AMERICAN KRATOM ASSOCIATION

POLICY REPORT

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

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ABSTRACT

The U.S. Food and Drug Administration ("FDA") claims it has submitted a recommendation to the Drug Enforcement Administration ("DEA") for the placement of the alkaloids in kratom into Schedule I of the Controlled Substances Act ("CSA"). The placement of drugs or other substances into schedules under the CSA is based upon the substance's medical use, potential for abuse, and safety or dependence liability[i]. The data on 44 deaths associated with kratom that has been publicly referenced by the FDA, and which FDA Commissioner Scott Gottlieb has affirmed is a part of the scientific and medical documentation submitted in support of its scheduling recommendation for kratom to the DEA.

A review of the available FDA data reveals the overwhelming majority of the cited deaths fails to provide a cohesive or reasonable scientific basis to conclude any of the deaths was caused by kratom, nor does the information released conclusively support any conclusion that kratom was associated to the cited death other than coincidentally. Only one case report released by the FDA suggests that the only substance detected in the decedent's blood was kratom, but that report provides no substantive detail other than the decedent's age and ethnicity, and provides no data on any underlying health condition that may have caused the death.

The FDA data source for the reported deaths purportedly associated with kratom is derivative of voluntary reports submitted by healthcare professionals and consumers to two separate adverse event reporting systems maintained by the FDA. There are 8 reported deaths associated with kratom from the CFSAN Adverse Event Reporting System (CAERS); and 25 reported deaths from the FDA Adverse Event Reporting System (FAERS) .

The CAERS database publishes the information "as reported[ii]" and claims the information does not represent any conclusion by the FDA about whether the product actually caused the adverse event. The CAERS database also recognizes 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. The FAERS database is also limited in that there is no certainty that the reported event was due to the product referenced in the report. FDA does not require that a causal relationship between a product and event be proven, and the FDA acknowledges publicly that the reports do not always contain enough detail to properly evaluate an event.

Yet, the FDA has clearly intentionally mischaracterized kratom using these unverified reports as the basis to recommend the effective ban on consumer access to kratom by placing kratom in Schedule I of the CSA. The FDA publicly argues its transparent campaign to require kratom products to be subject to FDA authority in the submission of a new drug application. The FDA's own data, however, fails to meet the criteria for CSA scheduling under Schedule I or any other schedule. Kratom remains a safe and suitable natural botanical for consumer use for products manufactured from the plant materials, including those crushed, chopped, powdered, or encapsulated. Additionally, products manufactured using

extracts of the constituent alkaloids of the kratom plant that use extraction methods approved by the FDA for dietary supplement products, are also safe for consumer use.

Kratom has been safely used for centuries by indigenous populations in Southeast Asia, with a very low number of confirmed adverse events. Kratom, which is used by three to five million Americans, has an extraordinarily safe public health profile. Indeed, given the significant volume of every-day consumer use of kratom and the recent focus on kratom use created largely by the FDA misinformation campaign, the safety signal for kratom use is extremely low, particularly when compared to adverse health events for a number of other dietary supplements and other consumer products that remain unscheduled under the CSA.

INTRODUCTION:

The DEA made its initial recommendation to place the alkaloids of kratom into Schedule I of the CSA on August 31, 2016 under the emergency scheduling authority of the CSA[iii]. The Notice of Scheduling cited nine deaths in Sweden "from the use of the kratom product 'Krypton'"; five additional deaths related to kratom exposure reported in scientific literature; and sixteen other deaths related to kratom exposure; for a total of 30 deaths attributed to kratom. The DEA withdrew this scheduling proposal on October 13, 2016 after receiving thousands of public comments challenging the proposal. DEA had previously requested a full 8-Factor Analysis ("8-FA") from the FDA[iv]. FDA has taken over a year to scour available sources in an effort to substantiate DEA's intention to ban kratom.

On November 14, 2017 the FDA issued a public health advisory on the use of kratom[v] and stated the FDA "is aware of reports of 36 deaths associated with the use of kratom-containing products."

On February 6, 2018 the FDA released an adverse events and scientific analysis of kratom's alleged opioid properties[vi], and released the reports of the 36 deaths referenced in the November 14, 2017 statement. In addition, the FDA increased its claim to 44 reported deaths associated with the use of kratom. The FDA claims it has released a total of 36 case reports (only 33 appear to have any data), and FDA claims it will release the remaining case reports in the near future.

