AMERICAN KRATOM ASSOCIATION

July 31, 2018

Nora D. Volkow, M.D.
Director
National Institute on Drug Abuse (NIDA)
6001 Executive Boulevard
Rockville, MD 20852

SENT VIA EMAIL AND REGULAR MAIL

Dear Director Volkow:

I am writing to address the controversy regarding updates to the NIDA "DrugFacts: Kratom" ("Fact Sheet") document that was, according to the posting, "Revised [in] July 2018." On July 30, 2018, the American Kratom Association (AKA) issued a press release that stated the NIDA had affirmed that, "Kratom by itself is not associated with fatal overdose", explaining that only when the natural ingredient is contaminated or "*laced with other compounds*" has it been associated with death.

That statement is true.

The NIDA press office apparently objected to the headline of the AKA media release that states: "Safety of Unadulterated Kratom Affirmed by The National Institute of Drug Abuse." This headline, when read in its proper context, correctly states that NIDA affirmed that kratom by itself is not associated with a fatal overdose as has been claimed repeatedly by the FDA.

The significance of the updates made by NIDA to the July 2018 Fact Sheet come in the face of a sustained effort by the FDA to mischaracterize kratom as an opioid, and more specifically, a "narcotic like opioid," involved in the deaths of 44 people, and poses a deadly risk to public health. The science, including recently published reports and including decades of evaluation in SE Asia and Malaysia, directly contradict the FDA's conclusions.

The NIDA Press Office issued a response to the AKA media release claiming, "*The section, Can a person overdose on kratom?"* had not been changed since the fact sheet was developed in February 2016."

That statement is simply incorrect.

That is why the AKA was encouraged by the reaffirmation of the NIDA position on the fact that kratom by itself is not associated with fatal overdose. The July 2018 update actually removed

the statement highlighted in the press release from a Section Header entitled "*What are the health effects of kratom*" and created an entirely new Section Header in the document entitled "*Can a person overdose on kratom?*" and then proceeded to reaffirm the previously stated position that "Kratom by itself is not associated with fatal overdose".

To be clear, there was no Section Header in the February 2016 kratom Fact Sheet as the NIDA Press Office claims in its response, and in fact that new Section Header in the 2018 Fact Sheet was a material change that highlighted the significance of the added emphasis on the question of whether a person can overdose on kratom. In addition, a **significant change** in the language was made to clarify that "***some forms of the drug packaged as dietary supplements or dietary ingredients can be*** laced with other compounds that have caused deaths" (***language change highlighted***). We believe the highlighting of this was especially important in light of FDA's repeated mischaracterizations of the risks of kratom since its November 14th, 2017 Advisory.

But the issue we believe was of equal or even greater significance is the change in the 2016 position where NIDA's characterized kratom as "*like other opioid drugs*" -- to the 2018 position that now characterizes kratom as "*like other drugs with opioid-like effects*." As NIDA now correctly concludes, kratom is not an opioid drug, and its addiction profile is associated with having "*opioid-like effects*" and some "stimulant effects that contribute to the "increased energy, sociability, and alertness instead of sedation" [a hallmark narcotic opioid effect] that NIDA correctly describes. Again, the science is clear that there are a number of non-scheduled substances that can have such effects despite the fact those substances are not classic "narcotic-like" opioids.

These distinctions in the July 2, 2018 update by NIDA is more closely aligned with the evolving science that demonstrates that although kratom's alkaloids bind to the same mu-receptors in the brain as classic opioids (as do other substances that are not scheduled), those kratom alkaloids do not suppress the respiratory systems of users as classic opioids do. The death toll of classic opioid abuse is largely due to respiratory suppression where the user literally suffocates.

Among the 42,000 opioid attributed deaths in 2016, we are not aware of a single death attributed to narcotic-like respiratory depression due to kratom. This is consistent with animal studies that are published and have been submitted to FDA's Office of Dietary Supplements and which do not demonstrate narcotic opioid-like toxicity.

