AMERICAN KRATOM ASSOCIATION

PETITION BY THE AMERICAN KRATOM ASSOCIATION REQUESTING THE STATE OF OHIO BOARD OF PHARMACY RESCIND ITS RESOLUTION ON THE PROPOSED CLASSIFICATION OF KRATOM AS A SCHEDULE I CONTROLLED SUBSTANCE

October 17, 2018

INTRODUCTORY STATEMENT

The American Kratom Association (AKA), represents the nearly 5 million consumers of the botanical kratom in the United States, and tens of thousands of kratom consumers in the State of Ohio. The AKA hereby files this Petition with the State of Ohio Board of Pharmacy (BOP) challenging the Proposed Classification of Kratom as a Schedule I Controlled Substance.

The AKA shows in this petition that the proposed Classification of Kratom as a Schedule I Controlled Substance fails to meet the standards for scheduling set in section 3719.44 of the Ohio Revised Code.

The BOP proposal to classify kratom as a Schedule I substance specifically relies upon outdated and unsubstantiated theories about the pharmacologic effects of the alkaloids in kratom that have been directly contradicted by new peer-reviewed published scientific literature. In addition, the BOP proposal is simply premature given the ongoing and presently unsettled review of the science to justify the scheduling of kratom's alkaloids at the federal level.

THE 8-FACTOR ANALYSIS ON KRATOM

The BOP is required pursuant to section 3719.44 to consider 8 criteria to determine the appropriateness of the scheduling of kratom. These 8 criteria mirror the federal substance scheduling benchmarks under the Controlled Substances Act (CSA). The current ongoing federal review by the Drug Enforcement Administration (DEA) is evaluating the new scientific research presented in this Petition.

An independent 8-Factor Analysis (8-FA) adhering to the CSA requirements was conducted by Jack Henningfield, Ph.D., Vice President of Research, Health Policy and Abuse Liability, at PinneyAssociates, and Adjunct Professor of Behavioral Biology, Johns Hopkins University School

of Medicine, and was submitted to the DEA on November 29, 2016 in response to a request from the DEA following its withdrawal of a proposed emergency scheduling notice on kratom.[1]

Dr. Henningfield's conclusions on the now withdrawn emergency scheduling notice by the DEA speaks directly to the basis for the current BOP proposal to classify kratom.

- Placement of kratom in the CSA is not warranted from a public health perspective and is more likely to cause public health problems that do not presently exist.

- Kratom consumption has not emerged as a public health or medical problem for adults or children despite more than two decades of rapidly increasing consumption by millions of Americans served by approximately 10,000 vendors.

- Kratom consumption appears to be primarily motivated by its perceived effects that enhance well-being, occupational performance, and social interactions, as well as serving as a natural "home remedy" that is preferred by millions of Americans to conventional medicines.

- The foregoing is consistent with the pharmacology of kratom and more specifically its alkaloids (MG and 7-HMG), which produce mixed pharmacological effects that are generally mild and caffeine stimulant-like at lower dosages. Consumption does not typically interfere with work or social activities and commitments, and in fact kratom is widely reported in the US, as in Southeast Asia, to contribute to work productivity, quality of life, and social relationships.

- Although the primary alkaloids of kratom, MG and 7-HMG, may demonstrate some characteristics considered for controlled substance scheduling, as do many other products including caffeine, nicotine, some antihistamines, and alcohol, despite decades of wide-spread consumption, there does not appear to be a public health risk that would warrant their scheduling.

- MG and kratom have very low toxicity, and thus a favorable safety profile. There have been few reports of serious adverse events or deaths associated with kratom and for most, the contribution of kratom is not clear. For example, in Sweden in about 2008-2009, a blend of herbals including kratom along with the opioid analgesic *O*-desmethyltramadol, and possibly co-administration of other drug substances was associated with nine deaths. Tramadol (including *O*-desmethyltramadol), in contrast to kratom, has been documented to carry a risk of severe respiratory depression and overdose death. To date, in the US, there have been no confirmed reports of death that can be considered "causatively" due to kratom overdose. How many, if any deaths, are

[1] Jack E. Henningfield, Reginald V. Fant, Daniel W. Wang, *The abuse potential of kratom according to the 8 factors of the controlled substances act: implications for regulation and research*, Psychopharmacology, https://doi.org/10.1007/s00213-017-4813-4, published online 23 December 2017.

"probably" classified as kratom poisoning deaths is not clear. This is consistent with the far larger and longer Southeast Asian experience of very few serious adverse events. In both the US and Southeast Asia, the low toxicity of kratom is in striking contrast to the experience with opioids.

- There appear to be remarkably low risk of serious adverse effects from kratom consumption as compared to opioids and other common drugs of abuse. Further, there is little evidence that kratom products are used by routes other than oral beverage or food consumption. In contrast, opioids and many other drugs of abuse are frequently used by high impact routes such as nasal insufflation, smoking, and injecting. Graduation from oral consumption to such other routes is common for opioids and other substances of abuse but not for kratom.

- Consumption of kratom products appears to provide positive benefits such as relief of pain and fatigue without the adverse consequences produced by other products that are used for similar purposes as reported in the appended testimonials and over a century or more of documented consumption in Southeast Asia. For example, liver disease caused deaths associated with the use of acetaminophen is a serious problem in the US, and there are problems of serious GI side effects and cardiovascular problems associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDS). At the far extreme, there is the inherent risk of overdose and serious addiction associated with the use of opioids. For those who manage various ailments with kratom instead of such products, the benefit to risk ratio appears favorable.

