

## **THE FDA DISINFORMATION CAMPAIGN REPEATEDLY PROMOTES “FAKE NEWS” ON KRATOM**

*A recent television news report in South Dakota shows how pervasive the FDA’s War on Kratom really is and the importance of setting the record straight.*



**STATEMENT:** “It (*kratom*) can have the same effect as opioids on the brain, yet anyone can buy it at the corner gas station or smoke shop.”

**RESPONSE: That statement is inaccurate.** The only similarity kratom has to opioids is that Kratom’s alkaloids hit the same mu receptor in the brain — as does chocolate, cheese, St. John’s Wort, and other commonly consumed products. The significant differences are that Kratom’s alkaloids do not produce any of the reinforcing euphoric effects as opioids do (that leads to addictions to opioids); and Kratom’s alkaloids do not have any effect on the respiratory system where respiratory suppression is the reason why drug overdoses commonly occur.

Specifically, opioids induce users to become addicted. Kratom does not have such attributes linked to addiction. A December 2019 peer reviewed published article, "Assessing physiological dependence and withdrawal potential of mitragynine using schedule-controlled behavior in rats" concluded that "findings suggest that MG does not induce physiological dependence but can alleviate the physical symptoms associated with morphine withdrawal which represent the desired characteristics of novel pharmacotherapeutic interventions for managing opioid use disorder (OUD) (*see <https://pubmed.ncbi.nlm.nih.gov/31832720/>*).

The National Institute on Drug Abuse (NIDA) concurrently funded two independent studies on the addiction liability of Kratom’s alkaloids, and those conclusions directly address why kratom is not scheduled today by the Drug Enforcement Agency (DEA) because it does not meet the scheduling criteria in the federal Controlled Substances Act:

- Abuse liability and therapeutic potential of the *Mitragyna speciosa* (kratom) alkaloids mitragynine and 7-hydroxymitragynine, Hemby, et. al., that concluded "present findings indicate that MG does not have abuse potential and reduces morphine intake, desired



characteristics of candidate pharmacotherapies for opiate addiction and withdrawal . . . “ (see <https://onlinelibrary.wiley.com/doi/abs/10.1111/adb.12639>)

- Abuse liability of mitragynine assessed with a self-administration procedure in rats, Yue, et. al., that concluded “these results suggest a limited abuse liability of mitragynine and potential for mitragynine treatment to specifically reduce opioid abuse. With the current prevalence of opioid abuse and misuse, it appears currently that mitragynine is deserving of more extensive exploration for its development or that of an analog as a medical treatment for opioid abuse. (see <https://pubmed.ncbi.nlm.nih.gov/30039246/>)

The US Food and Drug Administration (FDA) may have contributed to the misunderstanding of the health effects of most of kratom’s alkaloids. In its February 6, 2018 announcement, the agency stated that its computer modeling program predicted that 22 of the 25 most prevalent alkaloids found in kratom could bind to opioid receptors; thereby concluding that these alkaloids could be considered opioids [see *Gottlieb, S., 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. 2018, U.S. Food and Drug Administration: Rockville, MD*].

This simplistic analysis ignores the fact that substances that bind to mu-opioid receptors vary widely in their effects and safety. For example, the life-saving drug naloxone, the over-the-counter (OTC) antidiarrheal loperamide (Imodium®), and the addiction treatment buprenorphine, all bind to mu-opioid receptors. Although kratom’s compounds do in fact bind to mu-opioid receptors, real experimental data show that these compounds have unique signaling properties at mu-opioid receptors, and do not induce the same degree of respiratory depression or present the same risk of abuse as classical opioids. FDA’s approach also ignored the facts initially discovered primarily by South East Asia (SEA) researchers that most of kratom’s alkaloids have little biological activity and/or occur at such low levels [as exemplified by 7-HMG] to be of relatively little consequence with respect to use, effects, and safety [see *Prozialeck, W.C., Avery, B.A., Boyer, E.W., Grundmann, O., Henningfield, J.E., Kruegel, A.C., McMahon, L.R., McCurdy, C.R., Swogger, M.T., Veltri, C.A., and Singh, D., Kratom policy: The challenge of balancing therapeutic potential with public safety. Int J Drug Policy, 2019. 70: p. 70-77*].

