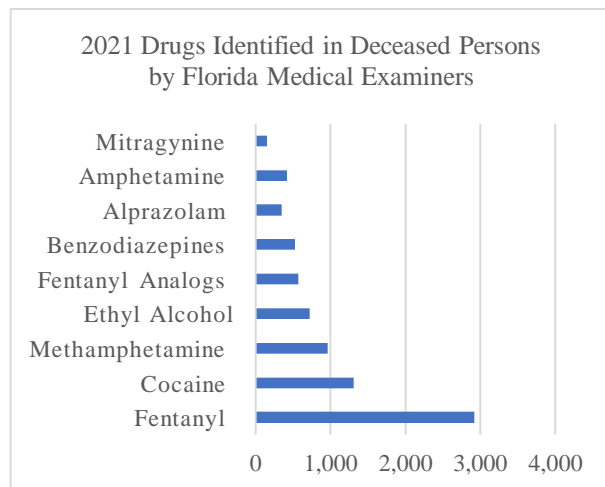

Factors to Consider Prior to Including Kratom or Mitragynine as Cause of Death

Medical examiners and coroners hold the difficult and complex responsibility to determine cause of death. Recently, kratom and its primary alkaloid, mitragynine, are listed as cause of death in more death investigations. The number of such cases remains small compared to the number of other drug deaths as noted in the 2021 Drugs Identified in Deceased Persons by Florida Medical Examiners (Florida Law Enforcement 2022). There were 7,756 cases in Florida where drugs were found, with the most frequently occurring drugs fentanyl (3,210), ethyl alcohol (3,132), benzodiazepines (2,081, including 773 alprazolam occurrences), cocaine (1,971), cannabinoids (1,915), fentanyl analogs (1,376), methamphetamine (1,338) and amphetamine (1,245). Drugs listed that caused the most deaths were fentanyl (2,920), cocaine (1,305), methamphetamine (962), ethyl alcohol (718), fentanyl analogs (574), benzodiazepines (526, including 349 alprazolam deaths) and amphetamine (421). In this same time frame there were only 154 mitragynine findings (0.02%) in the total number of reported deaths. In 106 of these mitragynine or

kratom was listed as cause of death (68.8%) and merely as present in 48 cases (31.2%). Considering the percentages of findings listed as cause of death, they ranged from the most common fentanyl 91.0%, methamphetamine 71.9%, mitragynine 68.8%, cocaine 66.2%, alprazolam 45.1%, fentanyl analogs 41.7%, amphetamine 33.8%, benzodiazepines 25.3%, ethanol 22.9%, and none for cannabinoids. Considering the low prevalence of mitragynine in postmortem death cases, why is there such a high propensity to list mitragynine as cause of death compared to more toxic compounds such as fentanyl analogs and cocaine when the toxicity of kratom or mitragynine in humans remains questionable?

Kratom comes from a tropical tree *Mitragyna speciosa* (Korth.) from the genus *Mitragyna* (Rubiaceae) native to Southeast Asia that also includes the coffee tree. Kratom leaf powders, tea-like decoctions, and extracts are taken primarily to fight fatigue from working in hot climates, for analgesia, improved mood and well-being, to reduce anxiety, including for posttraumatic stress disorder (PTSD), to eliminate opioid use for analgesia and to self-manage opioid withdrawal and use disorder by millions of people around the world. In 2020, Covvey et al (Covvey et al 2020) estimated there were 2.5 to 15 million kratom users in the United States. Mitragynine, the primary indole alkaloid (1-2%) in *Mitragyna speciosa* leaves, is a low affinity, partial μ -opioid receptor agonist ($K_i \sim 709$ nM), but also an antagonist at κ -opioid receptors, an agonist at α -adrenergic ($\alpha 1A$, $\alpha 1B$, $\alpha 1D$, $\alpha 2A$, $\alpha 2B$ & $\alpha 2C$), 5-HT_{1A}, 5-HT_{2C} & 5-HT₇ serotonin, D₂ dopamine and A_{2A} adenosine receptors. Mitragynine's pharmacological profile, botanical origin and its molecular structure clearly document that it is not an opioid. Another important



difference is that mitragynine does not activate the β -arrestin-2 pathway responsible for opioids' adverse respiratory depression and constipation effects.

