AMERICAN KRATOM ASSOCIATION

August 22, 2018

By Overnight Mail and Email

Uttam Dhillon
Acting Administrator
Drug Enforcement Administration (DEA)
Lincoln Place West
Room 12060
700 Army Navy Drive
Arlington, VA 22202

Dear Administrator Dhillon:

On behalf of the nearly five million kratom supporters in the United States, you will find attached a petition signed by more than 40,000 Americans who support continued access to the natural plant kratom (**see Exhibit 1**).[1] These petition signers respectfully request the DEA immediately return the scheduling recommendation the U.S. Food and Drug Administration (FDA) has submitted for kratom to be placed as a Schedule I substance for reanalysis and reconciliation of the emerging science that contradicts the basis claimed by the FDA for the scheduling of kratom.

The AKA asks the DEA to consider the following deficiencies in the FDA's scheduling recommendation:

1. **The FDA has failed to meet its evidentiary burden to demonstrate that kratom presents a risk to the public health.**

The FDA has submitted data to the DEA in support of its recommendation claiming there are 44 deaths "associated with the use of kratom." An independent analysis of those claimed deaths associated with kratom by Dr. Jane Babin, entitled "*FDA Fails to Follow the Science*," the FDA claims are characterized as follows (**see Exhibit 2**)[2]:

> "The key evidence the FDA has offered on the dangers of kratom as the basis for placing it in Schedule I are case reports on 44 deaths over a nine-year period

[1] See Exhibit 1 available at https://www.dropbox.com/sh/enle7tkvlux3khj/AABU0uHLfPWYNdKiSEmet-xma?dl=0

[2] See Exhibit 2 available at https://www.dropbox.com/sh/enle7tkvlux3khj/AABU0uHLfPWYNdKiSEmet-xma?dl=0

> world-wide associated with the use of kratom. However, the FDA did not independently verify or perform any due diligence on the death reports, and worse, FDA's own documents indicate that every reported case involved other factors. With no direct investigation by the FDA, and a clearly unprofessional review, those case reports are riddled with significant credibility issues. In addition, there are serious errors and omissions between the source reports and the data entered into the FDA FAERS database by FDA that are either deliberate, or so incredibly unskilled as to call into question the validity of any conclusions made by the FDA."

To illustrate, the FDA repeatedly references nine deaths that occurred over a twelve-month period in Sweden in 2009 after ingesting a powdered kratom product known as "Krypton." The FDA submitted those deaths as part of their 2016 justification for the scheduling of kratom as a Schedule I substance that was ultimately rejected by the DEA. The FDA has repeatedly referenced those deaths in (1) the issuance of an Import Alert on kratom in 2012 (updated in 2014 and 2016); (2) the FDA November 14, 2017 Public Health Advisory on kratom; (3) the FDA February 6, 2018 statement on the scientific evidence on the presence of opioid compounds in kratom; in regular communications with the National Institute on Drug Abuse (NIDA) to support the addition of kratom in the DrugFacts publication[3]; and (4) in communications to the DEA to support the addition of kratom on the Drugs and Chemicals of Concern.[4]

The FDA failed to disclose the publication of a peer-reviewed Case Report that was published in the *Journal of Analytical Toxicology* in May 2011 entitled "*Unintentional Fatal Intoxications with Mitragynine and O-Desmethyltramadol form the Herbal Blend Krypton*"[5] that concluded:

> "We believe that the addition of the potent mu-receptor agonist *O*-desmethyltramadol to powdered leaves from Kratom contributed to the unintentional death of nine cases presented and conclude that intake of Krypton is not as harmless as it often is described on internet websites."

The Krypton product that caused the deaths of these nine individuals resulted from the use of an adulterated kratom product, not because of ingesting the natural botanical kratom. There is no basis for scheduling a substance that has been adulterated and there is no intent of Congress to authorize the DEA to make such a scheduling decision because the evidence

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[3] *DrugFacts, Kratom*, National Institute on Drug Abuse, Revised July 2018; https://www.drugabuse.gov/publications/drugfacts/kratom

[4] *Drugs of Abuse, Kratom, A DEA Resource Guide: 2017 Edition*, U.S. Drug Enforcement Administration, page 84, https://www.dea.gov/factsheets/kratom

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

presented shows a consumer died from ingesting an adulterated product containing a toxic dose of a completely separate substance. The FDA has an obligation to present accurate and complete reports on the death data they use to fulfill their evidentiary burden in its 8-Factor Analysis (8-FA) to demonstrate kratom is a threat to public health. They have failed to meet any reasonable standard for proving the natural plant kratom poses a threat to the public health.

