

Kratom Crackdown: FDA Intensifies Warnings with Limited, Inconclusive Data

To Scientists, Kratom-Linked Salmonella Outbreak Signals Need for Quality Control, Not a Ban

By Connor Yearsley

On February 6, 2018, a statement from US Food and Drug Administration (FDA) Commissioner Scott Gottlieb, MD, reiterated the FDA's concerns about the supposed dangers of leaf preparations of the Southeast Asian tree kratom (*Mitragyna speciosa*, Rubiaceae).¹

"Kratom should not be used to treat medical conditions, nor should it be used as an alternative to prescription opioids," the statement reads. "There is no evidence to indicate that kratom is safe or effective for any medical use."¹

Kratom is a tropical, evergreen, broad-leafed tree that can grow to 25 meters (82 feet) tall. It is native to peninsular Thailand, southeastern Myanmar, Malaysia, Borneo, Sumatra, the Philippines, and New Guinea. The species belongs to the madder (Rubiaceae) family, a large plant family that also includes coffee (*Coffea arabica*, *C. canephora*). The name "kratom" originates from Thailand and likely derives from the Sanskrit *kadam*, a name that refers to *Neolamarckia cadamba* (Rubiaceae), a widespread tree that is sacred in Hinduism. Similar names are used for various related tree species in the region.²

Preparations of kratom leaves have been used for centuries in Southeast Asia for a wide range of purposes, including to treat cough, diarrhea, and diabetes; to manage pain and opioid withdrawal; and to stave off fatigue. Leaf preparations of the plant, including powders and teas, act on the central nervous system. At low doses, they can produce stimulant effects, while higher doses often produce sedative and intoxicating effects.²

In a previous FDA statement from November 14, 2017, in which the FDA urged consumers not to use kratom or any compounds from the plant, the FDA claimed it was "aware of reports of 36 deaths associated with the use of kratom-containing products."³ By the time of the February statement, that number had increased to 44 deaths. Also on February 6, the FDA released reports of the 36 deaths previously noted in November (though only 33 appear to include any data) and stated it would release the remaining reports soon.^{1,4-6}

Reports of the 36 deaths "underscore the serious and sometimes deadly risks of using kratom and the potential interactions associated with this drug," according to the FDA.¹ But, in most, if not all, of these cases, kratom's involvement is circumstantial, and it is difficult or impossible to establish a causal relationship between kratom and the deaths. Many of these cases involved other substances and decedents who had a history of misusing substances other than kratom.⁴⁻⁶ To the FDA, though, this raises concerns that potentially lethal interactions may occur when kratom is used with other substances.⁷

"If you were taking an FDA-approved opioid, you would know exactly what other drugs you're not supposed to be taking with it," an FDA spokesperson was quoted as saying. "We don't have that with kratom — nobody does."⁷

Among the 36 cases was someone who died by suicide after having struggled with bipolar disorder and depression; another who was murdered by a gunshot to the chest; and a third person with nine other substances in his system who fell from a window, suffered a broken arm, and refused medical treatment before dying.⁴⁻⁶ Also included are nine deaths that occurred in Sweden between 2009 and 2010 that were linked to a product called "Krypton." It has been documented that kratom-containing products sold under the name "Krypton" were also found to contain caffeine and *O*-desmethyltramadol, which is the main active metabolite of the prescription opioid tramadol and is a significantly more potent agonist (activator) of mu-opioid receptors (an opioid receptor subtype that is involved in producing analgesia and euphoria) than tramadol.^{2,4-6}

The FDA identified one case that it stated "was of particular concern. This individual had no known historical or toxicologic evidence of opioid use, except for kratom." However, because the February 6, 2018, FDA statement does not include the case ID number, it is unclear to which case report the FDA is referring, or whether the report for this case is even included among those that were released.¹