Dr. Henningfield's conclusions on his research speak directly to the current BOP proposal on kratom:

> "It's important to understand that although kratom has some mild effects similar to opioids, its chemical make-up is different, and it appears overall much safer, with apparently relatively small effects on respiration. In fact, kratom's analgesic effects and impact on energy, combined with its favorable safety profile supports continued access by consumers to appropriately regulated kratom products while research on its uses continues. Furthermore surveys suggest that kratom products are used by many former opioid users as a natural remedy to help them abstain from opioids."[2]

There is an important distinction between a dietary ingredient/supplement that a consumer may choose to safely use as a part of their health and well-being regimen

[2] Pinney Associates, *Pinney Associates' Scientific Abuse Potential Assessment of Kratom Finds Evidence of Public Health Benefit and Little Harm*, https://www.prnewswire.com/news-releases/pinneyassociates-scientific-abuse-potential-assessment-of-kratom-finds-evidence-of-public-health-benefit-and-little-harm-300392756.html, January 18, 2017.

which is perfectly legal, and manufacturers, distributors, and vendors who make impermissible health claims to increase sales and their own economic advantage.

EVALUATING KRATOM UNDER THE EIGHT CRITERIA

(1) The actual or relative potential for abuse.

The BOP solely cites the FDA's analysis of the chemical structures of kratom, the FDA's use of it's PHASE computational model, and "reports of adverse effects in humans"[3] to justify the FDA's confidence in characterizing kratom as an opioid.[4]

RESPONSE:

Kratom is not a classic opioid and does not have effects of classic opioids. The current body of credible research on the actual effects of kratom demonstrates that it is not dangerously addictive, nor is it similar to "narcotics like opioids" with respect to "addiction" and "death" as stated by the FDA. Equally important, four surveys indicate that kratom is presently serving as a lifeline away from strong, often dangerous opioids for many of the nearly 5 million Americans who use kratom. The alkaloids in Kratom can provide pain relief, but kratom's alkaloids binding to the opioid receptor in the brain is only a partial opioid agonist. Partial opioid agonists affect the same opioid receptors in the brain but do so in a much different fashion than opiates such as Heroin or Morphine) or Opioids like Oxycodone or Methadone. Kratom use is not associated with high-risk negative side effects of opioids such as dangerous addiction or respiratory failure.

One of the leading researchers on kratom is Andrew Kruegel, a Columbia University pharmacologist who has extensively studied kratom, pointed out the deficiencies in the FDA PHASE modeling system as follows:

- Researchers have already demonstrated that compounds in kratom bind to mu opioid receptors, including an article he co-authored and that was published in 2016,[5] which examines how compounds in kratom, particularly mitragynine, only partially activate certain opioid receptors, yet have distinct pharmacological properties.

---

[3] State of Ohio Board of Pharmacy, *Resolution: Classification of Kratom As A Schedule I Controlled Substance*, October 2018.

[4] Office of the Commissioner. (2018, February 6). Press Announcements - Statement from FDA Commissioner Scott Gottlieb, M.D., on the agency's scientific evidence on the presence of opioid compounds in kratom, underscoring its potential for abuse. Retrieved from https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm595622.htm

[5] *Synthetic and Receptor Signaling Explorations of the Mitragyna Alkaloids: Mitragynine as an Atypical Molecular Framework for Opioid Receptor Modulators***,** Andrew C. Kruegel, Madalee M. Gassaway, Abhijeet Kapoor, András Váradi, Susruta Majumdar, Marta Filizola, Jonathan A. Javitch, and Dalibor Sames**,** *Journal of the American Chemical Society* **2016** *138* (21), 6754-6764, DOI: 10.1021/jacs.6b00360

- Kratom does not appear to share the dangerous side effect of respiratory depression that other opioids have—that's when someone's breathing slows down and could stop completely.

- Opioids are, by definition, compounds that interact with opioid receptors. But not every opioid has the same effect. Naloxone, for example, binds to opioid receptors, but is actually used to reverse opioid overdoses.

- The problem with saying it's 'an opioid' without qualification is that it just paints everything with this broad brush, and obviously carries a negative connotation given what's going on in the country right now.[6]

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

The BOP relies exclusively on information published by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) in its conclusions on how kratom alkaloids are "selective and full agonists of the mu-opioid receptor" and the toxicity and pharmacologic profile of kratom's two primary alkaloids, mitragynine (MG) and 7-hydroxymitragynine.

RESPONSE:

The EMCDDA conclusions do not represent a scientific consensus on these issues and should not be the basis for a major public policy decision to schedule kratom as a Schedule I controlled substance.

The unique and distinct pharmacologic activity of kratom, along with the documented analysis of it being only a partial agonist on the mu-opioid receptors, is robustly examined in Dr. Kruegel's research[7] on how kratom's alkaloids act in an atypical fashion that contradicts the EMCDDA theory.