FDA points to 9 deaths in Sweden between 2009 and 2010 to support its claim of deaths associated with kratom use, but an independent scientific review of those cases concluded that the deaths were the result of spiking powdered kratom leaves with a lethal concentration of the mu opioid receptor agonist *O*-desmethyltramadol[vii]. Each of the remaining deaths attributed to kratom by the FDA have equally suspect association with kratom. Nearly all of the decedents were using multiple substances, and most included illicit or prescription drugs that carry well-known risks of fatalities.

Notable cases include a decedent who had hanged himself after struggling with depression and prescription drug abuse; a "death by homicide" resulting from a gunshot wound to the chest; and a man who had fallen out of a window, broken his arm and refused medical treatment before dying. These case reports appear to be derived from two separate adverse event reporting systems maintained by the FDA, but neither of these reporting systems have validation protocols in place to verify the integrity of the submitted data, and both databases have disclaimers that the information is not verified and should not be relied upon to draw a conclusion that the product actually caused the reported death. The data integrity is further challenged by the fact that as many as one-third were deaths that did not occur in the U.S.

It should be noted that the FDA concedes that the information used to support its claims on deaths has limitations. The FDA Adverse Event Reporting System (FAERS) webpage contains the following disclaimer:

> *FAERS data does have limitations. 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.*

ANALYSIS OF CLAIMED DEATHS:

The following data was released by the FDA on February 6, 2018 from the FAERS database:

Death #	*FDA Incident #*	*Reported Cause of Death*	*Substances Involved*	*Circumstances*
1	12639316	Death by Homicide	Citalopram Hydrobromide, Chlordiazepoxide, Mitragynine	Report completely redacted. A review of the FAERS "Listing of Cases" revealed that this death is recorded in as death by homicide due to a gunshot wound to the chest. The reports listed the decedent had suicidal ideation, suffered from alcoholism, and died from the chest and aortic injuries from the gunshot wound.
2	12639332	Heroin, alcohol, and benzodiazepines intoxication, manner of death is accident	Heroin, alcohol, benzodiazepines, THC, Citalopram, Morphine, Chlordiazepoxide, Demoxepam, Alprazolam, Mitragynine	On the evening of the death, decedent drank alcohol, smoked heroin, and took Xanex and Narco. The decedent had a history of heroin and alcohol abuse; the family requested no autopsy. The Medical Examiner did a toxicology test.
3	12639556	Ligature hanging; suicide	Alcohol, Benzodiazepines, Zolpidem, 7-Aminoclonazepam, Nordiazepam, Zolpidem, Mitragynine, Quetiapine	Decedent was found hanged by the neck with a nylon rope tied to a tree. The decedent suffered from Bipolar disorder, depression, anxiety, insomnia, and had suicidal ideations. Prior to the death, the decedent had started cutting himself.
4	13421666	Aspiration of chime	Fluoxetine, Etizolam, Lorazepam, Mitragynine, Olanzapine, Pipamperone, Pregabaline, Quetiapine, Triazolam, Fluoxetine	Decedent had fallen from a window but refused medical treatment despite reported intense pain resulting from the fall. A hematoma and humerus fracture of the left arm were confirmed in the autopsy. The benzodiazepine in the femoral blood was in a concentration range that was likely to result in toxic effects. Decedent's father reported his son was using an herbal substance known as kratom.
5	8121551	Accidental drug intoxication/overdose	Pregabalin, Amphetamine, Olanzapine, Diazepam, Fluoxetine, Nordiazepan, Norfluxoetine, Phenazon, O-desmythltramadol, Mitragynine	Decedent had a history of drug abuse, there was evidence of the use of the herbal preparation Krypton.
6	8121559	Accidental drug intoxication/overdose	Venlaflaxene, Zopiclone, O-desmythltramadol, Mitragynine	Decedent had a history of drug abuse, there was evidence of the use of the herbal preparation Krypton.
7	8121566	Accidental drug intoxication/overdose	Alimemazine, DMA, O-DMV, Mitragynine	Decedent had a history of drug abuse, there was evidence of the use of the herbal preparation Krypton.
8	8124388	Accidental drug intoxication/overdose	Amphetamine, THC, Alprazolam, O-desmethyltramadol, Mitragynine	Decedent had a history of drug abuse, there was evidence of the use of the herbal preparation Krypton.

