and made critical revisions to the manuscript. All authors read and approved the final version of this manuscript, and agree to be accountable for all aspects of the work.

Role of funding sources

Support for Dr. Griffiths was provided in part by NIDA Grant R01DA003889. Support for Dr. Dunn was provided in part by NIDA Grant R01DA035246.

Declaration of Competing Interest

The authors have no conflicts of interest to report.

Acknowledgment

The authors would like to thank Dr. Jack E. Henningfield for his comments on early drafts of the manuscript.

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12.05.2023

Kratom Science Update:
Evidence-Based Facts
Annual Update – December 2023

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Preface

Kratom science increased almost exponentially over the past decade with more than 450 new scientific publications addressing kratom safety, benefits, and abuse potential since early 2018, and more than 100 since the 2022 Kratom Science Update was developed.

The science provides evidence to guide consumer safety leading to kratom regulations now passed into law in eleven states, with many more states considering such laws. As discussed below, these new scientific findings also led the United States Department of Health and Human Services (US DHHS) to reverse its position on Controlled Substances Act (CSA) scheduling and, in August 2018, to rescind its earlier scheduling recommendation to the Drug Enforcement Administration (DEA).

More recently in 2021, the World Health Organization Expert Committee on Drug Dependence (WHO ECDD), thoroughly reviewed all the evidence for international scheduling including written and oral statements from scientists around the world. The WHO ECDD concluded there was insufficient evidence to recommend scheduling kratom, meaning the available data did not show public health risks of kratom warranting international restrictions.

- **What is clearly needed is balanced regulation to ensure that kratom products purchased by consumers are pure and unadulterated, meeting the same types of standards applied to other food products, and even bottled water.** Steps toward such standards were taken in states that passed their own versions of kratom consumer protection act laws. Ultimately, the Food and Drug Administration (FDA) needs to develop national performance standards for kratom as it does for other products. Such standards will help ensure access to kratom products that are appropriately marketed and are without contaminants and adulterants that might pose safety risks.

- **This is the first annual update of the October 2022 Kratom Science Update.** Many new studies related to kratom safety, the effects of its naturally occurring constituents, and the benefits reported by kratom consumers provide the basis for this 2023 update. The recent findings may also support implementation of regulatory efforts that were passed into law in many states. Updates are provided at the end of each subsection.

Specific regulatory and policy approaches supported by new evidence.

The Food and Drug Administration (FDA) request to schedule kratom (specifically, mitragynine and 7-hydroxymitragynine) in Schedule I of the Controlled Substances Act (CSA), was reversed by the lead Department of Health and Human Services (DHHS) official charged with Controlled Substances Act recommendations to the DEA, namely, the Assistant Secretary of Health, Dr. Brett Giroir. Dr. Giroir requested a review of the evidence pertaining to kratom scheduling and safety, and concluded in August 2018, that the evidence did not support Schedule I placement. See a summary of the findings of the review in Dr. Giroir's formal 2018 scheduling rescission letter to the DEA at:

https://static1.squarespace.com/static/54d50ceee4b05797b34869cf/t/60145eab6df59e7e36a7cfc1/1611947693695/dhillon-8.16.2018-response-letter-from-ash-radm-giroir.pdf.

As discussed in the scheduling rescission letter, the evidence in the FDA's 8-Factor Analysis was not sufficient to support scheduling. To the contrary, surveys and other data (see annotated bibliography) were sufficient to support the conclusion that many thousands of kratom consumers use kratom as a path away from opioids and would be at risk of returning to opioids if kratom was banned from licit markets. This led to the public health concern that "[Scheduling would lead to] … kratom users switching to highly lethal opioids… risking thousands of deaths…". Dr. Giroir raised other concerns including that placing kratom and mitragynine in Schedule I would discourage pregnant women and others from talking to their health care providers about their kratom use, discourage research, and more.

The conclusions of the Assistant Secretary of Health were consistent with those of the National Institute on Drug Abuse (NIDA), which states on its Kratom Facts webpage that "While there are no uses for kratom approved by the FDA, people report using kratom to manage drug withdrawal symptoms and cravings (especially related to opioid use), pain, fatigue and mental health problems.

NIDA supports and conducts research to evaluate potential medicinal uses for kratom and related chemical compounds." NIDA substantially expanded its kratom research support since 2017 and this research portfolio is rapidly expanding the evidence base for kratom regulation and possibly new kratom derived medicines in the years to come.

Similarly, at the international level, the large evidence base was reviewed in 2021 by the World Health Organization Expert Committee on Drug Dependence (WHO ECDD) to determine if kratom met criteria for being placed on a critical review pathway for international scheduling. The WHO ECDD came to essentially the same conclusions as the Assistant Secretary of Health and NIDA. After conducting a thorough pre-review and a public hearing with input from leading international experts, the ECDD reported to the United Nations Office of Drug Control that there was insufficient evidence to recommend kratom for critical review but that it should be kept under surveillance. It also stated, "(k)ratom is used for self-medication for a variety of disorders but there is limited evidence of abuse liability in humans…"

Addressing overdose risks, the ECDD noted:

"Although mitragynine has been analytically confirmed in a number of deaths, almost all involve use of other substances, so the degree to which kratom use has been a contributory factor to fatalities is unclear."

Both the Assistant Secretary, and the WHO ECDD also acknowledge beneficial uses to abstain from opioids. Without labeling this as "therapeutic use", the Assistant Secretary clearly acknowledges such use and the public health risks of banning kratom. This nuanced recognition of benefits of use, along with risks of banning access to use by Assistant Secretary Giroir, was absent in the 2017 and early 2018 position of FDA, but was since recognized by the Secretary of Health Becerra in a letter to Senator Mike Lee and Congressman Mark Pocan on March 16, 2022.[1]

[1] *https://assets.website-files.com/61e07df312afed13238eb7f1/6261ab303b46bb88f21b6d1a_HHS%20Kratom%20Response.pdf*

Regulatory update:

Uniform national regulation of kratom is vital because kratom product vendors vary widely in their product stewardship, quality control, and packaging and marketing related information and claims. Product testing revealed that some products were adulterated with dangerous substances and/or with high concentrations of mitragynine and other kratom alkaloids. Since October 2022, 4 additional states (West Virginia, Virginia, Florida, and Texas) enacted various laws to ensure continuation of legal kratom sales in their states, but with regulatory oversight laws generally referred to as the Kratom Consumer Protection Act (KCPA). This brings the total to 11 states that now have consumer protections in place. Several other states are considering similar regulatory frameworks.

Although the KCPA provisions and standards vary somewhat across states, most include the following requirements for all products sold in the state: (a) registration of products and vendors, (b) labeling that discloses that products contain kratom as well as the name and contact information of the distributing vendors, (c) products must be tested to show they are not contaminated with heavy metals and toxins, that are consistent with the standards for food products such as oatmeal, tea leaves and coffee, or adulterated with drugs or boosted levels of mitragynine and 7-hydroxymitragynine (7OHMG); (d) health claims are not permitted; and (e) the minimum age of purchase is either 18 or 21 years, depending on the choice of the state.

Several more states are in various stages of consideration and action on similar proposed KCPA laws. Federal KCPA regulatory oversight has bipartisan support in the U.S. Congress with the filing of S. 3039, sponsored by Senator Mike Lee (R-UT) and Senator Cory Booker (D-NJ), and H.R. 5905 sponsored by Congressman Mark Pocan (D-WI) and Congressman Jack Bergman (R-MI). The Federal Kratom Consumer Protection Act will provide a regulatory framework for kratom much like the Congress did in 1994 when they passed the Dietary Supplement Health and Education Act (DSHEA).

Specifically, among other provisions requiring the FDA to publish standards for the manufacturing and marketing of kratom products, the Federal KCPA will (1) require full transparency of all taxpayer-funded scientific research conducted on kratom; (2) require the FDA to add peer-reviewed published kratom research articles to their kratom website; and (3) require transcripts of public hearings where independent scientific testimony on kratom is provided. These requirements will allow the public to see a balanced perspective on current research on kratom related to its safety, benefits, and addiction liability profile.

What is the current state of kratom science and evidence?

Kratom was studied for decades, primarily in Southeast Asia (SEA), where kratom trees grow in abundance, but research escalated substantially in the US and globally with support by NIDA, SEA countries, and philanthropies. New science over the past 5-10 years includes investigations on kratom/mitragynine chemistry and medicinal development, neuropharmacology, brain imaging, preclinical and clinical studies, and surveys in the US and SEA. The rate of published kratom research continues to increase, along with presentations and symposia at a wide spectrum of national and international scientific meetings, such as the Society for Neuroscience, College on Problems of Drug Dependence, The International Conference on the Science of Botanicals, the International Association of Forensic Toxicologists and the Society of Forensic Toxicologists.

Kratom research effort update

The pace of kratom research and publication of peer-reviewed research remains rapid and continues to accelerate with expanded funding from government agencies in the US and internationally, as well as private sector efforts to support dietary supplement notifications and potential new drug applications derived from kratom. Since, October 2022, more than 450 new studies were published through October 2023, most supported by the National Institute on Drug Abuse (NIDA) and others from Southeast Asia. These studies provide the basis for the **"Science Updates"** noted at the end of each of the subsections in the November 2023 Kratom Science Update.

The following summary and conclusions are based on peer-reviewed scientific publications, many conducted by international leaders in kratom research and supported by NIDA. A bibliography with links to key articles is provided.

What is kratom?

Kratom is a tree in the coffee family. Not surprisingly, its diverse effects include coffee-like alerting, stimulating, and mood enhancing effects, which are quite distinct from the effects of morphine-type opioids. It also has some opioid-like effects that include pain relief, possible opioid withdrawal symptoms after chronic frequent use and unpleasant side effects like constipation, but without the potentially lethal respiratory depressing or highly addictive brain rewarding effects that are driving the opioid epidemic.

Is kratom an opioid?

While some naturally occurring substances in kratom act on opioid receptors**, kratom is not a prototypical opioid based on its chemical structure, botanical origins, or law** – nationally or internationally. Like many natural products it has diverse effects and mechanisms of action that contribute to these effects and the reasons people use kratom. Some kratom constituents bind to opioid receptors and relieve pain whereas others do not. Unlike opioids which sedate and can impair mental functioning, kratom is used by many people in place of coffee for its alerting, mental focusing, and occupational performance enhancing effects.

Animal and human studies, as well as neuropharmacology mechanisms of action studies, show that kratom does not carry the substantial opioid-like risks of deadly respiratory depression or powerfully addictive euphoria. A misunderstanding of one of kratom's self-reported beneficial uses, recognized by researchers and NIDA, providing relief of opioid withdrawal, is sometimes interpreted as evidence that it must be an opioid. In fact, the nonopioid adrenergic blocking drugs developed for treating high blood pressure, clonidine and lofexidine, were prescribed for decades to treat opioid withdrawal. FDA approved lofexidine (Lucemyra) for treating opioid withdrawal in 2018. Mitragynine, currently considered kratom's primary active compound, and other kratom constituents also produce adrenergic and other effects that might contribute to relief of withdrawal symptoms in people dependent on opioids, alcohol and stimulants.

Who uses kratom and why?

According to surveys in the US, most consumers are White adults, aged 35-55, with jobs and health care insurance, who report that their consumption is primarily for health and well-being. This includes consumption as an alternative to caffeinated products for alertness and increased focus, for the self-management of pain, and to improve mood. Many consumers state that kratom worked better for them, had fewer side-effects than the FDA-approved medicines they had taken, and/or that they preferred natural products. A smaller but important fraction of consumers are people who consider kratom as a "lifeline" or a path away from opioids. They use kratom to manage opioid withdrawal and reduce or eliminate opioid use.

Update. Continuing surveillance and studies monitoring individual kratom consumers confirm the 2022 Update findings summarized above. However, new research provides additional insights into the reasons for use and effects of use that are important to consider in regulatory efforts. In brief, users primarily report use for a broad range of perceived benefits including energy and productivity, as well as to self-manage withdrawal and addiction to stimulants, alcohol and other substances in addition to opioids that have been the primary focus of earlier studies. Studies from NIDA by Dr. Kirsten Smith and colleagues found that whereas the motivations of many kratom consumers to initiate use were to address specific health concerns, many continue to use for additional reasons such as increasing energy and productivity, relaxation, and mood.

Update: Kratom addiction related research findings.
The percentage of people who reported becoming "addicted to kratom" is small based on early studies and new research; however, there is currently no objective basis for estimating this percentage in the US. Estimates of the fraction of kratom consumers who report addiction are confounded by many factors including the following:

- Many people equate "withdrawal symptoms" with addiction or a substance use disorder and apparently are not aware that the American Psychiatric Association, FDA, NIDA, and the World Health Organization acknowledge that withdrawal can occur with many substances that are not ordinarily considered addicting, and that withdrawal alone is not the basis for a substance use disorder or "addiction" diagnosis, as discussed in reports from these organizations in the bibliography;

- Some people with prior addictions to opioids, stimulants, and alcohol used kratom to achieve abstinence from those substances and continue to use kratom, reporting addiction and difficulty discontinuing, in some cases in fear of returning to the far more deadly addictions that kratom helped them escape. Such use might be more appropriately considered "harm reduction" or therapeutic use, much as is maintenance of use of medicines such as antidepressants and approved addiction treatment medicines, such as buprenorphine and naltrexone, maintained long term to reduce the risk of relapse to the more deadly substances;

- Distinguishing between the mood enhancing effects of kratom reported as therapeutic or beneficial in surveys from recreational users, and reasons that are not necessarily to address a specific disorder are not always clear. This is also the case with respect to reported kratom use to "improve sexual health" and as part of exercise regimens;

- Finally, the factors that contribute to a diagnosis of a "substance use disorder" include personally and socially destructive aspects, and indicators of regular and compulsive use that are not necessarily a risk to personal health, violent crime, society, or the US drug overdose epidemic.

Withdrawal update. As discussed above, the potential for kratom to produce withdrawal and the relevance of withdrawal in kratom use, safety and addiction are widely misunderstood. To address this, a virtual kratom withdrawal think tank conference was convened in late 2022 and the results published in a leading peer-reviewed scientific journal specializing in addiction-related science – Drug and Alcohol Dependence Reports (see bibliography). The article is freely available by Open Access and provides details of the conference, conclusions and recommendations. Conclusions included: Animal studies confirm that chronic daily high mitragynine dosing can produce a level of dependence such that abrupt discontinuation is followed by withdrawal signs. However, the severity and duration of withdrawal are generally weaker and shorter than produced by morphine, and the signs are not identical to those produced by morphine-like opioids. Mitragynine alone and kratom tea preparations appeared effective in preventing and relieving opioid withdrawal with comparable efficacy to buprenorphine, an FDA-approved medication for treating opioid withdrawal.

Surveys and clinical studies confirm that kratom withdrawal can occur in some kratom consumers but is generally milder as compared to opioid and other drug withdrawal syndromes and generally self-manageable. Most kratom consumers do not experience withdrawal and although it is more likely in frequent multiple-times per day consumers, many such people do not report experiencing withdrawal upon discontinuation of kratom.

People with chronic opioid use histories report that kratom provides relief of opioid withdrawal. As was discussed, alleviation of opioid withdrawal may be due to some of kratom's effects that are not mediated by opioid receptors but also by effects that are similar to those of medicines used to treat high blood pressure including one that is FDA approved for treating opioid withdrawal – lofexidine. These results are consistent with human reports that kratom may be therapeutically useful for managing opioid withdrawal though FDA has not approved kratom for this or any other medical use. Clearly more research is needed to guide consumer use and potentially support applications to FDA for acceptance and approval for such use.

What led to increased kratom use in the United States?

Although kratom was taken as a natural traditional medicine in SEA for centuries, its use in the US was largely limited to Asian immigrants from the early 1970s through the 1990s. In the early 2000s, with a rising general interest in natural products as alternatives to conventional medicines and growing public access to information via the Internet, kratom use began to increase. Reasons for use appear generally similar from the US to SEA, as an alternative to coffee and tea for its alerting and mild stimulant effects, to improve mood and relieve pain, and to manage withdrawal and help people to reduce or discontinue use of opioids, alcohol and other addictive substances. Many survey respondents report that kratom was either more effective, carried fewer side effects of concern such as the sedating effects of opioid pain relievers, and/or that they prefer natural products over conventional medicine. Estimates of the present market vary widely. By 2014, there were an estimated 3-5 million kratom consumers, and marketing and SEA export estimates suggest that the present market is 15 million or more in the US. One federal survey estimated between 2-3 million kratom consumers, which might reflect its panel of respondents. The federal survey is designed to track substance abuse and might underrepresent middle aged and older people with lower rates of recreational substance use who might use kratom for other reasons.

Does kratom contain dangerous substances?

Like its botanical cousin coffee, kratom contains many substances referred to as alkaloids, which tend to be somewhat alkaline and bitter in flavor. More than 40 alkaloids are identified in kratom to date, with most having little or no known pharmacological effect, or occurring at such low levels as to be of little cause for harm or benefit. However, as is the case with other natural products, the naturally occurring mixture of substances likely contributes to the overall effects and natural variations in alkaloid composition may lead to varying pharmacological effects.

The main ingredient currently thought to account for most of the effects reported by kratom consumers is mitragynine, which does not have strong rewarding and addictive effects, nor respiratory depressant effects like opioids and conventional stimulants.

The second most widely recognized substance is 7OHMG that has stronger opioid effects but occurs at levels that are often nondetectable in fresh kratom leaves. However, 7OHMG is also a product of mitragynine metabolism and its gradual elevation in the blood following oral consumption may contribute to some of the effects of kratom that are desired by consumers.

In the absence of kratom regulation, some kratom makers boosted 7OHMG content far higher than that found in the native plant material, and this is a potential safety concern. States passing kratom consumer protection act laws ensure that legally marketed kratom does not contain boosted mitragynine or 7OHMG levels, contaminants, or other adulterants, thereby reducing public health risks. Additionally, dangerous substances like fentanyl and O-desmethyltramadol were found in adulterated kratom products. Regulation is needed from FDA to ensure that all US consumers are protected from risky exposure to contaminated or adulterated products.

Respiratory effects of kratom.

It is well understood that kratom's respiratory effects are not like those of morphine-like opioids; however, research since 2018 support the conclusion that kratom is not simply weaker than opioids with respect to respiratory depression. Specifically, mitragynine and other alkaloids in kratom act as partial agonists at opioid receptors, meaning that their maximal effects reach a ceiling beyond which higher doses produce little additional effect[ii]. This was demonstrated in several animal species (including cats, dogs, mice, and rats) with mitragynine doses increased to levels far beyond what is or can be consumed by even high intake chronic kratom consumers. The most recent study employed a sophisticated rodent model developed by FDA to compare a broad range of mitragynine doses to therapeutic and toxic oxycodone doses across blood gases and other parameters. Whereas oxycodone produced the signature dose-related plummeting blood oxygen levels and deaths, mitragynine produced no evidence of respiratory depression at any dose, and no life-threatening effects.

Can you overdose on kratom?

Kratom acts as a partial μ-opioid agonist that does not activate the β-arrestin 2 pathway involved in respiratory depression. Thus, kratom is much less likely to contribute to overdose deaths than heroin, fentanyl, oxycodone or other potent opioids. When mitragynine, the primary alkaloid in kratom, is identified in overdose cases, it is almost always found along with active central nervous system drugs with known lethal potential. Nevertheless, kratom consumers should not assume that kratom is without risk, especially when combined with other drugs.

The American Kratom Association recently published guidelines on factors to consider prior to naming kratom or mitragynine as cause of death. This was necessary because of the confusion following the FDA's announcement on February 6, 2018, that kratom was seriously harmful, with an opioid-like death risk. The FDA listed 44 deaths occurring in kratom consumers, but only 1 did not include other respiratory depressing substances or other conditions that likely contributed to the deaths. For example, further investigation determined that the one kratom only case was a motor vehicle fatality.

One of the most important guidelines to consider before naming kratom or mitragynine as cause of death is to ensure that comprehensive toxicology testing is performed. In many cases in which kratom is found at the scene or in the decedent's home, and in some cases with mitragynine detected in a blood sample, investigators concluded it must have been involved in the death. However, routine toxicology does not identify other drugs that are increasingly known to cause overdose death, such as novel fentanyl related and other psychoactive substances. Most laboratories do not include kratom or mitragynine in their routine testing because of the lack of reports of kratom overdoses and deaths, necessitating expensive analysis of autopsy specimens at reference laboratories. Thus, only kratom testing is ordered and the possible presence of other novel psychoactive substances is not identified due to the additional cost that cannot be borne by poorly resourced local and state forensic laboratories.

Centers for Disease Control scientists (2019) analyzed data from the State Unintentional Drug Overdose Reporting System (SUDORS) from 27 states over 18 months finding 152 or 0.56% of 27, 338 overdose deaths mentioning kratom in their postmortem toxicology reports.

However, kratom was listed as cause of death in 91 or 59.9% of these cases, despite only 7 or 4.6% having kratom only identified by toxicology. The authors stress that the presence of other drugs cannot be ruled out as contributing to cause of death. Eighty percent of decedents had a history of substance misuse. In cases when kratom was identified, 65.1% of fatalities also included fentanyl, 32.9% heroin, benzodiazepines 29.4%, prescription opioids 19.7% and cocaine 18.4%.

Gershman (2019) recently investigated 15 kratom-related deaths over 18 years and found 11 were multidrug deaths including opioids, and four were kratom only deaths and attributed by the coroners to kratom toxicity. Blood was available for comprehensive toxicology testing in 3 cases and additional toxic drugs were identified in all of these cases. The last case had no blood available for additional testing. Mitragynine concentrations ranged from 16 to 4800 ng/mL.

Some of the kratom associated death cases did not test for kratom but based the decision on crime scene investigation only, others had only a positive qualitative result confirming mitragynine exposures which varied widely from very low to very high levels.