The opioid epidemic in the United States claimed thousands of lives and has not yet abated, with more than 75.7% of 106,699 opioid deaths in 2021 due to opioid overdoses (Spencer et al 2022). In 2016, the Food and Drug Administration (FDA) requested the DEA to schedule kratom and mitragynine due to their posing an imminent danger to and the cause of death of many Americans. The DEA published its intent to schedule on August 31, 2016. In response, DEA received more than 23,000 comments from kratom consumers that kratom was important for their well-being and for others, kratom provided an alternative to opioids, offering a harm mitigation approach. On February 6, 2018, FDA released a report on 36 kratom-associated deaths supporting their request to schedule kratom (FDA 2018). These included a gunshot victim, a suicide, and a motor vehicle crash. Importantly, most cases included other drugs that were listed as the primary cause of death. The National Institute on Drug Abuse stated that there were multiple reports of deaths in people who had ingested kratom, but most involved other substances. Questions about causation of the fatalities reported by the FDA as kratom-caused deaths, and the comments indicating potential increased opioid deaths if kratom was scheduled and unavailable resulted in the DEA rescinding its intent to schedule kratom and mitragynine in September 2016 and requesting additional information from the FDA. On August 16, 2018, Admiral Brett Giroir, MD, Assistant Secretary of Health, US Department of Health and Human Services (HHS), formally withdrew HHS's request to schedule kratom and mitragynine based on a thorough review of the previous submitted evidence, new scientific findings and "concerns for unintended public health consequences." He referred to new scientific evidence of low abuse potential of kratom and mitragynine use by individuals with opioid use disorder to reduce the amount and frequency of their opioid intake. In addition, the Assistant Secretary stated that there is "still debate among

reputable scientists over whether kratom by itself is associated with fatal overdoses."

Olsen et al (2019) analyzed data from the State Unintentional Drug Overdose Reporting System (SUDORS) that records detailed data on unintentional and undetermined intent opioid overdose deaths from death certificates and medical examiner and coroner reports, including postmortem toxicology results. The authors from the Center on Disease Control and Prevention (CDC) state that kratom is not an opioid but is included in the SUDORS opioid reports. There were 27,338 overdose deaths that occurred during July 2016–December 2017 in SUDORS, and 152 (0.56%) of these decedents tested positive for kratom by toxicology. Medical examiners or coroners listed kratom as cause of death in 91 (59.9%) of the 152 kratom-positive decedents, including seven for whom kratom was the only substance to test positive on postmortem toxicology. Eighty percent of the 152 kratom-positive deaths were in individuals with a history of substance misuse. In most cases, multiple substances were detected including fentanyl and fentanyl analogs as the most frequently identified and determined to be the cause of death for 65.1% of kratom-positive decedents and 56.0% of kratom-involved decedents. Heroin was the second most frequent substance listed as a cause of death (32.9% of kratom-positive decedents), followed by benzodiazepines (22.4%), prescription opioids (19.7%), and cocaine (18.4%). Kratom or mitragynine positive deaths were less than 1% of SUDORS overdose deaths from July 2016 to December 2017.

Similarly, Gershman et al 2019 investigated all death certificates from Colorado deaths from 1999–2017. Kratom was mentioned as cause of death in 15 decedents in 19 years. Initially, 11 of the deaths reported multiple drugs, with mitragynine concentrations from 16 to 4800 ng/mL. Residual blood samples from three of the remaining four cases was available and subjected to more comprehensive toxicological testing. Additional drugs were identified that could have been responsible for the death. Blood was not available for confirmatory testing in the remaining kratom-

related death. The authors concluded that it is necessary to include comprehensive toxicology testing prior to concluding that kratom is the cause of death.

The National Institute on Drug Abuse's (NIDA) Director, Dr. Nora Volkow, recently discussed the use of kratom to help individuals manage their opioid use disorder at a US Congressional Appropriations hearing in May 2022. NIDA funded more than 30 million dollars of kratom and mitragynine research over the last few years to further understand the pharmacology of these compounds. Mitragynine or analogs potentially offer analgesia with less respiratory depression, and also may be useful as a harm reduction tool to reduce opioid overdose deaths.

The World Health Organization's Expert Committee on Drug Dependence (ECDD)

conducted an in-depth pre-review of kratom, mitragynine and 7-OH-mitragynine and received comments from scientists and health professionals around the world on the topic of whether kratom and mitragynine should be scheduled (WHO 2021). The ECDD advised the UN Commission on Narcotic Drugs that there was insufficient evidence to schedule kratom at the international level at this time and that they would continue monitoring kratom.