9	8124494	Accidental drug intoxication/overdose	Alprazolam, O-desmythltramadol, Mitragynine	Decedent had a history of drug abuse, there was evidence of the use of the herbal preparation Krypton.
10	8132531	Accidental drug intoxication/overdose	Alprazolam, Citalopram, THC, O-desmythltramadol, Mitragynine	Decedent had a history of drug abuse, there was evidence of the use of the herbal preparation Krypton.
11	12639302	Acute Mitragynine intoxication	Alcohol, Amphetamines, Mitragynine, Carbamazepine	Decedent had a history of drug abuse, and had a history of seizures with a recent hospitalization.
12	13934406	Suicide. Toxicity due to various agents	Bupropion, 3-Methoxyphencyclidine, Delorazepam, Ethanol, Mitragynine, Paroxetine	Patient was found unresponsive with fatal multi drug-intoxication.
13	12665817	Drug abuse	Loperamide HCL, Tramadol, Mitragynine	Decedent collapsed while playing basketball, could not be resuscitated.
14	12665823	Drug abuse	Loperamide HCl, Mitragynine	Decedent was researching natural ways to get high. Loperamide is known to allow users an opioid-like high if used in excess of recommended dose.
15	12665824	Drug abuse	Loperamide HCl, Mitragynine	Decedent was researching natural ways to get high. Loperamide is known to allow users an opioid-like high if used in excess of recommended dose.
16	12639421	Acute Mitragynine, Fentanyl, Alprazolam, and Clonazepam Intoxication	Benzodiazepines, Fentanyl, Cannabinoids, Mitragynine, Alprazolam, 7-Aminoclonazepam	Decedent had a history of alcohol, prescription medication, and illicit drug abuse.
17	12639579	Mixed Mitragynine, Methadone, and Alprazolam Intoxication	Benzodiazepines, Cannabinoids, Methadone, Mitragynine	Decedent had a history of drug abuse, and packaged syringes and a used syringe; half a Xanax tablet, a small unlabeled bottle with an unknown pink liquid; “Royal Kratom” capsules; “Maeng Da” kratom capsules; were found at the scene;
18	12639594	Pulmonary thromboemboli due to deep vein thrombosis. Obesity, dilated cardiomyopathy and chronic polysubstance abuse are listed as contributing factors	Opiates, Benzodiazepines, Cannabinoids, Oxycodone, Fluoxetine, Norfluxoetine, Trazodone, Alprazolam, Nordiazepan, Gabapentin, Mitragynine	Decedent is a 298-pound man who had a history of drug abuse, Tourette’s Syndrome, high blood pressure, rheumatoid arthritis, chronic back and shoulder pain, prescription medication abuse and alcohol abuse
19	14037602	Accidental drug intoxication/overdose	No specific report provided	Decedent had a history of drug abuse, there was evidence of the use of the herbal preparation Krypton.
20	8083892	Accidental drug intoxication/overdose	Mirtazapine, Buprenorphine, O-desmethyltramadol, Mitragynine, Alimemazine, Venlafaxine, Diazepam	Decedent had a history of drug abuse, there was evidence of the use of the herbal preparation Krypton. Several other psychotropic drugs were detected and “could have contributed to death.”

21	12569892	Accidental poisoning due to kratom and possibly in combination with other substances detected	Zopiclone, Citalopram, Lamotrigine, Mitragynine	Decedent had a history of substance abuse and well as psychiatric disease. Because of his drug habit, he had been subject to drug testing at work. In order to avoid testing positive, the decedent reportedly bought kratom on the internet.
22	10712257	Severe hypoxic encephalopathy complicating apparent mitragynine toxicity	Lamotrigine, Mitragynine, Paroxetine	The patient experienced generalized tonic-clonic seizure, tachycardia, cardio-respiratory arrest, anoxic brain damage, brain stem hemorrhage, pulmonary embolism, pulmonary infarct, hypoxic encephalopathy and subsequently died.
23	10708286	Cause of death rested "largely on the interpretation of the role mitragynine played in the case"	Clonazepam, Dextromethorphan, Temazepam, Diphenhydramine, Mitragynine	A well-established history of opioid abuse, and kratom use. The active compound of kratom was identified in the decedent's blood.
24	10698706	Mixed drug intoxication - primarily mitragynine	Alcohol, Omeprazole, Venlafaxine, Mirtazapine, Diphenhyramine, Mitragynine, Morphine	The decedent was a 24-year-old man whose medical history was significant for alcohol abuse and depression. He had been drinking alcohol since age 15, had several suicide attempts with pills and had been hospitalized for an accidental overdose.
25	7900650	Propylhexedrine toxicity	Propylhexedrine, Mitragynine, Acetaminophen, Morphine, Promethazine	The decedent, a 20-year-old Caucasian male, was found dead, under his bunk, in his living quarters. His roommate stated that it was not out of the ordinary for the decedent to sleep under his bunk. An investigation of the scene indicated no evidence of foul play. Thirty-nine separate nutritional supplements, herbal supplements, and prescription and nonprescription medications were found at the scene. Analysis of the decedent's computer and internet usage history indicated he had researched herbal supplements, particularly kratom, which he reportedly used to treat insomnia. Further investigation revealed the decedent had researched a procedure to concentrate propylhexedrine from over the-counter inhalers.