Recently, Papsun (2023) reviewed more than 5400 blood mitragynine postmortem kratom cases tested at NMS Labs over the last five years. Kratom identification in postmortem cases was 1.67-1.88% over the last 5 years. Mean and median blood mitragynine concentrations were 360 and 120 ng/mL, respectively, with a range of 5.4–11,000 ng/mL Most cases identified the presence of other drugs including fentanyl in 62%, methamphetamine 19%, cocaine 10% and others in 2022 cases. The authors concluded that “blood mitragynine concentrations of >1000 ng/mL are more often associated with severe adverse events, up to and including death.” However, there was no conclusion as to what dose of kratom or mitragynine alone might be considered “lethal” or to carry a high risk of mortality. Although kratom related deaths are low when compared to its widespread use, consumers should be aware of the potential dangers of combining multiple prescribed and recreational drugs with kratom.

For many substances, including those that account for the more than 100,000 annual drug overdose deaths in the US in recent years, the lethal doses are reasonably well established in animals as the LD50 and typical pathological lethal effects, e.g., respiratory depression for opioids and sedatives, and cardiovascular events for stimulants, are well known. For other substances such as caffeine, and marijuana’s tetrahydrocannabinol (THC) and cannabidiol (CBD), deaths attributable to acute overdose are rare and the lethal dose is not established.

A recent study compared the respiratory effects of up to 400 mg/kg oral mitragynine to up to 150 mg/kg oral oxycodone in rats according to the study design published by FDA. Oxycodone significantly depressed oxygen saturation and sedated the animals with two deaths at the higher doses. Mitragynine did not significantly depress respiration or produce life-threatening effects, even at these exceedingly high doses. Thus, the LD50 was not able to be established for kratom.

Although the lethal dose in humans remains unknown, consumers should not take excessive kratom doses, should not consume kratom with other CNS-active drugs and should consider their personal medical conditions.

Regulation with balanced evidence-based warnings is in the interest of personal and public health to minimize the risks of kratom without falsely equating it with “narcotics” or “opioids” and thereby discouraging its contribution to harm reduction.

Is kratom fueling the opioid overdose epidemic?

The US has the world’s most sophisticated and multi-pronged substance abuse and product safety monitoring network including the National Survey on Drug Use and Health (NSDUH), Monitoring the Future (MTF), Treatment Episodes Data Set, and the DEA’s National Forensic Laboratory Information System (NFLIS).

It also includes the Drug Abuse Warning Network (DAWN), which reported a variety of potential signals of emerging substance threats while kratom use was rapidly increasing from the 1990s through pre-2012 reports, as well as the “new” DAWN system that reported on 2021 data in its 2022 report. **None of these systems, nor more than 20,000 comments to the DEA, suggested that kratom contributed to the opioid epidemic.** Kratom was also never listed in DEA’s annual National Drug Threat Assessment, though DEA routinely monitors kratom as a “chemical of concern.” Despite over 10 years of monitoring, DEA has not listed kratom or mitragynine or 7OHMG as a national drug threat.

Key scientific findings in the past five years:

- Multiple state of the art animal studies found that kratom has low abuse potential. For example, mitragynine produces weak rewarding effects as compared to morphine and heroin. The authors of this fact sheet urge that as a precaution, consumers should monitor their kratom consumption to reduce the risk of dependence development.
- Surveys indicate that some people can become dependent upon kratom; however, many of these people were using kratom to abstain from opioids and/or other substances. Disentangling prior substance use disorders from kratom use is not always clear. Most people who report kratom dependence or withdrawal state that it is more readily self-manageable than dependence and withdrawal from opioids and other drugs of abuse.
- Mitragynine treatment results in reduced opioid (e.g., morphine and heroin) drug seeking and self-administration in animal models assessing the potential effectiveness of drug use disorder reduction and cessation. These findings are consistent with human reports that kratom consumption reduces their opioid cravings and served as a path away from opioids.
- In animals made physically dependent on morphine, kratom pretreatment reduced morphine withdrawal symptoms in several models for evaluating efficacy in the treatment of withdrawal. This is consistent with human reports that kratom consumption helps to manage opioid withdrawal and reduce opioid craving.
- Similarly, an intracranial brain self-stimulation study suggested low rewarding effects of kratom alkaloids as compared to drugs of abuse.
- Several national internet surveys found that kratom use was helpful in managing opioid withdrawal, reducing opioid cravings, and achieving abstinence from opioids.
- None of the national surveys relied upon by the FDA, Centers for Disease Control (CDC), NIDA, and DEA to determine if a substance poses an abuse-related threat to public health suggested that kratom poses a known or imminent risk to public health. Consistent with this, the DEA never listed kratom as a threat to public health in its annual National Drug Threat Assessment reports.[iii]
- Safety studies in several animal species demonstrated that even at extraordinarily high doses, mitragynine and kratom produced little evidence of respiratory depression or life-threatening effects in contrast to opioids such as morphine and oxycodone which produced substantial dose related decreases in respiration.

2023 UPDATES:

How kratom works, that is, its mechanisms of action, is amongst the most active areas of research in the US and globally with new studies published in journals or presented at scientific meetings seemingly every month. Much of this progress is summarized in original research and review articles listed in the bibliography. A few key findings are included below.

- Whereas 7OHMG is often discussed as a potentially dangerous kratom constituent, studies indicate that it is present at very low and often not detectable levels in fresh kratom leaf material. Thus, it is better thought of as a mitragynine metabolite that gradually emerges in the bloodstream, likely contributing to some of the effects of kratom. Products that contain artificially high levels of 7OHMG (e.g., higher than 2% of the total alkaloid content) have likely been “spiked” with added 7OHMG. Regulatory oversight should prohibit such products. Whereas 2% is the performance standard used presently in some states, it would seem ideal for FDA to develop an evidence-based standard that might be somewhat higher or lower, and with guidance for accepted testing methods.
- Whereas mitragynine is the primary or sole alkaloid present in many marketed kratom products, it increasingly appears likely that a variety of other naturally occurring alkaloids contribute to the effects ascribed to kratom.
- Although kratom use persists in the US with several million consumers estimated, clear signals of substantial public health risk remain lacking, while the preponderance of evidence suggests that use of naturally derived kratom products is more typically associated with perceived health benefits.

GENERAL CONCLUSION:

The rapid progress in understanding the risks and benefits of kratom and its potential for therapeutic use and public health benefits over the past decade is a tribute to visionary funding from NIH and other organizations in the US and globally, as well as the dedication and care of hundreds of researchers worldwide.

There clearly seems to be adequate scientific evidence to not only justify why regulation is warranted but also to guide regulatory efforts. For any regulation of food, dietary ingredients and pharmaceuticals, regulations need to be considered as an evolutionary process guided by emerging scientific evidence including laboratory and clinical studies, as well as real world surveillance to understand trends, patterns and emerging risks and benefits to health and well-being. Thus, the conclusion that more research is warranted should not be used as an excuse to delay regulatory implementation but rather a vital part of relevant and effective regulatory implementation and evolution.

Disclosure:

Through Pinney Associates, Drs. Henningfield and Huestis provide scientific and regulatory advising on new medicines, dietary supplements, cannabinoids, and tobacco/nicotine products for FDA regulation. This paid work includes leading the development and drafting of this kratom science facts summary for the American Kratom Association. Dr. Grundmann is a member of the advisory board of the Kratom Vendors Association and received an honorarium from the American Kratom Foundation for participation in a scientific discussion forum about kratom dependence. Dr. Garcia-Romeu is a paid scientific advisor to ETHA Natural Botanicals and received a speaking honorarium from the American Kratom Foundation.

Annotated Bibliography

Expert evaluations of kratom policy and regulation and risks & public health United Nations Commission on Narcotic Drugs, WHO Expert Committee on Drug Dependence (2021).

Implementation of the international drug control treaties: changes in the scope of control of substances Summary of assessments, findings and recommendations of the 44th World Health Organization's (WHO) Expert Committee on Drug Dependence (ECDD), 11–15 October 2021: Kratom, mitragynine, 7-hydroxymitragynine.

https://www.unodc.org/documents/commissions/CND/CND_Sessions/CND_64Reconvened/ECN72021_CRP12_V2108992.pdf.

Note:

This is a summary of the WHO Expert Committee on Drug Dependence pre-review of kratom concluding that the evidence does not support initiation of a full review of kratom for international drug scheduling considering its effects, safety, abuse related- risks and public health factors.

Assistant Secretary of Health Dr. Brett P. Giroir, Admiral (August 16, 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.

This formal DHHS scheduling rescission letter summarizes review of the evidence for FDA's 2017 recommendation to schedule kratom and concluded that FDA did not provide sufficient evidence to support scheduling, and also failed to consider the adverse public health consequences of Scheduling and thereby banning legal consumer access to kratom.

Gershman K, Timm K, Frank M, Lampi L, Melamed J, Gerona R, Monte AA.

Deaths in Colorado Attributed to Kratom.

N Engl J Med. 2019 Jan 3;380(1):97-98.

An important investigation of autopsy reports listing kratom only as cause of death and the importance of comprehensive toxicology to identify the presence of other toxic drugs contributing to the death. The range of mitragynine concentrations in kratom-related deaths includes low levels far below those reported in controlled kratom administration studies.

Henningfield JE, Rodricks JV, Magnuson AM, Huestis MA.

Respiratory effects of oral mitragynine and oxycodone in a rodent model.

Psychopharmacology 2022 Dec;239(12):3793-3804.

An exceedingly high dose of 400 mg/kg oral mitragynine did not significantly depress respiration or produce life-threatening effects in rats. The LD50 was not established for kratom. However, 60 and 150 mg/kg oral oxycodone significantly depressed oxygen saturation and sedated the animals resulting in two deaths.

Olsen EO, O'Donnell J, Mattson CL, Schier JG, Wilson N.

Notes from the Field: Unintentional Drug Overdose Deaths with Kratom Detected - 27 States, July 2016-December 2017.

MMWR Morb Mortal Wkly Rep. 2019 Apr 12;68(14):326-327.

Center for Disease scientists analyzed data from the State Unintentional Drug Overdose Reporting System finding that although kratom identifications in postmortem autopsy cases only represented 0.56% of overdoses, it was reported as cause of death (kratom-involved) in 59.9% of cases. Potent opioids were also identified in these kratom cases, 65.1% fentanyl, 32.9% heroin and 19.7% prescription opioids

Papsun D, Schroeder W, Brower J, Logan B.

Forensic Implications of Kratom: Kratom Toxicity, Correlation with Mitragynine Concentrations, and Polypharmacy.

Curr Addict Rep 10, 272–281 (2023).

After reviewing mitragynine concentrations in more than 5400 blood postmortem kratom cases over the last five years, mitragynine was identified in 1.67-1.88% cases, with a wide range of concentrations (5.4–11,000 ng/mL). Most cases identified the presence of other drugs including fentanyl in 62%, methamphetamine 19%, cocaine 10% and others. The authors concluded that "blood mitragynine concentrations of >1000 ng/mL are more often associated with severe adverse events, up to and including death." Although kratom related deaths are low when compared to its widespread use, consumers should be aware of the potential dangers of combining multiple prescribed and recreational drugs with kratom.

Prozialeck, W., Avery, B., Boyer, E., Grundmann, O., Henningfield, J., Krueger A., McMahon, L., McCurdy, C., Swogger, M., Veltri, C., and Singh, D. (2019).

Kratom Policy: The challenge of balancing therapeutic potential with public safety.

International Journal of Drug Policy, 70:70–77.

Note:

Leading kratom researchers discuss policy implications of state-of-the-art knowledge related to kratom's effects, uses, risks, and real-world public health benefits and risks.

Grundmann O, Garcia-Romeu A, McCurdy CR, Sharma A, Smith KE, Swogger MT, Weiss ST (2023).

Not all kratom is equal: The important distinction between native leaf and extract products.

Addiction. 2023 Oct 9. doi: 10.1111/add.16366. Epub ahead of print. PMID: 37814405.

This article addresses the fact that some manufactured extracts have high concentrations of mitragynine and other substances and do not include labeling that describes the concentrations, total content, or recommended serving sizes and the need for national regulation of such.

Swogger MT, Smith KE, Garcia-Romeu A, Grundmann O, Veltri CA, Henningfield J, Busch LY (2022)

Understanding kratom use: a guide for healthcare providers.

Front Pharmacol 13:801855.

Although there are no FDA approved uses for kratom, which is the case for most dietary supplements, this expert opinion article provides practical information for consideration by health care professionals whose patients are consuming kratom.

Henningfield JE, Grundmann O, Babin JK, Fant RV, Wang DW, Cone EJ (2019)

Risk of death associated with kratom use compared to opioids.

Prev Med. 128:105851.

This article compared estimates from FDA of deaths associated with kratom consumption in comparison with deaths associated with nonmedical opioid use concluding that the risk of death associated with kratom use is at least 1,000 times less than for opioids.

Henningfield JE, Wang DW, Huestis MA (2022)

Kratom abuse potential 2021: an updated eight factor analysis.

Front Pharmacol 12:775073.

This article is a published version of an assessment of kratom abuse potential according to the 8-factor analysis required for permanent scheduling by the Controlled Substances Act. It concludes that on the basis of all factors, including decades of surveillance in the US, and decades more globally, kratom does not warrant scheduling and, in fact, that scheduling kratom would carry adverse public health consequences. This is consistent with the position of the WHO Expert Committee on Drug Dependence and the DHHS review led by Assistant Secretary Giroir.

Kratom reasons for use surveys

Whereas there are several surveys that provide estimates of how many people use kratom with estimates ranging from about 2 to more than 15 million, those surveys provide no information about why people use kratom, or the consequence of their kratom use (See Henningfield JE, Grundmann O, Garcia-Romeu A, Swogger MT. We Need Better Estimates of Kratom Use Prevalence. Am J Prev Med. 2022;62(1):132-133).

- The following surveys are focused on why people use kratom and provide insights as to the risks and benefits of kratom consumption.
- Specifically, these surveys show that although there is some recreational use of kratom, most people use for reasons related to health and well-being including as approaches to self-manage opioid and other drug withdrawal and to reduce and discontinue opioid and other addictive drug use.

Coe MA, Pillitteri JL, Sembower MA, Gerlach KK, Henningfield JE.

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(PMID: 35389321)

(Feldman et al., 2023; Smith et al., 2023

Oliver Grundmann 1 2, Charles A Veltri 2, Diana Morcos 2, David Knightes 3rd 2, Kirsten E Smith 3, Darshan Singh 4, Ornella Corazza 5, Eduardo Cinosi 5 6, Giovanni Martinotti 5 7, Zach Walsh 8, Marc T Swogger 9Smith et al., 2023; and a few in 2022

Kratom abuse potential and assessment for treatment of dependence and withdrawal

Note: The following studies found that mitragynine is characterized by low abuse potential in classic models as compared to morphine and heroin. The Hemby et al. and Yue et al. studies also showed that mitragynine administration led to decreases in morphine and heroin self-administration, which is consistent with survey reports that kratom helps relieve opioid craving and discontinuation of opioid use. Hassan et al. is one of several recent studies demonstrating that (a) mitragynine withdrawal is less severe than morphine withdrawal, and (b) mitragynine provides effective relief of opioid withdrawal, which is a common use of kratom that is acknowledged by NIDA and claimed by many kratom consumers in the surveys of why people use kratom.

Wilson et al. demonstrates that a kratom tea like preparation was of relatively low risk and effective at reducing opioid withdrawal symptoms. It is also important to note that animal studies of single substances such as mitragynine cannot be interpreted as showing that kratom has no abuse or dependence potential – it does carry some abuse and dependence risk in humans as documented in the surveys, but these appear relatively low for most consumers as compared to opioids. These studies are also contrary to FDA's 2017 claims that mitragynine carried narcotic opioid like risks.

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At kratom doses far higher than those consumed by humans, respiratory depressant effects are substantially lower than opioids. This does not mean that kratom does not carry risks but rather that its overall risks appear much lower than those associated with opioids. Balanced regulation could help consumers minimize the risks of kratom use by banning medical claims, providing accurate labeling and warning labels, as is being implemented in states that passed kratom consumer protection act laws.

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Note:
this is a living and evolving repository of factual scientific information that may be useful to policy makers, regulators, consumers, and other researchers. It is an example of what would ideally be provided by NIH and FDA.



i Neither the US Food Drug and Cosmetic Act, nor the US CSA or the international drug control treaties define “therapeutic use” as being approved as drugs by FDA or the equivalent regulatory agencies in other countries. However that has become the de facto standard of the FDA, which therefore ignores self-reported beneficial use by dietary supplement consumers and states that they have no recognized therapeutic use, and thus, widespread use of kratom to stay off opioids was ignored as a benefit. The authors of this science update and the American Kratom Association agree that specific health claims should not be made by kratom marketers without supporting evidence, but neither should policy makers simply dismiss the benefits of kratom and the risks of removing licit kratom by millions of kratom consumers.

ii Contributing to the misunderstanding that kratom carries opioid-like risks of overdose and addiction is a misunderstanding of potency and strength. Strength refers to the maximum effect that a substance can produce, whereas potency refers to how much of the substance it takes to produce a given effect. Thus, alcohol is strong and actually results in approximately 2,000 overdose deaths annually in the US, however, it is relatively low in potency among central nervous system active substances and requires the equivalent rapid consumption of a quart or more of high percentage (proof) alcohol to produce death, though for young people it may take much less as suggested by fraternity hazing related deaths every year in the US. At the other extreme is fentanyl which can produce extremely strong euphoriant effects in humans, reinforcing effects in animals, and lethal respiratory depressant effects at very low doses of just a few mg. Kratom’s primary active alkaloid, mitragynine is both relatively weak and low in potency with respect to respiration as compared to morphine. In fact, it is a partial agonist with respect to respiratory depression, meaning that its maximal effects at all tested doses do not produce lethal respiratory depression. The mitragynine metabolite 7-hydroxymitragynine is more potent than morphine on the guinea pig ileum muscle twitching test but that test is not necessarily relevant to lethality, and 7-hydroxymitragynine, also appears to be a partial agonist with respect to its respiratory effects.

iii DEA has included kratom on its list of “drugs and chemicals of concern”, for the past decade, first listing it following reports of overdose deaths in Sweden among consumers of a kratom product that was later concluded to have been adulterated with lethal doses of O-desmethyltramadol. However, as mentioned in this science update, DEA never listed kratom as a threat to public health in its annual National Drug Threat Assessment reports. In fact, it has not listed kratom in its annual National Forensic Laboratory Reports since 2016, apparently, because the reports have remained low and not at the “threshold for reporting.” Whether and when DEA will remove kratom or kratom alkaloids from its drugs and chemicals of concern list is not clear since researchers agree that kratom use and epidemiology should continue to be monitored, but unfortunately, this listing implies a higher level of concern than has been expressed by any other DEA action since it withdrew its scheduling proposal in 2016.

frontiers | Frontiers in Public Health

TYPE Mini Review
PUBLISHED 30 May 2024
DOI 10.3389/fpubh.2024.1416689

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OPEN ACCESS

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RECEIVED 12 April 2024
ACCEPTED 17 May 2024
PUBLISHED 30 May 2024

CITATION
Green M, Vadiei N, Veltri CA, Grundmann O and Evoy KE (2024) Kratom as a potential substance use disorder harm reduction agent.
Front. Public Health 12:1416689.
doi: 10.3389/fpubh.2024.1416689

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Kratom as a potential substance use disorder harm reduction agent

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Substance use disorders contribute to considerable U.S. morbidity and mortality. While effective pharmacotherapy options are available to treat opioid and alcohol use disorders, for a variety of reasons, many patients lack access to treatment or may be reluctant to seek care due to concerns such as perceived stigma or a current lack of desire to completely curtail their substance use. Furthermore, treatment options are limited for patients with stimulant or polysubstance use disorders. Thus, there is considerable need to expand the substance use disorder harm reduction armamentarium. Kratom (*Mitragyna speciosa* Korth.) is an herbal substance that can produce both opioid and stimulant-like effects, and its use in the US is growing. Though there are concerns regarding adverse effects, dependence risk, and limited regulation of its manufacturing and sale, the pharmacology of kratom and early preclinical studies suggest a potential role as a harm reduction agent for various substance use disorders, and it has historically been used in Southeast Asia for such purposes. The goal of this review is to describe kratom's history of use, pharmacology, and early pre-clinical and observational research regarding its therapeutic potential in opioid use disorder, as well as alcohol, stimulant, and polysubstance use disorders, while also highlighting current concerns around its use, existing gaps in the literature, and directions for future research.

KEYWORDS

kratom, *Mitragyna speciosa*, mitragynine, substance use disorder, alcohol use disorder, opioid use disorder, stimulant use disorder, harm reduction

1 Introduction

Kratom leaves represent a natural herbal substance that can produce both opioid and stimulant-like effects (1). Increased United States (U.S.) kratom use has caused concern among clinicians regarding its risks, potential for misuse and dependence, and lacking regulation. However, a limited but growing body of literature purports kratom's potential as a harm reduction agent to mitigate overdose risk for individuals with substance use disorders (SUD). This review describes evidence for kratom's potential efficacy in helping to manage various SUDs and the need for additional research.

1.1 History and patterns of use

The tree used to produce kratom products, *Mitragyna speciosa* (Korth.,) Havil., is native to Malaysia, Indonesia, Borneo, Philippines, and New Guinea (2). Its leaves have historically been consumed by indigenous communities as a mild stimulant, an ethnomedicine to treat pain, diarrhea, fever, or mental health conditions, and as an alternative to opioids or stimulants, helping to reduce use or withdrawal symptoms (3).

U.S. kratom consumption has increased over the past two decades, with lifetime and past-year use estimates ranging from 0.5–6.1% and 0.7–4.1% of the population, respectively, with a higher prevalence among SUD populations (past-year and lifetime use: 10 and 21%, respectively) (4–9). Kratom user demographics skew toward employed White males in their late teens to middle-age adults, with at least some college education (6, 10, 11).