Moreover, the profile of effects in kratom users is radically different from opioids with respect to serious adverse events, and social and occupational functioning in U.S. and Asian/Malaysian studies. Here too, animal studies, including one by NIDA itself, show that the main alkaloid in kratom, mitragynine, looks more like placebo than the narcotic like opioids to which it was compared.

Thus, we commend NIDA for getting the science right in its July 2 Kratom Fact Sheet update.

To illustrate, here is a chart showing the differences between the 2016 and 2018 "DrugFacts: Kratom" documents published by NIDA.

2016	2018 (July 2, 2018 Update)
Is kratom addictive? Like **other opioid drugs**, kratom may cause dependence (feeling physical withdrawal symptoms when not taking the drug), and some users have reported becoming addicted to kratom.	**Is kratom addictive?** Like **other drugs with opioid-like effects**, kratom might cause dependence, which means users will feel physical withdrawal symptoms when they stop taking the drug.
What are the health effects of kratom? *[additional text describing reported health effects of using kratom]* Kratom by itself is not associated with fatal overdose, but commercial forms of the drug are sometimes laced with other compounds that have caused deaths.	**New Section Header:** **Can a person overdose on kratom?** Kratom by itself is not associated with fatal overdose, but some forms of the drug packaged as dietary supplements or dietary ingredients can be laced with other compounds that have caused deaths.

As you are aware, several symposia, lectures and posters on kratom were held in conjunction with The College of Problems on Drug Dependence (CPDD) at their 80th Annual Scientific Meeting on June 9-14, 2018 in San Diego, California, that included NIDA's International Forum and its kratom science symposium is included on the NIDA website as an official NIDA meeting.[1]

A NIDA funded research project conducted by Drs. Albert Garcia-Romeu, Kelly Dunn and Roland Griffiths of The Johns Hopkins Medical School concluded that data dictates "kratom is currently being used among White, educated, middle-aged Americans for symptoms of pain, anxiety, depression, and opioid withdrawal. Although daily use was common, moderate or severe

[1] https://www.drugabuse.gov/international/2018-nida-international-forum

kratom-related SUD and endorsement of being troubled by kratom use were very low. Thus kratom, whose effects are hypothesized to be opioid receptor-mediated, may differ from typical prescription and illicit opioids."[2]

This survey study was consistent with three other kratom surveys in the US which together reported data on more than 20,000 kratom users, a survey of people with opioid use disorder, 20,236 comments to the Drug Enforcement Administration in 2016, and oral and submitted comments to the April 17 FDA, and NIDA sponsored meeting on treatments for opioid use disorder, a letter to the White House and the Acting DEA Administrator signed by nine prominent scientists on February 8, 2018, and in a separate letter signed by those scientists to Congressional leaders on June 21, 2018.[3] [4] [5] [6] [7] [8] [9]

The NIDA-funded research conducted by Jay McLaughlin, Ph.D. of the University of Florida was particularly compelling in his findings: "Kratom was recently proposed for DEA Schedule I designation. However, data suggests that mitragynine and 7-OH mitragynine have analgesic properties with possibly fewer liabilities."

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[2] A survey study characterizing use of kratom (Mitragyna speciosa), Albert Garcia-Romeu, Johns Hopkins University School of Medicine, Financial Support: NIDA R01DA003889 & NIDA R01DA035246.

[3] Garcia-Romeu, Dunn, & Griffiths (2018 CPDD Poster) A survey study characterizing use of kratom (Mitragyna speciosa) Albert Garcia-Romeu, Kelly Dunn, Roland Griffiths Presented at College on Problems of Drug Dependence, 2018.

[4] Grundmann O. Patterns of Kratom use and health impact in the US-Results from an online survey. Drug Alcohol Depend. 2017 Jul 1;176:63-70.

[5] Pain Network Kratom Survey: https://www.painnewsnetwork.org/kratom-survey/

[6] FDA/NIDA Public Hearing Docket at https://www.regulations.gov/document?D=FDA-2018-N-0987-0001
Some relevant and specific comments to the docket are listed at:
https://www.regulations.gov/document?D=FDA-2018-N-0987-0026
https://www.regulations.gov/document?D=FDA-2018-N-0987-0068
https://www.regulations.gov/document?D=FDA-2018-N-0987-0017

[7] Letter to White House Counselor Kellyanne Conway and Acting DEA Administrator Robert W. Patterson from nine leading research scientists, February 8, 2018.