Had FDA considered the known pharmacology of these alkaloids and the biologically negligible levels of most alkaloids in kratom, it may have concluded that the only alkaloids known to produce any opioid mediated effects of significance in humans are MG and 7-HMG, and that their pharmacology sets them apart from morphine-like opioids across key factors related to abuse potential and safety.



No study has demonstrated that kratom's effects are stronger than morphine on any measure of significance. 7-HMG is more potent than morphine in some tests but it does not produce a more powerful effect. With morphine-like opioids, death can occur due to these substances' reliable, dose-related respiratory depressant effects. In contrast to morphine, 7-HMG works as a biased G-protein ligand with little evidence of reliable respiratory depression at any dose level. In contrast, because 7-HMG works as a biased G protein ligand, there has been little evidence of reliable respiratory depression at any dose test.

Additionally, another effect of classical morphine-like opioids is their ability to induce euphoria, which can drive habitual and addictive use. Recreational opioid users generally report that kratom is a poor substitute for morphine-like opioids and does not produce the strong euphoria readily achieved with opium, morphine, or heroin. Thus, investigators who have studied certain effects of MG and 7-HMG that partially mimic opioids have described them as "atypical opioids"[see Kruegel, A.C., Uprety, R., Grinnell, S.G., Langreck, C., Pekarskaya, E.A., Le Rouzic, V., Ansonoff, M., Gassaway, M.M., Pintar, J.E., Pasternak, G.W., Javitch, J.A., Majumdar, S., and Sames, D., *7-Hydroxymitragynine Is an Active Metabolite of Mitragynine and a Key Mediator of Its Analgesic Effects. ACS Cent Sci*, 2019. 5(6): p. 992-1001] because many kratom effects are different from and/or weaker than those produced by morphine-like opioids. This has been verified in studies of kratom's mechanisms of action, analgesia, receptor binding and other effects related to use, addiction potential and safety across a broad range of laboratory tests.

Because kratom is not an opioid based on its plant origin, the chemical structure of its alkaloids, or its full pharmacology, kratom is not regulated as a Controlled Substance by international treaties such as the 1961 Single Drug Convention or the 1971 Psychotropic Convention, nor by the US Controlled Substances Act. As discussed above, more recent scientific research provides additional evidence that kratom has low abuse and addiction potential as compared to morphine-like opioids and cocaine, and carries a relatively low mortality risk as compared to such drugs.

Recreational opioid users for whom morphine-like opioids are powerful and reliable euphoricants have reported that kratom is a poor substitute for producing similar morphine-like euphoria. However, many users have also reported use of kratom to reduce opioid cravings and eliminate opioid use, consistent with animal studies discussed below that have shown that mitragynine reduces morphine and heroin seeking. For such people, kratom is life-giving if not life-saving, as they are able to resume productive lives in the workplace, and restore their family and social lives as has also been documented in field studies in SEA conducted by researchers at the Centre for Drug Research (CDR), Universiti Sains Malaysia.



Furthermore, studies by the CDR, an international review of the mental health effects of kratom, and an evaluation of kratom’s abuse potential according to the US Controlled Substances Act requirements, along with many other studies, concur that the risks of addiction are far lower for kratom than for morphine like opioids, cocaine and other highly addictive substances. These studies also indicate that in people who are dependent on kratom as a pain management tool or as a harm reduction alternative to opioid addiction, kratom is more likely to help them resume full occupational functioning, and responsible social and family lives, than when they were using opioids and other addictive drugs. Moreover, when kratom use is discontinued, most readily tolerate and self-manage the withdrawal symptoms.

Kratom is available at all levels of retail outlets, and gas stations and smoke shops are only two of such outlets. I have provided photos of the kind of store that exclusively deals with kratom that should illustrate that the pejorative reference to “gas stations and smoke shops” was used obviously to mischaracterize kratom and its consumer base. We believe this reference, while not determinative on final conclusions, paints the visual that the story was crafted to create.



