POLICY BRIEF

AMERICAN KRATOM ASSOCIATION

WHAT IS KRATOM, AND WHAT IS IT USED FOR?

Kratom is a tree that grows naturally in South East Asia (SEA) and is a part of the coffee family. Kratom is typically used to brew a tea and has been used safely in SEA for centuries for an energy boost, increased focus, and general well-being. Kratom has also been safely used in the U.S. since the early 1970's.

At higher use levels, kratom has a sedating effect and it has been found by some to be an effective pain reliever for acute and chronic pain and as an alternative to highly-addictive and potentially deadly opioid medications. In the United States, where it is estimated more than 15 million American use kratom regularly, products are typically sold as powders, capsules, or liquid tinctures (similar to a 5-hour energy drink). Reports of kratom being smoked or injected intravenously are inconsistent with the pharmacology and use patterns of kratom's alkaloids and likely are derivative of attempts by drug addicts to add kratom to other substances they are using.

Importantly, SEA authorities have not reported any kratom overdose deaths. The reasons for kratom use in this region largely mirror those in the U.S., including use as a mild stimulant by agricultural workers and as an alternative to opioids for pain relief and addiction treatment. Such traditional use is reported to benefit quality of life, and improve social and occupational behavior, with little evidence of serious personal or social harm.

IS KRATOM A SCHEDULE I CONTROLLED SUBSTANCE IN THE UNITED STATES?

Kratom is not classified as a Schedule I controlled substance under the Controlled Substances Act (CSA). The Drug Enforcement Administration (DEA) has declined to accept the U.S. Food and Drug Administration's (FDA) repeated recommendations to schedule the two primary alkaloids in kratom, mitragynine (MG) and 7-hydroxymitragynine (7-HMG). In fact, the DEA rescinded the approval of an emergency petition for scheduling of kratom from the FDA published in the Federal Register in October 2016[i] when they determined the FDA had failed to meet the criteria to schedule kratom under that section of the Controlled Substances Act (CSA).

The FDA resubmitted its recommendation for scheduling of kratom's alkaloids on October 17, 2017 and despite the FDA claims that kratom presents an imminent public health threat, the DEA has not acted on that recommendation. If the FDA's assertions on the safety and pharmacological profile were credible, particularly with the claims of deaths and opioid-like effects of kratom, the DEA would have quickly published a Notice of Scheduling to protect the public health. The fact that more than two years has

elapsed since the FDA scheduling petition was submitted to the DEA without any scheduling action, when such requests are typically approved within 90 days, clearly demonstrates the DEA is not persuaded by the FDA's safety claims about kratom.

The American Kratom Association (AKA) strongly concurs with the testimony of the Director of the National Institute on Drug Abuse (NIDA), Nora Volkow, Ph.D., before the U.S. House of Representatives Committee on Appropriations where she responded to the question on how research would be adversely impacted if the DEA classified kratom as a Schedule I substance under the CSA: "Indeed, the moment that a drug gets a Schedule I, which is done in order to protect the public so that they don't get exposed to it, it makes research much harder" (*House Appropriations Committee Testimony, 2019*[ii]).

MG and 7-HMG do bind to the same mu pain receptors in the brain as opioids, which accounts for consumers safely using kratom as an alternative to opioids to manage pain. The significant difference is that there is no evidence that kratom has any negative impact on the respiratory system of a consumer. Opioid overdoses occur when the opiate user literally suffocates because these powerful drugs suppress the respiratory system.

DOES KRATOM PRODUCE OPIOID-LIKE EFFECTS?

The pharmacological effects of MG and 7-HMG are fundamentally different from morphine and other euphoriant opioids that induce respiratory suppression. MG and 7-HMG are G-protein biased, partial agonists whereas morphine is a non-biased, full agonist at mu opiate receptors. Furthermore, the binding profiles of MG and 7-HMG differ from morphine in terms of their affinities and selectivities for opiate and other receptors. Thus, whereas morphine serves as a robust reinforcer for animals, MG did not serve as a reinforcer in the two animal intravenous self-administration studies that have evaluated it (*Hemby et al., 2018; Yue et al., 2018*).

Morphine-like opioids are powerful and reliable euphoriants for recreational opioid users and whereas no formal human abuse potential studies have been conducted to support the conclusion, self-experimentation among recreational substance abusers, as reported on internet sites, indicate that kratom is not a morphine-like euphoriant.