[8] Letter to U.S. Congressional Leaders McConnell, Schumer, Ryan, and Pelosi from nine leading research scientists, June 21, 2018.

[9] Henningfield, J.E., Raffa, R., Garcia-Romeu, A., and Doshi, T., Kratom and its mitragynines in the opioid crisis: A path to or away from opioids. College on Problems of Drug Dependence, San Diego, June 9-14, 2018.FDA DEA Kratom Docket at https://www.deadiversion.usdoj.gov/fed_regs/rules/2016/fr0831.htm

The conclusion addresses the respiratory issue directly and the contrasts of kratom to classic opioids: "The kratom compounds produced more potent MOR-mediated antinociception with less tolerance and respiratory depression than morphine, and in the case of analog mitragynine pseudoindoxyl, no conditioned place preference. Overall, these data suggest that 7-OH mitragynine and mitragynine pseudoindoxyl have a superior side effect profile compared to the gold standard opioid analgesic, morphine.[10]

It is important to note that mitragynine is the only alkaloid of the many alkaloids that FDA designated as "opioids", that is present in virtually all major kratom products, including ground leaves and extracts, marketed in the U.S. and consumed in SE Asia, Malaysia and region.

Jack Henningfield, Ph.D., of Pinney Associates presented his research that concluded: "Surveys indicate that some of the more than 3 million US kratom consumers in 2017 were using kratom as a path away from opioids. The neurobiology and low abuse potential of kratom support the potential viability of this such use. Surveillance suggests that kratom is an asset, though of not yet determined magnitude, in reducing opioid use. Kratom may provide a harm-reducing substitute for opioids used for pain or due to addiction.[11]

In addition, I would direct your attention to the presentation made by Dr. Surash Ramanathan of the Centre for Drug Research at the Universiti Sains Malaysia at the CPDD Conference on data on case reports on Kratom poisoning and death, where the following findings were reported that are consistent with the FDA's own data on kratom deaths:

- No direct evidence of death related to Kratom
- Death: unintentional or accidental:
    - Due to adulterated kratom products (synthetic adulterants: amphetamines, benzodiazepines or opioids amitriptyline, oxycodone, etc.).
    - Most cases the victims are poly drug users of other substance abuse.
    - Underlying medical conditions, e.g., alcohol abuse, depression, anxiety disorder.

[10] Characterization of mitragynine and an analog for analgesia, tolerance, physical dependence and reinforcing liabilities in mouse models, Jay McLaughlin, University of Florida, Financial Support: NIDA (DA06214), McManus Charitable Trust, and Mayday Foundation (to GWP), DA 034106 (to SM), NCI CA008748 (to MSKCC) and the University of Florida (to JPM).

[11] Henningfield, J.E., Raffa, R., Garcia-Romeu, A., and Doshi, T. Kratom and its mitragynines in the opioid crisis: A path to or away from opioids. College on Problems of Drug Dependence, San Diego, June 9-14, 2018, Financial Support: none.

Similarly, at the same symposium, Drs. Marek C. Chawarski, Yale School of Medicine, and Vicknasingam B. Kasinather, University Sains Malaysia, concluded:

- There are no known reported severe toxicity or fatality incidents in Malaysia or Thailand where there are large populations of long-term, daily users or [of] kratom.

