Kratom Science Update: Evidence-Based Facts

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Preface

Kratom science has been increasing almost exponentially over the past decade with more than 100 new published studies addressing kratom safety, benefits, and abuse potential since early 2018. The science provides evidence to guide consumer safety leading to kratom regulations now passed into law in seven states, with many more states considering such laws. As discussed below, these new scientific findings also led the United States Department of Health and Human Services (US DHHS) to reverse its position on Controlled Substances Act (CSA) scheduling and, in August 2018, to rescind its earlier scheduling recommendation to the Drug Enforcement Administration (DEA). More recently, and with still more evidence, in 2021, the World Health Organization Expert Committee on Drug Dependence (WHO ECDD), reviewed the evidence for international scheduling and concluded that there was not sufficient evidence to recommend scheduling, meaning the available data did not show public health risks of kratom warranting international restrictions.

What is clearly needed is balanced regulation to ensure that kratom products purchased by consumers are pure and unadulterated, in other words meeting the same types of standards that apply to other food products, and even bottled water. Steps toward such standards were taken in states that passed their own versions of kratom consumer protection act laws. Ultimately, the Food and Drug Administration (FDA) needs to develop national performance standards for kratom as it does for other products. Such standards will help ensure access to kratom products that are appropriately marketed and are without contaminants and adulterants that might pose safety risks.

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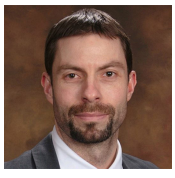

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Specific regulatory and policy approaches supported by new evidence

The DHHS request to schedule kratom and mitragynine was reversed by its lead official charged with Controlled Substances Act recommendations to the DEA, namely, the Assistant Secretary of Health, Dr. Brett Giroir. Dr. Giroir requested a review of the evidence pertaining to kratom scheduling and safety, and concluded in August 2018, that the evidence did not support Schedule I placement. See a summary of the findings of the review in Dr. Giroir's formal 2018 scheduling rescission letter to the DEA at https://static1.squarespace.com/static/54d50ceee4b05797b34869cf/t/60145eab6df59e7e36a7cfc1/1611947693695/dhillon-8.16.2018-response-letter-from-ash-radm-giroir.pdf.

As discussed in the scheduling rescission letter, the evidence was not sufficient to support scheduling, but was sufficient to support the conclusion that many thousands of kratom consumers use kratom as a path away from opioids. This led to the public health concern that "[Scheduling would lead to] … kratom users switching to highly lethal opioids… risking thousands of deaths…". Dr. Giroir raised other concerns including that placing kratom and mitragynine in Schedule I would discourage pregnant women and others from talking to their health care providers about their kratom use, discourage research, and more.

The conclusions of the Assistant Secretary of Health were consistent with those of the National Institute on Drug Abuse (NIDA), which states on its Kratom Facts webpage that "While there are no uses for kratom approved by the FDA, people report using kratom to manage drug withdrawal symptoms and cravings (especially related to opioid use), pain, fatigue and mental health problems. NIDA supports and conducts research to evaluate potential medicinal uses for kratom and related chemical compounds." NIDA substantially expanded its kratom research support since 2017 and this research portfolio is rapidly expanding the evidence base for kratom regulation and possibly new kratom derived medicines in the years to come.

Similarly, at the international level, the large evidence base was reviewed in 2021 by the World Health Organization Expert Committee on Drug Dependence (WHO ECDD) to determine if kratom met criteria for being placed on a critical review pathway for international scheduling. The WHO ECDD came to essentially the same conclusions as had the Assistant Secretary of Health and NIDA. After conducting a thorough pre-review and a public hearing with input from leading international experts, the ECDD reported to the United Nations Office of Drug Control that there was insufficient evidence to recommend kratom for critical review but that it should be kept under surveillance. It also stated, "(k)ratom is used for self-medication for a variety of disorders but there is limited evidence of abuse liability in humans…"[i]

Addressing overdose risks, the ECDD noted: "Although mitragynine has been analytically confirmed in a number of deaths, almost all involve use of other substances, so the degree to which kratom use has been a contributory factor to fatalities is unclear." Both the Assistant Secretary, and the WHO ECDD also acknowledge beneficial uses to abstain from opioids. Without labeling this as "therapeutic use", the Assistant Secretary clearly acknowledges such use and the public health risks of banning kratom. This nuanced recognition of benefits of use, along with risks of banning access to use by Assistant Secretary Giroir, was absent in the 2017 and early 2018 position of FDA, but was since recognized by the Secretary of Health Becerra in a letter to Senator Mike Lee and Congressman Mark Pocan on March 16, 2022.[1]

What is the current state of kratom science and evidence?