Critically relevant to the inappropriate characterization of kratom as a morphine-like opioid is its respiratory depressing and overdose risk – or lack thereof. Although kratom is estimated to be used by more than 15 million consumers in the U.S., in contrast to approximately 49,000 actually documented opioid deaths in 2017 (not known to include any in which kratom was the primary cause), it is not clear if there have been any direct kratom-related deaths in which pure kratom, MG, and/or 7-HMG were the primary cause of death, though the possibility that there has been one or more cannot be ruled out.

This is consistent with data from SEA, which was reported as follows at NIDA's International Kratom Science Symposium: "There are no known reported severe toxicity or fatality incidents in Malaysia or Thailand where there are large populations of long-term daily users of kratom". Moreover, animal safety and toxicology studies that have been published and/or known to have been provided to the FDA's Office

of Dietary Supplements in support of New Dietary Ingredient Notifications (NDI) for kratom have exposed several species of animals to doses of 100 or more times greater than human equivalent doses without evidence of respiratory overdose death.

Like a significant number of dietary ingredients and supplements currently on the market in the United States, no one can say that kratom has never caused or contributed to death, that kratom carries no risks, or that kratom and specific alkaloids cannot under some conditions cause respiratory depression. However, the science does not support the conclusion that it is a morphine-like opioid on this critical aspect of opioid pharmacology and toxicology.

The pharmacology of kratom is also at odds with the classic powerful soporific (i.e., "narcotic") effects of morphine that are among its defining characteristics for millennia. Although kratom can have relaxing effects that some people report are useful in helping to get to sleep, kratom is well known from decades of study in SEA and surveys in the U.S. to be more commonly used for alerting and focusing effects and sustaining occupational performance much as coffee and tea are used.

In February 2018 the FDA, using a poorly documented computational model, made the claim that kratom alkaloids are opioid analogues and concluded it was "confident in calling compounds found in kratom, opioids", thereby implying that such compounds are inevitably associated with all the same negative consequences of classical opioids (e.g., respiratory depression and addictive liability). This simplistic analysis ignores the fact that substances binding to mu-opioid receptors vary widely in their effects and safety. For example, the life-saving drug naloxone, the OTC antidiarrheal loperamide (Imodium®), and the addiction treatment buprenorphine, all bind to mu-opioid receptors. Although kratom's compounds do in fact bind to mu-opioid receptors, real experimental data show that these compounds have unique signaling properties at mu-opioid receptors and do not induce the same degree of respiratory depression or present the same risk of abuse as classical opioids.

A recent peer-reviewed published article (Henningfield, Grundmann, Babin, Fant, Wang, & Cone[iii]) found that opioids have at least a 1,000 times greater risk of overdose deaths than using kratom. The study emphasizes that more research on kratom safety and risks is needed, and regulation of commercial kratom products to ensure that consumers are informed by FDA labeling and that kratom products are not contaminated or adulterated with other substances.

IS KRATOM ADDICTIVE LIKE CLASSIC OPIOIDS?

Kratom's alkaloids, like caffeine in coffee, can result in a consumer developing a dependency with regular use. Kratom is not addictive because it does not produce the reinforcing euphoric high as opioids do. Withdrawal from kratom dependency generally matches caffeine withdrawal (4-5 days of mild headache, upset stomach, etc.)[iv]. Classic opioid withdrawal mostly involves severe symptoms and typically requires extensive in-patient detox treatment programs that can last months.

Importantly, kratom's alkaloids do not have a significant addiction liability as classic opioids do. Even then, kratom's alkaloids have been classified as "atypical opioids" (*Kruegel, et. al*.[v]) that do not have the same respiratory suppression effects as classic opioids like morphine. Most of the published literature

references to kratom's "opioid-like activity" is derived from findings in cell and animal studies where mitragynine has been found to bind to and activate opioid receptors and produce some analgesic effects (*Adkins, et. al.*[vi]*, Boyer et. al.*[vii]*, Kruegel, et. al.*[viii]), but there is strong evidence indicating that kratom's effects are distinct from those of classic opioids (*Henningfield, et. al.*[ix]*, Singh, et. al.*[x]*, Vicknasingam*[xi]).

The U.S. National Institutes of Health (NIH) and NIDA each commissioned an independent animal study, the gold standard in addiction research, to determine the addiction liability of kratom's alkaloids.