Consumption patterns are variable, with a wide range in frequency, dose, and administration route. Small doses tend to be consumed for mild stimulant effects or to mitigate health-related symptoms, while larger doses produce more pronounced psychoactive effects (12). This variable consumption, coupled with numerous preparations available and limited regulatory oversight, highlight both potential benefits and risks. Two areas of benefit reported by kratom users are to alleviate withdrawal symptoms and reduce opioid, stimulant, or alcohol cravings, emphasizing kratom's potential as a harm reduction agent for various SUDs (13–16). Furthering this potential is the notion that kratom confers less overdose or dependence risk and does not produce as potent of euphoric effects as traditional opioids (17, 18).

However, several concerns regarding kratom use warrant additional research before it can be recommended in clinical practice. Though generally tolerated at low and slowly titrated doses, kratom can produce adverse effects in line with their mild opioid and stimulant effects, including nausea, somnolence, confusion, agitation, hypertension, and tachycardia that are generally mild (10, 19). Case reports describe more serious, rare adverse events, including seizures, hepatotoxicity, cardiac arrest, or overdose (13, 20, 21). It is also well-established that routine kratom use can lead to dependence and withdrawal upon abrupt discontinuation (1). Controlled clinical studies are lacking to adequately assess adverse effect prevalence, and safety information is largely based on self-reported, observational data, spontaneous reporting systems, or case reports of rare events. U.S. poison control center data indicate increasing reported incidents in recent years, likely due to greater availability and use. Among 1,807 kratom-related reports from 2011 to 2017, 65% occurred between 2016 and 2017, and a subsequent analysis identified a 90% increase from 2017 to 2018 (22, 23). In a separate study, 7.4% of reported incidents were deemed major or life-threatening (19). There is also concern that, given the lack of regulatory oversight of kratom manufacturing and sales, available products are highly variable in content, may be mislabeled regarding the concentration of active compounds, and may contain toxic metals or potentially infectious microbes (24).

1.2 Current regulatory state

The US Food and Drug Administration (FDA) classifies kratom products as new dietary ingredients, meaning there is currently insufficient evidence to support medical use or provide assurance that it does not pose significant health risks when consumed (25). Kratom is not scheduled under the U.S. Controlled Substances Act and federal regulations and oversight are minimal. Regulations are instead at the state level through "Kratom Consumer Protection Acts" which focus on labeling, adulteration, and age restrictions. This has led to the medley of kratom products in the U.S. market, ranging from dried leaf preparations more representative of the plant's natural chemistry to highly concentrated extracts enriched with active alkaloids. This accentuates the need for better control of kratom-derived products and manufacturing practices and controlled clinical trials to establish safety, efficacy, and optimal dosing.

1.3 Pharmacology and medicinal chemistry

Kratom products contain many phytochemicals, including at least 40 distinct alkaloids (3). Mitragynine is the most abundant alkaloid (66%) and most associated with kratom's pharmacological and clinical effects, acting as a partial agonist at the μ-opioid receptor, a weak competitive antagonist at the κ- and δ-opioid receptors, and a partial agonist at several serotonin and α-adrenergic receptors (26, 27). Importantly, mitragynine does not recruit β-arrestin-2, thereby reducing its respiratory depression risk (28). Speciociliatine, speciogynine, paynantheine, and corynantheidine are structural isomers of mitragynine, making up 20% of the alkaloid content. These four alkaloids show greater affinity toward one of the three signaling pathways (nociceptive, serotonergic, or α-adrenergic) and weaker interactions with targets in the other two. Minor alkaloids (7-hydroxymitragynine, mitraciliatine, and isopaynantheine) also show opioid receptor-mediated antinociception. Notably, 7-hydroxymitragynine, both an oxidative degradation product of drying kratom leaves and a metabolite generated in the body, possesses 10-fold higher binding affinity than mitragynine (29). While mitragynine is only 25% as potent as morphine *in vivo*, 7-hydroxymitragynine possesses 10x times greater potency than morphine at opioid receptors. This complex mixture of active compounds and influence on signaling pathways points to kratom as a possible treatment for mitigating symptoms and withdrawal of various SUDs (30).

2 Opioid use disorder

In 2021, opioid overdoses caused more than 80,000 U.S. deaths (31). Many others develop communicable diseases from high-risk opioid administration. Despite availability of several FDA-approved pharmacologic agents for opioid use disorder (OUD, i.e., methadone, buprenorphine, and naltrexone), many patients lack access or do not seek assistance from healthcare providers. There remains a need to expand the harm reduction armamentarium.

Several pre-clinical studies confirmed antinociceptive effects of mitragynine and 7-hydroxymitragynine. Antinociceptive effects were determined in the hot plate test in rats using mitragynine or morphine (32). While morphine reduced operant response at low doses, mitragynine required higher doses. There is also evidence that at least some of its effects are not primarily mediated through opioid receptors (33, 34). Morphine antinociceptive effects were fully antagonized by

administration of the opioid antagonist naltrexone, whereas mitragynine could not be fully antagonized. However, another rat study determined that mitragynine withdrawal can be precipitated with the opioid receptor antagonist naloxone and rimonabant, a cannabinoid receptor-1 antagonist (35). Mitragynine and buprenorphine, a partial μ-opioid receptor agonist commonly used as a medication for OUD, both ameliorated morphine-induced withdrawal. This indicates that mitragynine can prevent morphine-precipitated withdrawal, potentially through actions at the opioid and cannabinoid receptors (35). Effects on the adrenergic receptors may also contribute, though this has yet to be evaluated in controlled studies. Less pronounced and shorter lasting precipitated mitragynine withdrawal indicates lower dependence and misuse potential versus classic opioids.

To further support lower misuse liability, a conditioned place preference (CPP) model compared continued self-administration of mitragynine to morphine. Whereas rats provided with morphine increased their intake over the duration of the study, animals provided mitragynine maintained their intake and reduced morphine intake if both were co-administered (36). In addition, precipitated withdrawal using pentylenetetrazole did not produce the anticipated anxiogenic effect for mitragynine that was observed for morphine (37, 38).

An important differentiator between pre-clinical animal studies and human studies is the administration route, which is primarily intravenous or intraperitoneal for animals, thus resulting in higher absorption and decreased alkaloid metabolism (39). Oral mitragynine bioavailability is low (30%) with subsequent metabolism to 7-hydroxymitragynine, mitragynine pseudoindoxyl, and inactive metabolites (40–42). The contribution of 7-hydroxymitragynine and mitragynine pseudoindoxyl to kratom's opioid-like effects remains unknown.

Whole kratom leaf products have not been well studied for OUD. One mouse study evaluated effects of lyophilized kratom tea containing 7.4 mg/g mitragynine, 3.5 mg/g speciociliatine, and 2.5 mg/g paynantheine (43). The tea, in oral doses of 100 and 1,000 mg/kg, produced antinociception lasting up to 60 min. Kratom tea had less pronounced, shorter-lasting respiratory depression than the morphine control, and did not present with CPP (an indicator of dependence) as morphine did. Furthermore, kratom tea administration following a four- or seven-day morphine induction significantly reduced several withdrawal behaviors, indicating that kratom tea can reduce opioid withdrawal symptoms.

One Malaysian kratom user study evaluated people with concomitant opioid and stimulant use disorders (44). Most reported using kratom to treat heroin withdrawal (77%), as a heroin replacement (59%), and to reduce heroin intake (58%), independent of how long they used kratom. Only 15% of 332 users reported consuming kratom for euphoric effects. This study supports traditional kratom use as an OUD harm reduction strategy versus using to obtain euphoric effects, though it's important to note potential sample selection bias and generalizability concerns given the study design.

3 Alcohol use disorder

Alcohol use disorder (AUD) is the most common SUD in the U.S., (45) yet has very few evidence-based treatments, each with only modest efficacy in reducing alcohol consumption and improving morbidity/mortality. A 2017 online survey conducted with support from the American Kratom Association studied 3,024 current and past kratom users (46). Of those currently using kratom ($N = 2,867$), 2.2% ($N = 64$) acknowledged mainly using kratom to reduce or quit alcohol consumption, whereas 18.0% ($N = 517$) included it among multiple reasons for using kratom.

Preclinical investigations have explored kratom efficacy in therapeutic AUD management. Animal studies suggest that kratom's delta opioid receptor (DOR) antagonistic activity may attenuate alcohol intake (47). Orally administered 50–100 mg/kg *Mitragyna speciosa* leaf extract doses reduced elevated dopamine levels in ethanol-dependent mice. Furthermore, kratom alkaloids exhibit activity at mu, delta, and kappa opioid receptors with negligible β-arrestin-2 recruitment, earning the G protein-biased partial agonist designation (48). Preclinical studies demonstrated that G protein-biased partial agonists targeting DOR reduced mouse alcohol intake, while increased β-arrestin-2 recruitment was linked to enhanced alcohol consumption (48). Another study revealed that 7-hydroxymitragynine modulates alcohol intake at the DOR in mice; however, its elevated potency at the mu opioid receptor (MOR) raises dependency, misuse, and adverse event concerns (48). Most recently, a preclinical study utilized kratom alkaloids with a lower MOR potency than 7-hydroxymitragynine (49). Wildtype mice displayed dose-dependent voluntary alcohol consumption reductions, while DOR knockout mice did not exhibit the same pattern. This corroborates previous research indicating involvement of G-protein biased agonism of DOR in AUD management.

Mitragynine also attenuated ethanol withdrawal symptoms in rats. Intragastric administration of 100, 300, and 500 mg/kg doses decreased immobility duration by 25% versus normal saline, without significant effect on spontaneous motor activity (50). 10 h after ethanol cessation, withdrawal-related behaviors remained suppressed. Another preclinical investigation determined that an alkaloid extract derived from *M. speciosa* reduced ethanol withdrawal symptom severity without inducing spontaneous motor activity (50).

These studies provide insights regarding kratom's potential application for AUD treatment; nevertheless, further research is required to comprehensively evaluate its efficacy, adverse effects, and optimal human dosing, as regular use may pose more risks than existing treatment options.

4 Stimulant use disorder

Global concern over stimulant misuse, specifically cocaine and amphetamines, is gradually increasing. Chronic stimulant misuse is linked to elevated mortality and adverse physical and psychological outcomes, including stroke, respiratory disease, bloodborne viruses, and neurocognitive alterations (51). Presently, available interventions to address stimulant dependence offer minimal to no resolution. There are no pharmacotherapies approved for the management of dependence and withdrawal.

Several reports have indicated Kratom's potential benefit for methamphetamine, cocaine, and polysubstance use disorder self-treatment. Among 332 Malaysian rehabilitation patients who concurrently used heroin and methamphetamine, 71% reported using kratom to reduce methamphetamine intake, while 59% used

it as a methamphetamine substitute (44). More than half (59%) viewed kratom as a safer alternative to methamphetamine and heroin.

Preclinical investigations also provided insights. Kratom alkaloid extract (80 mg/kg, containing 3.8 mg mitragynine) administration significantly reversed methamphetamine CPP and suppressed nucleus accumbens (NAc) gamma I and hippocampus delta signals in mice, where addictive behavior regulation predominantly occurs (52). Local field potential (LFP) signals (which record summated excitatory and inhibitory potentials from NAc and hippocampus neurons) were observed in mice administered methamphetamine, to explore neural signaling associated with drug craving and reward-seeking behavior. LFP and locomotor activity patterns were subsequently monitored following treatment with either kratom alkaloid extract, bupropion, or control. Kratom alkaloid extract significantly ameliorated methamphetamine CPP versus other treatments. Mice conditioned with methamphetamine exhibited a significant increase in the NAc gamma I power spectra; however, 80 mg/kg kratom alkaloid extract administration significantly reversed this effect. In the hippocampus, both 40 mg/kg and 80 mg/kg kratom alkaloid extracts suppressed methamphetamine-induced delta power increases. Elevated gamma I frequency activity range is associated with dopamine release and addiction, while heightened delta rhythms may reflect stress response regulation (52). Interestingly, a positive correlation was present between delta power and locomotor activity patterns, further suggesting kratom may attenuate stimulant craving behaviors. While additional preclinical studies depicting effects of chronic kratom administration are required, this information helps explain its potential efficacy in addressing physical and mental symptoms associated with stimulant dependence and withdrawal.

5 Polysubstance use disorders

Concurrent opioid and stimulant use is increasingly common and has been linked to increased overdose-related deaths (53, 54). Other substances, such as alcohol, benzodiazepines, and gabapentinoids are also commonly implicated in overdose-related deaths (53, 55). Prior research suggests stimulants are commonly mixed with depressants such as opioids/alcohol/benzodiazepines to offset their negative effects, namely withdrawal symptoms (53, 56). Unfortunately, fentanyl is also increasingly present in illicit stimulants, resulting in unintentional opioid overdoses (57).

For individuals with OUD, use of additional substances to offset their 'highs' or minimize withdrawal symptoms suggests need for harm reduction agents that can mitigate SUD symptoms without inducing opioid withdrawal or considerably increasing overdose risk. While there are highly effective OUD treatment options available, (58) they may not be viable for individuals looking to minimize withdrawal symptoms but unready to quit their preferred substance(s). Since methadone is a full opioid receptor agonist, use in conjunction with other opioids greatly increases overdose risk. Buprenorphine (a partial opioid agonist) and naltrexone (an opioid antagonist) induce opioid withdrawal if used concurrently with full opioid agonists (59, 60). Furthermore, for a variety of reasons, many patients lack access to effective OUD treatment or may be reluctant to seek care due to concerns such as perceived stigma surrounding SUD. Kratom could have potential utility for such patients.

In a latent class analysis of U.S. kratom users, utilizing data from the 2019 National Survey on Drug Use and Health (NSDUH), 412 adults reported using kratom in the past 12-months in addition to at least one of 11 additional substances (61). The three most distinct polysubstance user profiles identified were kratom users who also were using marijuana/alcohol/tobacco [63.3%], marijuana/alcohol/tobacco + psychedelics [19.3%], and marijuana/alcohol/tobacco + psychedelics/heroin/prescriptions [17.4%]. These data suggest most U.S. kratom users are polysubstance users. They may be using to offset negative effects of multiple substances or to manage common symptoms that drive individuals to use substances (e.g., comorbid mood disorders) (62). Given that data demonstrate kratom is mostly consumed by polysubstance users, and that it may have utility for multiple SUDs, further investigation into its utility as a harm reduction tool for polysubstance use disorders is warranted.

6 Discussion and conclusion

This review provides insight into kratom's pharmacological properties that indicate a possible role as a harm reduction agent for individuals with opioid, alcohol, stimulant, or polysubstance use disorders. However, much more research is needed before recommending kratom for clinical use. Future controlled clinical trials are necessary to investigate the impact of kratom in managing SUDs in human subjects, since current research is limited to heterogenous preclinical studies, case reports, and self-reported observational data (13). Furthermore, much work needs to be done to assess how to use kratom for such purposes, including studies to determine the ideal composition and optimal dose of the various chemical compounds found in kratom, the adverse effect profile and potential for drug interactions when used at these doses, and the impact of delivery route and what delivery systems would optimize its clinical effects while mitigating risks. There is also much work that needs to be done to standardize and regulate manufacturing and sale of available kratom products, to help ensure they are appropriately labeled to match the product content and are free of harmful contaminants. Despite concerns regarding misuse potential and safety, kratom use is on the rise; the development of novel kratom-derived compounds and improved regulatory standards would allow for further investigation into kratom's potential as a harm reduction agent for individuals with SUDs, a high-risk, vulnerable population with limited treatment options.

Author contributions

MG: Conceptualization, Writing – original draft, Writing – review & editing. NV: Conceptualization, Writing – original draft, Writing – review & editing. CV: Conceptualization, Writing – original draft, Writing – review & editing. OG: Conceptualization, Writing – original draft, Writing – review & editing. KE: Conceptualization, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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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)

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September 29, 2025

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List of Abbreviations

Abbreviation	Definition
B-arrestin-2	Beta (β)-arrestin-2
7-OH (7-OH-MG, 7-OH-MIT)	7-hydroxymitragynine
8-FA	8-Factor Analysis
CAMU	Commonly Accepted for Medical Use
CNS	Central nervous system
CPP	Conditioned place preference
CSA	Controlled Substances Act
CYP	Cytochrome P450 (i.e., 3A, 2D6, 3A4)
DAWN	Drug Abuse Warning Network
DEA	Drug Enforcement Agency
DHHS	Department of Health and Human Services
DOJ	Department of Justice
DOR	Delta (δ)-opioid receptor
ECDD	World Health Organization's Expert Committee on Drug Dependence
FAERS	Food and Drug Administration Adverse Event Reporting System
FDA	Food and Drug Administration
GI	Gastrointestinal
IC_{50}	Half-maximal inhibitory concentration
ICSS	Intracranial self-stimulation
IP	intraperitoneal
IQR	Interquartile range
IV	intravenous
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

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[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%).

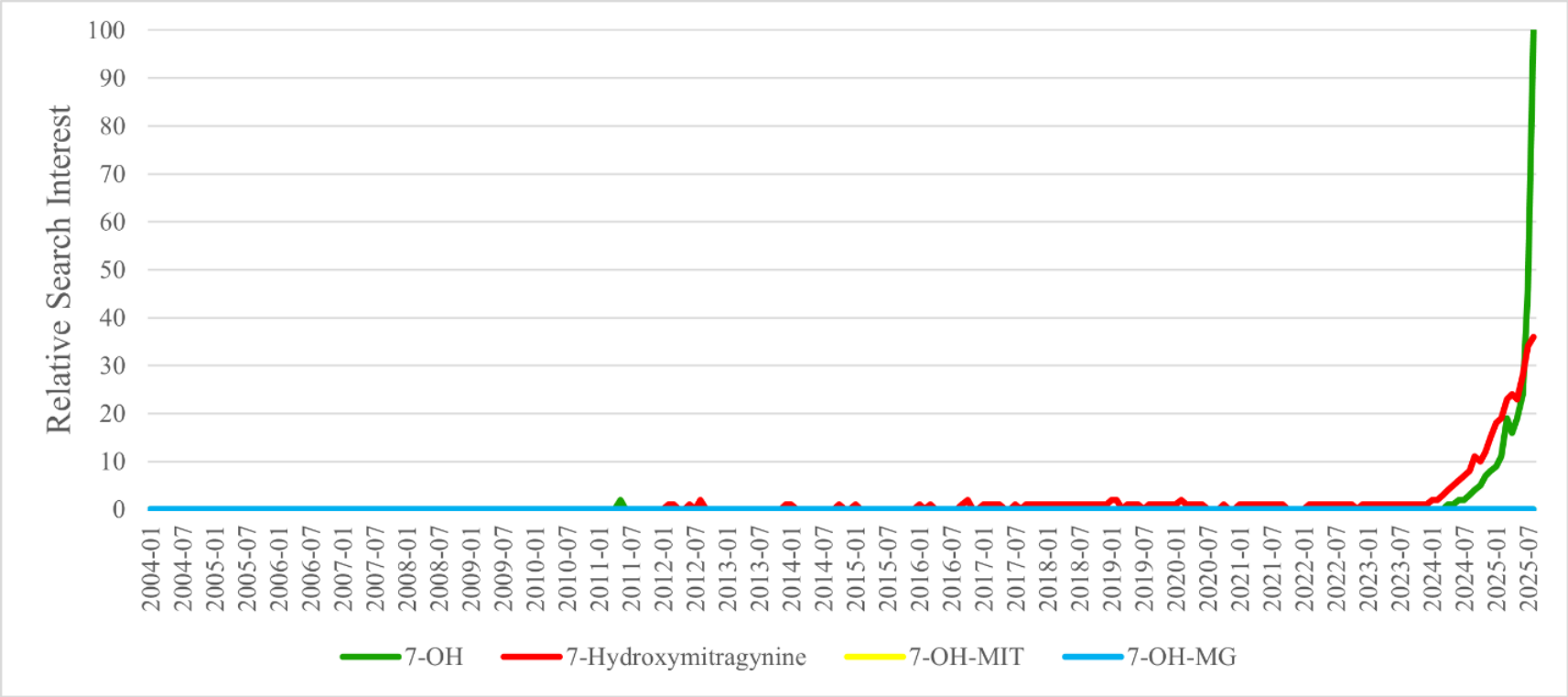
The following review of Reddit posts and comments on 7-OH is non-exhaustive. On Reddit, 7-OH was discussed in the Quitting Kratom subreddit (www.reddit.com/r/quittingkratom). Reddit posts and comments were much less descriptive than Erowid experience reports making inferences difficult. Nevertheless, 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.

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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	Experiment 1: 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 Experiment 2: 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

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FDA

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EXECUTIVE SUMMARY

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

7-OH is a naturally occurring substance in the kratom plant (*Mitragyna speciosa*), but only a minor constituent that comprises less than 2% of the total alkaloid content in natural kratom leaves. However, 7-OH demonstrates substantially greater mu-opioid receptor potency than kratom's primary alkaloid constituent mitragynine, as well as other classical opioids such as morphine. In vitro studies reveal 7-OH exhibits high binding affinity for mu-opioid receptors (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.

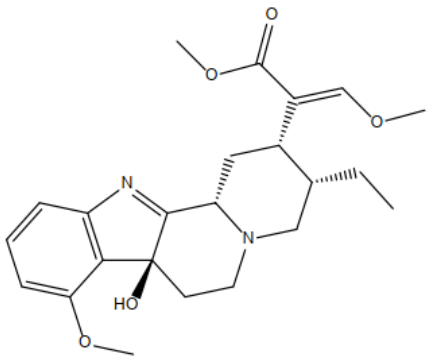


Figure 1. 7-Hydroxymitragynine Chemical Structure

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.