The following data on purported deaths associated with kratom from the CAERS database was released by the FDA on December 1, 2017. This information is drawn from the FDA's Center for Food Safety and Nutrition (CFSAN) Adverse Event Reporting System, and its webpage contains the following disclaimer:

> *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. Healthcare practitioners, firms, agencies, consumers, and others are encouraged to report suspected reactions; however, 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.

The reports submitted to FDA vary in the quality and reliability of the information provided. Some reports to FDA do not necessarily include all relevant data, such as whether an individual also suffered from other medical conditions or used other products or medications at the same time. Reports may not include accurate or complete contact information for FDA to seek further information about the event, or complainants may choose not to participate in a follow-up investigation. When important information is missing from a report, it is difficult for FDA to fully evaluate whether the product caused the adverse event or simply coincided with it.

Submission of an adverse event report does not constitute an admission that a product caused or contributed to an event. The information in these reports has not been scientifically or otherwise verified as to a cause and effect relationship and cannot be used to estimate incidence (occurrence rate) or to estimate risk.

Death #	*FDA Incident #*	*Reported Cause of Death*	*Substances Involved*	*Circumstances*
26	174035	No official documents were provided. "Voluntary Report" cited the following information: Cardiorespitory arrest versus drug intoxication/overdose	No medical record	Patient presented at the hospital unresponsive. Husband self-reported the patient had a history of heroin abuse, but had not used for 1-2 years. Husband reported the patient used kratom, but the hospital staff concluded the husband's information was not consistent throughout the hospital stay.
27	191303	Cardiac arrhythmia	O-desmythltramadol Mitragynine	Decedent died while swimming after suffering cardiac arrhythmia, a condition the patient had suffered from fot 2-3 years.
28	198584	No official documents were provided.	Zoloft Kratom	Father reported his son died on Sunday after consuming a kratom tea on Friday.
29	32266	Mitragynine intoxication, pulmonary edema	Mitragynine Lidocaine Naloxone Caffeine	Family reported use of kratom, limited marijuana and alcohol use in the last 1.5 years.
30	63579	No official documents were provided. "Voluntary Report" cited the following information: Terminal seizure	No report	Wife reported that husband was using kratom regularly for about 6 months for pain associated with knee surgery. Reported decedent had history of high blood pressure and onset seizure disorder of unknown origin.
31	63441	No official documents were provided.	None documented	Parent reported that the Coroner determined her son died from the toxic effects of kratom tea. He stopped breathing. Decedent reportedly had ulcerative colitis, smoked cigarettes and e-cigarettes, and drank alcohol daily.
32	60290	No official documents were provided.	None documented	Parent reported the Medical Examiner had concluded the death was caused by "Intoxication by Mitragynine

				(Kratom)". Decedent reportedly was taking kratom to "detox from opiates."
33	62885	No official documents were provided.	Lopid Metroprolol Kratom	Wife reported her husband died of a heart attack after taking kratom for several months. Decedent was a 40 year smoker, suffered from mild hypertension and borderline hyperlipidemia, but wife "strongly suspects" it was the herbal supplement.
34-44	No data provided by the FDA			

The FDA also presents an equally tenuous claim related to the addiction profile of kratom, and points to the fact that some kratom users report they use it as an alternative pain management option to more addictive and potentially deadly opioid products. A number of peer-reviewed published studies in the public literature directly contradict the FDA claims on the abuse profile for kratom, including its actual or relative potential for abuse; the history and current pattern of abuse; the scope, duration, and significance of abuse, and its psychic or physiological dependence liability.