It is possible, or perhaps probable, that the FDA was referring to the case of Matthew Dana. In September 2017, Franklin County (New York) Coroner Shawn Stuart ruled that the official cause of death of Dana, a police sergeant from Tupper Lake, New York, who died the previous month, was hemorrhagic pulmonary edema from an accidental overdose of mitragynine, one of the main chemical constituents of kratom. Dana reportedly had an extremely high amount of mitragynine in his blood (3,500 nanograms per milliliter) when he died, but no other foreign substances.⁸ "It's possible that we see more people die from drinking too much water every year. Or taking too much Tylenol," Stuart was quoted as saying. "All we're doing is reporting that in this case, kratom was the cause of death."⁷ Notably, this case may contradict the frequently mentioned claim that, at high doses, kratom induces vomiting, thus making it difficult to overdose.²

Eight of the deaths associated with kratom came from the Center for Food Safety and Applied Nutrition (CFSAN) Adverse Event Reporting System (CAERS), while at least 25 came from the FDA Adverse Event Reporting System (FAERS).⁶ Notably, both the CAERS webpage and the FAERS webpage include disclaimers about the limitations of the data.

The CAERS webpage states: “The adverse event reports about a product and the total number of adverse event reports for that product in CAERS only reflect information AS REPORTED and do not represent any conclusion by FDA about whether the product actually caused the adverse events. For any given report, there is no certainty that a suspected product caused a reaction.... The event may have been related to a concurrent underlying condition or activity or to co-consumption of another product, or it may have simply occurred by chance at that time.”⁹

Likewise, the FAERS webpage states: “First, there is no certainty that the reported event (adverse event or medication error) was due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event.”¹⁰

The significance of these data perhaps is obscured further because the deaths occurred over at least a nine-year period, and many occurred outside the United States.⁴⁻⁶ In the United States, kratom started gaining popularity about 15 to 20 years ago.² Now, an estimated three million to five million Americans reportedly use kratom regularly. Some kratom proponents contend that, considering this large number of regular kratom consumers in the United States and that people in the plant’s native range reportedly have used it safely for centuries,¹¹ the number of confirmed adverse events is seemingly very low, especially when compared to those caused by other products/substances that are widely available, including some that remain unscheduled under the Controlled Substances Act (CSA) of 1970.⁶ Still, kratom is now banned in seven states (Alabama, Arkansas, Indiana, Rhode Island, Tennessee, Vermont, and Wisconsin) and Washington, DC, because of disagreements about its safety and potential for misuse.^{2,12}

FDA Calls Kratom ‘an Opioid’ but Ignores Relevant Scientific Data

The FDA’s February 6 statement also describes how a then-unpublished computer model, which the FDA developed, was used to simulate how kratom’s constituents “are structured at a molecular level, how

they may behave inside the body, and how they can potentially affect the brain.” Using this model, FDA scientists evaluated the 25 most prevalent compounds in kratom and concluded: “The model predicted that 22 (including mitragynine) of the 25 compounds in kratom bind to mu-opioid receptors.”¹¹

Some have questioned the timing of this proclamation and claimed it may be another attempt to stigmatize kratom in light of the current opioid epidemic. After all, the fact that kratom contains opioid-like compounds is not news. This has been known since at least 1996 when an *in vivo* study on mitragynine was published.¹³ The study showed that mitragynine inhibited pain impulses in mice in a dose-dependent manner, and these effects were reversed by naloxone, a semi-synthetic opioid receptor antagonist (i.e., an inhibitor of receptor activity) that is used to reverse the effects of opioids in cases of overdose or postoperative sedation.¹⁴ A study published the following year showed that, through the opioid receptor, mitragynine inhibited the movement of isolated guinea pig intestines, and these effects also were reversed by naloxone.¹⁵

According to Oliver Grundmann, PhD, an associate professor of medicinal chemistry at the University of Florida College of Pharmacy who has co-authored a review of kratom pharmacology, the FDA’s computer model considers only whether compounds bind to opioid receptors. “It doesn’t take into consideration the data that we have obtained that distinguish the kratom alkaloids mitragynine and 7-hydroxymitragynine from the classical opioids,” he said (oral communication, June 4, 2018).