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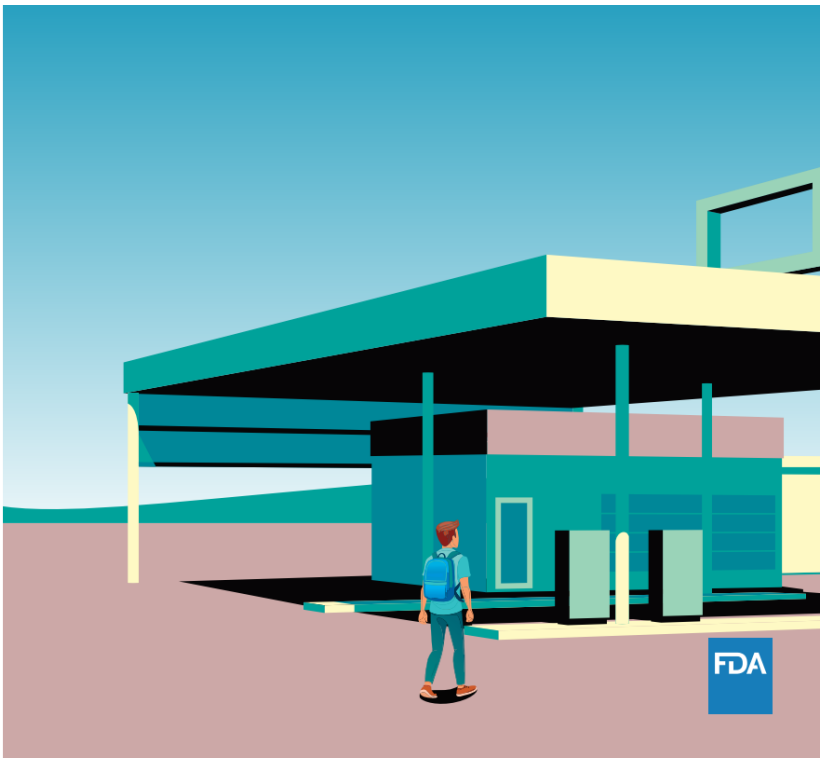
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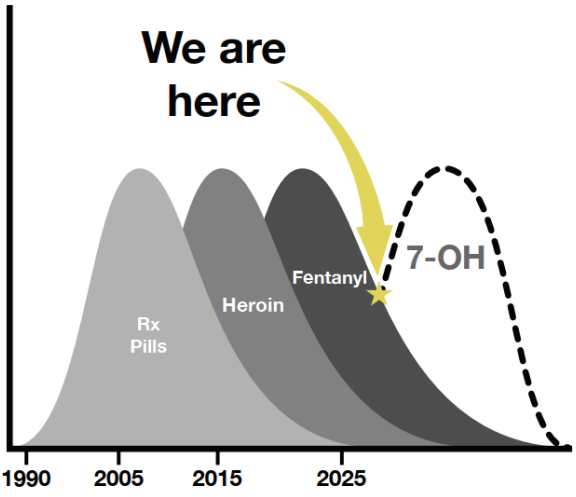
11.4 Appendix 4: FDA Slide Set: Preventing The Next Wave of the Opioid Epidemic: What You Need to Know About 7-OH

Preventing The Next Wave of the Opioid Epidemic:

What You Need to Know About 7-OH

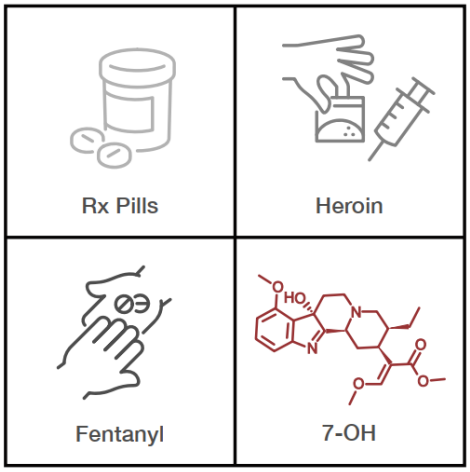


The Opioid Epidemic is Evolving with 7-OH. We Can and Must Act Now to Prevent a New Wave.



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

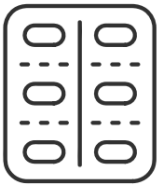


Note: These images are select illustrative examples and do not represent the full scope of 7-OH products on the market. Consumers should read packaging and labels carefully to determine whether a product contains 7-OH.

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

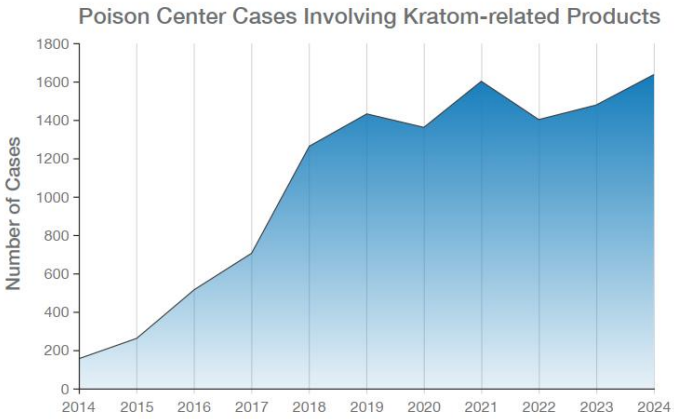
7-OH is 13x more potent than morphine.

High Risk

"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.





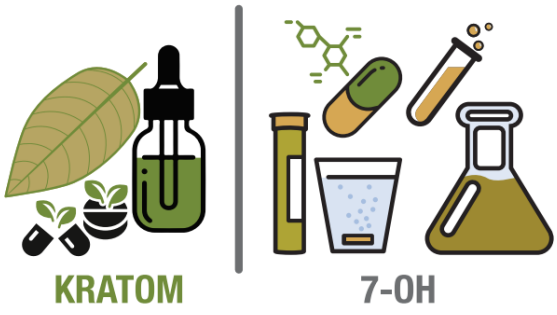
In 2025*, approximately 40% of 7-OH reports were among individuals abusing the drug.

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

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

From:	Matthew Lowe
To:	Board Coordination; David Wuest
Cc:	Walker Gallman
Subject:	Nevada Board of Pharmacy Workshop – April 15–16 | GKC Submission
Date:	Tuesday, April 7, 2026 4:28:28 AM
Attachments:	image001.png Nevada State Board of Pharmacy_6 April 2026_Signed.pdf

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Members of the Board,

On behalf of the Global Kratom Coalition, I am writing in advance of the Nevada State Board of Pharmacy's upcoming meeting and workshop scheduled for April 15–16, 2026, regarding proposed amendments to NAC 453 and NAC 639.

Please find attached our formal written submission in response to the Board's Notice of Proposed Regulation Workshop.

As outlined in our comments, we respectfully urge the Board to distinguish between natural kratom leaf and concentrated synthetic alkaloid products. The scientific record and recent federal actions support a targeted approach focused on higher-risk synthetic compounds, particularly concentrated 7-hydroxymitragynine, rather than a blanket classification of all kratom, including the natural leaf, as Schedule I.

We appreciate the opportunity to provide input and would welcome the opportunity to engage further during the workshop or answer any questions the Board may have.

Thank you for your time and consideration.

Regards,

GLOBAL KRATOM COALITION

Matthew Lowe
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April 6, 2026

Nevada State Board of Pharmacy
985 Damonte Ranch Pkwy, Ste 206
Reno, NV 89521

Members of the Board,

The Global Kratom Coalition (GKC) hereby responds to the Nevada Board of Pharmacy's March 26, 2026 request for Comment regarding the Notice of Proposed Regulation Workshop on amending Nevada Administrative Code 453, which would classify all kratom, without distinguishing between the natural leaf and novel concentrated synthetic alkaloid products, as a Schedule I controlled substance.

Natural kratom leaf is a botanical substance from Southeast Asia with centuries of safe, traditional use, and at least 50 years of use in the US. Today, 23.9 million people in the U.S. report consuming natural leaf kratom for its functional benefits. Kratom comes from a tropical evergreen tree, Mitragyna speciosa, native to Southeast Asia, where for centuries, it has been used for its functional benefits, primarily energy and focus. The tree belongs to the same family of plants as coffee and in its natural form is not intoxicating nor does it cause impairment. Natural kratom leaf is traditionally consumed in various forms, such as dried powders, fresh leaves, or brewed teas/decoctions.

Furthermore, the CDC recently released a new report addressing increases in Kratom-Related Reports to Poison Centers. Specifically, the report calls for surveillance to distinguish product types in order to properly assess risk. This is an implicit acknowledgment that lumping concentrated synthetic 7-hydroxymitragynine (7-OH) under the "kratom" label distorts the data and causes perverse outcomes for the 23 million natural kratom consumers across the country. Effectively, the data shows poison center calls were flat for six years — until concentrated synthetic 7-OH flooded the market in 2025.

This is an important nuance as news sources often cite a 1,200% rise in kratom-related poison center calls since 2015. However, they are missing the most important variable — what kind of product is actually driving the surge - the answer in this case is the introduction of concentrated synthetic 7-OH products.



Regarding the outright ban of natural kratom, as is being considered by the board, this issue has also already been adjudicated by the federal government. Specifically, in 2016, the DEA published notice of its intent to place kratom in Schedule I on an emergency basis. However, after failing to demonstrate that kratom was harmful and receiving numerous comments in opposition from Members of Congress and advocacy groups, DEA withdrew that notice. Part of the basis for rejecting the scheduling of kratom was that natural kratom did not meet the 8 factors required to demonstrate a substance is deserving of being a controlled substance.

As the science on natural kratom has advanced, it has become overwhelmingly clear consumers should not be prevented from accessing this natural botanical. There have been 18 clinical studies conducted on kratom in addition to hundreds of non-clinical studies. Of particular note is FDA's own clinical study which confirmed natural leaf kratom is well tolerated in humans, even at large doses. The FDA, the DEA and the WHO have all reviewed natural kratom and have concurred that natural kratom leaf does not meet any of the 8 factors required for scheduling a substance.

Recently, two new 8 factor analyses have been published on natural kratom and both reach the same conclusion—**natural kratom leaf does not meet the 8 factors for scheduling**. These 8 factor analyses were conducted by Dr. C. Michael White and separately by Dr. Jack Hennigfield, who are leading experts in this field.

We recognize that not all products marketed as 'kratom' are equal. Concentrated synthetic 7-OH products, which are up to 13 times more potent than morphine, pose serious risks and bear no resemblance to natural kratom leaf. That is why in July 2025, the FDA, HHS, and DEA jointly moved to schedule these synthetic concentrated products as Schedule I substances, while explicitly preserving access to natural kratom leaf. States like Kentucky and Florida have followed suit by also moving forward with the emergency scheduling of concentrated synthetic 7-OH while maintaining access to natural leaf kratom. In each instance they scheduled any product that contains a level of 7-OH above 400 parts per million by dried weight

With that in mind, Nevada should not seek to preempt federal regulators at the exact moment they are refining a targeted approach. Nevada should allow that process to



move forward and, if the state acts, it should do so in a way that aligns with the Federal government's focus on higher-risk products like concentrated synthetic 7-OH, not a blanket prohibition.

In light of the science and the actions of the Federal Government, **we urge you to remove mitragynine from scheduling consideration and instead focus on products that contain isolated synthetic alkaloids such as such as mitragynine pseudoindoxyl and 7-OH in concentrations above 400 ppm.**

Sincerely,

Matt Lowe

Matthew Lowe
Executive Director
Global Kratom Coalition

From: carder.run-5l@icloud.com
To: Board Coordination
Subject: Regarding Kratom usage and regulation
Date: Wednesday, April 15, 2026 9:19:56 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

"Please oppose scheduling kratom alkaloids as Schedule I. Natural kratom leaf has a demonstrated history of safe use and is not comparable to Schedule I substances. Regulate dangerous synthetic 7-OH products — not natural kratom."

I use natural kratom tablets from superspeciosa.com very effectively to reduce nerve pain for restless leg and peripheral neuropathy. I have absolutely no side effects or withdrawal effects. I use it regularly but not everyday and it doesn't cause me any problem nor does it impair my judgement or body in any way. There is no mental high in my use of the product and that is why I like to use it.

Sincerely

Michael Pieretti

From:	Michele Ross
To:	Board Coordination
Subject:	Oppose Scheduling mitragynine, 7-hydrxoxymitragynine, or mitragynine pseudoindoxyl
Date:	Tuesday, April 14, 2026 10:44:27 AM
Attachments:	Oppose Scheduling of Any Kratom Alkaloids - Nevada Board of Pharmacy - Dr. Michele Ross.pdf Who Uses 7-OH Research Results Infographic.pdf 7-OH 8-FA analysis & Federal Policymaker Brief - 7-HOPE Alliance.pdf

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Members of the Nevada Board of Pharmacy,

I am writing to submit the attached letter for your consideration rejecting any proposal to classify kratom or its alkaloids as Schedule I substances in Nevada.

I'm an addiction neuroscientist with over 20 years of experience studying chronic pain, substance use disorder, and alternative therapeutics. I serve as Chief Scientific Advisor to the 7-HOPE Alliance and have worked extensively with individuals using kratom as a harm-reduction tool.

My attached letter and resources outline the scientific, clinical, and public health concerns associated with scheduling kratom alkaloids, including mitragynine, 7-hydroxymitragynine (7-OH), and mitragynine pseudoindoxyl.

In brief, I would emphasize three key points for the Board's consideration:

First, prohibition does not eliminate demand. Evidence from other jurisdictions shows that restricting access to kratom predictably shifts some individuals toward illicit opioids, increasing overdose risk and public health burden.

Second, kratom is widely used as a harm-reduction tool. Many individuals rely on it to manage chronic pain or to avoid relapse to heroin, fentanyl, or prescription opioids. Abrupt loss of access risks destabilizing these individuals.

Third, the pharmacology of kratom alkaloids differs meaningfully from classical opioids. These compounds exhibit partial agonism and functional bias at the mu-opioid receptor, which is associated with a lower risk profile relative to full agonists when used alone.

Given these considerations, I respectfully urge the Board to prioritize regulatory approaches over prohibition, including age restrictions, product standards, and labeling requirements. These measures better align with public health goals while preserving access for responsible adult consumers.

I appreciate your time and careful review of the attached materials. I am available to provide additional scientific input or answer any questions the Board may have.

Sincerely,
Dr. Michele Ross, PhD, MBA
Scientific Advisor, 7-HOPE Alliance
michele@7hopealliance.org
www.7hopealliance.org

OPPOSE Scheduling Kratom Alkaloids
April 16, 2026

Dear Nevada Board of Pharmacy,

My name is Dr. Michele Ross. I am an addiction neuroscientist who has studied chronic pain, substance use disorder, and alternative medicines including kratom for over two decades. I am the author of *Kratom Is Medicine* and serve as the Chief Scientific Advisor to the nonprofit 7-HOPE Alliance. I work with kratom consumers across the United States, including individuals using kratom to manage chronic pain or to maintain recovery from opioid use disorder.

I am writing to strongly oppose making kratom or any of its alkaloids, including mitragynine, 7-hydroxymitragynine (7-OH), or mitragynine pseudoindoxyl, a Schedule 1 controlled substance in Nevada.

Experience from other jurisdictions and the literature shows that banning kratom does not eliminate demand—it displaces it. Removing lawful access to kratom and its alkaloids predictably drives some users toward far more dangerous illicit opioids, increasing overdose risk, emergency department utilization, and strain on public health systems.

Forced withdrawal from kratom is not benign. Many consumers report using kratom specifically to avoid returning to heroin, fentanyl, or misused prescription opioids. A Schedule I ban would undermine harm-reduction efforts and risks reversing progress made in addressing opioid-related mortality.

Kratom is used by over 20 million people nationwide with over a decade of mainstream use in the United States. There are roughly **200,000 kratom users in Nevada and at least 10,000 consumers of 7-OH products**. The primary use of kratom is chronic pain relief and the secondary use is recovery from opioid use disorder (OUD).

The primary active alkaloids in kratom, mitragynine and 7-hydroxymitragynine (7-OH), are atypical opioids both in chemical structure and because they both function as **G protein-biased *partial* mu opioid agonists**, meaning they can never activate the opioid receptor to the same magnitude as a traditional opioid like fentanyl, morphine, or oxycodone that are *full* mu opioid agonists.

This translates to minimal euphoria and even dysphoria at higher doses of kratom or 7-OH, little activation of the beta-arrestin pathway that causes respiratory depression, and low likelihood of overdose and death when taken alone. Compare this to traditional opioid drugs with very real risk of addiction, overdose and death. Kratom and kratom alkaloid products are the *safer* option with established therapeutic use.

Kratom is not a recreational drug of abuse nor is it a drug that teens are using. The average age of both traditional kratom users and alkaloid products such as 7-OH is over 40. Teens are not using kratom products, as the Monitoring The Future (MTF) survey data collected by the federal

government shows less than 1% of high school students have experimented with it. On the other hand, 11% of teens have used delta-8-THC vapes. The argument that kratom or 7-OH needs to be banned to protect the children simply isn't valid here, and instead warrants regulations such as age-gating to 21+ and child resistant packaging.

Finally, I urge the Board to follow science, not fear and to ignore the misleading attacks you may hear from certain kratom industry groups specifically on 7-OH. These individuals are being misinformed by industry members seeking market control, not consumer safety, and they do not represent the experiences of the many Nevadans who rely on kratom and 7-OH responsibly every day.

Instead of criminalizing consumers of kratom and kratom alkaloids including mitragynine, 7-OH, and mitragynine pseudoindoxyl. I urge the Board to support reasonable regulation, quality standards, and transparent labeling - approaches that protect consumers while preserving access to an important natural alternative.

Please follow the science, not fear, and do not schedule kratom or any of its alkaloids. I am available for any questions you may have.

Sincerely,

Dr. Michele Ross PhD, MBA
Scientific Advisor, 7-HOPE Alliance
michele@7hopealliance.org
www.7hopealliance.org

7-HOPE Alliance
7-Hydroxy Outreach For Public Education

THE REAL FACES OF 7-OH CONSUMERS

7-HOPE Alliance
7-Hydroxy Outreach For Public Education

~20 Million Americans Use Kratom and 7-OH

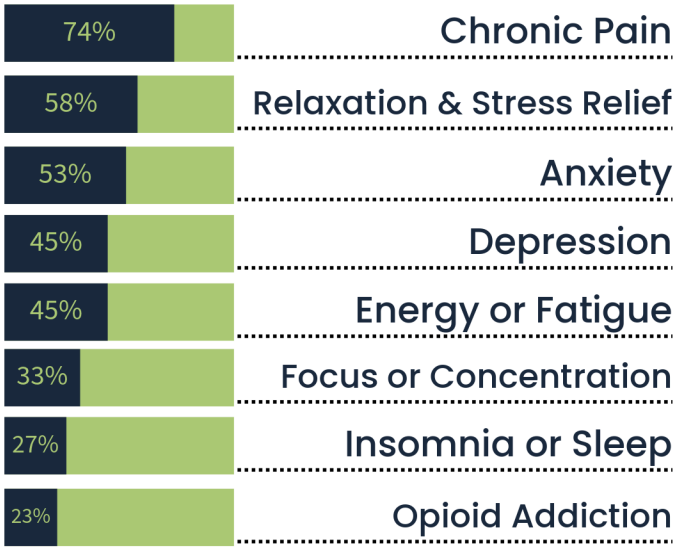
THE AVERAGE CONSUMER IS A WHITE 41 YEAR OLD, FULL-TIME EMPLOYED, COLLEGE EDUCATED DAD



7-OH CONSUMERS ARE PUBLIC SERVICE PROFESSIONALS

Healthcare	12%
Veterans	8%
Law Enforcement	2%

TOP 8 REASONS WHY CONSUMERS ARE USING 7-OH



7-OH WITHDRAWAL SYMPTOMS ARE MILD

1 Mild — 4 — 10 Severe

31% experienced no 7-OH withdrawal symptoms

BANS HARM 7-OH CONSUMERS



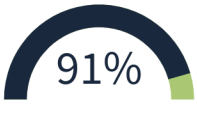
Would purchase 7-OH from illegal markets if banned

Would go back to using illicit drugs like heroin or fentanyl

Would consider suicide

97%

of consumers who use 7-OH for chronic pain find it effective



Think 7-OH should be available as a dietary supplement without a prescription



Think it would be harmful to society to make 7-OH illegal

Ross, M. N., et al. (2026). Impact of 7-OH on public health: National survey of 1,521 adult consumers [Manuscript in preparation]. Infused Partners.

Policymaker Brief: Do Not Make 7-OH a Schedule 1 Drug

Historically, under the Controlled Substances Act, substances have been placed into Schedule I only after a formal scientific and medical evaluation and recommendation from the U.S. Food and Drug Administration and the U.S. Department of Health and Human Services, followed by rulemaking by the Drug Enforcement Administration. This process reflects Congress's intent that federal scheduling decisions be grounded in a structured review of scientific evidence, abuse patterns, and public health risk.

At the state level, most jurisdictions historically align their controlled substance schedules with federal determinations under the Controlled Substances Act. Rather than acting as first movers, many states wait for federal scheduling decisions and then adopt conforming updates to their own controlled substance schedules through statutory or administrative harmonization. This approach promotes national consistency in drug control policy and ensures that scheduling decisions are informed by the full federal scientific and regulatory review process.

The federal scheduling framework also requires a formal Eight-Factor Analysis prior to placement of a substance into Schedule I. These factors are codified in 21 U.S.C. § 811(c) and form the scientific and evidentiary basis for determining whether a substance meets the statutory criteria for control.

The eight factors include:

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

This framework is intended to ensure that Schedule I placement - the most restrictive category under the Controlled Substances Act - is reserved for substances with high abuse potential, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use under medical supervision. As a result, scheduling decisions are expected to be supported by a comprehensive scientific record addressing each statutory factor.

7-HOPE Alliance has prepared an abbreviated Eight-Factor Analysis for the purpose of informing state and federal policymakers regarding the public health impact of kratom and 7-OH

product use and the evidentiary considerations relevant to placing 7-OH into Schedule I.