The FDA has repeatedly highlighted its claims that kratom's two primary alkaloids, mitragynine (MG) and 7-hydroxymitragynine (7-OH) are associated with deaths. In the FDA Adverse Event Reporting System (FAERS) database, from which the FDA claims the 44 deaths referenced earlier, contains two specific reports on what the FDA claims are deaths associated with kratom use that occurred in Germany; FAERS ID No. 13407030 and ID No. 1342166, reference a published article that purportedly supports the FDA claim that these two deaths were associated with the use of kratom. However, the referenced article, *Mitragynine concentrations in two fatalities,*[6] authored by Domingo, Roider, Graw, Misshoff, and Sachs, 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."

It is unexplainable why the FDA used this documentation for two deaths they claim to be associated with kratom (unless the FDA analysts only read the title of the article, as opposed to actually reviewing its content), but the inclusion of these two deaths in their list of 44 deaths illustrates the deep flaw in the FDA justification for its argument that kratom is a risk to public health.

[6] Domingo, Roider, Stover, Graw, Mussoff, Sachs, Bicker; *Mytragynine concentrations in two fatalities*, Forensic Science International, 2017

More important, the FDA has widely circulated the false claim that any level of mitragynine in a toxicological report is properly classified by a medical examiner or coroner as a "kratom associated death". The Domingo, *et. al.* report focused on the fact that one of the deaths "presents with one of the highest postmortem mitragynine concentrations to date," but it did not "have to be the direct cause of deaths in such fatalities as a result of acute overdose."

Despite this damning conclusion that undermines the premise of the FDA's argument on the threat of kratom to the public health, the FDA continues to disseminate the false information that any level of mitragynine in a decedent's blood constitutes a kratom associated death. What has predictably followed is an increase of reported deaths associated with kratom where toxicology reports and autopsies show only the presence of kratom in the blood, not any actual causality because these medical examiners and coroners are acting on the false information provided by the FDA.

The FDA also repeatedly references the reports from the Centers for Disease Control and Prevention (CDC) showing that U.S. poison control centers received a tenfold increase in calls on kratom from 2010 to 2015.[7] The increase in reports coincides with an increase in use of kratom in the United States during the study period, so that data is neither surprising nor determinative of any public health threat. An important test would be whether the reports of kratom exposure resulted in significant health events that are attributable to kratom exclusively, as opposed to co-ingestants that could result in a serious health impact.

An article published in The American Journal of Emergency Medicine on the Clinical outcomes after Kratom exposures: A poison center case series informs this discussion with the observation that "kratom use has increased recently; likely a combination of its unscheduled status in the United States, availability from local stores or the internet, and the current opioid use epidemic." [8] That accounts for the increase in the number of calls to the poison control centers, but the findings of this research show the critical fact that there were no fatalities or intensive care admissions from the use of kratom itself.

In fact, the CDC report found that the effects were relatively mild and reported only one death in a person who was exposed to the medications paroxetine (an antidepressant) and lamotrigine (an anticonvulsant and mood stabilizer) in addition to kratom. This finding is consistent with a significant number of deaths reported by the FDA "associated with kratom" involving polydrug use, not kratom alone.

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[7] Anwar and Schier; *Notes from the Field:* Kratom (*Mitragyna speciosa*) Exposures Reported to Poison Centers — United States, 2010–2015, Morbidity and Mortality Weekly Report (MMWR), July 29, 2016/65(29); 748-749.

[8] Clinical outcomes after Kratom exposures: A poison center case series, Cumpston, Kirk L. et al. The American Journal of Emergency Medicine , Volume 36 , Issue 1 , 166 - 168

2. <u>The FDA has failed to meet its evidentiary burden to demonstrate that kratom has a history and current pattern of abuse; the scope, duration, and significance of abuse; or kratom's psychic or physiological dependence; kratom has an actual or relative potential for abuse, or whether kratom is an immediate precursor of an already-controlled substance.</u>

The FDA's claims that kratom meets the Controlled Substances Act (CSA) criteria on abuse is refuted by numerous scientific reports, including the following peer-reviewed publications:

- Henningfield, Fant, and Wang; *The abuse potential of kratom according to the 8 factors of the controlled substances act: implications for regulation and research*; Psychopharmacology, December 23, 2017.[9]
- Swogger and Walsh; *Kratom use and mental health: A systematic review*; Drug and Alcohol Dependence, December 2017.[10]
- Grundmann, Brown, Henningfield, Swogger, and Walsh; *The therapeutic potential of kratom*; Addiction, June 2018.[11]
- Hemby, McIntosh, Leon, Cutler, and McCurdy; Abuse liability and therapeutic potential of the Mitragyna speciosa (kratom) alkaloids mitragynine and 7-hydroxymitragynine; Addiction Biology, 2018.[12]
- Kruegel and Grundmann; *The medicinal chemistry and neuropharmacology of kratom: A preliminary discussion of the promising medicinal plant and analysis of its potential for abuse*; Neuropharmacology, 2017.[13]
- Kruegel, Gassaway, Kapoor, Varadi, Majumdar, Filizola, Javitch, and Sames; *Synthetic and Receptor Signaling Explorations of the Mitragyna Alkaloids: Mitragynine as an*

[9] Henningfield, et. al.; *The abuse potential of kratom according to the 8 factors of the controlled substances act: implications for regulation and research*, Psychopharmacology, 23 December 2017

[10] Swogger and Walsh; *Kratom use and mental health: A systematic review*; Drug and Alcohol Dependence, 2018

[11] Addiction: Society for the Study of Addiction, Letter to the Editor, *The Therapeutic potential of kratom*, June 28, 2018, Oliver Grundmann, Paula Brown, Jack Henningfield, Marc Swogger, Zach Walsh

[12] *Abuse Liability and therapeutic potential of the Mitragyna speciosa (kratom) alkaloids mitragynine and 7-hydroxymitragynine*, Addiction Biology; Hemby, McIntosh, Leon, Cutler & McCurdy, published on June 27, 2018.

[13] Kruegel and Grundmann; *The medicinal chemistry and neuropharmacology of kratom: A preliminary discussion of a promising medicinal plant and analysis of its potential for abuse,* Neuropharmacology, 2017.

Atyptical Molecular Framework for Opioid Receptor Modulators; Journal of American Chemistry, 2016.[14]

- Henningfield; *FDA-NIDA Opioid Use Disorder Docket*, May 18, 2018.[15]

The term "abuse" is not defined in the CSA, but the legislative history of the CSA provides guidance for analyzing a substance's abuse for purposes of scheduling under the CSA.[16] Considerations include: evidence that individuals are taking the substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or the community; diversion of the substance from legitimate channels; evidence that individuals are taking the substance on their own initiative rather than on the basis of medical advice from a practitioner; and whether the substance is so related in its action to a drug already listed as having a potential for abuse to make it likely that the substance will have the same potential for abuse. Together, these considerations demonstrate that kratom does not demonstrate a high potential for abuse similar to fentanyl or oxycodone – but, rather, shares characteristics of unscheduled, naturally-derived substances such as caffeine.

The cumulative evidence on why the FDA scheduling recommendation utterly fails to meet its burden on the science is articulated in a letter co-signed by nine leading scientists who are subject matter experts on kratom to Congressional Leadership (Brown, Raffa, Griffiths, Garcia-Romeu, Grundmann, Kruegel, Walsh, Henningfield, Swogger) on June 21, 2018 (**see Exhibit 3**)[17].

3. **The FDA has failed to meet its evidentiary burden to demonstrate kratom's actual or relative potential for abuse.**

FDA Commissioner Gottlieb, in an apparent response to the previously referenced Babin report that offered a scathing review of the FDA's claimed deaths associated with kratom, stated the following:

[14] Kruegel, Gassaway, Kapoor, Varadi, Majumdar, Filizola, Javitch, and Sames; *Synthetic and Receptor Signaling Explorations of the Mitragyna Alkaloids: Mitragynine as an Atypical Molecular Framework for Opioid Receptor Modulators,* Journal of the American Chemical Society, December 2016.

[15] FDA Docket FDA-2018-N-0987 comments submitted by Jack E. Henningfield, VP of Research and Policy at PinneyAssociates, and Adjunct Professor of Behavioral Sciences at The Johns Hopkins University School of Medicine, May 18, 2018.

