

June 21, 2018

The Honorable Mitch McConnell
Majority Leader
United States Senate
Washington, D.C. 20510

The Honorable Paul Ryan
Speaker
United States House of Representatives
Washington, D.C. 20515

The Honorable Charles Schumer
Minority Leader
United States Senate
Washington, D.C. 20510

The Honorable Nancy Pelosi
Minority Leader
United States House of Representatives
Washington, D.C. 20515

Dear Leader McConnell, Leader Schumer, Speaker Ryan, and Leader Pelosi:

We write today to address the U.S. Food and Drug Administration's (FDA) recommendation to the Drug Enforcement Administration (DEA) to schedule the kratom plant and its two biologically active alkaloids, mitragynine and 7-hydroxymitragynine, under Schedule I of the Controlled Substances Act (CSA). Based on the substantial science and safety signal data, we conclude that kratom does not meet the statutorily mandated criteria for Schedule I substances based on their potential for abuse, safety, dependence liability, and medical use (if any).

Therefore, we strongly recommend that the DEA return the scheduling recommendation to the FDA for additional review and research and encourage the FDA's Office of Dietary Supplements to appropriately regulate kratom products. This matter is urgent because there is a foreseeable negative public health consequence if legal kratom is banned: thousands of former opioid users will be at risk of returning to high-risk opioid use and may add to our nation's opioid overdose epidemic.

We urge you to do all you can to convince the DEA and FDA to take these needed actions. We need the FDA taking every reasonable step to reduce opioid overdose deaths, which includes not risking feeding the epidemic by banning kratom.

Contrary to the FDA's public statements, four internet surveys of more than 20,000 kratom users and 20,236 comments on the DEA's docket in the federal register suggest that most kratom consumers are not opioid abusers, are not using kratom to get high, and no federal survey has detected kratom abuse as a public health problem. In fact, people with opioid experience generally report kratom as a poor alternative to opioids for getting high and are not motivated, as they are with classical opioids, to intensify the experience by injecting, smoking, or snorting the substance. Most people use it in food or beverage form for health and well-being. Major reasons for use include increased general alertness and focus (similar to caffeinated products), use to relieve depression and anxiety, use to relax and as a sleeping

aid, and use to relieve pain in place of over-the-counter and prescription pain relievers, including opioids. The nearly 14,000 respondents to the three internet surveys that collected demographic information found that U.S. kratom users largely represent a cross-section of the middle-aged adult population having at least some college education, who are employed and have health care coverage.

An additional motivation for kratom use that warrants particular attention in the midst of our nation's opioid emergency is the use of kratom in place of classical opioids for pain and/or addiction. This is a major reported reason for use among the more than 43,000 survey respondents and comments to the FDA. At a time that our nation is experiencing more than 115 opioid overdose deaths each day, or more than 42,000 per year, we would expect the FDA and the Centers for Disease Control (CDC) to welcome this potential safer alternative to classical opioids. Indeed, the FDA's dockets, including its April to June Opioid Use Disorder treatment development docket, include testimonials from kratom users who are "terrified" that obstacles to kratom access will lead to a relapse of opioid use disorder.

It is with these people in mind that we write to you. This is a truly urgent matter.

Let us tell you more about the science related to how kratom works, what it does, its relative safety, and public health implications to help you understand why we assert that FDA is wrong on the science, and wrong in its efforts to ban legal kratom by placement in Schedule I of the Controlled Substances Act.

There is a long history of kratom use; it has been used safely for centuries in the Southeast Asia (SEA) region, where it grows in the wild, and for at least a decade in the United States. Importantly, SEA authorities have not reported any kratom overdose deaths. The reasons for kratom use in this region largely mirror those in the U.S., including use as a mild stimulant by agricultural workers and as an alternative to opioids for pain relief and addiction treatment. Such traditional use is reported to benefit quality of life, and improve social and occupational behavior, with little evidence of serious personal or social harm.