In addressing the 2016 recommendation to schedule kratom under the emergency scheduling authority of the CSA, Jack E. Henningfield conducted an 8-FA that concluded "There has been no documented threat to the public health that would appear to warrant emergency scheduling of the products and placement in Schedule I of the CSA carries risks of creating serious public health problems.[viii]"

The low safety signal for kratom was reported by Oliver Grundmann in *Drug and Alcohol Dependence* that concluded "Negative or adverse effects requiring outpatient treatment or hospitalization due to Kratom consumption were only reported by 51 users indicating a low incidence of 0.65%.[ix]"

The FDA has cited an increase in the number of calls to Poison Control Centers as an indicator of kratom abuse to support is scheduling recommendation, but that data was rebutted by O. Hayden Griffin, III, Ph.D., J.D. and Megan E. Webb, M.S., M.P.A. in the *Journal of Psychoactive Drugs*, concluding "although there is a one-year difference, the 263 calls for kratom would have represented roughly 0.000091% of all calls to poison control, a very small proportion. Comparatively, there were roughly 381.7 times as many calls for analgesics, there were approximately 195.2 times more calls for alcohol than kratom, and even 12.4 times more calls for battery ingestion than kratom. The average number of calls per month for kratom in 2015 was 21.9. Thus, at least from the poison control data, there did not seem much of a necessity for the emergency scheduling of kratom.[x]"

The FDA also relies on the claim that kratom and its alkaloids bind to the mu-opioid receptors in the brain, and impute from that data that kratom is an opiod. However, the FDA's computational model analysis is contradicted by Andew C. Kruegel who concluded his research "revealed that opioid activity in the mitragynine scaffold is quite sensitive to structural modification and suggested that the *Mitragya* alkaloids adopt a unique binding pose at MOR, distinct from that of classical opioids.[xi]"

FDA also asks the DEA to accept its conclusion that kratom has the same effects as an opioid, and therefore poses a danger to users because the addiction and safety profile matches opioids. Marc T. Swogger and Zack Walsh directly dispute this FDA assumption in their research published this year in *Drug and Alcohol Dependence* where they conclude "unlike opioids, kratom use does not appear to result in significant respiratory depression (Kruegel et al., 2016) and is thus far less likely to cause fatal overdose" and "this comprehensive review of a preliminary, scant, and diverse literature yields no indication that kratom use carries significant mental health risks beyond the possible development of kratom dependence, which is generally mild compared to that of opioids.[xii]

CONCLUSION:

None of the case reports released to date support the evidentiary standard required by the CSA to prove there is a risk to the public health that relies primarily on the FDA claim of "numerous deaths associated with kratom." In fact, the data shows only that a relatively small number of individuals died from a variety of actual causes related to underlying health issues, abuse of prescription or illicit drugs either at toxic doses or taken in combination when contraindicated. The use of kratom by these individuals has no medical or statistical significance in assessing the safety signal required for scheduling.

A policy decision of this import should be based on valid statistical analysis developed from empirical evidence, and its interpretation should be in accordance with scientific methods. The FDA's attempt to use an unproven theory to justify the scheduling of kratom fails to meet any reasonable or credible scientific standard to prove a public health risk from the use of kratom. Numerous scientific studies (including the published reports FDA relies upon) directly contradict the FDA claims of deaths being caused by kratom, and the adoption of a less-rigorous and poorly defined standard of deaths being "associated with kratom" substitutes very weak opinion for medical or scientific conclusions on the cause of any death. This data weakness is highlighted by the FDA's own acknowledgment that the data they rely upon has not been validated.

FDA Commissioner Gottlieb implicitly acknowledged the fatal defect in the validity of the conclusions drawn by the FDA in support of the 8-FA they have submitted to the DEA when he stated on February 6, 2018 as follows:

> "Overall, many of the cases received could not be fully assessed because of limited information provided; . . ."