Kratom has been studied for decades, primarily in Southeast Asia (SEA), where kratom trees grow in

[1] https://assets.website-files.com/61e07df312afed13238eb7f1/6261ab303b46bb88f21b6d1a_HHS%20Kratom%20Response.pdf

abundance, but research escalated substantially in the US and globally with support by NIDA, SEA countries, and philanthropies. New science over the past 5-10 years includes investigations on kratom/mitragynine chemistry and medicinal development, neuropharmacology, brain imaging, preclinical and clinical studies, and surveys in the US and SEA. The rate of published kratom research continues to increase, along with presentations and symposia at national and international scientific meetings, such as the College on Problems of Drug Dependence in June 2022 that included a kratom symposium and a clinical study report in the late breaking hot topics research sessions.

New evidence

What is the new evidence that is so compelling to result in the Assistant Secretary's withdrawal of an earlier scheduling recommendation, and support the WHO ECDD findings accepted by the United Nations Office of Drug Control? In short, more than 100 new studies since early 2018 addressing kratom safety, abuse potential, mechanisms of action, and reasons for use, with most kratom users reporting that use is primarily motivated by health and well-being related benefits and not for recreational purposes. Much of this research was supported by NIDA and conducted in the US, but extensive additional research was conducted internationally with generally similar findings.

The following summary and conclusions are based on peer-reviewed scientific publications, many conducted by international leaders in kratom research and supported by NIDA. A bibliography with links to the articles is provided.

What is kratom?

Kratom is a tree in the coffee family. Not surprisingly, its diverse effects include coffee-like alerting, stimulating, and mood enhancing effects, which are quite distinct from the effects of morphine-type opioids. It also has some opioid-like effects that include pain relief, possible opioid withdrawal symptoms after chronic frequent use and unpleasant side effects like constipation, but without the potentially lethal respiratory depressing or highly addictive brain rewarding effects that are driving the opioid epidemic.

Is kratom an opioid?

While some naturally occurring substances in kratom act on opioid receptors, kratom is not a prototypical opioid based on its chemical structure, botanical origins, or law – nationally or internationally. Like many natural products it has diverse effects and mechanisms of action that contribute to these effects and the reasons people use kratom. Some kratom constituents bind to opioid receptors and relieve pain whereas others do not. Unlike opioids which sedate and can impair mental functioning, kratom is used by many people in place of coffee for its alerting, mental focusing, and occupational performance enhancing effects. Animal and human studies, as well as neuropharmacology mechanisms of action studies, show that kratom does not carry the substantial opioid-like risks of deadly respiratory depression or powerfully addictive euphoria. A misunderstanding of one of kratom's self-reported beneficial uses, recognized by researchers and NIDA, providing relief of opioid withdrawal, is sometimes interpreted as evidence that it must be an opioid. In fact, the nonopioid adrenergic blocking drugs developed for treating high blood pressure, clonidine and lofexidine, were prescribed for decades to treat opioid withdrawal. FDA approved lofexidine (Lucemyra) for treating opioid withdrawal in 2018. Mitragynine and other kratom constituents also produce adrenergic effects.

Who uses kratom and why?

According to surveys in the US, most consumers report are White adults, aged 35-55, with jobs and health care insurance, who report that their consumption is primarily for health and well-being. This includes consumption as an alternative to caffeinated products for alertness and increased focus, for the self-management of pain, and to improve mood. Many consumers state that kratom worked better for them, had fewer side-effects than the FDA-approved medicines that had been taken, and/or that they preferred natural products. A

smaller but especially important fraction of consumers are people who consider kratom as a "life-line" or a path away from opioids. They use kratom to manage opioid withdrawal and reduce or eliminate opioid use.

What led to increased kratom use in the United States?