> The alkaloids of the Southeast Asian plant Mitragyna speciosa, represented by the prototypical member mitragynine, are an unusual class of opioid receptor modulators with distinct pharmacological properties. Here we describe the first receptor-level functional characterization of mitragynine and related natural alkaloids at the mu-, kappa-, and delta-opioid receptors. These results show that mitragynine and the oxidized analog 7-hydroxymitragynine, are partial agonists of the human mu-opioid receptor and competitive antagonists at the kappa- and delta-opioid receptors. We also show that mitragynine and 7-hydroxymitragynine are G-protein-biased agonists of the mu-opioid receptor,

[6] Tonic, Jesse Hicks, February 8, 2018, The FDA Called Kratom an Opioid, Which is Pretty Misleading.
[7] *Synthetic and Receptor Signaling Explorations of the Mitragyna Alkaloids: Mitragynine as an Atypical Molecular Framework for Opioid Receptor Modulators***,** Andrew C. Kruegel, Madalee M. Gassaway, Abhijeet Kapoor, András Váradi, Susruta Majumdar, Marta Filizola, Jonathan A. Javitch, and Dalibor Sames**,** *Journal of the American Chemical Society* **2016** *138* (21), 6754-6764, DOI: 10.1021/jacs.6b00360

> which do not recruit β-arrestin following receptor activation. Therefore, the Mitragyna alkaloid scaffold represents a novel framework for the development of functionally biased opioid modulators, which may exhibit improved therapeutic profiles. Also presented is an enantioselective total synthesis of both (-)- mitragynine and its unnatural enantiomer, (+)-mitragynine, employing a proline-catalyzed Mannich-Michael reaction sequence as the key transformation. Pharmacological evaluation of (+)-mitragynine revealed its much weaker opioid activity. Likewise, the intermediates and chemical transformations developed in the total synthesis allowed the elucidation of previously unexplored structure-activity relationships (SAR) within the Mitragyna scaffold. Molecular docking studies, in combination with the observed chemical SAR, suggest that Mitragyna alkaloids adopt a binding pose at the mu-opioid receptor that is distinct from that of classical opioids.

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

The Ohio BOP cites a case of a man who fatally overdosed propylhexedrine and kratom, and noted that the postmortem mitragynine concentrations ranged from 0.01 mg/kg to 1.20 mg/l.[8] In addition, BOP restates its reliance on the PHASE methodology to assert that (1) "there is no evidence that kratom is safe or effective for any medical use," and (2) that compounds in kratom were found to bind to mu-opioid receptors similar to other opioids; and (3) the FDA found serious side effects associated with kratom, including seizures and respiratory depression.[9]

RESPONSE:
The kratom plant itself does not contain either of the referenced alkaloids at dangerous levels. It is the adulteration of kratom products that impacts the "identity, purity, and quantity" of those alkaloids that leads to uncertainty and inconsistency of kratom products, and it is those adulterants that pose a threat to public health. An article that was published in *Addiction Biology* in June 2018 authoritatively addresses this issue and concludes that MG "does not have abuse potential and reduces morphine intake"[10] and that 7-HMG potentially has abuse potential, but only in purified or concentrated adulterants. One of the world's experts on addiction and the behavioral, cognitive, and central nervous system effects of drugs, Jack E. Henningfield, Ph.D., emphasized the importance of these findings.

> "This is an important study that addresses the addictiveness of kratom," says Jack E. Henningfield, Ph.D., at Pinney Associates, a health consulting firm. "It

---

[8] The European Monitoring Centre for Drugs and Drug Addiction. Kratom (Mitragyna speciosa) drug profile. http://www.emcdda.europa.eu/publications/drug-profiles/kratom#pharmacology

[9] Office of the Commissioner. (2017, November 14). Press Announcements - Statement from FDA Commissioner Scott Gottlieb, M.D. on FDA advisory about deadly risks associated with kratom. Retrieved from https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm584970.htm

[10] Hemby *et al*. "*Abuse liability and therapeutic potential of the Mitragyna speciosa (kratom) alkaloids mitragynine and 7-hydroxymitragynine,"* Addiction Biology, 27 June 2018, doi: 10.1111/adb.12639

> shows that the major naturally occurring constituent responsible for the health-related effects of kratom, mitragynine, is of very low abuse potential. A second substance, 7-HMG, which naturally occurs at such low levels in kratom that it might be of minimal health consequence, has higher abuse potential. This has at least two regulatory implications. First, the findings do not support the FDA's claim that kratom is a narcotic-like opioid. Second, in regulating kratom products, the FDA could set standards to ensure that no kratom product contain levels of 7-HMG exceeding those that are commonly present in kratom leaves and products."[11]

The issue of the toxicity of MG at postmortem concentrations is predicated on the premise advanced by the FDA that any level of MG in a toxicology screen is dangerous or fatal. The question of whether a high level of MG in a decedent's bloodstream is addressed conclusively in peer-reviewed research article, Mitragynine concentrations in two fatalities, authored by Domingo, Roider, Graw, Misshoff, and Sachs,[12] actually directly contradicts the FDA conclusion:

> "Two cases of fatalities are reported of which the recreational use of Mitragyna speciosa ("kratom") could be confirmed. One of these cases presents with one of the highest postmortem mitragynine concentrations published to date. Our results show that even extremely high mitragynine blood concentrations following the consumption of kratom do not necessarily have to be the direct cause of death in such fatalities as a result of an acute overdose (emphasis added). The two cases are compared with regard to the differences in mitragynine concentrations detected and the role of mitragynine in the death of the subjects. Irrespective of the big differences in mitragynine concentrations in the postmortem blood samples, mitragynine was not the primary cause of death in either of the two cases reported here (emphasis added). Additionally, by rough estimation, a significant difference in ratio of mitragynine to its diastereomers in the blood and urine samples between the two cases could be seen."

(4) The history and current pattern of abuse.

