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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.

Kratom as a substitute for opioids: Results from an online survey.

Drug Alcohol Depend. 2019;202:24-32.

Garcia-Romeu A, Cox DJ, Smith KE, Dunn KE, Griffiths RR.

Kratom (Mitragyna speciosa): User demographics, use patterns, and implications for the opioid epidemic.

Drug Alcohol Depend. 2020;208:107849.

Grundmann O.

Patterns of Kratom use and health impact in the US-Results from an online survey.

Drug Alcohol Depend. 2017;176:63-70.

Smith KE, Rogers JM, Dunn KE, et al.

Searching for a Signal: Self-Reported Kratom Dose-Effect Relationships Among a Sample of US Adults With Regular Kratom Use Histories.

Front Pharmacol. 2022;13:765917.

Smith KE, Rogers JM, Schriefer D, Grundmann O.

Therapeutic benefit with caveats?: Analyzing social media data to understand the complexities of kratom use.

Drug Alcohol Depend. 2021;226:108879.

Swogger MT, Walsh Z.

Kratom use and mental health: A systematic review.

Drug Alcohol Depend. 2018;183:134-40.

Exploring the self-reported motivations of kratom (Mitragyna speciosa Korth.) use: a cross-sectional investigation

Grundmann et al. 2022

(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.

Behnood-Rod A, Chellian R, Wilson R, Hiranita T, Sharma A, Leon F, et al.

Evaluation of the rewarding effects of mitragynine and 7-hydroxymitragynine in an intracranial self-stimulation procedure in male and female rats.

Drug Alcohol Depend. 2020;215:108235.

Hassan R, Pike See C, Sreenivasan S, Mansor SM, Müller CP, Hassan Z.

Mitragynine attenuates morphine withdrawal effects in rats-a comparison with methadone and buprenorphine.

Front Psychiatry. 2020;11:411.

Hemby SE, McIntosh S, Leon F, Cutler SJ, McCurdy CR.

Abuse liability and therapeutic potential of the Mitragyna speciosa (kratom) alkaloids mitragynine and 7-hydroxymitragynine.

Addict Biol. 2019;24(5):874-85.

Yue K, Kopajtic TA, Katz JL.

Abuse liability of mitragynine assessed with a self-administration procedure in rats.

Psychopharmacology (Berl). 2018;235(10):2823-9.

Wilson LL, Harris HM, Eans SO, Brice-Tutt AC, Cirino TJ, Stacy HM, et al

Lyophilized kratom tea as a therapeutic option for opioid dependence.

Drug Alcohol Depend. 2020;216:108310.

Kratom pharmacology studies help understand its effects that contribute to reasons for use and safety

Note: The following studies are representative of several dozen other studies published since 2018 that help understand the effects, and potential benefits and risks of kratom's constituents including mitragynine.

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.

Avery BA, Boddu SP, Sharma A, Furr EB, Leon F, Cutler SJ, et al.

Comparative pharmacokinetics of mitragynine after oral administration of Mitragyna speciosa (kratom) leaf extracts in rats.

Planta Med. 2019;85(4):340-6.

Chakraborty S, DiBerto JF, Faouzi A, Bernhard SM, Gutridge AM, Ramsey S, et al.

A novel mitragynine analog with low-efficacy mu opioid receptor agonism displays antinociception with attenuated adverse effects.

J Med Chem. 2021;64(18):13873-92.

Hill R, Kruegel AC, Javitch JA, Lane JR, Canals M.

(2022) The respiratory depressant effects of mitragynine are limited by its conversion to 7-OH mitragynine.

Br J Pharmacol. 179(14):3875-3885.

Kruegel AC, Grundmann O.

The medicinal chemistry and neuropharmacology of kratom: A preliminary discussion of a promising medicinal plant and analysis of its potential for abuse.

Neuropharmacology. 2018;134(Pt A):108-20.

Macko E, Weisbach JA, Douglas B

(1972) Some observations on the pharmacology of mitragynine [in cats, dogs and monkeys].

Arch Int Pharmacodyn Ther 198(1):145.

Maxwell EA, King TI, Kamble SH, Raju KSR, Berthold EC, Leon F, et al.

Pharmacokinetics and safety of mitragynine in beagle dogs.

Planta Med. 2020;86(17):1278-85.

NIDA.

2022, March 25. Kratom. Retrieved from

https://nida.nih.gov/research-topics/kratom on December 5, 2023

Obeng S, Kamble SH, Reeves ME, Restrepo LF, Patel A, Behnke M, Chear NJ, Ramanathan S, Sharma A, León F, Hiranita T, Avery BA, McMahon LR, McCurdy CR.

Investigation of the Adrenergic and Opioid Binding Affinities, Metabolic Stability, Plasma Protein Binding Properties, and Functional Effects of Selected Indole-Based Kratom Alkaloids.

J Med Chem. 2020 Jan 9;63(1):433-439.

Obeng S, Wilkerson JL, Leon F, Reeves ME, Restrepo LF, Gamez-Jimenez LR, et al.

Pharmacological comparison of mitragynine and 7-hydroxymitragynine: In vitro affinity and efficacy for mu-opioid receptor and opioid-like behavioral effects in rats.

J Pharmacol Exp Ther. 2021;376(3):410-27.

Sharma A, McCurdy CR.

Assessing the therapeutic potential and toxicity of Mitragyna speciosa in opioid use disorder.

Expert Opin Drug Metab Toxicol. 2021;17(3):255-7.

Vicknasingam B, Chooi WT, Rahim AA, Ramachandram D, Singh D, Ramanathan S, et al.

Kratom and pain tolerance: A randomized, placebo-controlled, double-blind study.

Yale J Biol Med. 2020;93(2):229-38.

Chakraborty S, DiBerto JF, Faouzi A, Bernhard, SM, Guttridge, AM, Ramsey, S et al.

.(2021). A Novel Mitragynine Analog with Low-Efficacy Mu Opioid Receptor Agonism Displays Antinociception with Attenuated Adverse Effects.

J Med Chem. 2021;64(18):13873-13892.

McCurdy C, Grundmann O, McLaughlin

J (2020) Kratom Resources. Department of Pharmacodynamics, College of Pharmacy, University of Florida.

https://pd.pharmacy.ufl.edu/research/kratom/. Accessed 8 March 2022.

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.