This science strongly supports NIDA's 2016 conclusions and its 2018, July 2 update. It is particularly troubling to read in the response from the NIDA Press Office to the AKA media release that NIDA "consulted with the FDA regarding the overdose information on the Fact Sheet" and reported the "FDA is concerned that there have been deaths related to kratom that could be overdoses; while acknowledging that many of the products are adulterated, and many deaths result from mixing Kratom with other drugs." It should also be pointed out that, that kratom involved deaths reported by FDA include 9 Swedish *O*-desmethyltramadol deaths from nearly a decade ago[12], a homicide victim, and people with major life-threatening illnesses and/or other drug use.[13]

NIDA is the leading U.S. organization and voice on the effects of addictive drugs and substances like kratom and its 2016 and 2018 Drug Facts statements, though appropriately very cautious, are an important contrast to the mischaracterization of kratom as a deadly risk and narcotic like opioid by the FDA. We hope that NIDA will continue to stand as an independent voice, basing its conclusions on science, and its understanding of and obvious concern for people who actually suffer from opioid addiction and risk of overdose.

We are concerned that NIDA may be under pressure from purely political requests or demands being made by the FDA related to kratom that are not supported by the science, including research done by NIDA and its research contractors. The NIDA position is also supported by an 8-Factor Analysis on kratom conducted by Henningfield, Fant, and Wang[14] ; the Yue, Kopajtic, and Katz research on the abuse liability of mitragynine[15]; the Kruegel, et.al. research on the

[12] Robert Kronstrand, Markus Roman, Gunilla Thelander, and Anders Eriksson, Unintentional Fatal Intoxications with Mitragynine and *O*-Desmethyltramadol from the Herbal Blend Krypton, Journal of Analytical Toxicology, Vol. 35, May 2011.

[13] Jane Babin, Ph.D., Esq., 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, American Kratom Association Policy Report, March 2018.

[14] Henningfield, J.E., Fant, R.V., and Wang, D. The abuse potential of kratom according the 8 factors of the controlled substances act: implications for regulation and research. Psychopharmacology, 235:573–589, 2017.

[15] Yue K, Kopajtic, Katz, Abuse liability of mitragynine assessed with a self-administration procedure in rats, Pyschopharmacology, 2018, https://www.ncbi.nlm.nih.gov/pubmed/30039246

kratom alkaloids[16]; and Varadi et. al.[17]; as well as the Swogger and Walsh research on kratom use and mental health.[18]

The original NIDA statement is factually correct, as shown by all of the referenced studies conducted by dedicated and credible scientists in the U.S. and SE Asia. Deviation from this body of scientific evidence to accommodate a purely political agenda by the FDA on kratom would undermine public confidence in the independence NIDA is entrusted with in protecting the integrity of the regulatory review processes.

The scientific evidence is overwhelming that adopting the FDA's current bias against kratom will create a more dangerous safety signal where kratom users will be forced to either more dangerously addictive and potentially deadly opioids or to the black market where the adulterated kratom products will likely result in even more deaths.

Please accept our request for a meeting with you and your staff to discuss this matter, and to allow us to present the scientific basis for why listing kratom in Schedule I of the Controlled Substances Act, along with heroin, would actually pose a deadly risk for public health and is contrary to the science of kratom. We believe that NIDA, if not FDA, understands such science, as well as the science of addiction and the challenges facing those with actual opioid addiction.

Respectfully submitted,

David Herman
Chairman
American Kratom Association

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[16] Kruegel AC, Gassaway MM, Kapoor A, Váradi A, Majumdar S, Filizola M, Javitch JA, Sames D. Synthetic and Receptor Signaling Explorations of the Mitragyna Alkaloids: Mitragynine as an Atypical Molecular Framework for Opioid Receptor Modulators. J Am Chem Soc. 2016 Jun 1;138(21):6754-64.

[17] Váradi A,Marrone GF, Palmer TC, Narayan A, SzabóMR, Le Rouzic V, Grinnell SG, SubrathWE, Kalra S,Hunkele A, Pagirsky J, Eans SO, Medina JM, Xu J, Pan YX, Borics A, Pasternak GW, McLaughlin JP, Majumdar S (2016) Mitragynine/Corynantheidine Pseudoindoxyls as opioid analgesics with Mu Agonism and Delta antagonism, which do not recruit β-Arrestin-2. J Med Chem 59(18): 8381–8397.

[18] SWOGGER M. T., WALSH Z. Kratom use and mental health: A systematic review, Drug Alcohol Depend 2018: 183: 134-140.

Contact information:

Email: dave.herman@americankratom.org