The Ohio BOP cites (1) the expanded use of kratom in the United States; (2) FDA regulatory actions against three marketers and distributors of kratom products for illegally selling unapproved kratom-containing drug products; (3) using unproven medical claims for those kratom products; (4) increases in kratom exposures reported to poison control centers[13]; (5)

---

[11] High Point University, *Professor's Research Shows Therapeutic Potential for Kratom,* June 29, 2018, http://www.highpoint.edu/blog/2018/06/professors-research-shows-therapeutic-potential-for-kratom/

[12] Domingo, Roider, Stover, Graw, Mussoff, Sachs, Bicker; *Mytragynine concentrations in two fatalities*, Forensic Science International, 2016, http://dx.doi.org/10.1016/j.forsciint.2016.12.020

[13] United States Drug Enforcement Administration. Schedules of Controlled Substances: Temporary Placement of Mitragynine and 7-Hydroxymitragynine Into Schedule I. https://www.federalregister.gov/documents/2016/08/31/2016- 20803/schedules-of-controlled-substances-

that no marketer has sought to develop a drug that includes kratom in the U.S.; (6) that several states and local jurisdictions have banned kratom[14]; and (7) that the DEA has listed kratom as a Drug and Chemical of Concern.[15]

Response:

The FDA has been engaged in a significant anti-kratom campaign since 2012 when it imposed its first Import Alert on kratom in 2012, and has widely disseminated misleading, incomplete, inaccurate, and demonstrably false information to various federal agencies, the Congress, state legislatures and state regulatory agencies, and the public on the addiction and safety profile of kratom.

There are now four U.S. surveys, including some funded with grants from NIDA, along with thousands of signed testimonials cited in the comments submitted to the DEA during the public comment period that ended on December 1, 2016, that collectively document significant fears among kratom consumers that the government will wrongfully ban kratom. The survey results demonstrate that any kratom ban would force many of these consumers to the illicit contraband market to find alternative pain management therapies, and that would pose a far higher safety risk to the public than the current marketplace where kratom is available.

In this context, the AKA commissioned a survey[16] of kratom consumers that was recently completed and the preliminary results confirm two earlier cited surveys that many consumers would turn to prescription drugs if kratom were no longer available. The survey results document a perverse and unintended consequence resulting from the FDA's public health advisory on kratom, and if the Ohio BOP recommendation on scheduling kratom is adopted, where the threat to public health, adverse events, and deaths would occur because of any kratom ban. Specifically, the survey concluded that if kratom were no longer legally available, more than one-quarter of survey respondents said they would try to get it even if it were illegal. About one-in-five survey respondents said they would start using "something else" and approximately two-thirds of these respondents said that "something else" would be "prescription drugs," and about one-third would consider using "illicit or illegal drugs."

It is inconceivable that the Ohio BOP would favor a policy that would foreseeably force a patient who has been weaned from opioid addition back to dangerously addictive and potentially deadly opioid prescription medications. These facts clearly support the AKA's position that the FDA's public health advisory creates an unusual situation requiring an immediate review in the public interest and requiring the FDA to explain and support its alleged evidence supporting its positions on kratom.

---

temporary-placement-of-mitragynine-and-7-hydroxymitragynine-into?utm_campaign=pi+subscription+mailing+list&utm_medium=email&utm_source=federalregister.gov

[14] What's Kratom, and Why Are States Banning It? Governing Magazine. http://www.governing.com/topics/health-human- services/sl-kratom-state-ban.html

[15] DEA Drug Fact Sheets (2017). Retrieved from https://www.dea.gov/factsheets/kratom

[16] Grundmann et al., Drug and Alcohol Dependence, 2017; Pain Network News, 2017

The public interest continues to be harmed by the FDA's willful dissemination of misinformation on kratom to inform the opinions and actions of a variety of other public entities, including the U.S. Congress, state legislators, and a myriad of local government counties, cities and towns. In fact, the BOP cites the fact that kratom has been "banned in several states including Alabama, Arkansas, Indiana, Vermont, Rhode Island, Wisconsin and the District of Columbia have banned kratom, along with at least three cities — Denver, San Diego and Sarasota, Florida." But, the BOP fails to acknowledge that these bans are a direct result of a long-standing anti-kratom misinformation campaign promulgated by the FDA, and the DEA at the behest of the Agency, and the current bans merely document the necessity of the correction of the inaccurate information disseminated by the FDA.

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

The Ohio BOP relies on various reports to document expanded distribution and consumer use of kratom in the United States, including shipment seizures resulting from the FDA Import Alert on kratom.[17] In addition, the BOP cites reports from forensic laboratories showing an increase in the number of toxicology reports showing the presence of kratom/mitragynine and concludes this proves "widespread abuse and trafficking" activity, and demonstrates the presence of these substances on the recreational drug market.[18]

In addition, the BOP points to reports they have received that kratom users have reported the "most common route of administration for kratom is intravenous injection (aka "shooting"). Participants in the Akron-Canton region estimated that out of 10 kratom users, seven would shoot the drug and three would orally consume the drug (including drinking it as a tea).[19]

RESPONSE:

There is no disagreement that the popularity of kratom has grown in the United States, and that includes the activities of unscrupulous smoke shop or illegal street drug dealers who are blending kratom into dangerous drug products that are used in the recreational drug market. The best evidence of this condition in the marketplace is the report that seven of ten kratom