8-Factor Analysis of 7-hydroxymitragynine (7-OH)

Introduction

Kratom is a botanical product made from the leaves of the Southeast Asian tree *Mitragyna speciosa*, which has been used for generations for pain relief, energy, and to ease opioid withdrawal symptoms. The kratom plant contains more than 50 naturally occurring alkaloids, of which mitragynine is the most abundant.

7-hydroxymitragynine (7-OH) is one of these naturally occurring alkaloids and is present in small amounts in the plant. It is known to have pain relieving, anti-inflammatory, antioxidant, and even anti-cancer abilities, showing promise as a therapeutic for HER2+ breast cancer (Akbar et al., 2025; Arief et al., 2025; Kampmeyer et al., 2025). In addition, 7-OH is formed in the human body as a metabolite of mitragynine following kratom ingestion, meaning exposure to 7-OH occurs whenever kratom is consumed.

In recent years, some manufacturers have produced products containing standardized or concentrated amounts of 7-OH, which exist alongside traditional kratom leaf products and differ in formulation and dose. This analysis evaluates 7-OH in light of its biological origins, pharmacology, real-world use, and public health impact to determine whether it meets the statutory criteria for Schedule I placement under Federal or state law.

Factor 1: Actual or Relative Potential for Abuse

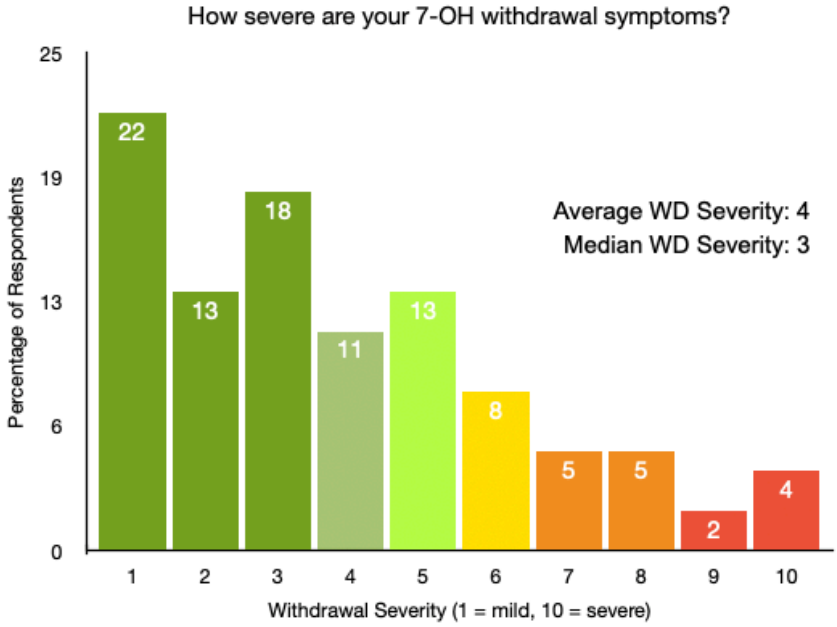
The available evidence does not support the conclusion that products containing isolated or concentrated 7-hydroxymitragynine (7-OH) have an abuse potential comparable to substances traditionally placed in Schedule I. Substances placed in Schedule I are typically associated with rapid escalation of use, strong reinforcement, compulsive binge patterns, widespread diversion, and significant public safety impacts. These features have not been demonstrated for 7-OH products at the population level.

Mechanistic and behavioral evidence supports a dose- and formulation-dependent risk profile rather than an inherently high abuse liability. Pharmacological studies show that 7-OH is a G protein-biased partial mu-opioid receptor agonist with low intrinsic efficacy, poor oral bioavailability of approximately 2.5%, restricted penetration into the brain, and constrained engagement of reward pathways associated with high-abuse opioids (Obeng et al., 2021; Chiang et al., 2025; Yusof et al., 2019).

Neurochemical and behavioral studies further indicate that 7-OH does not robustly activate mesolimbic dopamine signaling or enhance brain reward function in the manner observed with heroin or fentanyl, and at higher doses may impair reward signaling rather than reinforce it (Behnood-Rod et al., 2020; Gutridge et. al., 2020; Manus et al., 2025). These properties mechanistically limit the magnitude and reinforcement profile of 7-OH relative to full opioid agonists, even where opioid-like effects are present. 7-OH was even found to reduce binge alcohol drinking in mice (Gutridge et. al., 2020). This does not mean 7-OH is risk-free, but it does distinguish its abuse potential from that of high-efficacy opioids.

Human behavioral data are consistent with this interpretation. Available sales and consumer-use data indicate repeated, measured use patterns, most commonly for self-treatment of chronic pain (74%) and mental health symptoms, rather than rapid escalation, widespread diversion, or compulsive binge use that typically precipitates emergency scheduling actions (Ross, 2025; Ross, 2026).

In an October 2025 research survey of 1,521 adults who had used 7-OH products, most respondents did not consider themselves addicted, 31% reported no withdrawal symptoms at all, and reported withdrawal severity was predominantly mild to moderate rather than severe (Ross, 2026). No respondents reported overdose requiring medical attention despite widespread and repeated use. These patterns are more consistent with substances such as kratom, cannabis, or caffeine than with heroin or fentanyl, and they indicate the presence of manageable risk rather than the uncontrolled abuse profile implied by Schedule I placement.



(Ross, 2026)

Observational studies of kratom use, in which 7-OH exposure occurs both naturally and metabolically, show that problematic use is more strongly associated with frequency and cumulative exposure than with specific alkaloids or formulations (Garcia-Romeu et al., 2020; Rogers et al., 2024). Although these studies are not specific to isolated 7-OH products, they provide important context for evaluating abuse potential at the population level and caution against assuming Schedule I–level risk absent clear epidemiological signals.

Taken together, the current scientific and behavioral evidence indicates that any abuse potential associated with 7-OH products is context-specific and dose-dependent, not categorical or extreme. On this record, Factor (1) does not support placement of 7-hydroxymitragynine in Schedule I.

Factor 2: Scientific Evidence of its Pharmacological Effects

The pharmacological effects of 7-hydroxymitragynine (7-OH) are often oversimplified and misrepresented in policy discussions. 7-hydroxymitragynine (7-OH) interacts with the mu-opioid receptor, but its pharmacological effects differ in meaningful and well-documented ways from classical opioids typically placed in Schedule I. In multiple human receptor systems, 7-OH behaves as a partial agonist with lower intrinsic efficacy than full opioid agonists such as morphine or fentanyl, meaning it produces a ceiling on receptor activation even at higher receptor occupancy (Obeng et al., 2021).

In head-to-head functional assays using human mu-opioid receptors, the maximal effect of 7-OH is substantially lower than that of morphine, placing it closer to partial agonists like buprenorphine than to high-efficacy opioids (Obeng et al., 2021; Kruegel et al., 2016). In addition, 7-OH is an antagonist at the delta opioid receptor and kappa opioid receptors, reinforcing its utility to reduce alcohol and substance abuse, rather than promote it (Guttridge et. al., 2020).

Claims that 7-OH is unusually potent or dangerous relative to morphine are not supported by modern, human-relevant pharmacological evidence. Widely repeated assertions that 7-OH is “13x more potent than morphine,” including those disseminated by the U.S. Food and Drug Administration (FDA), rely on a 24-year-old guinea pig gut tissue assay (Takayama et al., 2002). Potency estimates derived from this *ex vivo* smooth-muscle model are highly context-specific and not considered translational measures of human opioid risk. Subsequent research using human mu-opioid receptor systems and contemporary functional assays consistently shows that 7-OH is a partial agonist with lower intrinsic efficacy and reduced maximal opioid signaling compared to morphine, producing ceiling effects that constrain pharmacological impact (Kruegel et al., 2016; Váradi et al., 2016; Obeng et al., 2021). Conflating assay-specific potency with clinical danger has therefore materially distorted public and regulatory discussions of 7-OH and does not reflect the totality of the pharmacological evidence.

Pharmacokinetic evidence further constrains the real-world implications of 7-OH's receptor activity. Orally administered 7-OH exhibits poor bioavailability due to extensive first-pass metabolism, with only a small fraction of the dose reaching systemic circulation (Chiang et al., 2025; Maxwell et al., 2021). Studies examining blood-brain barrier transport show that 7-OH has limited penetration into the central nervous system and restricted distribution within brain tissue compared with mitragynine and classical opioids, reducing its ability to engage central pathways involved in reward and respiratory control (Yusof et al., 2019).

Importantly, available toxicological data do not demonstrate a defined lethal dose for orally administered 7-hydroxymitragynine. In supplementary toxicology studies reported by Smith et al. (2019), oral administration of 7-hydroxymitragynine to mice did not produce a calculable LD50, meaning that a lethal dose could not be established under the conditions tested. This finding is notable because orally active opioids with high intrinsic toxicity typically exhibit a measurable LD50 in standard rodent models. While absence of an LD50 does not imply absence of risk, it indicates that acute oral lethality occurs at doses beyond those tested and contrasts with the toxicity profiles of classical opioids used as Schedule I comparators.

Consistent with these pharmacological constraints, there is no controlled human evidence demonstrating that oral 7-OH produces respiratory depression, overdose risk, or lethality comparable to morphine. Assertions of heightened respiratory danger derive primarily from intravenous rodent models or isolated human case reports involving extreme dosing and multiple co-ingested substances, which cannot be used to establish human-equivalent risk (Hill et al., 2022; Zuarth Gonzalez et al., 2025; Pullman et al., 2025). Taken together, the primary scientific evidence shows that while 7-OH has opioid activity and is not risk-free, its pharmacological profile does not support treating it as a high-efficacy opioid comparable to Schedule I substances.

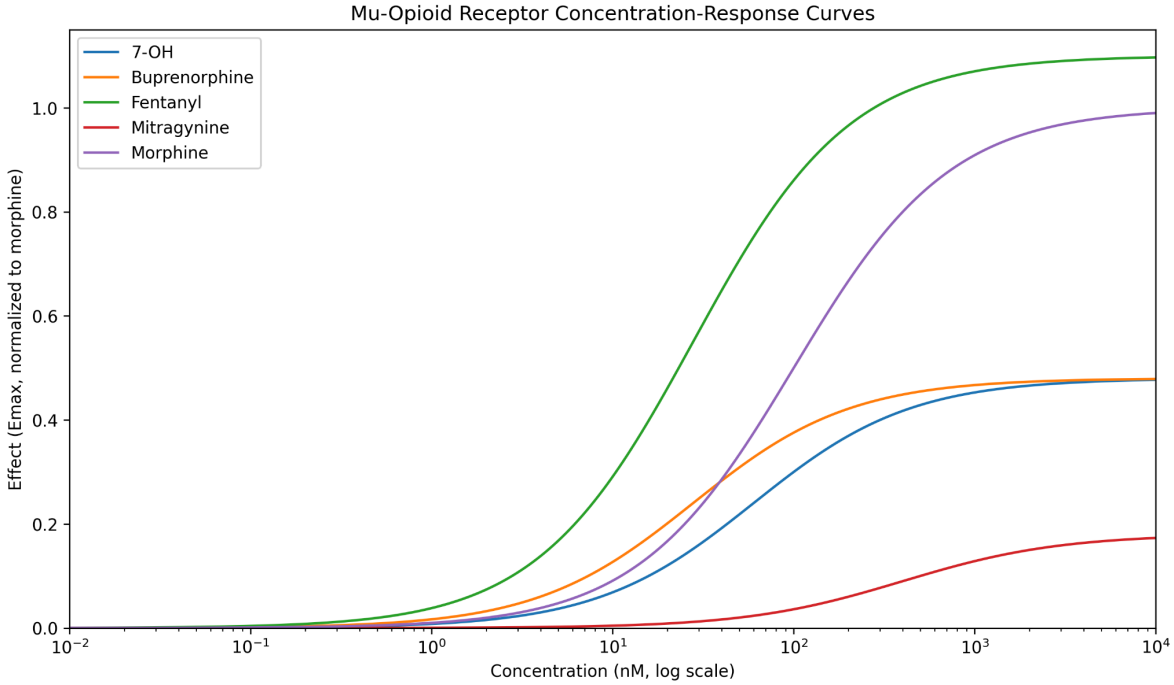
Factor 3: Current State of Scientific Knowledge

The current scientific understanding of 7-hydroxymitragynine (7-OH) is incomplete, evolving, and frequently mischaracterized in policy discussions. While there is a substantial preclinical literature describing receptor binding, signaling pathways, and pharmacokinetics, there is a relative absence of controlled human data establishing dose-response relationships, comparative addiction risk, or population-level public health outcomes specific to isolated or concentrated 7-OH products. As a result, claims that the risks of 7-OH are well established or settled are not supported by the structure of the existing evidence base.

A significant source of confusion has been the repeated propagation of incorrect or oversimplified pharmacological claims through secondary sources. Most notably, the assertion that 7-OH has "14–22 times greater" mu-opioid receptor binding affinity than morphine is false and reverses what primary receptor-binding data show. In the most relevant head-to-head human receptor studies, morphine binds the mu-opioid receptor far more tightly than 7-OH, with

Ki values differing by approximately one to two orders of magnitude in favor of morphine (Obeng et al., 2021; Váradi et al., 2016; Todd et al., 2020). This numerical inversion appears to have arisen from confusion between comparisons of 7-OH versus mitragynine and later misapplication of that ratio to morphine. Once repeated in reviews, case reports, and regulatory summaries, the error has taken on the appearance of scientific consensus despite being directly contradicted by primary data.

Beyond binding affinity, the scientific literature makes clear that receptor binding alone does not determine clinical risk. Functional efficacy, signaling bias, route of administration, metabolism, and central nervous system exposure all materially influence real-world effects. Primary functional assays show that 7-OH behaves as a partial mu-opioid receptor agonist with lower maximal efficacy than morphine or fentanyl in human receptor systems and functions more closely to buprenorphine, an opioid abuse treatment (Obeng et al., 2021; Kruegel et al., 2016). Pharmacokinetic studies further demonstrate poor oral bioavailability and restricted brain penetration, which limit the magnitude, speed, and duration of central opioid signaling (Yusof et al., 2019; Chiang et al., 2025). These constraints are well documented in the literature but are often omitted from policy summaries that focus narrowly on opioid receptor interaction.



(adapted from Varadi, 2021)

Importantly, there is no robust human clinical literature establishing that 7-OH produces rates of addiction, overdose, or respiratory depression comparable to Schedule I opioids. Existing human evidence consists primarily of isolated case reports involving extreme dosing, non-representative formulations, or multiple co-ingested substances, which cannot be

generalized to typical use of oral tablets or used to establish population-level risk (Reif et al., 2025; Pullman et al., 2025). Animal studies, particularly those using intravenous administration, provide valuable mechanistic insight but do not establish human-equivalent risk when divorced from route, exposure, and pharmacokinetic context (Hill et al., 2022; Zuarth Gonzalez et al., 2025).

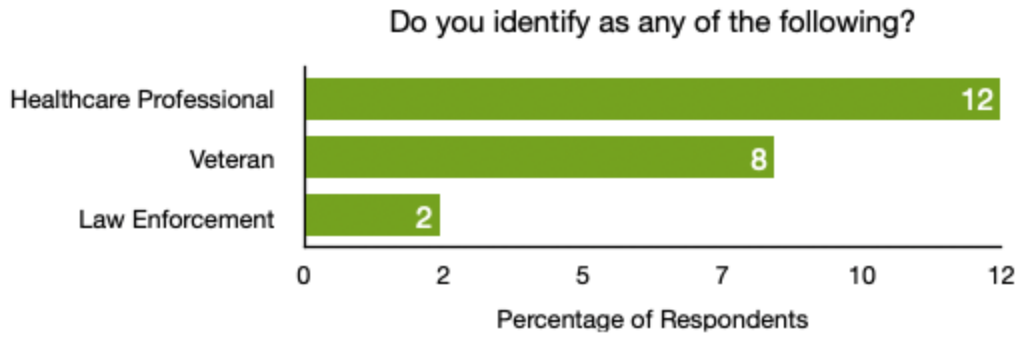
Taken together, the current state of scientific knowledge supports a cautious and proportionate regulatory approach rather than categorical conclusions. The evidence base does not justify treating 7-OH as a well-characterized, high-risk substance analogous to heroin or fentanyl. Instead, it reflects an emerging and still-developing literature with known uncertainties, documented misstatements, and clear gaps in human data. In this context, Schedule I placement would outpace the science rather than reflect it.

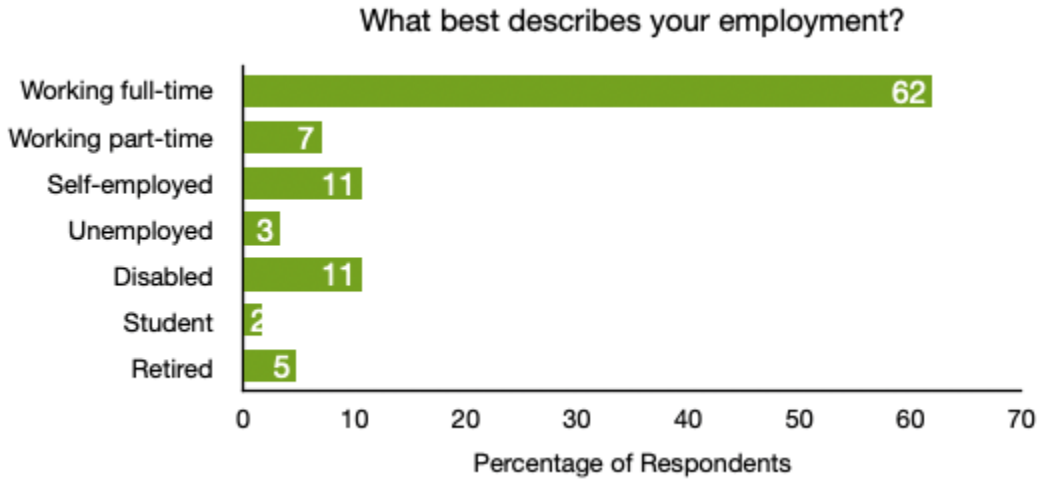
Factor 4: History and Current Pattern of Abuse

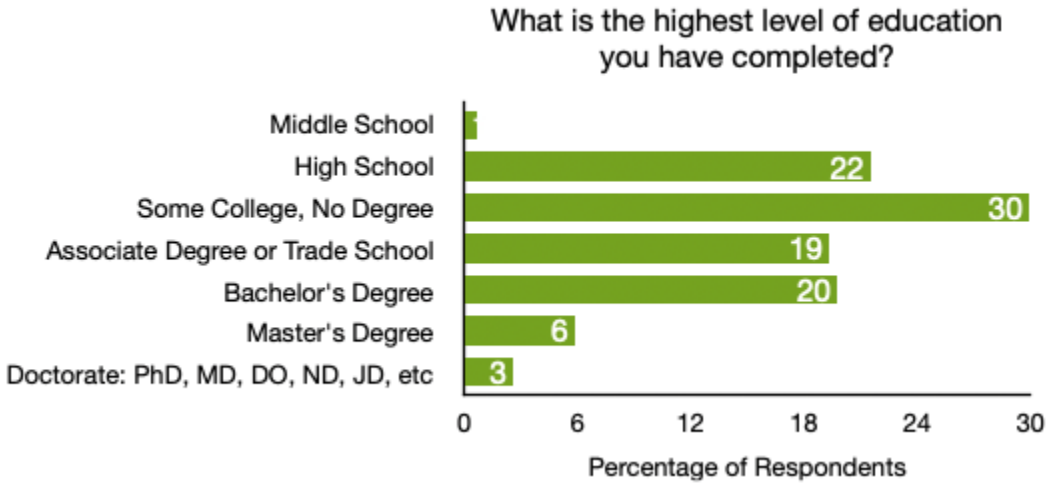
The history and current pattern of use associated with 7-hydroxymitragynine (7-OH) do not resemble the abuse trajectories of substances traditionally placed in Schedule I. Exposure to 7-OH has occurred for many years through kratom consumption, which is estimated to involve more than 20 million users nationwide. During this period of widespread and sustained exposure, there has been no corresponding emergence of a distinct pattern of severe abuse, rapid escalation, or population-level harm attributable specifically to 7-OH.

Since late 2023, higher-concentration 7-OH products have emerged, with an estimated one million consumers nationwide and over one billion servings sold. Despite this scale of exposure, there is no documented pattern of widespread diversion, escalating compulsive use, or community-level harm comparable to heroin, fentanyl, or other Schedule I substances. While isolated adverse events and dependency concerns warrant regulatory attention, the overall history and current pattern of use indicate managed, consumer-driven use rather than uncontrolled abuse, supporting targeted regulation rather than Schedule I classification.

The average consumer of 7-OH products is a 41-year-old employed, college-educated caucasian male with children, versus a young adult or unemployed person (Ross, 2026). This is similar to published research on kratom users (Garcia-Romeu et al., 2020). Surprisingly, 12% of 7-OH consumers surveyed were healthcare professionals, 8% were veterans, and 2% were current or retired law enforcement (Ross, 2026).