**STATEMENT: “However, our KELOLAND News investigation talks with an Aberdeen mother whose son overdosed on kratom, as overdose deaths from the substance continue to rise nationwide.”**

**RESPONSE: This statement is misleading and incomplete.** The report states the reporter talked to a mother “whose son overdosed on kratom” does not qualify that statement as a claim by the mother, but rather treats the claim as if it is a fact. Unless Angela has seen an autopsy report on this death that documents that the medical examiner concluded the death was caused by an “overdose of kratom” then the proper characterization should more appropriately states as “**the reporter talked with an Aberdeen mother who BELIEVES HER SON OVERDOSED ON KRATOM.**”

The AKA would welcome the receipt of the autopsy report and toxicology screen on this death and, if available, will submit it for examination by an independent expert and we will immediately share the results with your team. We have had the FDA’s reported 44 deaths independently examined by an expert and the conclusion was that, with the exception of 1 death where no blood data exists for review, the remaining deaths the FDA reported as associated with kratom were actually caused by polydrug use, adulterated kratom products, or



underlying medical conditions. One of the deaths the FDA claims to be associated with kratom was, when a readable copy of the autopsy report was discovered, was actually caused by two gunshot wounds to the chest.

The statement that “**overdose deaths from the substance [kratom] continue to rise nationwide**” is, as you described, based on the CDC report (*Notes from the Field: Unintentional Drug Overdose Deaths with Kratom Detected — 27 States, July 2016 — December 2017*). **The statement is, at best, misleading.** The title specifically states the overdose deaths had “kratom detected.”

There have been multiple reports of deaths in people who had ingested kratom, but most have involved other substances. A 2019 paper analyzing data from the National Poison Data System found that between 2011-2017 there were 11 deaths associated with kratom exposure. Nine of the 11 deaths reported in this study involved kratom plus other drugs and medicines, such as diphenhydramine (an antihistamine), alcohol, caffeine, benzodiazepines, fentanyl, and cocaine. Two deaths were reported following exposure from kratom alone with no other reported substances. In 2017, the FDA identified at least 44 deaths related to kratom, with at least one case investigated as possible use of pure kratom. The FDA reports note that many of the kratom-associated deaths appeared to have resulted from adulterated products or taking kratom with other potent substances, including illicit drugs, opioids, benzodiazepines, alcohol, gabapentin, and over-the-counter medications, such as cough syrup. Also, there have been some reports of kratom packaged as dietary supplements or dietary ingredients that were laced with other compounds that caused deaths. People should check with their health care providers about the safety of mixing kratom with other medicines.”

Moreover, animal safety and toxicology studies have been published and/or known to have been provided to FDA’s Office of Dietary Supplements (ODS) in support of New Dietary Ingredient Notifications (NDIN). **These studies have exposed several species of animals to doses of 100 or more times greater than human equivalent doses without evidence of respiratory overdose death.**

In the US a recent comparison of the mortality risk of kratom with that of morphine-like opioids is consistent with the use of kratom as harm reduction substitute for many opioid users. **Specifically, an October 2019 peer-reviewed article examined the relative risks of death associated with kratom use compared to opioids and concluded that the risk of overdose death is more than 1000 times greater for opioids than for kratom** [see Henningfield, J.E., Grundmann, O., Babin, J.K., Fant, R.V., Wang, D.W., and Cone, E.J., *Risk of death associated with kratom use compared to opioids. Prev Med, 2019. 128: p. 105851*].



To the extent that kratom consumers are successfully using kratom to reduce opioid use, or to wean off opioid use entirely, the data strongly suggests that removal of kratom from the marketplace will result in more opioid-related deaths that will add to the opioid crisis in the US.

Note, we do not contend that kratom has never caused or contributed to death, that kratom carries no risks, or that kratom and specific alkaloids cannot under some conditions cause respiratory depression. However, the science does not support the conclusion that it is a morphine-like opioid on this critical aspect of opioid pharmacology and toxicology.

Leading international researchers from the Universiti Sains CDR presented their studies at the 2018 United States National Institute on Drug Abuse (NIDA) International Kratom Science Symposium where they concluded as follows: "There are no known reported severe toxicity or fatality incidents in Malaysia or Thailand where there are large populations of long-term daily users of kratom".