---

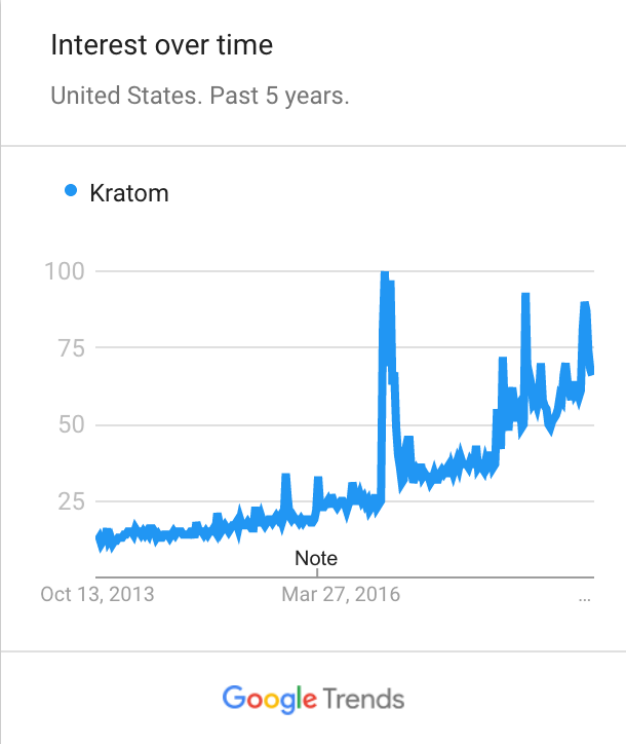
[17] United States Drug Enforcement Administration. Schedules of Controlled Substances: Temporary Placement of Mitragynine and 7-Hydroxymitragynine Into Schedule I. https://www.federalregister.gov/documents/2016/08/31/2016- 20803/schedules-of-controlled-substances-temporary-placement-of-mitragynine-and-7-hydroxymitragynine-into?utm_campaign=pi+subscription+mailing+list&utm_medium=email&utm_source=federalregister.gov

[18] United States Drug Enforcement Administration. Schedules of Controlled Substances: Temporary Placement of Mitragynine and 7-Hydroxymitragynine Into Schedule I https://www.federalregister.gov/documents/2016/08/31/2016- 20803/schedules-of-controlled-substances-temporary-placement-of-mitragynine-and-7-hydroxymitragynine-into?utm_campaign=pi+subscription+mailing+list&utm_medium=email&utm_source=federalregister.gov

[19] Ohio Department of Mental Health and Addiction Services [OhioMHAS] (2018). Ohio Substance Abuse Monitoring Network: Surveillance of Drug Abuse Trends in the State of Ohio: June 2017 - January 2018. Columbus, OH: State of Ohio.

users “shoot the drug” because the pharmacologic activity of kratom would have no effect in such a mode of administration. It would have to be other substances in an adulterated mixture for kratom to be administered in this manner.

it is also true that kratom use is rising in the United States and that has led to a dramatic increase in the number of searches done on kratom as anecdotal reports of its efficacy in treating pain, mental health disorders, and opioid addiction have spread.



The kratom plant itself does not contain either of the referenced alkaloids at dangerous levels. It is the adulteration of kratom products that impacts the “identity, purity, and quantity” of those alkaloids that leads to uncertainty and inconsistency of kratom products, and it is those adulterants that may pose a threat to public health. An article that was published in *Addiction Biology* in June 2018 authoritatively addresses this issue and concludes that MG “does not have abuse potential and reduces morphine intake”[20] and that 7-HMG potentially has abuse potential, but only in purified or concentrated adulterants. One of the world’s experts on addiction and the behavioral, cognitive, and central nervous system effects of drugs, Jack E. Henningfield, Ph.D., emphasized the importance of these findings.

> “This is an important study that addresses the addictiveness of kratom,” says Jack E. Henningfield, Ph.D., at Pinney Associates, a health consulting firm. “It shows that the major naturally occurring constituent responsible for the health-

[20] Hemby *et al*. “*Abuse liability and therapeutic potential of the Mitragyna speciosa (kratom) alkaloids mitragynine and 7-hydroxymitragynine,”* Addiction Biology, 27 June 2018, doi: 10.1111/adb.12639.

> related effects of kratom, mitragynine, is of very low abuse potential. A second substance, 7-HMG, which naturally occurs at such low levels in kratom that it might be of minimal health consequence, has higher abuse potential. This has at least two regulatory implications. First, the findings do not support the FDA's claim that kratom is a narcotic-like opioid. Second, in regulating kratom products, the FDA could set standards to ensure that no kratom product contain levels of 7-HMG exceeding those that are commonly present in kratom leaves and products."[21]

(6) The risk to the public health.

The Ohio BOP cites death data published by the FDA alleging 44 deaths,[22] and recent data from the Ohio Department of Health linking 6 deaths between 2016 and 2017 where "Kratom was indicated as the primary cause of death."[23]

The BOP also reported on concerns about the conditions "under which the drug is produced" where there was a recent multi-state recall of kratom products that tested positive for salmonella contamination.[24]

Response:

Despite the clear record of safe use, the FDA claims there are 44 deaths globally that they characterize as "kratom associated deaths." The data supporting this claim, in an independent analysis conducted by Jane Babin, Ph.D., Esq., was found to be filled with exaggerated claims, discredited research, and distorted data that fails to meet the evidentiary standard for placing kratom as a Schedule I controlled substance.

> "A review of the available FDA data reveals the overwhelming majority of the cited deaths fails to provide a cohesive or reasonable scientific basis to conclude any of the deaths was caused by kratom, nor does the information released conclusively support any conclusion that kratom was associated to the cited death other than coincidentally. Only one case report released by the FDA suggests that the only substance detected in the decedent's blood was kratom,

---

[21] High Point University, *Professor's Research Shows Therapeutic Potential for Kratom,* June 29, 2018, http://www.highpoint.edu/blog/2018/06/professors-research-shows-therapeutic-potential-for-kratom/

[22] Office of the Commissioner. (2018, February 6). Press Announcements - Statement from FDA Commissioner Scott Gottlieb, M.D., on the agency's scientific evidence on the presence of opioid compounds in kratom, underscoring its potential for abuse. Retrieved from https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm595622.htm

[23] Ohio Department of Health, Violence and Injury Prevention Program. State Unintentional Drug Overdose Reporting System (SUDORS). Received August 24, 2018.