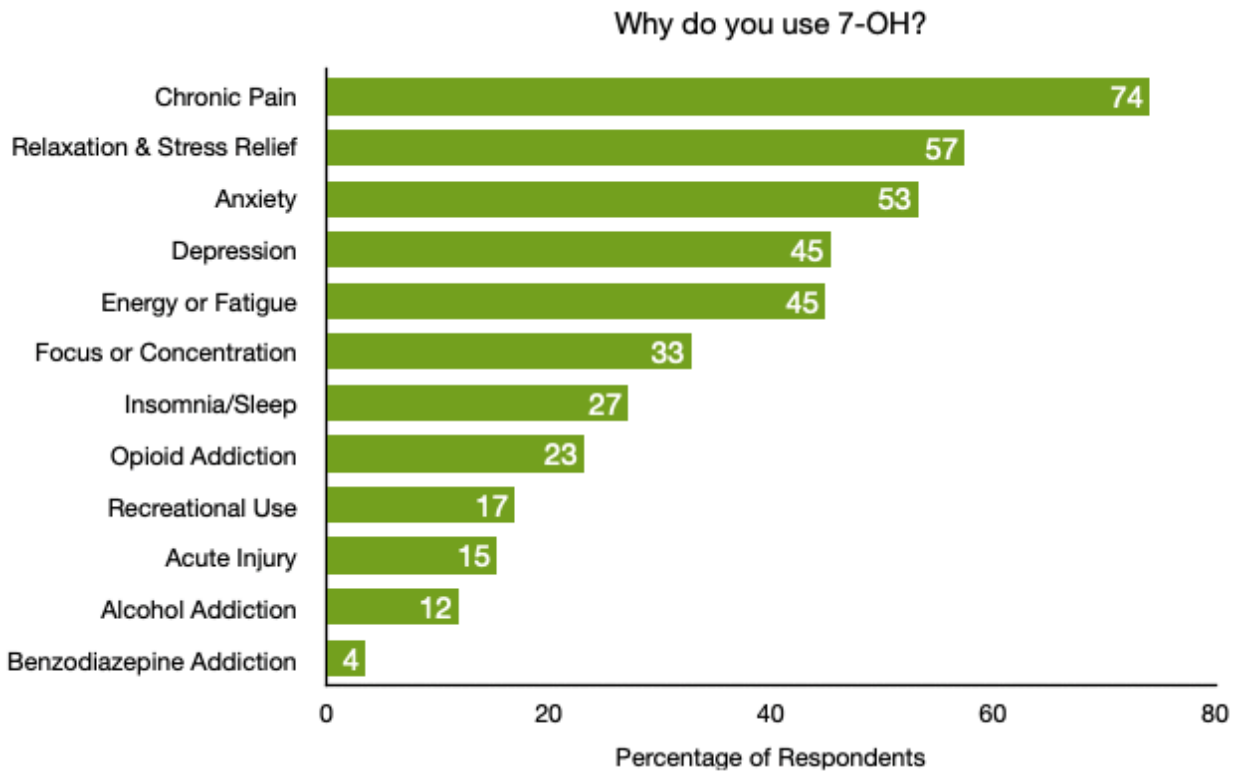

Do you identify as any of the following?
Healthcare Professional
Veteran
Law Enforcement
12
8
2
0
2
5
7
10
12
Percentage of Respondents


What best describes your employment?
Working full-time
Working part-time
Self-employed
Unemployed
Disabled
Student
Retired
62
7
11
3
11
2
5
0
10
20
30
40
50
60
70
Percentage of Respondents


What is the highest level of education you have completed?
Middle School
High School
Some College, No Degree
Associate Degree or Trade School
Bachelor's Degree
Master's Degree
Doctorate: PhD, MD, DO, ND, JD, etc
22
30
19
20
6
3
0
6
12
18
24
30
Percentage of Respondents

(Ross, 2026)

Available data indicate that these products are primarily used by adults for self-management of chronic pain (74%), mental health symptoms, or as substitutes for prescription or illicit opioids (23%), rather than for recreational intoxication (Ross, 2026). 97% of people using 7-OH for chronic pain found it very effective (Ross, 2026).



(Ross, 2026)

Reported use patterns are generally stable and intentional, not characterized by binge use, widespread diversion, or the types of compulsive behaviors that historically prompt emergency scheduling actions (Ross, 2026). This pattern is consistent with survey findings and observational research on kratom-related products more broadly (Garcia-Romeu et al., 2020; Rogers et al., 2024).

Public discussion has highlighted a small number of overdose deaths in Los Angeles County in which 7-OH was reported as present. In these cases, mitragynine was also detected, no quantitative concentrations were disclosed, and no evidence of specific 7-OH product use was documented. Each death involved multiple co-ingested substances independently associated with overdose risk such as alcohol, cocaine, and benzodiazepines. Under accepted forensic toxicology standards, these cases are consistent with polysubstance overdoses in which 7-OH detection may reflect ordinary kratom use and expected metabolism rather than a distinct

pattern of 7-OH product abuse (Hughes et al., 2024; Los Angeles County Department of Medical Examiner records).

Overall, the historical record shows sustained and widespread exposure to 7-OH without evidence of an emerging abuse epidemic or a shift toward high-risk use patterns. The available data support the conclusion that current patterns of use do not meet the threshold implied by Schedule I placement and are more appropriately addressed through targeted regulatory oversight rather than criminal prohibition.

Factor 5: Scope, Duration, and Significance of Abuse

The scope and duration of exposure to 7-hydroxymitragynine (7-OH) are substantial, but the scope and significance of abuse are not. Millions of Americans have been exposed to 7-OH for many years through kratom use, and more recently through 7-OH products, without evidence of sustained, large-scale abuse patterns comparable to substances in Schedule I. At least 20 million Americans use kratom products. Nationally, more than one million adults are estimated to have used 7-OH kratom alkaloid products, with over one billion servings sold. If 7-OH abuse were widespread, severe, or escalating, that signal would be evident at this scale of exposure.

Instead, available evidence indicates that problematic use occurs in a minority of users and is generally limited in severity (Ross, 2026). Only 9% of survey respondents reported feeling high after using 7-OH, and this is correlated with a small percentage of consumers who may be abusing the compound (Ross, 2026).

Reported adverse outcomes are rare relative to the size of the exposed population, and there is no evidence of sustained increases in emergency department utilization, overdose mortality, motor vehicle accidents, or criminal activity attributable specifically to 7-OH (Kedzierski, 2023). The absence of a population-level harm signal over a prolonged period of exposure weighs strongly against the conclusion that 7-OH abuse is significant in scope or duration.

Isolated adverse events, including the Los Angeles County deaths that have received public attention, do not alter this assessment. These cases lack quantitative toxicology, confirmed product exposure, and causal attribution, and all involved multiple co-ingested substances known to drive overdose risk. Such cases are not evidence of a widespread or significant abuse problem and should not be used to infer population-level risk.

Taken together, the scope and duration of 7-OH exposure are large, while the scope and significance of abuse remain limited. This disparity is inconsistent with Schedule I classification, which is reserved for substances that produce widespread, severe, and socially disruptive abuse. The evidence instead supports proportionate regulatory approaches that address specific risks without criminalizing a large and identifiable consumer population.

Factor 6: The Risk to Public Health

The public health risk associated with 7-hydroxymitragynine (7-OH) must be evaluated in terms of both direct harms from use and indirect harms resulting from regulatory action. The available evidence does not show that 7-OH use is driving a population-level public health crisis comparable to those associated with Schedule I opioids. Despite widespread exposure over many years, there is no evidence of sustained increases in overdose mortality, emergency department utilization, or community-level harm attributable specifically to 7-OH (Garcia-Romeu et al., 2020; Rogers et al., 2024).

Kratom use is estimated at about 7% of Americans, yet mitragynine and/or 7-hydroxymitragynine appears in only about 2% of fatal drug overdoses (Centers for Disease Control and Prevention [CDC], 2025). This means kratom and/or 7-OH products are roughly 70% underrepresented in overdose deaths relative to population exposure. From a public health lens, that pattern is inconsistent with a primary overdose driver and is more consistent with incidental detection or co-exposure in fentanyl-dominated polysubstance fatalities.

National toxicology surveillance data provide important context regarding relative public health risk. In 2023, the National Poison Data System recorded only 1,490 kratom-related exposure calls in the US out of more than 2,080,659 total Poison Control Center Call cases, just 0.07 percent (America's Poison Centers, 2024). By contrast, nearly 278,501 cases, over 13 percent, involved analgesics, including prescription opioid painkillers and common over-the-counter drugs like Tylenol. Even with an estimated one million 7-OH consumers nationwide, adverse events remain rare relative to use. This is not the profile of a substance driving a public safety or public health crisis.

Where adverse outcomes have been reported, they overwhelmingly involve polysubstance use. This includes the Los Angeles County deaths in which 7-OH was detected alongside multiple central nervous system depressants, stimulants, or illicit drugs, without quantitative toxicology or confirmed product exposure. Epidemiological and forensic literature consistently show that polysubstance use, particularly combinations involving alcohol, benzodiazepines, and opioids, is the dominant driver of fatal overdose risk (Jones et al., 2014; Kandel et al., 2021). Attributing such outcomes to a single detected compound in the absence of concentration data risks misdirecting public health interventions away from the true sources of harm.

Consistent with this, controlled animal toxicology studies have not identified a lethal oral dose for 7-hydroxymitragynine, further distinguishing its acute toxicity profile from that of high-risk opioids driving overdose mortality (Smith et al., 2019).

The potential public health consequences of placing 7-OH in Schedule I are substantial and foreseeable. Prohibition would criminalize a large population of adults who currently use kratom or 7-OH products for pain management or to reduce reliance on illicit opioids, displacing them into unregulated markets with far higher overdose risk. Extensive evidence from opioid policy

demonstrates that sudden loss of access to lower-risk alternatives increases transitions to fentanyl and other illicit opioids, with predictable increases in morbidity and mortality (Cicero et al., 2014; Wakeman et al., 2019). This is not just theory, as there was a **300% increase in overdose deaths in Florida following an Emergency Schedule 1 ban of 7-OH** in August, 2025.

Population-level epidemiologic evidence further indicates that prohibiting kratom-related products may worsen opioid-related outcomes rather than reduce them. Blair, 2022 found that enactment of kratom bans was associated with statistically significant increases in opioid overdose mortality in multiple states, including Indiana, Vermont, Wisconsin, Arkansas , and Alabama, with no protective effect observed in any state. The author concluded that public health policies banning kratom, implemented with the intent of reducing addiction and harm, did not mitigate the opioid epidemic and in several cases were associated with increased opioid mortality (Blair, 2022).

More broadly, evidence shows that Controlled Substances Act scheduling does not reliably reflect real-world drug harms. Broman, 2025 found a weak negative correlation between CSA schedule placement and expert-assessed harm (Broman et al., 2025). Drugs responsible for the greatest mortality and social harm, including fentanyl, methamphetamine, crack cocaine, heroin, and alcohol, ranked highest in overall harm, while several Schedule I substances ranked among the least harmful. These findings demonstrate that punitive scheduling frequently misclassifies risk and can amplify harm through criminalization and legal consequences rather than reduce it. In this context, placing 7-OH in Schedule I would replicate a well-documented policy failure by prioritizing classification over evidence-based public health outcomes.

For individuals who do not transition to illicit opioids following a 7-OH ban, unmanaged pain, psychological distress, and increased suicide risk represent additional, well-documented harms. These concerns were explicitly cited by the U.S. Department of Health and Human Services in 2018 as reasons for declining to recommend Schedule I placement of mitragynine and 7-hydroxymitragynine (Grior, 2018).

Over 32,837 people signed a Change.org petition urging lawmakers to halt a proposed national ban on 7-OH, indicating public resistance to prohibition-oriented policy actions (7-HOPE Alliance, 2025).

In this context, Schedule I placement is likely to increase public health risk rather than reduce it. A regulatory approach focused on product standards, dosage limits, labeling, and surveillance would better protect public health while preserving the ability to monitor and respond to emerging risks. The evidence does not support treating 7-OH as an immediate public health threat warranting the most restrictive classification available under state or federal law.

Factor 7: Psychic or Physiological Dependence Liability

The evidence indicates that 7-hydroxymitragynine (7-OH) can produce some degree of physical dependence at sufficient doses, but its dependence liability is constrained and does not resemble that of Schedule I opioids such as heroin or fentanyl. At the pharmacological level, 7-OH functions as a partial mu-opioid receptor agonist with lower intrinsic efficacy than full agonists, a property associated with a ceiling effect on receptor activation and reduced severity of dependence and withdrawal compared with high-efficacy opioids (Kruegel et al., 2016; Obeng et al., 2021). This mechanism limits the intensity of neuroadaptations that typically drive severe opioid dependence.

Human behavioral data reinforce this distinction. In a survey of 1,521 adults who reported using 7-OH products, most respondents did not consider themselves addicted, and reported withdrawal symptoms were predominantly mild to moderate rather than severe (Ross, 2026). Only a minority reported functional impairment related to dependence, and no respondents reported overdose requiring medical intervention despite repeated use (Ross, 2026). These findings are inconsistent with the dependence profile seen in heroin or fentanyl users and are more closely aligned with substances such as kratom, cannabis, or caffeine, where physical dependence may occur but is generally manageable and non-disabling.

Observational research on kratom use provides additional context, as 7-OH exposure occurs both naturally and metabolically in that population. Studies consistently report that while some users experience tolerance and withdrawal, symptoms are typically limited in severity and rarely meet criteria associated with severe opioid use disorder (Garcia-Romeu et al., 2020; Smith et al., 2022). Case reports describing problematic 7-OH product use involve atypical exposure scenarios, extreme dosing, or co-occurring substance use disorders and do not establish generalizable dependence risk for the broader population (Reif et al., 2025).

The presence of some dependence liability does not justify Schedule I placement. Many legally regulated substances produce physical dependence and withdrawal yet are managed through dosage controls, labeling, and clinical guidance rather than prohibition. The combined mechanistic evidence and human survey data indicate that any dependence potential associated with 7-OH is dose-dependent, limited in severity for most users, and amenable to risk mitigation through regulation. On this record, Factor (7) does not support classifying 7-hydroxymitragynine as a Schedule I substance.

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

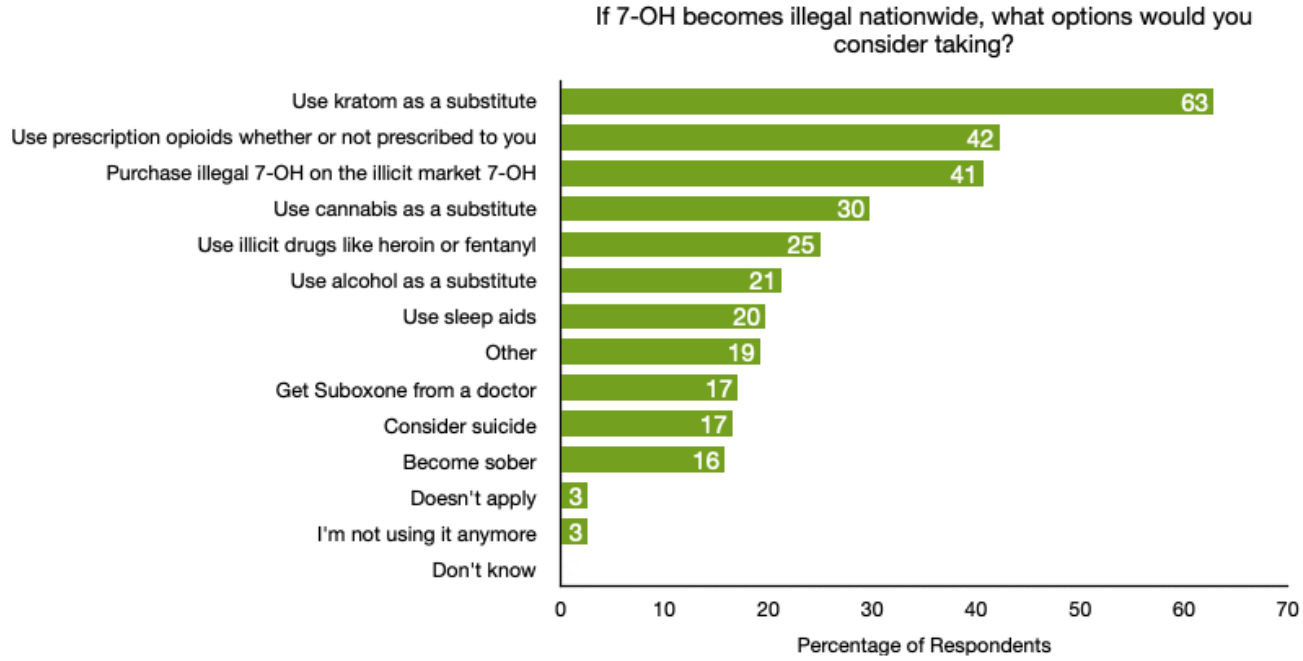
7-hydroxymitragynine (7-OH) is not an immediate precursor to any substance controlled under federal law. It is not used to manufacture heroin, fentanyl, or any other drug listed in the

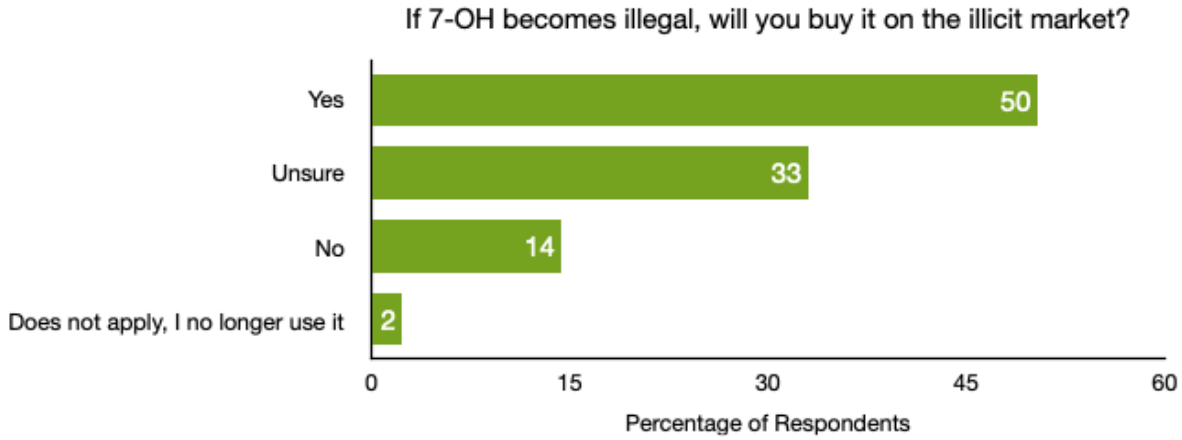
Controlled Substances Act (CSA), and it does not function as a chemical intermediate or feedstock in the production of any scheduled substance.

Fiscal Impact of Scheduling

The fiscal consequences of this approach are substantial. Removing access to 7-OH for more than 1 million Americans risks driving increased opioid overdoses, higher emergency room utilization, expanded demand for addiction treatment, greater Medicaid expenditures, lost workforce participation, and increased disability and unemployment. There are also severe human costs with direct fiscal impacts, including elevated suicide risk among individuals who lose effective pain or withdrawal management.

In fact, a recent survey of 1521 7-OH consumers completed in October 2025 found **17% of 7-OH consumers would consider suicide if 7-OH was banned**, **25% said they would use illicit drugs like heroin or fentanyl, and the majority said they would buy 7-OH from the illicit market.** The downstream costs of overdose care, long-term addiction treatment, and preventable death far exceed any speculative benefit of prohibition and will ultimately be borne by taxpayers.





(Ross, 2026)

Scheduling Recommendation

Based on the totality of the evidence across all eight factors, 7-hydroxymitragynine (7-OH) does not meet the statutory or scientific criteria for placement in Schedule I. The record does not demonstrate a high or uncontrollable abuse potential, severe or widespread public health harm, or dependence liability comparable to Schedule I opioids. Instead, the evidence shows a pharmacologically constrained compound with dose- and formulation-dependent risks, substantial uncertainty in the human data, documented misstatements in secondary sources, and a long history of widespread exposure without population-level harm.

A Schedule 1 ban of 7-OH is the most punitive regulatory outcome at a time when the evidence base is still evolving. Schedule 1 is not a temporary measure; it is a rigid framework that restricts research, eliminates regulatory flexibility, and makes policy correction difficult even if assumptions prove wrong. A no vote does not endorse unregulated access. It preserves the Legislature's ability to evaluate evidence, distinguish between product types, and pursue solutions that genuinely improve public safety. Exercising restraint here reflects responsible governance and ensures that federal and state government do not impose irreversible criminal penalties without clear, compelling, and quantitative evidence that such action is necessary.

This conclusion is reinforced by epidemiologic evidence showing that state-level kratom bans have been associated with increased opioid overdose mortality rather than reductions in harm (Blair, 2022). This risk is compounded by evidence that the Controlled Substances Act (CSA) itself is poorly aligned with expert assessments of drug harms, making Schedule I placement an unreliable and often counterproductive public health tool (Broman et al., 2025). For these reasons, scheduling or banning 7-OH is not recommended.

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From: Michael White
To: Board Coordination
Subject: Potential Ban of Mitragynine, 7-Hydroxymitragynine and Mitragynine Pseudoindoxyl in NV
Date: Thursday, April 2, 2026 10:54:28 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

I am C. Michael White, Pharm.D., FCP, FCCP, FASHP, Distinguished Professor and Chair of Pharmacy Practice at the UConn School of Pharmacy and Chair of the Kratom Consumer Advisory Council. The KCAC is an independent board of consumers helped or hurt by kratom derived products. We try to define best practices for public health regarding kratom derived products.

I see that you are considering scheduling mitragynine, 7-hydroxymitragynine, and mitragynine pseudoindoxyl. I recently presented at the NASCSA and the Addiction Policy Forum Understanding 7-OH – Science, Risks, and Real-World Impact about this topic. If you think my expertise could be of value, please let me know. I would be happy to present to your group and/or answer any questions you might have.

Additionally, I have conducted an 8-Factor Analysis Eight-Factor Analysis of Natural Kratom Leaf — Global Kratom Coalition™ that could be useful as NV considers the potential benefits and risks of different actions. I would assume that NV would want their pharmacy experts to construct something similar. This is a complex area and one that requires understanding nuances of pharmacology, illicit drug products, and vulnerable patients with limited to no access to healthcare.

The FDA and HHS both agree that concentrated isolated 7-hydroxymitragynine, mitragynine pseudoindoxyl, and MGM-15 should be banned. However, these public health governmental organizations specifically recommend against banning natural leaf kratom and NIDA and the WHO also have not supported or enacted bans on the natural leaf after their reviews. I think this is the prudent action to take at the present time as I describe in the 8-Factor Analysis. Natural leaf kratom is not risk free, and there needs to be public health protections but a host of regulations can reduce the risk without resorting to a blanket ban.