“We know from studies that have been conducted by Christopher McCurdy at the University of Florida and Andrew Kruegel at Columbia University that, after they bind to the opioid receptor, the downstream activation and the downstream signaling are different for the kratom alkaloids,” Grundmann continued.^{16,17}



Kratom *Mitragyna speciosa*
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That is, the kratom alkaloids do not recruit the beta-arrestin-2 protein that seems, at least partly, to influence respiratory depression and opioid tolerance. Instead, the kratom alkaloids seem “biased” toward the G-protein signaling pathway and therefore do not seem to cause respiratory depression the way that other opioids, like morphine, do.^{2,16-18}

David Kroll, PhD, a pharmacologist and medical writer who has written articles about kratom for *Scientific American* and *Forbes.com*, also noted that “the FDA’s computer modeling did not take into account that the 20+ other kratom compounds predicted to have opioid activity are highly unlikely to reach meaningful concentrations in the blood of kratom consumers. The limited published data on kratom in human volunteers suggests that mitragynine may be the only kratom alkaloid that can reach blood levels that would lead to meaningful activity at the mu-opioid receptors” (email, July 24, 2018).

Grundmann added: “I understand that the FDA has safety concerns, but what we have seen so far with kratom is that, for one, the extracts are not being abused in the manner that heroin or morphine or some of the other classical opioids are being abused. They do not seem to be injected. The kratom alkaloids are not being extracted and used as pure substances, like fentanyl or heroin, and then being injected. That is not happening.”

In addition, kratom alkaloids are partial agonists of mu-opioid receptors, meaning their maximal effect is lower than that of a full agonist like morphine. The pharmacological actions of the kratom alkaloids more closely resemble those of buprenorphine than those of other, more common opioids. Buprenorphine is a semisynthetic opioid that gradually has been replacing methadone in opioid maintenance therapy for recovering opioid addicts.^{2,13,17-18}

“I agree that we need a better system to allow more traditional medicines or supplements, like kratom, to undergo clinical trials,” Grundmann added. “There needs to be a pathway for such supplements to be recognized and have a path forward through the regulatory system to be recognized as potential treatment options.”

There are countless anecdotal reports of people who claim to have benefitted from kratom. These people have used kratom for a broad variety of purposes, including to cope with post-traumatic stress disorder (PTSD), manage fibromyalgia and other chronic pain conditions, and recover from alcoholism.² The FDA, however, is concerned that people are using kratom to self-medicate, without guidance from trained medical professionals.^{1,19} Instead, the FDA urges kratom users to seek FDA-approved medications, like methadone, which have undergone extensive review and for which the FDA continuously tracks emerging safety data.¹ Kratom proponents contend that these medications often are inaccessible to the uninsured, don’t work for everyone, and can be dangerous.⁷ Methadone, for example, causes about 5,000 overdose deaths per year.²

While there is hope about the potential for new therapeutics derived from kratom to become safe and effective pain-relievers and opioid recovery aids, there, unfortunately, seems

to be little financial incentive to investigate kratom constituents as new drugs. In the United States, the only paths for kratom are as a new dietary ingredient (NDI) or a botanical drug. For NDIs, the FDA requires adequate safety data before the ingredient can be used in supplement products, but the FDA does not believe this requirement has been met for kratom. In addition, no company has submitted the necessary information for a kratom product to become a botanical drug.^{2,13}

Herbal products can be sold as long as no disease-treatment claims are made and as long as the FDA does not consider them unsafe. In kratom’s case, however, the FDA formally has recommended that the US Drug Enforcement Administration (DEA) place the kratom alkaloids in Schedule I, the most restrictive and punitive schedule, of the CSA.^{6,7,19} This, in effect, would mean that possession and distribution of any kratom preparations would be illegal and could result in criminal prosecution. In August 2016, the DEA announced its intention to temporarily place the compounds in Schedule I, but significant backlash from the public and members of Congress convinced the DEA to withdraw that proposal (covered extensively in *HerbalGram* issue 112).² Now, the DEA has hinted it could make a decision as early as summer 2018.¹⁹

“When the FDA comes to us and says a certain substance should be a medicine, we are bound by that,” DEA spokesperson Rusty Payne was quoted as saying. “When something is deemed a threat, we act.”⁷