[16] Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No. 91-1444, 91st Cong., Sess. 1 (1970) reprinted in U.S.C.C.A.N. 4566, 4603

[17] See Exhibit 3 available at https://www.dropbox.com/sh/enle7tkvlux3khj/AABU0uHLfPWYNdKiSEmet-xma?dl=0

> "These deaths are just one measure of kratom's risk. They don't account for the many people who may be initiated on, and addicted to, opioids because of the easy access to kratom."[18]

There is not a single credible study that has been published that supports this claim by Dr. Gottlieb. In fact, the overwhelming scientific literature directly contradicts the assertion by Gottlieb and shows that a segment of kratom users actually use the plant as an alternative to dangerously addictive and potentially deadly opioid medications. While Dr. Gottlieb is entitled to his personal opinion, any major public policy decision for scheduling of a substance in Schedule I must be grounded in science.

The FDA argues that kratom shares certain characteristics with classic opioids, and specifically referenced its analysis of kratom using its "Public Health Assessment via Structural Evaluation (PHASE)" computer modeling system as follows:

> "The computational model also predicted that some of the kratom compounds may bind to the receptors in the brain that may contribute to stress responses that impact neurologic and cardiovascular function. The agency has previously warned of the serious side effects associated with kratom including seizures and respiratory depression.[19]

Reactions from the science community were swift, with a response reported in a publication form the Harvard Law Bill of Health blog by the Petrie-Flom Center:

> "The FDA has published few details on how its PHASE simulation model works, how the software was validated, and the scope of data on which it was trained. Aside from the lack of transparency with respect to PHASE, it is strange that the FDA chose to do this kind of modeling in the first place because the binding of kratom's active ingredients to mu and delta opioid receptors is already well established. Numerous scientific articles report that kratom's most active ingredients, mitragynine and 7-hydroxymitragynine, bind to mu and kappa opioid receptors. According to Andrew Kruegel, a research chemist at Columbia University, the FDA's use of computer modeling is significantly less rigorous than the methods used in previous kratom studies. Furthermore, according to Kruegel, the FDA's claim that kratom has risks comparable to morphine is akin to

[18] *Advocates Skewer FDA over 'junk science' blaming kratom for deaths*, Kimberly Leonard, August 14, 2018, Washington Examiner.

[19] 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, February 6, 2018.

> "saying that all opioid agonists have the same effect, which is not true based on what we've learned about these compounds." Instead of lumping kratom in with classic opioids such as morphine and heroin, Kruegel prefers to call it an atypical opioid because it may have different effects, and a preferable side-effect profile, compared to classic opioids." [20]

The science here is important to the FDA's claims regarding the binding of MG and 7-OH to the mu-receptors. The binding is only the first step in the progression of effects caused by classic opioids, and there is no scientific evidence upon which the FDA can credibly claim that kratom's alkaloids have the same effects as those classic opioids. In fact, kratom does not exhibit the binding profile associated with the reinforcing qualities that lead to opioid addiction and abuse. Mitragynine[21] binds to several non-opioid receptors, and demonstrates both agonist and antagonist effects at the opioid receptors, limiting the "high" that can be achieved with kratom and, with it, the potential for abuse.[22] Kreugel et al. found that mitragynine "acted as a partial agonist" for the mu-opioid receptor, but did not bind the delta-opioid receptor or the kappa-opioid receptor.[23] At the kappa receptor, mitragynine "was a competitive antagonist, fully inhibiting the activity of the reference agonist." Mitragynine was also an antagonist at the delta opioid receptor, although with lower potency than at the kappa receptor.

The key issue here is that classic opioids, after binding to the mu-opioid receptor, then affect the portions of the brain controlling the respiratory functions. The World Health Organization documented the effects of classic opioids reporting that "[D]ue to their effect on the part of the brain which regulates breathing, opioids in high doses can cause respiratory depression and death."[24] No such activity on the respiratory system has been documented from the use of kratom, and that accounts for why there are no fatalities reported from kratom overdoses in the scientific literature.

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[20] Mason Marks; Simulated Side Effects: FDA Uses Novel Computer Model to Guide Kratom Policy, posted on February 8, 2018, http://blogs.harvard.edu/billofhealth/2018/02/08/fda-uses-novel-computer-simulation-to-guide-kratom-policy/

[21] Andrew C. Kruegel et al., *Synthetic and Receptor Signaling Explorations of the Mitragyna Alkaloids: Mitragynine as an Atypical Molecular Framework for Opioid Receptor Modulators*, 138 J. Am. Chem. Soc. 6754, 6762 (2016). See, e.g., Kruegel et al. at 6756 (reporting that it was "not possible to isolate any measurable quantity" of 7-hydroxymitragynine)

[22] *Id.* at 6754.

[23] *Id.* at 6756.