From:	Matthew Winterhawk
To:	Board Coordination
Subject:	Public Comment, April 15–16, 2026 Hearing, Kratom / 7-OH Regulation
Date:	Wednesday, April 15, 2026 8:30:03 AM
Attachments:	BOP Proposed regulation public safety concerns MW Public Comment.pdf Public Comment For Pharmacy Board 4_16_2026.pdf

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Name: Matthew Winterhawk **Date:** April 15, 2026
Regarding: Proposed regulation / public safety concerns, kratom derivatives (7-OH)

My name is Matthew. I'm a Nevada resident, a father, and someone who has worked closely around the retail and trade environments where these products are introduced and scaled.

I want to speak today about **kratom derivatives, specifically high-potency products containing 7-hydroxymitragynine, or 7-OH.**

Over the past several years, especially after COVID, I witnessed firsthand a shift in the industry. At national trade shows and within retail supply chains, we saw a strong push toward **concentrated kratom products** being marketed for pain relief, mood, and energy.

At that time, I raised concerns directly with vendors and chose to step away from participation because the trajectory was clear:
increasing potency, increasing accessibility, and no meaningful regulatory framework.

Today, these products are widely available in **smoke shops and gas stations**, with:

- No standardized dosing
- No consistent labeling of alkaloid content
- And no real consumer protections

At the same time, communities are now dealing with:

- **Dependence and withdrawal**
- Individuals seeking help for kratom-related use
- And growing groups of affected families and recovering users

This is not a future concern, this is already happening.

My concern is that we are operating in a **post-reaction model**, where substances reach widespread use before meaningful oversight is applied.

I am here to respectfully urge this Board to consider a more **proactive approach**.

Specifically:

- Evaluate **scheduling of high-potency kratom derivatives, including 7-OH**
- Consider **removal of these concentrated products from general retail environments like smoke shops**
- And establish **clear regulatory standards before widespread harm occurs**

If a substance:

- Interacts with opioid receptors
- Has demonstrated dependency risk
- And is being sold without medical oversight

Then it should not exist in an unregulated retail space.

We have seen what happens when regulation comes too late.

We have an opportunity here to **act before this grows further**.

I appreciate the work being done, and I strongly encourage this Board to move toward **front-end regulation instead of reactive enforcement**, for the safety of Nevada's communities.

Thank you for your time.

Matthew Winterhawk
Candidate for Governor of Nevada
Primary Election: June 9, 2026
General Election: November 3, 2026
[W4Nevada.com](https://www.W4Nevada.com)
winterhawk@w4nevada.com
(702) 381-4295
Battle Born. People First. Nevada Always.

Follow the campaign:
X: @W4Nevada | Instagram: @W4Nevada | Facebook: @W4Nevada

Good morning, and thank you to the Nevada State Board of Pharmacy for the opportunity to speak.

My name is Matthew Winterhawk, I am a Nevada resident, a father, and someone who has spent years working directly in community-facing industries where these products are sold and marketed.

I am here today to speak specifically about **kratom-derived products, and more importantly, the rise of highly concentrated derivatives such as 7-hydroxymitragynine, commonly referred to as 7-OH.**

Following COVID, I witnessed a major shift at national trade shows, particularly in the counterculture and smoke shop supply industry.

Events like CHAMPS began heavily promoting **enhanced kratom products**, including extracts and concentrated forms that go far beyond traditional leaf use.

At that time, I personally raised concerns with vendors and organizers about:

- The **potency** of these products
- The **lack of labeling standards**
- And the **clear risk of dependency and misuse**

I made the decision to **walk away from participation** because I believed the industry was moving in a dangerous direction.

That direction has now materialized.

Today, these products are:

- Widely available in **smoke shops and gas stations**
- Sold with **little to no standardized dosing guidance**
- Marketed as **legal alternatives for pain relief, mood, and energy**

At the same time, we are now seeing:

- Increasing reports of **dependence and withdrawal**
- Individuals seeking help for **kratom and 7-OH-related use disorders**
- Community groups, like the one I recently joined, made up of **survivors, families, and recovering individuals directly impacted**

This is not theoretical.
This is already happening at the community level.

What concerns me most is that these substances exist in a **regulatory gray area**.

They:

- Interact with **opioid receptors**
- Carry **real dependency risk**
- Yet are sold without the safeguards applied to other substances with similar effects

At the same time, the burden of dealing with the consequences is falling on:

- Families
- Communities
- And treatment systems that are now seeing the impact firsthand

I am not here to advocate for fear or overreach.

I am here to ask for **responsible oversight**.

At a minimum, I urge this Board to consider:

- **Mandatory product testing and labeling standards**
- **Clear disclosure of alkaloid concentrations, including 7-OH**
- **Age restrictions and point-of-sale controls**
- And a review of whether highly concentrated derivatives should remain **unregulated retail products**

Because right now, accessibility has outpaced safety.

We have seen this pattern before in this country.

The difference today is that we have the opportunity to respond **before it escalates further**.

I spoke up about this years ago when it was beginning.

I am speaking again now because the consequences are no longer coming, they are here.

Please do not wait until this becomes something we wish we had acted on sooner.

Thank you for your time.

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I am here to respectfully urge this Board to consider a more **proactive approach**.

Specifically:

- Evaluate **scheduling of high-potency kratom derivatives, including 7-OH**
- Consider **removal of these concentrated products from general retail environments like smoke shops**
- And establish **clear regulatory standards before widespread harm occurs**

If a substance:

- Interacts with opioid receptors

- Has demonstrated dependency risk
- And is being sold without medical oversight

Then it should not exist in an unregulated retail space.

We have seen what happens when regulation comes too late.

We have an opportunity here to **act before this grows further**.

I appreciate the work being done, and I strongly encourage this Board to move toward **front-end regulation instead of reactive enforcement**, for the safety of Nevada's communities.

Thank you for your time.

From: nickcaruso25@everyactioncustom.com on behalf of Nick Caruso
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Saturday, April 11, 2026 4:18:36 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

My Own Personal Experience with Kratom:

Kratom has been a life saver for me and many others I know. It is infinitely safer than prescription opiates or legal drugs like alcohol/tobacco.

It is incredibly frustrating that the pharmaceutical industry continues to try banning kratom. This would be an absolute disaster for the citizens of Nevada and it is NOT the will of the people.

Governor Lombardo vetoed a bill that overwhelmingly passed to regulate kratom in Nevada. There has been an aggressive misinformation campaign against kratom and I can say as a long-time user of it that it is incredibly safe. I am very healthy and if I did not have kratom my quality of life would be harmed significantly. It is a tool for pain and addiction. It helps people get off alcohol, pain medication and live better lives.

Sincerely,
Nick Caruso

From: niconess@everyactioncustom.com on behalf of Nicholas Gruschow
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Thursday, April 16, 2026 2:09:52 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

Please no making mitragynine unlawful substance for adults. Thank you for reading. s s

Sincerely,
Nicholas Gruschow

From: Nathan Hinkel
To: Board Coordination
Subject: Kratom Ban Hearing Public Comment
Date: Wednesday, April 15, 2026 1:06:37 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Hello,

Kratom has had immense benefit to my life. In 5 years of daily use, nothing about it has ever been a danger to me. I'm able to work because of how it helps me manage my otherwise disabling sciatica. Please do not make illegal the thing that allows me to work painlessly enough that I can support my family.

I do not oppose the regulation of sythetic 7-OH products: those are entirely different conversation. They must be deliniated from regular kratom leaf.

Thank you,
Nathan Hinkel
Henderson, NV

From: The Happys
To: Board Coordination
Subject: Kratom my story.
Date: Monday, April 13, 2026 12:04:44 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Hey guys I was an addict of drugs my name is Nick Petty, I was addicted to Percocet from an injury, and benefited off kratom for chronic pain. 7OH I get getting banned, but just the plant alone has helped me a lot. Please do not ban regular Kratom it's associated with the coffe plant. 7OH is 50 -100 stronger. Please ban stepped on and high potency kratom only.

16 years I've been off drugs, and using low amounts of kratom. Please don't mess it up for the good people and construction workers.

From:	Pharmacy Board
To:	Board Coordination
Subject:	Fw: Public Comment - Kratom Ban Opposition in Nevada
Date:	Monday, April 20, 2026 8:30:05 AM
Attachments:	Outlook-gz2czclb.png

Thank you.

Nevada State
Board of Pharmacy
985 Damonte Ranch Pkwy Suite 206
Reno, NV 89521
Office: 775-850-1440
Fax: 775-850-1444
Web Page: https://bop.nv.gov/

This information is provided as a courtesy on behalf of the Nevada State Board of Pharmacy. This information does not constitute legal advice and does not override the specific provisions of Nevada law as applied to a particular set of facts.

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From: Parker Flowers <[redacted]@gmail.com>
Sent: Thursday, April 16, 2026 10:15 AM
To: Pharmacy Board <pharmacy@pharmacy.nv.gov>
Subject: Public Comment - Kratom Ban Opposition in Nevada

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My written testimony - In OPPOSITION of a KRATOM BAN

Please enter into the record

My name is Parker Flowers. I am representing myself

I do personally use kratom for a sense of wellbeing and pain management due to a few action sports accidents when I was younger. Not daily, but consistently, as a part of my life.

I also come from a family with a history of addiction. I've seen what drugs like heroin and fentanyl can do—I've watched lives be lost and families torn apart.

But I've also seen something different.

My mother was estranged from her sisters for years due to addiction. Today, she's rebuilding those relationships—and kratom played a role in giving her the stability to do that.

My brother went down a very dark path after our father passed—gang involvement and heroin addiction. Today, he's been on a path to reform for over three years, and kratom has been part of that turnaround.

These aren't statistics to me—this is my family.

That's why I'm here in opposition of a full ban on kratom

Because banning doesn't remove demand—it pushes people into the shadows.

As a father, that's what scares me most.

If responsible access is taken away, people won't just stop—they'll look elsewhere. And that means unregulated products, unknown potency, and far greater risk.

For many people, kratom is not the problem—it's part of the solution.

It's helped people move away from substances that were far more destructive—including even some of the prescriptions meant to help them overcome addiction.

And when we talk about public health, perspective matters. A quick look at CDC data shows cigarettes are associated with roughly 480,000 deaths each year in the U.S., and alcohol with over 178,000.

By comparison, reports involving kratom are significantly lower and often involve multiple substances—not kratom alone.

And while I’m not here representing any company today, I’ve spent enough time around this space and in the industry to understand how quickly things can go wrong without clear standards.

My point is not to minimize risk—but to emphasize the need for balanced, responsible regulation.

Protect consumers. Set standards. And don’t take away something that is helping people rebuild their lives.

I’m asking you, as a responsible kratom user myself to please protect a plant that has been used for centuries.

Thank you for your time.

Parker Flowers

From:	Dwane M
To:	Board Coordination
Subject:	PLEASE REJECT KRATOM SCHEDULE I PROPOSAL - SUPPORT RESPONSIBLE REGULATION
Date:	Friday, April 10, 2026 4:21:15 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Members of the Nevada Board of Pharmacy,

I hope this email finds you well. My name is Robert Manning. I have family and friends living in Nevada, and I am writing because this issue affects them and many others across the state.

Many Nevada citizens, especially veterans and those with chronic pain, benefit greatly from access to safe kratom. I respectfully urge you to REJECT the proposal to schedule kratom alkaloids as Schedule I. This would effectively ban kratom entirely, which would only drive the market underground and remove access for responsible consumers who rely on it for pain management and wellness. Responsible consumer protections, such as age restrictions, clear labeling requirements, and standards to prevent the sale of adulterated or unsafe products, would be far more effective than prohibition.

Over the years, I have undergone six major operations due to debilitating spinal issues. Kratom has been instrumental in helping me transition away from major opiates, significantly improving my quality of life. Thanks to this natural substance, which is in the same family as coffee and has proven to be the safest option I have tried, I have been able to return to work and contribute productively to our community.

Safe, natural kratom is a substance often used by many as an alternative to stronger and more dangerous pain medications, by senior citizens dealing with aches and recurring pain, and by veterans suffering from service injuries. The internet is full of misinformation on kratom, and even news stories regularly mix it up with other products.

Nevada should follow the science and reject this Schedule I proposal in favor of responsible regulation to keep kratom safe and appropriately regulated.

I would like the opportunity to share my story with you in more detail if that would be helpful. This public comment is submitted in advance of the April 16, 2026 Board of Pharmacy workshop.

Thank you for your time, dedication, and service to the people of Nevada. I appreciate your consideration of this important matter and my public comment.

Sincerely,

Robert Manning

From: trinamarieb@everyactioncustom.com on behalf of Trina Montgomery
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Monday, April 13, 2026 1:02:09 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

In 1993, I hurt my back while on the job. Throughout the last 20 years, I have had numerous surgeries. Attended countless doctors ' appointments and physical therapy. I have been on every pain killer on the market. I received epidurals and cortisone shots every few months. I would end up in the ER with back spasms almost monthly. Nothing seemed to take the pain away. Fast forward to 2016. I lost my 9 year old daughter to cancer. I was devastated. I honestly felt like i could not go on without her. I was in constant pain and then had severe depression and anxiety from losing her. A friend of mine said I should try Kratom. I started taking it and have never looked back. My back pain has become non existent. I no longer see a physician for it. I am off all medications. I havent been to the ER in years. It has also helped my depression. I no longwr take anti depressants or anxiety medications. Of course, I still miss my daughter but at least i am not in the same dark place that I was in. Please, I beg you. Do not take this wonderful product away from me and so many others who depend on Kratom to survive. Help us protect it.
Thank you so much for your time.
wn Personal Experience with Kratom:

Sincerely,
Trina Montgomery

From:	robertrutter@everyactioncustom.com on behalf of Robert Rutter
To:	Board Coordination
Subject:	Oppose Mitragynine Scheduling
Date:	Monday, April 13, 2026 6:00:04 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

I'm writing to support kratom consumer protection legislation and to ask you to keep kratom safe in Nevada. Kratom criminalization efforts are based on fear mongering and misinformation. Natural kratom is used by many Nevada citizens safely for over a decade.

Also, I want to share my personal experience with kratom.

For me personally, I have dealt with chronic pain from a car accident in 2009. I was taking painkillers for years and my insides were taking a beating. I was slowly dieing, I'm sure. As I was trying to get off of painkillers for about the tenth time, I ran across a movie on Prime about Kratom and ordered some the very next day. It saved my life. Kratom helps with the pain but doesn't have all of the ugly side effects that pills do. The problems painkillers cause outweigh the good that they do, in my opinion. I still deal with chronic back pain and if it wasn't for Kratom, I'd surely be dead by now. PLEASE keep kratom legal! There are many of us who would end up either suffering immensely or dieing without it. Thank you for your time.

Sincerely,
Robert Rutter

From: sansevererobert@everyactioncustom.com on behalf of Robert Sansevere
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Friday, April 10, 2026 11:22:49 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

My Own Personal Experience with Kratom: After 11years on opioids for arthritis I was able to get off of them when I discovered kratom. It was an easy transition without any withdrawal effects. Please keep kratom safe for all those like me. Thank you.
Robert Sansevere

Sincerely,
Robert Sansevere

From: beckyrwines1@everyactioncustom.com on behalf of Rebecca Wines
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Friday, April 10, 2026 11:46:10 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

My Own Personal Experience with Kratom:. I'm a 53 year old mother, grandmother & a kratom consumer for almost 8 years. Kratom has been life changing for my chronic pain& allows me to live a normal productive life. It has been life saving for so many others as well & it would be devastating if it could no longer be accessed. Prohibition has never worked& is very dangerous because it will only cause devastation by spiking the opioids epidemic, over doses from deadly street drugs, suicides etc. Absolutely no good will come from banning kratom. I hope you will please consider the actual scientific data instead of the false information being spread about it. Natural leaf kratom is safe& should not be banned. It should be regulated instead to insure its safe. I hope you will please make the right decision by keeping it legal. Thank you for taking the time to read my testimony.

Sincerely,
Rebecca Wines

From: Sean Cervantez
To: Board Coordination
Subject: Kratom Ban Hearing Public Comment
Date: Wednesday, April 15, 2026 1:37:27 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

To whom it may concern,

Hello I understand that Kratom is once again on the chopping blocks as a schedule one drug. As a former opioid addict, I am writing this letter on behalf of myself and other natural pure kratom users that this has been so beneficial to my life.
It has kept me from relapsing and going back to harder things that now may include fentanyl.

I fell into opioid addiction during the height of the epidemic, and it took me a few relapses to finally pull myself together and stay sober.
That being said I have used pure Kratom powder to keep me off of street drugs; and it has been successful. Granted I am trading one chemical dependence for another but considering the only option is fentanyl laced pills on the street I pick the lesser of two evils.
Your proposed bill would turn me into a criminal overnight, With no other options except to turn to the street.
As a working adult male who has insurance that does not cover mental health or chemical dependency I am out of options.
With your proposed bill, I go from a tax paying citizen who is a working high functioning adult to a criminal with no incentive to stay the straight and narrow course.
It is completely insane to propose a bill like this with no alternative treatments to those who have already chose this path. When it comes to chemical dependency, you cannot just stop because something became illegal. This is a humanitarian issue. And to alienate a portion of the population overnight and turn them into criminals with no outlet or solution is not the government that we want in office.
I understand the synthetics and potent extracts are creating issues just like the synthetic marijuana did. Please don't demonize the entire industry for a small villainous segment that needs to be nipped in the bud. I do agree with passing laws on extracts and synthetics, and especially in advertising them in places like convenience stores in purview of children.
However, that being said, turning a natural and medicinal plant into a schedule, one drug overnight over the basis of synthetic and extracts made from it is not the way proper government should function.
Please, please please I beg of you protect us; the people! Don't turn us into criminals. We want to contribute to society that's why we run from our Pain. Please don't turn us into something we are not. Please don't alienate us from society.
I stand with you regarding extracts and synthetics. Please stand with us in the medical aspects of the whole natural unprocessed plant.

Thank you for your time and consideration

Sean Cervantez

From: Scott Elingburg
To: Board Coordination
Subject: Keep kratom legal in Nevada
Date: Wednesday, April 15, 2026 8:32:07 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear madam or sir,

Thank you for taking the time to read my message. I write to you today to ask you to help keep kratom legal in Nevada. I travel to the great state of Nevada twice a year and each time I feel safe knowing that kratom is legal in the state.

As a user of kratom for nearly eleven years, I must tell you that any action to ban kratom will harm many law-abiding citizens.

Many people--and many veterans--use kratom to help manage anxiety, chronic pain conditions, PTSD, and sleep issues. For many of us, the point is simple: kratom has saved our lives and makes our lives incredibly meaningful. Without kratom -- and my wife and daughter will tell you the same thing -- I would not be alive today.

I understand that there is a lot of miscommunication and outrage over what kratom is and what it actually does and does not do. Banning it will send it underground and, more importantly, it will not stop citizens from using it. It will merely criminalize the ones who do.

I work daily with veterans from all over our state and I've seen the good that this small leaf can do for many of us. Please don't remove our safe and responsible access to it.

Thank you for reading and thank you for your service to this great country.

God bless America and God bless our freedoms.

-- --
Scott Elingburg

From: 5thhouserevelations
To: Board Coordination
Subject: Kratom Schedule 1
Date: Sunday, April 19, 2026 11:29:54 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Hello Nevada board of Pharmacy team,

My name is Scarlett,

I am a lifelong resident of Northern California so I'm not from Nevada, but I have been watching what has been going on with the schedule I recommendation that is currently under review in regard to the Kratom plant and its alkaloids. I am writing to you today to respectfully urge you to please consider the ramifications that come with rendering Botanical Kratom a schedule 1 substance, as it will end up criminalizing many innocent people who responsibly have utilized pure leaf Kratom to maintain their health.

There is a lot of fear and negativity surrounding Kratom now because of what has happened with chemically manipulated synthetic products such as 7OH. Most of us botanical Kratom users are seeking the removal of synthetics such as 7OH from the marketplace because we are aware of their harmful consequences, but we are also fighting to keep our access to pure leaf Kratom, which is being unfairly demonized. What has happened has completely disrupted our peace and stability; we have been fighting nonstop to protect the safe consumption so many of us have maintained over decades. Choosing to categorize all Kratom as a schedule 1 substance is not only misinformed... it kicks us while we are already down - us being the people governments are supposed to be serving.

What follows this fearful reaction to the 7OH controversy (and perhaps, you could say, crisis) is a complete injustice in the form of blanket bans that are centered upon scientific misinformation and promote emotional appeals over evidence. I would like to say here, again, that most botanical Kratom users support a ban of synthetically produced 7OH, which is a compound found within the natural Kratom leaf at a rate of less than 1%, and is only highly present in certain products that have been altered in very irresponsible ways, for very manipulative reasons.

I want to ask you this: do you really want to punish people who have done nothing wrong, and who have merely turned to a natural plant product to assist in their struggles? What will it look like later on when the science catches up to this decision and at best it looks like regulators were foolishly duped by fear mongering, and *at worst* corruption is discovered? I do not wish to accuse you of anything, but I am trying to put this into perspective in a way that is truthful. Do you really want to go after natural plant medicine in a time when the world population is beginning to distrust the practices of corporate medicine?

I am going to share some of my story with you; mine is encased within the tapestry of millions of others who complete the picture of exactly who uses botanical Kratom and why. I am 35 years old now with a healthy and happy family, with healthy relationships, and I am living in a completely functional home. I am a responsible mother of a 5 year old boy. I am productive and very active, and I have no level of emotional or mental instability. Compare this to how I was 13 years ago, right before discovering pure leaf Kratom.