In addition, the FDA uses invalid and circuitous reasoning to justify its concern about kratom, stating that the FDA is "not alone in our evaluation and our public health concerns" because other "states and cities have banned kratom from entering their jurisdictions." The basis for existing bans on kratom in any state or city likely resulted from the misinformation about kratom disseminated by the FDA itself, starting with a Import Alert in 2012 based on the now discredited 9 deaths resulting from an *O*-desmethylltramadol overdose in Sweden, and including the characterization of kratom as a "synthetic" drug lumped together with truly dangerous synthetic substances such as bath salts and synthetic cannabinoids that are banned under federal law.

Of significant note is the fact that FDA has never before sought to ban or schedule a substance because it has been mixed or blended with a toxic dose of another substance or substances. The suggestion that there are "risks" associated with combining kratom with "certain drugs" is unsupported by the data released by the FDA, which shows only that the cause of death in each of the released reports is associated with the toxicity of an illegal street drug, the use of a prescription drug in combination with other prescription drugs that are specifically contraindicated, or the use of one or more potentially fatal prescription drugs above the recommended dosage. No reliable scientific data currently exists to show that unadulterated kratom leaf itself is toxic, or that its use in combination with other substances that are ingested or inhaled can be attributed in any way to the kratom plant itself.

The FDA recommendation for the scheduling of kratom is supported only by exaggerated claims, discredited research, and distorted data, that in total fail to meet the evidentiary standard for placing kratom as a Schedule I controlled substance. It is clear that if an applicant seeking FDA approval for a drug or dietary supplement marketing approval presented such evidence in support of their application, it would be summarily rejected, and future consideration would require credible science and well-controlled studies to document the claims made by the applicant.

The DEA should decline further consideration of the FDA recommendation for the scheduling of kratom, and return it to the FDA with the direction that future recommendations must meet the same rigorous standards it requires for research prior to making any substantive public policy decision. At present, the overwhelming data strongly suggests the scheduling of kratom would result in the perverse outcome of kratom users either being forced to the black market for kratom products, where the risk of adultration and contamination is exponentially higher, or to more dangerously addictive and potentially deadly opioids.

[i] 21 U.S.C. §§ 811-812.

[ii] CFSAN Adverse Event Reporting System (CAERS), U.S. Food and Drug Administration, https://www.fda.gov/Food/ComplianceEnforcement/ucm494015.htm

[iii] 21 USC 801 *et seq*. The CSA provides for "temporary scheduling to avoid imminent hazards to public safety," commonly referred to as the "emergency" scheduling process.

[iv] Department of Justice, Drug Enforcement Administration, 21 CFR Part 1308, Withdrawal of Notice of Intent to Temporarily Place Mytragynine and 7-Hydroxymitragynine Into Schedule I, Federal Register, Vol. 81, No. 198, Thursday, October 13, 2016/Proposed Rules.

[v] https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm584970.htm

[vi] https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm595622.htm

[vii] 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.

[viii] Jack E. Henningfield & Reginald V. Fant & Daniel W. Wang, The abuse potential of kratom according the 8 factors of the controlled substances act: implications for regulation and research," Pyschopharmacology, published online, 23 December 2017, https://doi.org/10.1007/s00213-017-4813-4

[ix] Oliver Grundmann, Patterns of Kratom use and health impact in the US − Results from an online survey, Drug and Alcohol Dependence, July 1, 2017, Volume 176, pages 63-70, http://www.drugandalcoholdependence.com/article/S0376-8716(17)30182-5/pdf

[x] O. Hayden Griffin, III, Ph.D., J.D. and Megan E. Webb, M.S., M.P.A., The Scheduling of Kratom and Selective Use of Data, JOURNAL OF PSYCHOACTIVE DRUGS, June 2017, https://doi.org/10.1080/02791072.2017.1371363

[xi] C. Kruegel, Madalee M. Gassaway, Abjijeet Kapoor, András Váradi, Susruta Majumdar, Marta Filizola, Jonathan A. Javitch, and Dalibor Sames, Synthetic and Receptor Signaling Explorations of the *Mitragyna* Alkaloids: Mitragynine as an Atypical Molecular Framework for Opioid Receptor Modulators, Journal of the American Chemical Society, May 18, 2016, 138 (21), pp 6754 – 6764, https://pubs.acs.org/doi/ipdf/10.1021/jacs.6b00360

[xii] Marc T. Swoggera, Zach Walsh, Kratom use and mental health: A systematic review, Drug & Alcohol Dependence , Volume 183 (2018), 134 – 140, www.drugandalcoholdependence.com/article/S0376-8716(17)30558-6/fulltext