**STATEMENT:** Kratom affects the **same opioid brain receptors as morphine and can be addictive**. It can also have a stimulant effect in low doses.

**RESPONSE:** **These statements are inaccurate.** The National Institute on Drug Abuse (NIDA) conducted two animal studies on the addiction liability of Kratom's alkaloids, mitragynine and 7-hydroxymitragynine, and both concluded there was not significant addiction liability — see *Hemby and Yue studies referenced above*. Certainly a consumer can become dependent and experience relatively mild withdrawal symptoms similar to weaning off of caffeine. In fact, kratom is a part of the coffee family and it should not be surprising that it can be a stimulant in low doses, much like coffee.

For context, I would refer you to the published article "Kratom use and mental health: A systemic review," Swogger, et al. This study concluded that "Findings indicate kratom's potential as a harm reduction tool, most notably as a substitute for opioids among people who are addicted. Kratom also enhances mood and relieves anxiety among many users. For many, kratom's negative mental health effects - primarily withdrawal symptoms - appear to be mild relative to those of opioids." (see <https://pubmed.ncbi.nlm.nih.gov/29248691/>)



Another important study, "Self-treatment of opioid withdrawal using kratom (*Mitragynia speciosa korth*)" concluded "one striking finding of this report is the extent to which kratom attenuates potentially severe opioid withdrawal, yet cessation of kratom administration itself appears to be associated with modest abstinence symptoms," Boyer et al. (see <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3670991/> )

**The stated association to morphine and its well-recognized addiction profile and Kratom's addiction potential simply are inaccurate and misleads viewer about the effects kratom actually has.**

With regard to the "stimulant effect" reference, like most substances in the dietary supplement and drug product arena, kratom's effects are reported to be dose-dependent, with smaller doses producing mild stimulant-like effects that are more like coffee and tea than cocaine. Indeed, surveys in the US and SEA show that a major use of kratom is to increase occupational productivity and mental focus.

Larger doses can produce relaxing effects and serve as aids for some people to get to sleep but these effects are not as pronounced as are readily produced by pharmaceutical sedatives and opioids.

These uses are consistent with the characterization of its main active alkaloid MG, as well as the minor alkaloid 7-HMG, as G-protein-biased partial agonists of the mu-opioid receptor. At low to moderate doses, kratom has mild stimulant properties, unlike the sedating effects often exhibited by opioids. In addition, kratom does not seem to produce an intense high or euphoria at typical doses [see Cinosi, E., Martinotti, G., Simonato, P., Singh, D., Demetrovics, Z., Roman-Urrestarazu, A., Bersani, F.S., Vicknasingam, B., Piazzon, G., Li, J.H., Yu, W.J., Kapitany-Foveny, M., Farkas, J., Di Giannantonio, M., and Corazza, O., *Following "the Roots" of Kratom (Mitragynia speciosa): The Evolution of an Enhancer from a Traditional Use to Increase Work and Productivity in Southeast Asia to a Recreational Psychoactive Drug in Western Countries. Biomed Res Int, 2015. 2015: p. 968786*].

The most significant difference from opioids is that, even at very high doses, kratom is much less likely to depress respiration (to a fatal degree) than classical opioids [see Varadi, A., Marrone, G.F., Palmer, T.C., Narayan, A., Szabo, M.R., Le Rouzic, V., Grinnell, S.G., Subrath, J.J., Warner, E., Kalra, S., Hunkele, A., Pagirsky, J., Eans, S.O., Medina, J.M., Xu, J., Pan, Y.X., Borics, A., Pasternak, G.W., McLaughlin, J.P., and Majumdar, S., *Mitragynine/Corynantheidine Pseudoindoxyls As Opioid Analgesics with Mu Agonism and Delta Antagonism, Which Do Not Recruit beta-Arrestin-2. J Med Chem, 2016. 59(18): p. 8381-97*]. Further, at the molecular level, mitragynine has a chemical structure that is quite different



*from classical opioids such as morphine, which are mostly derived from the alkaloids of the opium poppy*[4, 6, 22, 25].