I was a drug addict who could not build anything and yes, like so many others, I was hooked on opiates. My pill addiction took over my entire life; I started coming to people I knew with Vicodin prescriptions out of desperation because my own prescription for a chronic spinal condition had run out. People I cared deeply for abandoned me, rightfully so, because they could not handle seeing me struggle with my addiction. It was just when I was going to turn to Heroin that Kratom came into my life and totally subverted it as a focus. Very, very shortly after starting Kratom use I was off the pills completely, and with absolutely no side effects - not even opiate withdrawal.

Fast forward to now, when I am still a Kratom user and I am still off of the pills that would have killed me if I stayed on them because, as an addict, I had no self control. Here is a big misconception - well, one of them: regulators act as though Kratom users are hopelessly addicted and have no self control, to such an extent that we

need to have our plant taken away in a punitive fashion. The truth is that I have more self control and willpower now than I ever have before in my life. I never went back to my addiction, not since Kratom was introduced into my life.

There's one more thing I'd like to share with you before ending this letter here. Now at age 35 - thirteen years into using pure leaf Kratom with no side effects - I have a chronic, painful inflammatory condition called Endometriosis. It is some of the most debilitating pain I have experienced, and once again Kratom saves me because of how beneficial it is for pain. If anyone has done the slightest amount of true research they would know that even the federal government has been unable to find a lethal dose of pure Kratom, per their own experiments, therefore it is a Godsend to have a natural product for chronic pain that one can take as needed without the real possibility for overdosing or death.

If you have read all of this so far I really appreciate it. I hope and pray that you reconsider turning responsible Kratom users such as myself into criminals, and I pray you deeply reflect before further stigmatizing us, when all we are doing is struggling through life like everyone else, but we have found something natural that helps. Thank you again for your time, and I apologize if at any point in this letter Is sound disrespectful,

~Scarlett Logan

From: SCOTT LOMILL
To: Board Coordination
Subject: I oppose scheduling Kratom
Date: Tuesday, April 14, 2026 7:15:23 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

I oppose scheduling kratom alkaloids as Schedule I. Natural kratom leaf has a demonstrated history of safe use and is not comparable to Schedule I substances. Regulate dangerous synthetic 7-OH products — not natural kratom
Scott Lomill

From:	Stephen McIntosh
To:	Board Coordination
Subject:	Opposition to 4/16 Agenda Item 15 (Re: Kratom)
Date:	Wednesday, April 15, 2026 1:21:09 AM
Attachments:	MCINTOSH_NVBOP.pdf

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

To the Board of Pharmacy and staff,

I am writing to voice my OPPOSITION to the proposal to schedule kratom. I have included my testimony to be entered into the record as an attachment. I will make every effort to be present on April 16 in person or remotely.

Sincerely,

--
Stephen McIntosh, MBA
Retired Software Developer and Instructor of Computer Information Systems

To the Nevada Board of Pharmacy:

My name is Stephen McIntosh. I am medically retired and permanently disabled with advanced heart failure and chronic pain. I am writing to voice my **OPPOSITION** for **Agenda Item 15** that would designate mitragynine, et. al. to Schedule I.

Nevada already has regulation on kratom that was passed by the legislature. It is grossly inappropriate for an unelected board to go behind the legislature and criminalize an entire product class the legislature has sought to regulate (NRS 597.998) and preserve for adult consumers.

The Board of Pharmacy should exempt botanical products that were on the market in 2019 when the legislature passed NRS 597.998, which would include botanical kratom.

High 7-hydroxymitragynine (7-HMG) and other semi-synthetic products are already illegal under NRS 597.998 as they are adulterated and unsafe. AB 322 (vetoed) did not prohibit botanical kratom for adult consumers and would have further defined the limit and capped 7-HMG levels and synthetic products.

The legislature has never put forth a bill that would schedule natural botanical kratom, or any other derivative for that matter. Such as decision will have significant impacts to local consumers, retailers, travelers, and enforcement costs which are matters where legislative oversight is important. Consumers should not have to worry that their local or state regulators will side-step the legislature over and over again as BOP has considered in past years.

I use botanical kratom to manage acute and chronic pain and have since 2018 when my pain medication was stopped against my will. It allows me to perform basic housework, and the PT exercises recommended by cardiology to preserve cardiac function. Without adequate pain management I am unable to do these things and am substantially more impaired.

I suffered a massive heart attack in 2010, with 99% occlusion of the LAD artery. My heart stopped for nearly 4 minutes. Against odds, I was revived but with significant damage. This lead to my early retirement despite genuine effort to return to work, largely due to unplanned absences due to CHF exacerbation, unstable angina, and insomnia due to pain. Unfortunately, I still experience significant and constant chest pain to this day that is not responsive to nitrates. The medications I was taking before the heart attack for unrelated lower back pain (NSAIDs) are no longer advisable.

Like many Americans, I have very few choices when it comes to healthcare. Our middle-class (married) household income is too high to qualify for Medicaid and for subsidized insurance though the ACA Marketplace. I am too young for Medicare. My only healthcare option is though the HMO offered through my wife's employer. My insurance only covers seeing HMO physicians and only covers prescription drugs prescribed by their doctors or a dentist. It is financially insurmountable to seek out-of-network pain management where no visits, procedures, or drugs would be covered—if they are even willing to do anything my existing provider originally was, or some other option.

Before kratom, I was either in the ER or hospital 14-30 days per year. This has been reduced to 0-3 each year since using it. Every hospital or ER visit costs me at minimum $100, and costs the health plan (and ultimately rate-payers) a minimum of $8000 per incident if they do the absolute bare minimum cardio workup.

Most pain management tools are unavailable to me, contraindicated for cardiac patients or cardiac patients with pacemakers, did not work, or had significant side effects. While I am glad it is an option, medical cannabis has not been effective, erratic, and very impairing.

Kratom is my last available resource for managing pain. During my use my cardiovascular, liver, and kidney labs have remained stable. My imaging studies have remained stable. My AICD/defibrillator has never fired and paces less than 1% of the time. By all accounts, despite being at higher risk than many, my use has been utterly inconsequential.

I personally do not use, and will not use, high 7-HMG (“7-OH”) products that are inaccurately and misleadingly sold as kratom products.

Again, I ask you to defer to the legislature, and barring that to exempt botanical kratom from any prohibition in a manner that other states do (such as a 7-HMG safe-harbor limit of 2% by alkaloid fraction or 800 ppm). This is an important product for me and people like me who have no other viable options to do the kinds of things that most people take for granted and to have some reasonable quality of life.

I hope that you never experience profound disability, but if you do I hope this option will be available for you, especially if you are under-served or unsatisfied with your medical options.

Sincerely,

SIGNED
STEPHEN MCINTOSH
2026-APR-15 00:44:57

Stephen C. McIntosh, MBA
(Ret.) Software Developer and Instructor of Computer Information Systems
smcintosh@mcintosh-household.org

From: sandy wilson
To: Board Coordination
Subject: Workshop #15B
Date: Wednesday, April 8, 2026 8:55:22 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Hello members, my name is Sandra Wilson.

My son died from mitragynine toxicity. The only substance found in his system was Kratom. Nothing else.

We did not see this coming.

Kratom is sold in gas stations, smoke shops, and convenience stores. It is marketed as natural. It is presented as safe. But it was not safe for my son.

He was 31 years old. He had a life. He had people who loved him deeply. And now he is gone.

As his mother, I live every day with a pain that cannot be described. I replay everything in my mind. I ask myself questions no parent should ever have to ask. All because a substance that can be bought so easily took his life.

This is not political for me. This is personal.
My son is gone.

There needs to be a total ban. No more warnings. No more age restrictions. No more pretending this is harmless. If it can take my healthy, young son with nothing else in his system, it can take someone else's child too.

I am sharing this as his mother.

I am sharing this because silence helps no one.

I am sharing this because no family should feel this kind of heartbreak.

A forever grieving mom

From: Terry Hill
To: Board Coordination
Subject: Please hear my story about how Kratom save my life
Date: Wednesday, April 15, 2026 3:39:26 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

To Whom It May Concern,

I am writing to share my personal experience regarding the botanical kratom and the vital role it plays in my daily health and sobriety.

For thirty years, I lived with early-onset rheumatoid arthritis. This condition stripped away my mobility and left me in a state of chronic suffering that conventional prescription medications could not adequately address. For much of my life, I also struggled with a 40-year history of substance dependency, including narcotics, alcohol, and cigarettes.

Since discovering kratom, my life has been fundamentally restored:

- **Physical Mobility:** I have regained the ability to perform essential daily tasks, such as walking and grocery shopping, which were previously impossible due to pain.
- **Recovery and Sobriety:** Kratom provided the support I needed to move away from narcotic pain relievers and successfully end a four-decade cycle of addiction.
- **Quality of Life:** Unlike the fleeting and often ineffective relief of previous treatments, this botanical has offered a consistent foundation for my health recovery.

I am a retired individual who has worked hard for 40 years, and I am now finally able to enjoy my life and maintain my independence. I humbly ask that you protect the access to this botanical for those of us whose quality of life depends on it.

Sincerely,

Terry Hill

Yahoo Mail: Search, Organize, Conquer

From:	Tori Johnson
To:	Board Coordination
Subject:	My public comment on 7oh products
Date:	Wednesday, April 15, 2026 3:31:53 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada Board of Pharmacy,

I am writing as a consumer to share my experience and perspective on products related to kratom and 7-hydroxymitragynine (7-OH).

I began using kratom products because I was looking for an alternative to prescription painkillers following a surgery. I knew that this surgery would leave me taking painkillers for an extended period of time and I have done that before with a previous surgery and it was very difficult on my body and even more difficult to get off of. For me, these products have helped with treating my post-op pain and they actually help treat the pain more than the prescription options ever did. Not only that, these products are much easier to taper down from and get off of.

What I have learned is that 7-OH is not something new or synthetic being introduced into the body. It is a compound that naturally occurs in the kratom plant and is also produced in the body after consuming kratom. This makes it different from many drugs that are entirely foreign to the body.

I am concerned that if 7-OH is banned or treated as a Schedule I substance, it will:

- Take away a tool that people like me rely on
- Push people toward more dangerous substances
- Drive these products into unregulated markets

I have met many people in the 7oh community who are using it for harm reduction purposes, so I decided to try that within my own family.

My brother was a fentanyl addict living on the streets, and my family had tried everything — interventions and rehab but nothing worked. So I asked him to give 7oh a try. That was October 2024 and he has been clean ever since. Now he is finally healthy. He has a good job, a happy relationship and his own home. I watched 7oh save his life.

I support reasonable regulation to ensure products are safe and properly labeled. But I do not support banning or over-restricting access to something that has been helpful in my life and in my brother's life. I worry every day about what would happen to him (and the many others who have changed their lives) if these products were to be banned.

Please consider keeping 7-OH within a regulated framework rather than removing access entirely.

Thank you for considering my perspective.

Sincerely,
Tori Johnson

From: Tarah K
To: Board Coordination
Subject: Against Kratom ban for NV
Date: Thursday, April 16, 2026 8:59:24 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

I am a Nevada resident who is completely against the Kratom ban especially because there is a difference between natural and synthetic. Natural Kratom has brought healing and peace for many.
Here's my story

AKA

In 2018 a friend randomly informed me of Kratom, I had no clue what this was. After she described it I had to try it out and look into it. After doing tons of research I decided to give it a try. I am someone who USED to struggle with stomach pains, so bad I could no longer handle the pain and doctors refused to help me in pain management and could not figure out what my issue was. I literally had diarrhea every single day, all day it was taking a toll on me. On top of that I was dealing with a lot of stress and bad anxiety. When I tried kratom for the first time I was absolutely amazed and so grateful. My diarrhea completely went away, pain was managed and my anxiety was gone. It was such a happy day for me and I have taken it since. I LOVE kratom so much, I am so grateful for something natural and plant based. I refuse to use pharmaceutical drugs that cause extreme side effects and with kratom you can not overdose, also if not taken it does not cause horrid side effects like pharmaceutical drugs. With this being said I pray and hope you will take the time to listen to us kratom fans, supporters and lovers for this beautiful leaf that helps so many more than just me. Thank you for taking the time to read

From: trinamarieb@everyactioncustom.com on behalf of Trina Montgomery
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Monday, April 13, 2026 1:02:09 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

In 1993, I hurt my back while on the job. Throughout the last 20 years, I have had numerous surgeries. Attended countless doctors ' appointments and physical therapy. I have been on every pain killer on the market. I received epidurals and cortisone shots every few months. I would end up in the ER with back spasms almost monthly. Nothing seemed to take the pain away. Fast forward to 2016. I lost my 9 year old daughter to cancer. I was devastated. I honestly felt like i could not go on without her. I was in constant pain and then had severe depression and anxiety from losing her. A friend of mine said I should try Kratom. I started taking it and have never looked back. My back pain has become non existent. I no longer see a physician for it. I am off all medications. I havent been to the ER in years. It has also helped my depression. I no longwr take anti depressants or anxiety medications. Of course, I still miss my daughter but at least i am not in the same dark place that I was in. Please, I beg you. Do not take this wonderful product away from me and so many others who depend on Kratom to survive. Help us protect it.
Thank you so much for your time.
wn Personal Experience with Kratom:

Sincerely,
Trina Montgomery

From: Travis Priestley
To: Board Coordination
Subject: Don"t Outlaw Kratom
Date: Saturday, April 18, 2026 2:47:36 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Please don't outlaw this. Kratom has helped me manage my back pain without pain killers and helped me kicked them so I can work and lead a normal life. Please don't ban it.

From: conradrosejr97@everyactioncustom.com on behalf of Thomas Rose
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Tuesday, April 14, 2026 3:59:49 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

My Own Personal Experience with Kratom: I have 5 herniated discs in my neck. I use to take hydrocodone and morphine by the handful. I had a good friend recommend that I try Kratom from a trusted source that uses AMKA to verify the contents. I settled on super speciosa online and it saved my life! I take 5 grams of powder twice a day and have been doing so for 6years now. I own a business in las Vegas. Since starting Kratom I have not had to take ANY pain killers at all. I was on deaths door from Opioid's. When I would run out I would go to the street for pills like 90% of people in chronic pain. Doctors think everyone is an addict so they never give you enough to truly kill the pain. Since starting Kratom my blood pressure has normalized and I don't have the need for opioids any longer. Please reconsider banning kratom. It has allowed me to have a normal life again and my jewelry store is doing great. Morgan Taylor Jewelers 7995 west Sahara ave suite 103. Please feel free to come in or contact me for any reason at all! # 702-259-8011 is the store Number. My personal cell # is [redacted]

Sincerely,
Thomas Rose

From: Wendy Chamberlain
To: Board Coordination
Subject: Kratom
Date: Thursday, April 9, 2026 10:11:26 AM
Attachments: KDA Letter.pdf

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Members of Board of Pharmacy

My name is Wendy Chamberlain, and I am the founder of Kratom Danger Awareness, Inc.

I understand there will be a hearing April 16. I would like to virtually testify if you allow ..

This issue is deeply personal to me. My son, Joseph S. Lumbrazo, died on August 30, 2020 from mitragynine toxicity after using a product marketed as “safe,” “natural,” and widely available. He was not seeking opioids—he used kratom for energy, believing it was harmless. There were no meaningful warnings, no protections, and no public awareness of the risks.

What I have learned since his death is alarming:

- Kratom is not approved by the FDA for any medical use
FDA: https://www.fda.gov/news-events/public-health-focus/fda-and-kratom

- The FDA has identified kratom’s primary compounds (mitragynine and 7-hydroxymitragynine) as having opioid-like effects and potential for abuse
FDA Scientific Statement: https://www.fda.gov/news-events/public-health-focus/fda-and-kratom

- Kratom products are often sold in gas stations, smoke shops, and online with misleading claims of safety and without standardized dosing or oversight
FDA Warning Letters & Safety Concerns: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/kratom

- Products vary widely in potency and may be contaminated with heavy metals or pathogens such as salmonella
CDC Salmonella Outbreak Linked to Kratom: https://www.cdc.gov/salmonella/kratom-02-18/index.html

- Kratom has been associated with addiction, withdrawal, serious health effects, and death
CDC MMWR Report: https://www.cdc.gov/mmwr/volumes/68/wr/mm6814a2.htm

- Updated federal data show over 1,800 kratom-involved deaths reported between 2016–2022
CDC SUDORS Data Summary: https://www.cdc.gov/overdose/data/sudors/index.html

Communities across the country are beginning to recognize that regulation has not worked. Age limits, labeling, and so-called “consumer protection” laws do not address the core issue: this is an unapproved, psychoactive substance being sold with little oversight and significant risk.

Local action matters. By passing this ordinance, Nevada has the opportunity to protect families, prevent future harm, and take a leadership role in public health and safety.

No family should have to learn about kratom the way mine did—through tragedy.

Thank you for your time, your service, and your commitment to protecting your community.

Sincerely,
Wendy Chamberlain
Founder & Chair
Kratom Danger Awareness, Inc.
https://linkprotect.cudasvc.com/url?a=https%3a%2f%2fwww.kratomdangerawareness.org%2f&c=E,1,qGq-WqHSJKU3WtGTDoApqvHRsmPlmJcms209z51D2MHaDhuLXJbMapkHFBBwjsVFguqU8lMK_KoUfwJVw1LoYMzLWjQDzgCBe2o0QrHZJJOeXnfI9eWE&typo=1

U.S. Department of Justice
Drug Enforcement Administration

Office of the Administrator *Springfield, VA 22152*

Kratom Danger Awareness
[redacted]

Dear Kratom Danger Awareness:

This is in response to your September 8, 2025, letter petitioning the Drug Enforcement Administration (DEA) to initiate rulemaking proceedings pursuant to 21 U.S.C. 811(a) to amend 21 CFR 1308.11 to place *Mitragyna speciosa* and all its naturally occurring, synthetic, and semi-synthetic alkaloids into schedule I of the Controlled Substances Act.[1] In the petition, you specifically used the following language parallel to the scheduling of marijuana: "*Mitragyna speciosa* (commonly known as kratom), including its leaves, stems, roots, bark, flowers, seeds, and any other part of the plant, whether growing or not; and any compound, manufacture, salt, derivative, mixture, extract, preparation, or conversion thereof, whether naturally occurring or synthetic; including but not limited to the alkaloids mitragynine, 7-hydroxymitragynine, mitragynine pseudoindoxyl, speciogynine, paynantheine, corynantheidine, and speciociliantine; regardless of concentration, formulation, or intended use." Pet. at 3.

Because the petition substantially complies with the procedural requirements of 21 CFR 1308.43(b), and the grounds upon which the petition relies can be readily understood, DEA accepts the petition for filing under 21 CFR 1308.43(c). In regard to *Mitragyna speciosa,* mitragynine, and 7-hydroxymitragynine specifically, DEA will begin the process of gathering the necessary data under 21 U.S.C. 811(b). As DEA gathers the necessary data, if the petitioner obtains additional information regarding *Mitragyna speciosa,* mitragynine and 7-hydroxymitragynine, please provide such supporting data to DPE@dea.gov.

With respect to the other alkaloids present in *Mitragyna speciosa*, however, the petition fails to provide any relevant medical or scientific evidence to support the request for all other naturally occurring, synthetic, and semi-synthetic alkaloids found in *Mitragyna speciosa*. For example, no data was provided for mitragynine pseudoindoxyl, speciogynine, paynantheine, corynantheidine, and speciociliantine. Upon review, DEA has determined that the data provided to support the scheduling of these alkaloids is insufficient to justify the initiation of proceedings at this time. Therefore, under 21 CFR 1308.43(c), the petitioner's request to initiate proceedings for these other alkaloids is denied. However, DEA invites the petitioner to resubmit the petition to schedule those other alkaloids present in *Mitragyna speciosa* and

[1] A drug or other substance is included in schedule I if it has "a high potential for abuse," "no currently accepted medical use in treatment in the United States," and "a lack of accepted safety for use . . . under medical supervision." 21 U.S.C. 812(b)(1)(A)-(C).

include data which specifically indicates the pharmacological profile, abuse potential, and the threat to public safety for these substances.

If you should have further questions relating to your petition, please feel free to contact the Diversion Control Division's Dug and Chemical Evaluation Section at (571) 362-3249 or DPE@dea.gov.

Sincerely,

OCT 2 9 2025

Terrance Cole,
Administrator

From:	Wade Goodman
To:	Board Coordination
Subject:	Kratom helps me live a better and healthier life, please don"t take away my right to choose what I put in my body
Date:	Tuesday, April 14, 2026 7:58:36 AM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Hello,
I live in Nevada and I use Kratom almost every day to make my life better, I would like to attend the hearing on Thursday but I will be at work, so I am writing this to voice my opinion.

I have used Kratom almost everyday for the last 8 years. I take 100% kratom leaf, not the concentrated or synthetic products. I use it to give me energy in the morning, improve my mood, and for pain relief. It has been so much more effective than any synthetic or pharmaceutical drug I have tried in the past to treat my symptoms. The only side effects I've experienced are minor dehydration and constipation, which are much better than the major side effects I have experienced from other medications. I strongly believe it should not be Schedule 1, it is a natural option for pain relief and many other beneficial medical uses.

I am so happy that I have the option to treat my symptoms by consuming 100% natural plant leaves. Please don't take that away from me and others who need it. I actually feel proud that I live in a state that allows people the option to choose this natural medication.

I agree with the following statement wholeheartedly: "Please oppose scheduling kratom alkaloids as Schedule I. Natural kratom leaf has a demonstrated history of safe use and is not comparable to Schedule I substances. Regulate dangerous synthetic 7-OH products — not natural kratom."

Thank you for reading this and taking it into consideration.
Sincerely,
Wade Goodman

From: walter_weisberg@everyactioncustom.com on behalf of Walter Weisberg
To: Board Coordination
Subject: Oppose Mitragynine Scheduling
Date: Sunday, April 12, 2026 2:56:46 PM

WARNING - This email originated from outside the State of Nevada. Exercise caution when opening attachments or clicking links, especially from unknown senders.

Dear Nevada BOP,

I am writing to respectfully oppose making mitragynine a controlled substance.

My Own Personal Experience with Kratom:

Sincerely,
Walter Weisberg