Although kratom has been taken as a natural traditional medicine in SEA for centuries, its use in the US was largely limited to Asian immigrants from the early 1970s through the 1990s. In the early 2000s, with a rising general interest in natural products as alternatives to conventional medicines and growing public access to information via the Internet, kratom use began to increase. Reasons for use appear generally similar from the US to SEA; as an alternative to coffee and tea for its alerting and mild stimulant effects, to improve mood and relieve pain, and to manage withdrawal and help people to reduce or discontinue use of opioids, alcohol and other addictive substances. Many survey respondents report that kratom was either more effective, carried fewer side effects of concern such as the sedating effects of opioid pain relivers, and/or that they prefer natural products over conventional medicine. Estimates of the present market vary widely. By 2014, there were an estimated 3-5 million kratom consumers, and marketing and SEA export estimates suggest that the present market is 15 million or more in the US. One federal survey estimated between 2-3 million kratom consumers, which might reflect its panel of respondents. The federal survey is designed to track substance abuse and might underrepresent middle aged and older people with lower rates of recreational substance use who might use kratom for other reasons.

Does kratom contain dangerous substances?

Like its botanical cousin coffee, kratom contains many substances referred to as alkaloids, which tend to be somewhat alkaline and bitter in flavor. More than 40 alkaloids are identified in kratom to date, with most having little or no known pharmacological effect, or occurring at such low levels as to be of little cause for harm or benefit. However, as is the case with other natural products, the naturally occurring mixture of substances likely contributes to the overall effects and natural variations in alkaloid composition may lead to varying pharmacological effects. The main ingredient currently thought to account for most of the effects reported by kratom consumers is mitragynine, which does not have strong rewarding and addictive effects, nor respiratory depressant effects like opioids and conventional stimulants.

The second most widely recognized substance is 7-hydroxymitragynine that has stronger opioid effects but occurs at non-detectable levels in fresh kratom leaves. However, 7-hydroxymitragynine is also a product of mitragynine metabolism. In the absence of kratom regulation, some kratom makers boosted 7-hydroxymitragynine content far higher than that found in the native plant material. States passing kratom consumer protection act laws ensure that legally marketed kratom does not contain boosted 7-hydroxymitragine levels, contaminants, or other adulterants, thereby reducing public health risks. Additionally, dangerous substances like fentanyl, heroin, and morphine were found in adulterated kratom products, and these can be harmful. Regulation is needed from FDA to ensure that all US consumers are protected from risky exposure to contaminated or adulterated products.

Respiratory effects of kratom

It is well understood that kratom's respiratory effects are not like those of morphine-like opioids; however, studies since 2018 support the conclusion that kratom is not simply weaker than opioids with respect to respiratory depression. Specifically, mitragynine and other alkaloids in kratom act as partial agonists at opioid receptors, meaning that their maximal effects reach a ceiling beyond which higher doses produce little additional effect.[ii] This was demonstrated in several animal species (including cats, dogs, mice, and rats) with mitragynine doses increased to levels far beyond what is or can be consumed by even high intake

chronic kratom consumers. The most recent study employed a sophisticated rodent model developed by FDA to compare a broad range of mitragynine doses to therapeutic and toxic oxycodone doses across blood gases and other parameters. Whereas oxycodone produced the signature dose-related plummeting blood oxygen levels and deaths, mitragynine produced no evidence of respiratory depression at any dose, and no life-threatening effects.

Can you overdose on kratom?

It is possible that kratom contributed to some deaths occurring in kratom consumers but the overall risk appears at least 1,000 times lower for kratom as compared to opioids. There were no deaths in which either the FDA or CDC confirmed as appropriately categorized as due to kratom consumption, though the possibility cannot be ruled out. Kratom consumers should not assume that kratom is without risk. Nonetheless, the CDC did not list kratom as a cause of any of the more than one hundred and eight thousand drug overdose deaths in 2021, or in any other year of which we are aware. In contrast, opioids were concluded by the CDC and NIDA to account for more than 80,000 overdose deaths in 2021. Overdose is possible with many readily available consumer substances, including caffeine, but kratom's most common side-effect, transient stomach upset and nausea, also limits intake and is discomforting but not seriously harmful. In February 2018, after announcing that kratom carried opioid-like death risk, the FDA noted that only one of 44 deaths occurring in kratom consumers did not involve other respiratory depressing substances. Further investigation found that the final cause was a motor vehicle fatality involving a kratom consumer.

In fact, NIDA, FDA, US DHHS, and WHO ECDD all concluded that most kratom-associated deaths involved other substances. This is also true in SEA where scientists' conclusions were similar to those of the US Assistant Secretary of Health, Dr. Brett Giroir. As summarized by Dr. Giroir in the previously mentioned 2018 DHHS scheduling rescission letter, "There is still debate among reputable scientists over whether kratom by itself is associated with fatal overdoses."