[24] Center for Food Safety and Applied Nutrition. (2018, April 19). Outbreaks - FDA Investigates Multistate Outbreak of Salmonella Infections Linked to Products Reported to Contain Kratom. Retrieved from https://www.fda.gov/Food/RecallsOutbreaksEmergencies/Outbreaks/ucm597265.htm

> but that report provides no substantive detail other than the decedent's age and ethnicity, and provides no data on any underlying health condition that may have caused the death."[25]

Any deaths alleged to be associated to the use of kratom merely document the possible use of kratom products at the time of the occurrence of a death caused by other specific factors, i.e., where the cause of death is related to a gunshot wound; a suicide related to mental health issues; physical injuries that caused ancillary medical issues resulting in a fatality; use of an illegal drug; polydrug use of prescription and/or illegal drugs at toxic dose levels; and deaths that are related to other unrelated medical conditions that have no relationship to kratom use, i.e., a death from deep vein thrombosis.

Of the 44 claimed deaths, the FDA identifies only a single death as being kratom-related involving an individual who "had no known historical or toxicologic evidence of opioid use, except for kratom." The FDA reported in a media release on February 6, 2018 that it was actively investigating that single death. Now, after 8 months of investigation, the FDA still refuses to release any additional information on the death other than the subject's age and ethnicity and provides no information on how kratom was determined to have contributed to the death.

The FDA repeatedly cites a cluster of 9 deaths that occurred in Sweden over a 12-month period in 2009. The FDA failed, however, to adequately disclose and account for material facts from the peer-reviewed Case Report of nine deaths in Sweden that was published in 2011 in the Journal of Analytical Toxicology.[26]

That Case Report concluded the deaths were actually the result of adulteration of kratom powder with a toxic dose of *O*-desmethyltramadol rather than being associated with the use of kratom, other than the kratom powder being the product adulterated by a bad actor seeking to market a product for economic gain to those seeking a recreational high. *O*-desmethyltramadol is a highly toxic and dangerous chemical used in the production of the opioid, Tramadol.

The science is extremely important to resolve the claims by the FDA about deaths being associated with kratom. If kratom is not the primary causative substance in the death report, the fact that a decedent used kratom along with some other substance at the time of the death is not a sufficient basis to seek a scheduling recommendation for kratom.

Under existing reporting protocols for toxicology reports, laboratories simply report the presence of mitragynine in the decedent's blood. There is no assessment of the levels of

---

[25] American Kratom Association, *The FDA Kratom Death Data: Exaggerated Claims, Discredited Research, and Distorted Data Fail to Meet the Evidentiary Standard for Placing Kratom as a Schedule I Controlled Substance*, Jane Babin, Ph.D., Esq., March 2018.

[26] Kronstrand *et al.*, "*Unintentional Fatal Intoxications with Mitragynine and O-Desmethyltramadol from the Herbal Blend Krypton*", J Anal Toxicol 35: 242-47 (2011).

mitragynine in the toxicology report, and there has been no study to determine the level at which mytragynine might become toxic and play a role in a death.

The fallacy of using a baseline that any level of mitragynine in a toxicology report is illustrated in the Domingo study that showed that even the highest levels of mytragynine concentrations in the postmortem blood samples recorded prior to the date of publication, "mitragynine was not the primary cause of death."[27]

The CSA was enacted to remove truly dangerous substances from the market. There are important reasons why kratom does not cause overdose deaths, and the evaluation of the science should be the determinative factor in any scheduling decision.

First, as demonstrated through numerous studies in animals, kratom has very low toxicity. In such studies, even extremely high doses—doses that, when adjusted for humans, would be difficult to consume—do not cause death or significant toxic effects.28

The intent of the CSA was to reduce the potential for deaths resulting from dangerous substances. Yet, the proposed scheduling of kratom would actually have the perverse and unintended result of actually elevating the safety threat. Nine leading scientists, in a February 8, 2018 letter to Kellyanne Conway, the Counselor to the President on the Opioid Crisis, and Robert W. Patterson, Acting Administrator of the DEA, issued a chilling warning about the consequences of scheduling kratom as proposed by the FDA.

> "It is our collective judgment that placing kratom into Schedule I will potentially increase the number of deaths of Americans caused by opioids because many people who have found kratom to be their lifeline away from strong opioids will be vulnerable to resumption of that opioid use, whether their prior opioid use was for relief of pain or due to opioid addiction. This opinion is supported by four national surveys conducted in the past two years, as well as decades of studies in the US and in Southeast Asia, where kratom has been used as a safer alternative to opioids for more than a century. Failure to evaluate this potential outcome of any proposed scheduling of kratom would directly contradict the expressed purpose of the enactment of the CSA by the U.S. Congress, to protect the safety of consumers. Perversely, it is foreseeable that such an action may lead to the deaths of people and worsen the opioid crisis, not mitigate it."

---

[27] Domingo, Roider, Stover, Graw, Mussoff, Sachs, Bicker; *Mytragynine concentrations in two fatalities*, Forensic Science International, 2016, http://dx.doi.org/10.1016/j.forsciint.2016.12.020

[28] *See*, *e.g.*, M.S.A. Kamal et al., *Acute toxicity study of standardized Mitragyna speciosa Korth aqueous extract in Sprague Dawley rats*, J. PLANT STUD. 2012;1(2):120-129; A. Sabetghadam et al., *Subchronic exposure to Mitragynine, the principal alkaloid of Mitragyna speciosa, in rats*, J. ETHNOPHARMACOL. 2013 Apr. 19;146(3):815-23; Henningfield at 4 (citing studies).