A recent study in rodents compared blood gases, observable signs and pharmacokinetics of 20, 40, 80, 240 and 400 mg/kg oral mitragynine and 6.75, 60 and 150 mg/kg oral oxycodone hydrochloride over 12 h (Henningfield et al 2022). The study followed the recommendations published by US Food and Drug Administration (FDA) scientists on evaluating respiratory depressants against oxycodone as the prototypical opioid control (Xu et al 2020). Oxycodone administration produced significant dose-related respiratory depressant effects including decreases in oxygen saturation and increases in partial pressure of carbon dioxide

blood gas levels. In addition, oxycodone produced pronounced sedation with one death each at 60 and 150 mg/kg. Mitragynine did not yield any significant dose-related respiratory depressant or life-threatening effects even at 400 mg/kg. Sedative-like effects, milder than those produced by oxycodone, were evident at the highest mitragynine dose. Consistent with mitragynine's pharmacology that includes partial μ -opioid receptor agonism without recruitment of the respiratory depressant activating β -arrestin pathway, mitragynine produced no evidence of respiratory depression at doses many times higher than known to be taken by humans.

Another consideration is potential adulteration of unregulated kratom with toxic substances. Kronstrand et al 2011 described nine overdose deaths in which kratom was listed as the cause of death. Upon further toxicological investigation, they identified O-desmethyltramadol in all nine decedents. These individuals unknowingly used a kratom product adulterated with a toxic dose of the powerful μ -receptor agonist O-desmethyltramadol. US News and World Report in March 2019 commented on the need for appropriate regulation on kratom noting "whenever products like kratom are not regulated, there is a risk for adulteration and contamination. There have been some instances of products being sold as kratom that are adulterated with potentially dangerous substances in order to artificially increase quantity and weight." There are other reports of kratom adulterated with its more potent 7-OH-mitragynine metabolite and more recently, adulteration of kratom with novel psychoactive substances including designer opioids. The Kratom Consumer Protection Act currently adopted by 8 states and recently introduced into the US Congress December 27, 2022, regulates kratom production and eliminates adulteration of the natural product.

Kratom and mitragynine science is advancing rapidly but much more data are needed to understand kratom and mitragynine's effects in humans. Human studies following mitragynine administration are just beginning. Prior to assigning causation of death to mitragynine, a complete toxicological analysis is needed to identify other

... "whenever products like kratom are not regulated, there is a risk for adulteration and contamination."

potential contributors to death. Novel psychoactive substances including designer opioids and designer benzodiazepines were frequently identified in cases where kratom or mitragynine was also found. Approximately one-third of kratom users state in surveys that they take kratom to self-manage their opioid use disorder; hence the finding of fentanyl, fentanyl analogs, heroin and prescription opioids in conjunction with kratom or mitragynine, and potential identification of kratom at the scene of death if the individual was taking kratom to reduce opioid use, but unfortunately relapsed.

For the many reasons described above, standardization is needed in postmortem investigations prior to listing kratom as the cause of death.

Factors for listing kratom or mitragynine as cause of death

1. Initially, at a minimum, perform the laboratory's postmortem toxicology tests as specified in ANSI-ASB Standard #119 entitled "Standard for the Analytical Scope and Sensitivity of Forensic Toxicological Testing of Blood Medicolegal Death Investigations." The minimum standards for the analytical scope and sensitivity of forensic toxicological testing of blood in medicolegal death investigations is based on the current prevalence and availability of drugs in the United States.
2. Perform a thorough scene investigation to identify the presence of potentially toxic compounds, including mitragynine.
3. Expand the list of drugs investigated to include drugs commonly found in the jurisdiction that might not be common throughout the United States and hence, absent from ANSI-ASB Standard #119.
4. Consider all the circumstances of death.
5. Investigate the decedent's past drug use history, past medical history of overdoses, rehabilitation stays, law enforcement records etc. to determine potential additional relevant drugs to test, including those that may require testing at a reference laboratory.
6. Test for novel psychoactive substances that could be the cause of death.
7. Quantify all drugs found in initial postmortem toxicology, potentially toxic prescription and illegal drugs found at the scene, drugs identified by past drug use history, including mitragynine, and if possible, 7-OH-mitragynine its active metabolite, and novel psychoactive substances to document total drug exposure.
8. Review the current scientific data on mitragynine pharmacology.

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