Is kratom fueling the opioid overdose epidemic?

The US has the world's most sophisticated and multi-pronged substance abuse and product safety monitoring network detecting signals of gateway drug use and ways in which one substance may contribute to the abuse and risks of another. US monitoring systems include the National Survey on Drug Use and Health (NSDUH), Monitoring the Future (MTF), Treatment Episodes Data Set, and the DEA's National Forensic Laboratory Information System (NFLIS). It also includes the Drug Abuse Warning Network (DAWN) which reported a variety of potential signals of emerging substance threats while kratom use was rapidly increasing from the 1990s through its pre-2012 reports, as well as the "new" DAWN system that reported on 2021 data in its 2022 report. None of these systems, nor more than 20,000 comments to the DEA, suggested that kratom contributed to the opioid epidemic. Kratom was also never listed in DEA's annual National Drug Threat Assessment, though DEA routinely monitors kratom as a "chemical of concern" Despite over 10 years of monitoring, DEA has not listed kratom or mitragynine or 7-hydroxymitragynine as a national drug threat.

Key scientific findings in the past five years:

- Multiple state of the art animal studies found that kratom has low abuse potential. For example, mitragynine produces weaker rewarding effects compared to morphine and heroin. The authors of this fact sheet urge that as a precaution, consumers should monitor their kratom consumption to reduce the risk of dependence development.

- Surveys indicate that some people can become dependent upon kratom; however, many of

these people were using kratom to abstain from opioids and/or other substances. Disentangling prior substance use disorders from kratom is not always clear. Most people who report kratom dependence or withdrawal state that it is more readily self-manageable than dependence and withdrawal from opioids and other drugs of abuse.

- Mitragynine treatment results in reduced opioid (e.g., morphine and heroin) drug seeking and self-administration in animal models assessing the potential effectiveness of drug use disorder reduction and cessation. These findings are consistent with human reports that kratom consumption reduces their opioid cravings and served as a path away from opioids.

- In animals made physically dependent on morphine, kratom pretreatment reduced morphine withdrawal symptoms in several models for evaluating efficacy in the treatment of withdrawal. This is consistent with human reports that kratom consumption helps to manage opioid withdrawal and reduce opioid craving.

- Similarly, an intracranial brain self-stimulation study suggested low rewarding effects of kratom alkaloids as compared to drugs of abuse.

- Several national internet surveys found that kratom use was helpful in managing opioid withdrawal, reducing opioid cravings, and achieving abstinence from opioids.

- None of the national surveys relied upon by the FDA, Centers for Disease Control (CDC), NIDA, and DEA to determine if a substance poses an abuse-related threat to public health suggested that kratom poses a known or imminent risk to public health. Consistent with this, the DEA never listed kratom as a threat to public health in its annual National Drug Threat Assessment reports.[iii]

- Safety studies in several animal species demonstrated that even at extraordinarily high doses, mitragynine and kratom produced little evidence of respiratory depression or life-threatening effects in contrast to opioids such as morphine and oxycodone which produced substantial dose related decreases in respiration.

Disclosure:

Through Pinney Associates, Drs. Henningfield and Huestis provide scientific and regulatory advising on new medicines, dietary supplements, cannabinoids, and tobacco/nicotine products for FDA regulation. This paid work includes leading the development and drafting of this kratom science facts summary for the American Kratom Association. Dr. Grundmann is a member of the advisory board of the Kratom Vendors Association and has received an honorarium from the American Kratom Foundation for participation in a scientific discussion forum about kratom dependence. Dr. Garcia-Romeu is a paid scientific advisor to ETHA Natural Botanicals and has received a speaking honorarium from the American Kratom Foundation.