On February 8, 2018, two days after the FDA’s statement, Grundmann and eight other top kratom researchers submitted a letter to DEA Acting Commissioner Robert W. Patterson and Counselor to the President Kellyanne Conway in which they urged them to consider the effects that banning kratom might have on current kratom users. “We believe strongly that 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,’” the scientists wrote. “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.”²⁰

The scientists also claimed that failure to consider possible negative consequences of scheduling would contradict the purpose of the enactment of the CSA (to protect the safety of consumers) and that scheduling would have a “profound and pervasive chilling effect” on additional kratom research.²⁰

Salmonella Outbreak

On February 20, 2018, the US Centers for Disease Control and Prevention (CDC) announced it was investigating a *Salmonella* outbreak it claimed was linked to kratom. Twenty-eight people from 20 states were reported to have been infected with a type (or serovar) of *Salmonella* designated I 4,[5],12:b:-. Because whole genome sequencing revealed that *Salmonella* samples from infected individuals were closely related geneti-

cally, the CDC concluded the outbreak likely was caused by a single source. Interviews with some infected people then led the CDC to conclude that kratom was the likely source, even though no kratom products had been shown to be contaminated at the time.²¹

A CDC spokesperson explained: “Health officials use questionnaires to ask sick people in an outbreak what they ate in the week before illness. Eight out of 11 people interviewed reported kratom use, which is a much higher percentage than would be expected for a healthy group of people. That epidemiologic evidence is strong enough to link the outbreak to kratom. There were no other common foods reported at such a higher than expected frequency. In outbreak investigations, it is normal for some people to not report eating the suspected food item, which could be for a variety of reasons. For instance, they might forget what they ate, it isn’t specifically asked on the questionnaire, or they got secondary transmission from caring for someone else who was sick.”²²

The *Salmonella* serovar in question reportedly has been found previously in humans, reptiles, and fish, and even in spices and dried mushrooms. Furthermore, a CDC spokesperson confirmed that “*Salmonella* I 4,[5],12:b:- is often seen in countries in Southeast Asia [where kratom is native]. We have seen other outbreaks with this serotype linked to other products, such as frozen shredded coconut and frozen raw tuna.”²²

On March 1, the CDC announced that 12 more people from seven states had been infected with the *Salmonella* serovar in question, bringing the total to 40 people from 27 states. Notably, analyses of leftover and unopened kratom products from ill people in North Dakota and Utah confirmed that both samples were contaminated with the serovar in question.²¹

Two weeks later, the CDC announced that 47 more people from 25 states had been added to the investigation, bringing the total to 87 people from 35 states. Analyses of kratom products from retailers where ill people purchased kratom confirmed that samples were contaminated with additional *Salmonella* serovars. By the end of the investigation on May 24, 199 infected people had been identified from 41 states. Implicated products were recalled, but the investigation was not able to identify a single, common source of contaminated kratom. The CDC warns that contaminated kratom products may still be available for purchase or in people’s homes. No deaths were reported.²¹

A group of scientists suggested that, by issuing its kratom import alerts several years ago, the FDA may have inadvertently contributed to the *Salmonella* outbreak, because these alerts significantly reduced the number of available kratom products and thus forced some kratom users to turn to inferior products.²³ In 2012, the FDA issued an import



Kratom

Mitragyna speciosa

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alert notifying field personnel that they could detain kratom-containing products listed in the alert without physical inspection because these products were considered unapproved and/or misbranded drugs. In February 2014, the FDA issued a separate import alert regarding kratom-containing dietary supplements and bulk dietary ingredients.²⁴

“This *Salmonella* contamination of kratom products underscores the need for responsible manufacture of products, implementation of current Good Manufacturing Practices (cGMPs) in compliance with the mandatory 2007 rule for dietary supplements, and FDA enforcement, not scheduling [under the CSA],” Paula N. Brown, PhD, director of applied research in biosciences at the British Columbia Institute of Technology, was quoted as saying.²³

Grundmann also said: “Whenever there is a food contamination, that doesn’t mean that all of a sudden we would prohibit lettuce as a food item, for example. That’s not happening. If we establish quality control measures for herbal supplements the same way we do for our food chain products, then we can ensure that products consistently meet necessary standards and prevent contamination.” HG

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