Recent studies indicate that even though mitragynine acts on opioid receptors, its overall molecular actions are quite different from those of classical opioids. Two recent studies demonstrated that mitragynine and several related compounds act as G protein-biased agonists at the mu-opioid receptor [see Kruegel, A.C., Gassaway, M.M., Kapoor, A., Varadi, A., Majumdar, S., Filizola, M., Javitch, J.A., and 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. 138(21): p. 6754-64*]. In other words, although they activated G protein-mediated signaling pathways, much like classical opioids, they did not activate the  $\beta$ -arrestin-2 signaling pathway, which has been implicated as a mediator of some opioid-induced side effects, including respiratory depression [see Raehal, K.M. and Bohn, L.M., *beta-arrestins: regulatory role and therapeutic potential in opioid and cannabinoid receptor-mediated analgesia. Handb Exp Pharmacol, 2014. 219: p. 427-43*]. Accordingly, the avoidance of  $\beta$ -arrestin-2 activation may in part explain the apparent respiratory safety of kratom, despite other mild opioid-like effects.



**STATEMENT:** You can also buy it [kratom] online. But there's absolutely no regulation of the plant

**RESPONSE:** This statement is incorrect. Kratom is subject to all of the misbranding and labeling requirements of the Food Drug & Cosmetic (FD&C) Act, and the FDA has taken action against kratom vendors to market their products using impermissible health claims because they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, including opiate withdrawal and addiction, and/or because they are intended to affect the structure or function of the body. Such marketing of kratom products allows the FDA to classify them as "new drugs" under section 201(p) of the FD&C Act, 21 U.S.C. 321(p), because they are not generally recognized as safe and effective for use under the conditions prescribed, recommended, or suggested in their labeling. Under section 505(a) of the FD&C Act, 21 U.S.C. 355(a), new drugs may not be introduced or delivered for introduction into interstate commerce without prior approval from FDA. No approved application pursuant to section 505 of the FD&C Act, 21 U.S.C. 355, is in effect for these products. Accordingly, the introduction or delivery for introduction into interstate commerce of these products violates sections 301(d) and 505(a) of the FD&C Act, 21 U.S.C. 331(d) and 355(a).



(see <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/cali-botanicals-llc-575320-06112019>).

Kratom products are also required to be manufactured under Current Good Manufacturing Practices (CGMPs) to ensure the safety of food — which is the proper classification of pure kratom. In 1969, FDA established CGMPs in the Code of Federal Regulations (CFR) (21 CFR Part 110). In September 2015, the agency modernized the CGMPs and established them in new Part 117 (21 CFR Part 117), along with new requirements for hazard analysis and risk-based preventive controls which were issued as part of the implementation of the FDA Food Safety Modernization Act (FSMA).



**STATEMENT:** “It’s legal. You can get it at the corner gas station and at the smoke shops. But it should be a Schedule I. It can be abused so easily,” Kathy Boschee said.

**RESPONSE: This statement is misleading.** This quote from Ms. Boshee is the only one published with no counter position offered. On its face, it leaves viewers with only that opinion with no balancing counter-point despite substantial evidence — including the plain fact the DEA has elected not to schedule kratom despite their authority to do so if the evidence merited such a decision – that a scheduling decision is not merited.



**STATEMENT:** While the feds have called for it to be classified as a Schedule I drug, that hasn’t happened, although it is illegal in six states.

**RESPONSE: This statement is misleading.** The FDA is the only “feds” to be calling for kratom to be classified as a Schedule I drug. NIDA has abandoned support for the recommendation to schedule kratom, and the U.S. Congress called for more research into kratom and recognized the significant number of kratom consumers reporting success with using kratom to wean off of highly addictive and potentially deadly opioids.