Annotated Bibliography

Expert evaluations of kratom policy and regulation and risks & public health

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Henningfield JE, Grundmann O, Babin JK, Fant RV, Wang DW, Cone EJ (2019) Risk of death associated with kratom use compared to opioids. Prev Med. 128:105851. *Note: This article compared estimates from FDA of deaths associated with kratom consumption in comparison with deaths associated with nonmedical opioid use concluding that the risk of death associated with kratom use is at least 1,000 times less than for opioids.*

Henningfield JE, Wang DW, Huestis MA (2022) Kratom abuse potential 2021: an updated eight factor analysis. Front Pharmacol 12:775073. *Note: This article is a published version of an assessment of kratom abuse potential according to the 8-factor analysis required for permanent scheduling by the Controlled Substances Act. It concludes that on the basis of all factors, including decades of surveillance in the US, and decades more globally, kratom does not warrant scheduling and, in fact, that scheduling kratom would carry adverse public health consequences. This is consistent with the position of the WHO Expert Committee on Drug Dependence and the DHHS review led by Assistant Secretary Giroir.*

Prozialeck, W., Avery, B., Boyer, E., Grundmann, O., Henningfield, J., Krueger A., McMahon, L., McCurdy, C., Swogger, M., Veltri, C., and Singh, D. (2019). Kratom Policy: The challenge of balancing therapeutic potential with public safety. International Journal of Drug Policy, 70:70–77. *Note: Leading kratom researchers discuss policy implications of state-of-the-art knowledge related to kratom's effects, uses, risks, and real-world public health benefits and risks.*

Swogger MT, Smith KE, Garcia-Romeu A, Grundmann O, Veltri CA, Henningfield J, Busch LY (2022) Understanding kratom use: a guide for healthcare providers. Front Pharmacol 13:801855. *Note: Although there are no FDA approved uses for kratom, which is the case for most dietary supplements, this expert opinion article provides practical information for consideration by health care professionals whose patients are consuming kratom.*

United Nations Commission on Narcotic Drugs, WHO Expert Committee on Drug Dependence (2021). Implementation of the international drug control treaties: changes in the scope of control of substances Summary of assessments, findings and recommendations of the 44th World Health Organization's (WHO) Expert Committee on Drug Dependence (ECDD), 11–15 October 2021: Kratom, mitragynine, 7-hydroxymitragynine. https://www.unodc.org/documents/commissions/CND/CND_Sessions/CND_64Reconvened/ECN72021_CRP12_V2108992.pdf. *Note: This is a summary of the WHO Expert Committee on Drug Dependence pre-review of kratom concluding that the evidence does not support initiation of a full review of kratom for international drug scheduling considering its effects, safety, abuse related- risks and public health factors.*

Kratom reasons for use surveys

Note: Whereas there are several surveys that provide estimates of how many people use kratom with estimates ranging from about 2 to more than 15 million, those surveys provide no information about why people use kratom, or the consequence of their kratom use (See Henningfield JE, Grundmann O, Garcia-Romeu A, Swogger MT. We Need Better Estimates of Kratom Use Prevalence. Am J Prev Med. 2022;62(1):132-133). The following surveys are focused on why people use kratom and provide insights as to the risks and benefits of kratom consumption. Specifically, these surveys show that although there is some recreational use of kratom, most people use for reasons related to health and well-being including as approaches to self-manage opioid and other drug withdrawal and to reduce and discontinue opioid and other addictive drug use.

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Garcia-Romeu A, Cox DJ, Smith KE, Dunn KE, Griffiths RR. Kratom (Mitragyna speciosa): User demographics, use patterns, and implications for the opioid epidemic. Drug Alcohol Depend. 2020;208:107849.

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Smith KE, Rogers JM, Dunn KE, et al. Searching for a Signal: Self-Reported Kratom Dose-Effect Relationships Among a Sample of US Adults With Regular Kratom Use Histories. Front Pharmacol. 2022;13:765917. https://doi.org/10.3389/fphar.2022.765917 *Note: This review article examines the results of 129 surveys of kratom use in the United State, with attention to trends use and effects related to duration (e.g., weeks and months) and daily consumption levels. As stated by the authors, "Acute kratom effects were largely reported as compatible with, and sometimes helpful in, meeting daily obligations."*

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Kratom abuse potential and assessment for treatment of dependence and withdrawal

Note: The following studies found that mitragynine is characterized by low abuse potential in classic models as compared to morphine and heroin. The Hemby et al. and Yue et al. studies also showed that mitragynine administration led to decreases in morphine and heroin self-administration, which is consistent with survey reports that kratom helps relieve opioid craving and discontinuation of opioid use. Hassan et al. is one of several recent studies demonstrating that (a) mitragynine withdrawal is less severe than morphine withdrawal, and (b) mitragynine provides effective relief of opioid withdrawal, which is a common use of kratom that is acknowledged by NIDA and claimed by many kratom consumers in the surveys of why people use kratom. Wilson et al. demonstrates that a kratom tea like preparation was of relatively low risk and effective at reducing opioid withdrawal symptoms. It is also important to note that animal studies of single substances such as mitragynine cannot be interpreted as showing that kratom has no abuse or dependence potential – it does carry some abuse and dependence risk in humans as documented in the surveys, but these appear relatively low for most consumers as compared to opioids. These studies are also contrary to FDA's 2017 claims that mitragyine carried narcotic opioid like risks.