- A NIH funded peer-reviewed and published study concluded (1) that **kratom is not dangerously addictive** and does not act in the same way as classic opioids in suppressing the respiratory system of the consumer, and (2) that the **alkaloids in kratom actually have the effect of reducing the cravings in the animals for morphine** (*Hemby, Addiction Biology, 27 June 2018*[xii]*)* That finding helps explain why so many struggling with opioid use disorder in the United States are attempting to use kratom to reduce their opioid use or wean off opioids entirely, and helps us understand why kratom shows up in toxicology screens of opioid overdose victims who apparently had turned to kratom for its potential benefits in fighting their opioid addictions.

- A second intramural NIDA study confirmed that kratom **is not dangerously addictive** and concluded that more research needed to be done on the value kratom could have as an alternative pain management therapy to opioids (*Yue, Psychopharmacology, July 2018*[xiii]).

NIDA has currently funded more than $10 million in kratom research studies, including two grants totaling $6.9 million over the next 5 years at the University of Florida[xiv] that will investigate the potential for kratom's alkaloids to treat opioid withdrawal. The University of Florida research team supported in their grant submissions affirming that "studies indicate that mitragynine does not exhibit abuse-related effects and can attenuate opioid intake"[xv].

Additionally, the U.S. House of Representatives has called on NIH to expand studies on kratom (*House Committee on Appropriations LHHS, 2020*[xvi]*)*, and specifically opposed a ban on kratom that would significantly impede needed new research. The House Report also stated the Committee "is aware of the potential promising results of kratom for acute and chronic pain patients who seek safer alternative to sometimes dangerously addictive and potentially deadly prescription opioids".

WHY IS KRATOM CURRENTLY BANNED IN 6 STATES?

In 2009, there were 9 people who died in 12-month period in Sweden reportedly from consuming a powdered kratom product called "Krypton." A cluster of that many deaths in a short time period caught the attention of public health officials around the world. The FDA disseminated this information widely to the states, and between 2009 and 2016 the states of Alabama, Indiana, Wisconsin, Vermont, Rhode Island, and Arkansas enacted bans on kratom.

The FDA did not disclose that a peer-reviewed article on those 9 deaths in Sweden published in 2011 concluded the Sweden deaths actually were caused by adulterating the kratom product with a lethal dose

of the powerful chemical *O*-desmethyltramadol.[xvii] If the same amount of *O*-desmethyltramadol were added to a cup of coffee or a glass of orange juice the consumer would be dead in minutes.

In November 2019, the Rhode Island Director of the Department of Health opened a formal review of the kratom ban there, and the Wisconsin State Senate Health Committee unanimously voted to open a bill file on replacing the kratom ban with a regulatory scheme to allow consumers over the age of 21 access to pure unadulterated kratom.

In addition, in 2019, Utah, Georgia, Arizona, and Nevada all enacted legislation known as the Kratom Consumer Protection Act (KCPA) that requires manufacturers to adhere to current good manufacturing practices (CGMP) for kratom products; limits alkaloid content to that proportion of alkaloid content present in the natural plant; restricts any adulteration or synthesizing of kratom's alkaloids; requires labeling to allow consumers to be informed on product ingredients; and imposes an age restriction to ensure consumers have access to safe kratom products. Another 21 states have KCPA legislation pending in the 2020 legislative season.

The FDA claims kratom can have unknown adverse interactions with prescription drugs. The Food, Drug & Cosmetic Act (FD&CA) requires any adverse event from a prescription drug, over-the-counter drug, or dietary supplement to be reported to the FDA Adverse Event Reporting System (FAERS) database. For dietary ingredients and dietary supplements, no studies are required in advance of marketing to determine any contraindications with prescription drugs. Whenever credible reports are received by the FDA on adverse events associated with the use of any marketed product, and if the investigation finds a contraindication, then a warning label is required to advise consumers of possible contraindications.

To date, there have been no significant adverse events reported from the use of pure kratom when used along with any prescription drug or dietary supplement that would require any warning label. Given that kratom has been safely used in SEA for centuries, and in the United States at least since the early 1970's, the likelihood that kratom has significant contraindications is unlikely. If such adverse events are observed in the future, the appropriate response is the warning label protocol provided by existing law.

The presence of kratom in the toxicology screens of polydrug users who have overdosed is not surprising given many opioid addicts report using kratom to reduce or wean off of opioid use, but is not an indication of any contraindication or adverse event derivative of any interaction with kratom.

IS KRATOM COMPLETELY SAFE FOR CONSUMER USE?

Pure kratom used responsibly, like thousands of other dietary supplements and over-the-counter drugs, is safe for use. It is estimated that about a quarter of kratom consumers use it to manage acute and chronic pain as an alternative to dangerous opioids or to reduce or wean off of opioids entirely.