A review of the available medical records for each of the 44 total deaths the FDA claims are "attributable to kratom" shows that none of those deaths have been clearly established as a kratom-caused overdose poisoning. Importantly, what is missing from the FDA data is a pattern of deaths that look opioid-like (i.e., acute respiratory depression); or alcohol or sedative-like (acute sedation and respiratory depression); or cocaine and methamphetamine-like (i.e., cardiovascular types of deaths); which would typically be included in data submitted to the DEA supporting a scheduling recommendation. Rather, the data are comprised of an unusual mix of alleged "kratom-associated" deaths including various unrelated causes, such as, (1) polydrug use of toxic doses of illegal and/or prescription drugs; (2) an underlying medical condition that contributed to the death (e.g., leg thrombosis in an obese person); (3) the use of an adulterated or contaminated kratom product; or (4) non-drug related

circumstances (e.g. suicide and homicide). For example, the FDA consistently points to 9 deaths that occurred over a 12-month period in 2009 in Sweden resulting from the use of an internet drug known as “Krypton.” Krypton is a concoction that contains powdered kratom leaves adulterated with *O*-desmethyltramadol (a potent opioid analgesic). Researchers concluded that this *O*-desmethyltramadol adulterant was the cause of death in each of these 9 cases. In the case of the reported homicide, the decedent was shot in the chest resulting in his death, and he happened to be a kratom user at the time of his death. The science does not support the conclusion that kratom causes deaths on its own. Even if the FDA were correct in its estimate of 44 kratom-caused deaths world-wide over a decade of use by many millions of people, that would indicate a very low risk compared to many OTC drugs, dietary supplements, and even household cleaning products.

Further, the recently publicized health risks associated with bacterial contamination of kratom products are not unique. In fact, romaine lettuce, cantaloupes, chicken, and many common food products have been recently identified as contaminated with salmonella, *E. coli*, or other pathogens. In each case, the FDA and CDC have the statutory authority and regulatory tools to identify the source, remove contaminated products from the marketplace, and take appropriate steps to protect the public safety. FDA regulation of kratom as a dietary supplement could greatly reduce such risks in the future.

Accordingly, there are no safety data to support the conclusion that kratom poses an imminent public health risk to consumers that would justify its scheduling

Available scientific data also fail to support placement of kratom in Schedule I of the CSA. The CSA scheduling authority is premised on the pharmacology of the substance and it is incumbent on the FDA to submit valid scientific data supporting its scheduling recommendation to the DEA. The pharmacology of the alkaloids isolated from kratom has been studied enough to undermine the FDA’s claims that kratom has a high potential for abuse, as statutorily required for Schedule I placement.

The seemingly mild to moderate effects of the raw kratom plant in humans may be explained by the observation that mitragynine, while representing the most abundant active compound in the plant, is typically found in concentrations of only ~1-2% by weight of the dried leaf. Further, mitragynine is a low potency partial agonist of the mu-opioid receptor. In contrast, the more potent 7-hydroxymitragynine occurs in only trace quantities in kratom, suggesting that this compound does not play a major direct role in the pharmacological activity of raw kratom or its extracts. Relatedly, the low concentrations of the relevant compounds in the kratom plant are expected to limit the risk of adverse medical outcomes from its consumption. Likewise, there is no evidence that the compounds mitragynine and 7-hydroxymitragynine are available in a pure form to consumers, even via the black market, and thus, any potential dangers of such pure compounds are not relevant to any scheduling review of kratom itself.

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, this 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 “narcotic-like” opioids to which the FDA compared kratom in their public pronouncements in November 2017.

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

A 2017 panel at the prestigious American College of Neuropsychopharmacology meeting addressed analogues of mitragynine and like substances as potentially safer, minimally addictive pain relievers of the future. The panelists pointed to the substantial body of scientific studies both in the U.S. and globally that show that such “G protein-biased” substances are very different from narcotic-like opioids with respect to addiction profile and potential lethality, and that analogues of these substances might be among the next generation of safer medications. Much of the current research in this area will come to a halt if kratom is placed in Schedule I; another serious adverse consequence of scheduling.