It is true Kratom is banned in six states, but it is legal in 44 other states. As we discussed, the six states passed their bans between 2012 and 2016 when the FDA was filling the information pipeline to state legislatures, health agencies, and law enforcement agencies highlighting the 9 deaths in Sweden in a 12 month period where the decedents consumed a powdered kratom product known as “Krypton.” What the FDA did not disclose were the findings of Swedish researchers, Kronstrand, et al., published in the Journal of Toxicology in May 2011 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 the nine cases presented and conclude that intake of Krypton is not as harmless as it often is described on internet websites.” (see <https://pubmed.ncbi.nlm.nih.gov/21513619/>)

It is also worthy to note the while the report referenced six states that have banned kratom, no mention is made of the four states who passed the Kratom Consumer Protection Act (KCPA), Utah, Georgia, Arizona, and Nevada — all of which were passed in 2019. In the current legislative session, the KCPA was under consideration in 21 states, and prior to the COVID shutdown it was clear more than a dozen states were on track to pass the KCPA. In South Dakota, the Legislature defeated a proposal to ban kratom sales in 2020.



**STATEMENT:** Millions of proponents say kratom is a good alternative to opioids to help relieve pain. However, kratom has caused nearly 100 overdose deaths in 27 states.

**According to the CDC another 61 fatal drug overdoses were found to have kratom in their bloodstreams, although other drugs may have been responsible for the deaths.**

**RESPONSE:** This statement is inaccurate and misleading. During our phone conversation, Angela read from the CDC report that states “deaths in which **kratom was detected** on postmortem toxicology testing and deaths **in which kratom was determined by a medical examiner or coroner to be a cause of death** in 11 states during July 2016 — June 2017 and states during July —December 2017. I have attached an analysis of the CDC report for your review (*A Reply to CDC Report on Unintentional Drug Overdose Deaths with Kratom Detected (2019); appropriate regulation of kratom and improved postmortem testing protocols are needed immediately, Jack E. Henningfield, Ph.D.; Jane K. Babin, Ph.D., Esq.; Oliver Grundmann, Ph.D.; Geoffrey Laredo, MPA; and Edward Cone, Ph.D.*)



The following points directly address the conclusion in the broadcast report that kratom overdose deaths are increasing nationwide:

Here are the top-line conclusions that the CDC data actually supports:

- The 91 “kratom-involved” deaths found multiple substances detected in “almost all decedents,” with fentanyl and fentanyl analogs as the most frequently identified cooccurring substances. These findings support the NIDA review of the FDA-claimed 44 kratom deaths, which concluded that “most kratom associated deaths appear to have resulted from adulterated products or taking kratom along with other potent substances.” The public policy mandate from this data is that the FDA should use its existing statutory authority to interdict manufacturers and marketers who deliberately adulterate kratom products with dangerous substances that cause death.
- Medical examiners and coroners are incorrectly reporting kratom-involved deaths as deaths caused by kratom. The lack of a consistent postmortem testing protocol to accurately pinpoint the extent kratom contributes to a death has exacerbated the grossly inaccurate and overstated FDA public narrative on the potential dangers of kratom. There is a critical need for the publication of standards for postmortem toxicology testing to avoid inaccurate findings by medical examiners and coroners, such as kratom allegedly being the cause of death and comprehensively identify substances that are not detected in routine testing for drugs of abuse.
- The report accurately states that “kratom is not an opioid” and notes that nonopioid substances are included in the State Unintentional Drug Overdose Reporting System (SUDORS), but the system records all substances testing positive on postmortem toxicology testing (including those that did and did not contribute to death). In fact, kratom critically differs from conventional opioids on the two signature features of conventional opioids that contribute to the opioid epidemic: It does not cause the powerfully addicting brain rewarding effects or the lethal respiratory depressing effects of conventional “narcotic-like” opioids”. However, the repeated claims by the FDA that kratom is an opioid and advisories claiming kratom has caused overdose deaths have clearly contributed to incorrect determinations by medical examiners and coroners that the presence of even the tiniest amount of kratom in postmortem toxicology screens was the cause of a death.

It is my sincere hope that you will consider an “educational” story on kratom and help to correct the factually incorrect statements and the misleading conclusions in the earlier story —



that are derivative of your good-faith reliance on the FDA position on kratom. In this instance, as I emphasized was the case in the early 1990's when the FDA made the same safety and policy arguments to ban vitamins and dietary supplements, the FDA is wrong on the science and wrong on the policy on kratom.