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Kratom pharmacology studies help understand its effects that contribute to reasons for use and safety

Note: The following studies are representative of several dozen other studies published since 2018 that help understand the effects, and potential benefits and risks of kratom's constituents including mitragynine. At kratom doses far higher than those consumed by humans, respiratory depressant effects are substantially lower than opioids. This does not mean that kratom does not carry risks but rather that its overall risks appear lower than those associated with drugs such as opioids that kratom substitutes for. Balanced regulation could help consumers minimize the risks of kratom use by banning medical claims, providing accurate labeling and warning labels, as is being implemented in states that passed kratom consumer protection act laws.

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drugs singly and in combination. It compared the same doses of an opioid as used by FDA and with the same objective respiratory measures to 5 doses of mitragynine that included a dose within the range of human consumption to doses many times higher than consumed by humans. Oxycodone produced striking dose related decreases in blood oxygen levels and death at the two higher doses, whereas mitragynine did not produce respiratory depression or life-threatening effects at any dose. This does not mean kratom can be used without harm or risk of death but as discussed in the publication it is consistent with other studies showing that mitragynine is substantially less likely to produce overdose than opioids of abuse.

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[i] Neither the US Food Drug and Cosmetic Act, nor the US CSA or the international drug control treaties define "therapeutic use" as being approved as drugs by FDA or the equivalent regulatory agencies in other countries. However that has become the de facto standard of the FDA, which therefore ignores self-reported beneficial use by dietary supplement consumers and states that they have no recognized therapeutic use, and thus, widespread use of kratom to stay off opioids was ignored as a benefit. The authors of this science update and the American Kratom Association agree that specific health claims should not be made by kratom marketers without supporting evidence, but neither should policy makers simply dismiss the benefits of kratom and the risks of removing licit kratom by millions of kratom consumers.

[ii] Contributing to the misunderstanding that kratom carries opioid-like risks of overdose and addiction is a misunderstanding of potency and strength. Strength refers to the maximum effect that a substance can produce, whereas potency refers to how much of the substance it takes to produce a given effect. Thus, alcohol is strong and actually results in approximately 2,000 overdose deaths annually in the US, however, it is relatively low in potency among central nervous system active substances and requires the equivalent rapid consumption of a quart or more of high percentage (proof) alcohol to produce death, though for young people it may take much less as suggested by fraternity hazing related deaths every year in the US. At the other extreme is fentanyl which can produce extremely strong euphoriant effects in humans, reinforcing effects in animals, and lethal respiratory depressant effects at very low doses of just a few mg. Kratom's primary active alkaloid, mitragynine is both relatively weak and low in potency with respect to respiration as compared to morphine. In fact, it is a partial agonist with respect to respiratory depression, meaning that its maximal effects at all tested doses do not produce lethal respiratory depression. The mitragynine metabolite 7-hydroxymitragynine is more potent than morphine on the guinea pig ileum muscle twitching test but that test is not necessarily relevant to lethality, and 7-hydroxymitragynine, also appears to be a partial agonist with respect to its respiratory effects.

[iii] DEA has included kratom on its list of "drugs and chemicals of concern", for the past decade, first listing it following reports of overdose deaths in Sweden among consumers of a kratom product that was later concluded to have been adulterated with lethal doses of O-desmethyltramadol. However, as mentioned in this science update, DEA never listed kratom as a threat to public health in its annual National Drug Threat Assessment reports. In fact, it has not listed kratom in its annual National Forensic Laboratory Reports since 2016, apparently, because the reports have remained low and not at the "threshold for reporting." Whether and when DEA will remove kratom or kratom alkaloids from its drugs and chemicals of concern list is not clear since researchers agree that kratom use and epidemiology should continue to be monitored, but unfortunately, this listing implies a higher level of concern than has been expressed by any other DEA action since it withdrew its scheduling proposal in 2016.