If kratom were banned, these scientists argue kratom users who use kratom as an alternative pain management option, or as a way to reduce classic opioid use, would be put at far greater safety risk. The use of over-the-counter non-steroidal anti-inflammatory drugs (NSAIDS) have significant adverse health impacts, including serious liver toxicity issues, and the use of classic opioids puts users at significant risk for dangerous addiction and potential death. The following data was extracted from the FAERS database for the same time period used by the FDA to report the 44 kratom associated deaths.

Analysis of Adverse Events Reported on the FAERS Public Dashboard From 2008 – 2017 for Pain Management Therapies[29]

Product	Total Cases	Serious Cases (including deaths)	Deaths
Mytragynine/herbal	64	44	44
Ibuprofen	46,209	26,910	4,068
OxyContin	16,940	11,666	2,250
Tramadol	10,703	9,183	3,301
Fentanyl	47,925	25,753	8,233

The only option left for an individual using kratom as an alternative pain management option who does not want to use NSAIDS or a classic opioid, would be to turn to the black market for kratom that is well-documented to be rife with adulterated kratom products. The FDA and NIDA have documented that adulterated kratom products that have been spiked with synthetic chemicals or highly-toxic classic opioid medicines can be and often are deadly.

Kratom exhibits very low bioavailability—only about 3% when taken orally. For comparison, oral morphine shows bioavailability between 20 and 25%,[30] fentanyl ranges from 50% to almost 70%,[31] and oral codeine is approximately 90% bioavailable.[32] Kratom's low bioavailability also reduces the extent to which any effect, positive or negative, can be achieved, and substantially

[29] https://fis.fda.gov/sense/app/777e9f4d-0cf8-448e-8068-f564c31baa25/sheet/45beeb74-30ab-46be-8267-5756582633b4/state/analysis

[30] P.J. Hoskin et al., *The Bioavailability and Pharmacokinetics of Morphine after Intravenous, Oral and Buccal Administration in Healthy Volunteers*, 27 J. Clin. Pharmacol. 499 (1989).

[31] Abstral Clinical Pharmacology Review, NDA 22510 (Mar. 11, 2010); *see also* M. Darwish et al., *Absolute and Relative Bioavailability of Fentanyl Buccal Tablet and Oral Transmucosal Fentanyl Citrate*, 47 J. Clin. Pharmacol. 343 (2007).

[32] *See, e.g.*, Clinical Pharmacology and Biopharmaceutics Review at 5, NDA 202245, Codeine Sulfate oral solution (Dec. 6, 2010).

reduces the possibility of overdose because a user would need to ingest an overly large (and likely aversive) amount to achieve a euphoric "high."

As described by Walter C. Prozialeck, a professor of pharmacology at Midwestern University who has studied kratom extensively, "[T]he amount [of kratom] that a person has to take in to get any severe effects is ridiculously high. You're talking 10 to 15 grams of raw leaf. Most people who are using kratom for pain management don't take that much. Most people can't take that much."[33] Indeed, an intoxicating effect can be achieved with lower doses of dextromethorphan or nutmeg.[34]

Finally, unlike potent opioid substances, kratom does not carry a high risk of respiratory depression, which is generally the cause of death in cases of opioid overdose.[35] The "[r]espiratory depressant effects appear substantially lower than those produced by opioids and this would be consistent with the absence of verified kratom caused overdose death."[36] Moreover, because kratom does not produce the euphoric "high" that drives addiction to opioids and other drugs, it is less likely to be abused at high doses, also lessening the risk of respiratory depression.

Salmonella causes approximately 1.2 million illnesses, 23,000 hospitalizations, and 450 deaths in the United States every year.[37] Nevertheless, CDC only investigates and alerts the public to a small fraction of these cases. The rest remain unexplained. The following Salmonella product contaminations have been reported in 2018[38]:

Product	*Reported Cases*	*States*	*Hospitali-zations*	*Deaths*	*Recall*
Ground Beef	57	16	14	0	Yes
Gravel Ridge Farms Shell Eggs	38	7	10	9	Yes
Chicken	17	4	8	1	No
Raw Turkey Products	90	26	40	0	No
Hy-Vee Spring Pasta Salad	101	10	25	0	Yes

[33] Nick Wing, *Some Say Kratom Is A Solution to Opioid Addiction. Not If Drug Warriors Ban It First*, Huffington Post, updated Sept. 7, 2016, 8:38 am, http://www.huffingtonpost.com/entry/kratom-ban-drugpolicy_us_56c38a87e4b0c3c55052ee3f.

[34] Henningfield at 6.

[35] *See* Kruegel at 6754-55 ("Unfortunately, acute [mu-opioid receptor] activation is also associated with serious side effects, including respiratory depression, constipation, sedation, nausea, and itching. At sufficiently high doses, the evoked respiratory depression may be fatal.").

[36] Henningfield at 6.