[24] Information sheet on opioid overdose, Management of substance abuse, World Health Organization, August 2018, http://www.who.int/substance_abuse/information-sheet/en/

Indeed, rather than resembling the classic opioids, kratom's pharmacological action is often described as similar to caffeine. According to Dr. Henningfield, "in many respects, the factors that appear important in sustaining kratom use appear more similar to those that sustain dietary caffeine use, namely to better manage fatigue and daily life demands and provide mild effects considered enhancing to quality of life."[25] Moreover, many common products including caffeine such as soda, coffee, and over-the-counter medicines contain enough caffeine in a single unit to produce reinforcement,[26] while one would need to consume doses "far higher than those commonly ingested by people in the United States" to achieve reinforcement through kratom.[27]

Kratom also differs from classical opioids in terms of its very low bioavailability, as only 3% is bioavailable when taken orally. This is a fraction of the bioavailability of scheduled opioids such as morphine, fentanyl, and codeine, with oral bioavailability of approximately 20-25%, 50-70%, and 90%, respectively. Dr. Henningfield describes the oral absorption of mitragynine as "slow, prolonged and [] incomplete."[28] Kratom's exceptionally low bioavailability limits the extent to which a user could experience a "high," reduces the possibility of overdose, and limits reinforcement. These pharmacological characteristics of kratom suggest that it is a very poor candidate for abuse, and this is reflected in the absence of actual abuse observed in the United States.

This point was highlighted in a letter submitted to Congressional Leadership on June 21, 2018 as follows:

> "Importantly, even in their pure form, the active compounds of kratom have been found to be safer than classical opioids. Studies in multiple animal species have shown that mitragynine does not depress the respiratory system as strongly as classic opioids, which is the main cause of death from opioid overdose. These findings are consistent with the lack of acute overdose deaths induced by kratom in humans. Kratom also does not provide "addictive reward" in animal studies as compared to addictive opioids (e.g., morphine). In fact, two intravenous drug self-administration studies in animals have shown that mitragynine acts more like saline placebo control than morphine or heroin. Therefore, available data clearly does not demonstrate a high potential for abuse, as required for placement of a substance in Schedule I of the CSA. In sum,

[25] Henningfield at 7.

[26] *Id.* at 9-12

[27] *Id.* at 6.

[28] *Id.* at 8.

> his work, reported at recent scientific meetings and conducted in part by scientists at the National Institute on Drug Abuse (NIDA), shows a radically different profile in terms of abuse potential and side effects from that of "narcoticlike" opioids to which the FDA compared kratom in their public pronouncements in November 2017."[29]

The current patterns of use do not reflect the telltale patterns of abuse associated with substances that carry a high and dangerous level of abuse liability. Kratom presents a wholly different picture. That is distinctly different than adverse health outcomes resulting from adulterated kratom products that the FDA currently has adequate statutory tools to interdict, and that is where they should focus their regulatory efforts to protect public health.

Several million law-abiding consumers use kratom just as they would any other botanical or natural remedy they see on the commercial market. There is little to no evidence of experimentation with alternative routes of administration; with criminal activity associated with its production and use; or with debilitating reinforcing effects that pose a threat to the community or to the individual. Indeed, there are far more reports of kratom users being able to lead normal lives, than reports of quintessential destructive behaviors associated with highly abused substances.

Finally, on the issue of those kratom consumers who are using kratom as an alternative pain management option for chronic or acute pain; as an alternative to dangerously addictive and potentially deadly opioid medicines; or even as a step-down from opioid addiction, we believe both the FDA and DEA should welcome this potential safer alternative to classic opioids given that our nation is experiencing more than 115 opioid overdose deaths each day, or more than 42,000 per year. The public record in the April to June Opioid Use Disorder treatment development document includes testimonials from kratom users who are "terrified" that obstacles to kratom access will lead to the relapse of opioid use disorder.

We ask you to carefully review the pleas of the more than 40,000 Americans who signed the attached petition to you urging the DEA to return the FDA 8-FA request for scheduling of kratom to the FDA for additional analysis and a reconciliation of the clear science that rebuts its claims. These petition signers hail from every state, the U.S. territories, and the District of Columbia. Please Follow the Science, and require the FDA to do the same.

[29] Letter to Congressional Leadership, June 21, 2018, see Exhibit 2.

Respectfully submitted,

David Herman
Chairman
American Kratom Association

Contact information:

Email: dave.herman@americankratom.org

cc: FDA Commissioner Scott Gottlieb
HHS Secretary Alex M. Azar
NIDA Director Nora Volkow
Members of the U.S. Congress