We strongly recommend an inquiry to NIDA to determine if kratom is appropriately designated a “narcotic-like” opioid with respect to risk of addiction and death. Addressing the broader public health issue, NIDA could be asked to evaluate reports of using kratom as a replacement for opioids. NIDA should also be asked to conduct a nationally projectable survey determining whether a ban on legal kratom increases the risks of exposure to black market kratom or opioid overdose for some fraction of kratom users and if so, how many.

The preceding discussion should not be construed to suggest that consumption of kratom itself is risk free. It is true that nothing, not candy, vitamins, probiotics, or caffeine are free from risk; but those risks should not be exaggerated to advance public health policy initiatives which, although well intentioned, are likely to have unintended negative consequences.

While we do not believe there is a legitimate basis for Schedule I placement of kratom under the criteria of the CSA, we do believe there is an appropriate role for FDA regulatory regimens in each of the kratom categories of use that reflect current consumer use.

Kratom Leaf as a Food: There is an extensive history of use of kratom leaves as conventional foods in SEA and under the Federal Food, Drug, and Cosmetic Act (FFDCA) Section 413(a)(1), traditional kratom leaf preparations are exempt from the premarket notification requirements as they were present “in the food supply in a form that has not been chemically altered.” Importantly the plain language of the FFDCA recognizes history of use “could be from the United States or another country, as long as the substance was consumed as a food, dietary supplement, or, in the case of foreign history of use, category of product comparable to a dietary supplement in the U.S.” As such, consumers have a right to unfettered access to traditional kratom leaf products that meet food standards. FDA can and should apply all applicable food regulations to kratom leaf products prepared as per traditional use (ground leaf either directly ingested or prepared as a tea, which accounts for the majority of current use in the US).

Manufactured Kratom Products as Dietary Supplements: Extracts prepared from Kratom leaves that demonstrate the constituents in the dietary ingredient have not been chemically altered, should be considered as a Dietary Supplement under the Dietary Supplement Health and Education Act of 1994 (DSHEA). Ensuring Kratom products in the market place meet all requirements under DSHEA for Current Good Manufacturing Practices (CGMP), including specifications for identity and purity, and maximum allowable levels of alkaloids, is essential for ensuring the public has access to products that are of high quality and not contaminated or otherwise adulterated.

Adulterated Kratom Products: Any kratom product that is adulterated with undeclared substances or deleterious agents, fails to meet Dietary Supplement CGMP, or where a manufacturer asserts impermissible health claims for a kratom product, each should be appropriately addressed by FDA through its statutory authorities. The FDA and DEA currently have sufficient authority and regulatory tools to interdict and remove such illegally marketed and dangerous products. This means that under FDA regulation, consumers would have some assurance that their products are not adulterated and if they are, that they will be recalled. Without FDA regulation there is no such consumer protection, and this is appropriately terrifying to

kratom users who feel they benefit from kratom and fear an unregulated black market as their only kratom source.

We strongly urge the Congress to protect the freedom of American consumers to make informed decisions on products they safely use for their general health and well-being and allow for use of a safer alternative pain management product for those suffering from acute or chronic pain. The natural kratom plant does not kill consumers when used responsibly. The FDA and DEA should focus their regulatory efforts in dealing with dangerous adulterated products that pose a real threat to public safety.

The FDA has a range of regulatory tools that can be used to reduce risks of dietary products. This includes setting standards for maximum allowable levels of active constituents, screening for potential toxicants, packaging, labeling, and consumer information. The FDA can track and trace regulated marketers and it can withdraw from the market products that are not made or marketed to agreed upon standards.

With FDA regulation, purchasers of lawfully marketed products have the same reassurance that they do for other FDA-regulated dietary supplements and foods. Our nation's kratom consumers deserve an FDA-regulated market. The increasing use of kratom as a path away from opioids is an especially important one, which we hope you will help to address by asking the FDA, DEA, and NIDA to work together to preserve kratom product access while accelerating research, surveillance, and balanced regulation.

Respectfully submitted,



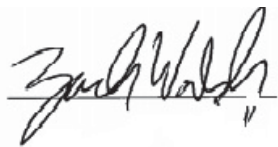
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