[37] CDC, "*Salmonella*," https://www.cdc.gov/salmonella/general/index.html

[38] https://www.cdc.gov/salmonella/outbreaks-2018.html

Kellogg's Honey Smacks Cereal	135	36	34	0	Yes
Pre-cut melon	77	9	36	0	Yes
Shell Eggs	45	10	11	0	Yes
Dried Coconut	14	8	3	0	Yes
Chicken Salad	265	8	94	1	Yes
Kratom	199	41	50	0	Yes
Raw Sprouts	10	3	0	0	No
Frozen Shredded Coconut	27	9	6	0	Yes
Romaine Lettuce	210	36	96	5	No

Salmonella contamination is not unique to the natural plant or kratom products, and the solution is for better regulation of the supply chain for food and dietary ingredient products. It has not been a custom or practice of the government to seek to schedule any of these products, other than kratom, because the product has had a Salmonella contamination.

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

The Ohio BOP again points to the FDA's PHASE computer modeling program to conclude there is "no evidence to indicate that kratom is safe or effective for any medical use. The compounds in kratom were found to bind to mu-opioid receptors similar to other opioids." Reference is also made to EMCDDA analyses that regular kratom use can produce dependence, and that such dependence produces withdrawal symptons.

Response:

Kratom is used as a dietary ingredient/supplement and is currently subject to FDA regulation. It has been reported that some kratom vendors have either made impermissible health claims related to kratom products, or have allowed consumers to make such claims on comment forums or blogs on the vendors' websites. In each case, the FDA has issued appropriate warning letters and acted to remove such medical claims from those vendors' websites to resolve this issue.

The dependence and withdrawal profile of kratom is not accurately characterized in the EMCDDA analysis. Regarding physical dependence, ethnographic studies in SE Asia, some testimonials appended to the Pinney Associates 8-factor analysis, and the surveys by Grundmann (2017)[39] and the Pain News Network (2017)[40] suggest that abrupt discontinuation

[39] Grundmann O (2017) Patterns of Kratom use and health impact in the US-results from an online survey. DrugAlcohol Depend 176:63–70. https://doi.org/10.1016/j.drugalcdep.2017.03.007

[40] Pain News Network (2017) Kratom survey. https:/ /www.painnewsnetwork.org/kratom-survey/. Accessed 15 July 2017

may be accompanied by withdrawal symptoms that are qualitatively similar but generally weaker than those observed following discontinuation of opioids.[41]

Research published in the Journal of Psychoactive Drugs reported that "findings showed that regular kratom users do not experience major impairments in their social functioning, despite being dependent on kratom for prolonged periods. Our findings suggest that chronic kratom administration does not significantly impair social functioning of users in a natural context in Malaysia."[42]

In an analysis published in the *American Chemical Society Medicinal Chemistry Letters* in 2017, where a discussion observing that withdrawal from kratom is milder than withdrawal from opiates, the "most significant advantage of kratom is that it has not caused any overdose deaths."[43]

(8) Whether the substance is an immediate precursor.

The Ohio BOP properly concluded that kratom is not known to be an immediate precursor.

Conclusion:

The AKA respectfully requests the Ohio BOP to rescind its Resolution for the Classification of Kratom as a Controlled Substance because the justification for such an action as presented by the Board fails to meet the statutory burden for such scheduling.

Kratom does not have a high potential for abuse, and recently published peer-reviewed studies (Hemby, June 2018; and Yue, July 2018) have properly concluded that MG does not have abuse potential, and actually reduces morphine intake.

Kratom is a dietary ingredient/supplement that is being used safely by nearly 5 million Americans. To the extent any manufacturer, distributor, or vendor is marketing kratom products as a medicine, the FDA currently has sufficient authority to seize such products and refer these individuals or corporations to the Department of Justice for prosecution.

Kratom has an excellent safety profile and the only safety issues arise when the natural kratom plant is adulterated or contaminated. The FDA currently has sufficient authority to seize such

---

[41] Jack E. Henningfield, Reginald V. Fant, Daniel W. Wang, *The abuse potential of kratom according to the 8 factors of the controlled substances act: implications for regulation and research*, Psychopharmacology, https://doi.org/10.1007/s00213-017-4813-4, published online 23 December 2017

[42] Darshan Singh, Christian P. Müller, Balasingam K. Vicknasingam & Sharif M. Mansor (2015) Social Functioning of Kratom *(Mitragyna speciosa)* Users in Malaysia, Journal of Psychoactive Drugs, 47:2, 125-131, DOI: 10.1080/02791072.2015.1012610

[43] Genevieve M. Halpenny, *Mitragyna speciosa: Balancing Potential Medical Benefits and Abuse,* American Chemical Society Medicinal Chemistry Letters, 2017.

products and refer these individuals or corporations to the Department of Justice for prosecution.

Kratom does not pose a significant risk to the public health for the citizens of Ohio. It is not dangerously addicitive (it has a similar addiction profile as caffeine); and withdrawal from it is similar to weaning from an addiction to coffee or caffeinated sodas.

The DEA has not taken any action on an FDA recommendation to schedule despite its submission nearly a year ago. The emerging and recent scientific studies directly contradict the FDA's conclusions on kratom having the same effects as classic opioids; and document that safety issues are grounded in adulterated kratom products. In addition, safety data relied upon in the BOP's scheduling recommendation rely upon deaths that are actually caused by polydrug use, underlying medical conditions, or adulteration of kratom products with toxic doses of other dangerous substances.

Neither the Federal CSA nor the Ohio CSA contemplate scheduling of products because they have been adulterated with other dangerous substances.

For additional information:

Charles M. Haddow
Senior Fellow on Public Policy
American Kratom Association
mhaddow1@verizon.net
571-294-5978

The undersigned supporters of keeping kratom legal for the safe use of consumers respectfully asks the Ohio Board of Pharmacy to rescind its proposed scheduling of kratom.