Some unscrupulous bad actors in the kratom marketplace have found a lucrative market for dangerously adulterated kratom products spiked with fentanyl, heroin, morphine and other opioids to deceive consumers by giving the kratom product an "opioid kick" when they think they are purchasing pure kratom. These spiked kratom products should be banned from the marketplace just like any other

adulterated or misbranded drug. NIDA conducted its own review of the deaths reported by the FDA to be associated with kratom and concluded that all resulted from polydrug use or adulterated kratom products, and even the FDA now concurs with that assessment[xviii]. One death cited by the FDA associated with the use of pure kratom has been investigated but there is no blood data in the autopsy to confirm that claim.

There were several media reports in April 2019 claiming that "CDC reported 91 kratom overdose deaths"[xix]. In actual fact, CDC reported on claims made by medical examiners and the CDC proceeded to provide an analysis that concluded most of the kratom detected in toxicology screens from the reported deaths, where data was available, involved polydrug use. For the few death reports that did not find other drug use might have missed other drugs because the medical examiners did not properly test for them.

Importantly, the CDC made no conclusion about how many deaths (if any) in which kratom was reported by medical examiners could actually be attributed primarily, if at all, to kratom. The CDC report offered the following conclusion: "Kratom was determined to be a cause of death (i.e., kratom-involved) by a medical examiner or coroner for 91 (59.9%) of the 152 kratom-positive decedents, including seven for whom kratom was the only substance to test positive on postmortem toxicology, although the presence of additional substances cannot be ruled out. In approximately 80% of kratom-positive and kratom-involved deaths in this analysis, the decedents had a history of substance misuse, and approximately 90% had no evidence that they were currently receiving medically supervised treatment for pain. Postmortem toxicology testing detected multiple substances for almost all decedents." These media reports misrepresent the CDC article and there is no question that the risk of kratom is far lower than carried by opioids and other drugs that are substituted for by many users.

Consumers currently are put at unacceptable risk by an unregulated kratom marketplace where it is the "wild west" where no appropriate regulatory scheme is in place to ensure kratom products are pure and unadulterated.

DOES KRATOM CONTAMINATED WITH SALMONELLA OR HEAVY METALS POSE A THREAT TO CONSUMERS?

The FDA, the U.S. Department of Agriculture (USDA), and the Centers for Disease Control (CDC) monitor foodborne illness caused by Salmonella. The FDA actively monitors levels of metals -- such as arsenic, lead, cadmium, mercury and others – that are found in the food supply. Some kratom products in 2018 and early 2019 were found to have Salmonella and levels of heavy metals that raised concerns.

While Salmonella is common to plant-based food products, improvements in harvesting, drying, and grinding machines used to process kratom raw material in Indonesia (where 95% of the kratom imported to the U.S. originates) have reduced kratom raw material exposure of both Salmonella and heavy metals, and U.S. based kratom manufacturers have implemented rigorous testing for these contaminants. These contaminants are not unique to kratom, and adherence to CGMPs has proven to significantly reduce potential exposure to consumers.

WHAT KIND OF KRATOM REGULATIONS SHOULD BE ADOPTED?

The AKA strongly supports consumer protections already authorized under the FD&CA and believes the FDA should publish standards for the manufacturing and marketing of kratom products to consumers as a dietary ingredient or dietary supplement. The FDA has refused to recognize kratom as a dietary ingredient and insists that it is an unapproved drug that must be subject to a New Drug Application (NDA) and can only be marketed as a prescription drug if approved.

The AKA strongly endorses consumer protections that require kratom manufacturers to follow current CGMP regulations; restrict any alteration of the proportion of alkaloids found in the natural plant; not allow any dangerous substance to be added to a kratom product that would be injurious to a consumer; require compliant labeling to inform consumers of the content; impose age restrictions; and not permit any therapeutic marketing claims that are not supported with approved clinical trial evidence.

Given the unwillingness of the FDA to regulate kratom as a dietary ingredient or supplement, the AKA has advocated for these consumer protections to be enacted by individual states. The AKA also expects federal legislation will be filed to require the FDA to recognize kratom as a dietary ingredient or supplement to ensure consumers are protected by empowering them in a regulated marketplace that increases their confidence in kratom product safety.

The American Kratom Association (AKA), a consumer-based non-profit organization, advocates for the more than 15 million kratom consumers in the United States to possess and consume safe and natural kratom.

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BACKGROUND RESEARCH

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