



POLICY REPORT

The FDA has failed to provide credible data and science to justify the scheduling of kratom as a Schedule I substance

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EXECUTIVE SUMMARY

The U.S. Food and Drug Administration (FDA) has failed to meet its evidentiary burden for the scheduling of kratom as a Schedule I substance under the Controlled Substances Act (CSA). To meet this burden, the FDA must submit an 8-Factor Analysis (8-FA) that conclusively demonstrates with scientific evidence that kratom is dangerously addictive and presents a risk to the safety of the public.

The FDA has established two pillars for its arguments to the U.S. Drug Enforcement Administration (DEA) seeking a Schedule I designation for kratom: (1) kratom use is associated with 44 deaths and therefore presents an unacceptable risk to public health; and (2) kratom is an opioid with the same addiction profile of other opioids and has the same or similar adverse effects on the health of users. The 8-FA must rely upon all published literature addressing these issues, including peer-reviewed published research that addresses the critical issues on the addiction profile and safety of kratom and its alkaloids, mitragynine (MG) and 7-hydroxymitragynine (7-HMG).

The CSA provides broad discretion in making the determination on the addiction and safety profile of any candidate substance for scheduling, but it does not contemplate any abuse of that discretion by presenting arguments for scheduling that are not grounded in credible science. Additionally, the FDA's claims on the 44 deaths associated with the use of kratom uses documentation that proves that some deaths have resulted from use of adulterated kratom products, but the majority of the death data relied upon by the FDA implicates polydrug use and underlying health conditions of the decedents that are completely unrelated to any pharmacologic activity of kratom. The DEA has never accepted a scheduling recommendation for any substance because it is adulterated with a toxic or dangerous drug.

The FDA has presented its argument that kratom is an opioid with the same effects as classic opioids because the primary alkaloids of kratom, MG and 7-HMG, bind to the same mu-opioid receptors in the brain. The key element in this argument the FDA must prove is that these alkaloids have the same or similar addiction profiles

as classic opioids that create a public health risk. The FDA claims that MG and 7-HMG bind to the same mu-opioid receptors has been known since studies were published in the early 1990s, but there is no scientific evidence that demonstrates the kratom alkaloids are either dangerously addictive or have the same effects as classic opioids that lead to deaths. Peer-reviewed published scientific literature clearly demonstrates that the alkaloid levels in the natural plant kratom are not dangerously addictive, and do not have the same pharmacologic effects as classic opioids that attack the respiratory system of users. In fact, there is no credible scientific literature that proves kratom has any effect on the respiratory system of any user that is typically associated with deaths from the use of classic opioids.

Beginning in 2009 and continuing today, the FDA has aggressively disseminated incomplete and inaccurate information to federal agencies, state law enforcement agencies and pharmacy boards, state legislatures, local governments, and the media that has demonized kratom and advocated for regulatory action at all levels of government. That propaganda campaign led to six states enacting bans on kratom that the FDA then used to justify part of its argument, coupled with incomplete and inaccurate claims of deaths associated with kratom use, for the DEA to publish its Notice of Intent on August 31, 2016 to schedule kratom under the emergency scheduling provisions of the CSA. The scientific community and kratom advocacy groups provided substantial credible evidence that contradicted the FDA claims, and that led the DEA to withdraw its Notice of Intent on October 13, 2016.

The FDA's current scheduling recommendation to the DEA on kratom merely restates its claims on the threats to public health of kratom that is based on much of the same flawed death data it submitted in 2016, supplemented with new data that is equally unsound, and relying on unprovable claims on the addiction profile of kratom's alkaloids. The science on kratom conclusively proves the FDA claims have failed to meet their evidentiary burden for kratom to be scheduled.

THE ADDICTION PROFILE OF KRATOM'S ALKALOIDS, MG AND 7-HMG

The primary alkaloids of kratom, MG and 7-HMG, have been targeted by the FDA as the "bad actors" in the addiction discussion on kratom, and asserts that "[b]ased on the variability of the mitragynine concentration in each product, users may experience differing effects when consuming similar amounts of different products."¹ The FDA relies primarily on the following claim:

"Since abusers obtain kratom, which contains the main active alkaloids mitragynine and 7-hydroxymitragynine, through unknown sources, the identity, purity, and quantity of these substances are uncertain and inconsistent, thus posing significant adverse health risks to users. Several studies have analyzed the concentrations of mitragynine \3\ and/or 7-hydroxymitragynine \4\ in different kratom products. The studies showed that there were inconsistencies in the levels of the opioid mitragynine present in similar kratom products, and some products contained other psychoactive substances (see 3-factor analysis). Based on the

¹ Federal Register/Vol. 81, No. 169/Wednesday, August 31, 2016/Proposed Rules, Docket No. DEA-442, Schedules of Controlled Substances: Temporary Placement of Mitragynine and 7-Hydroxymitragynine into Schedule I, page 59932.

variability of the mitragynine concentration in each product, users may experience differing effects when consuming similar amounts of different products.”²

The kratom plant itself does not contain either of the referenced alkaloids at dangerous levels. It is the adulteration of kratom products that impacts the “identity, purity, and quantity” of those alkaloids that leads to uncertainty and inconsistency of kratom products, and it is those adulterants that pose a threat to public health. An article that was published in *Addiction Biology* in June 2018 authoritatively addresses this issue and concludes that MG “does not have abuse potential and reduces morphine intake”³ and that 7-HMG potentially has abuse potential, but only in purified or concentrated adulterants. One of the world’s experts on addiction and the behavioral, cognitive, and central nervous system effects of drugs, Jack E. Henningfield, Ph.D., emphasized the importance of these findings.

“This is an important study that addresses the addictiveness of kratom,” says Jack E. Henningfield, Ph.D., at Pinney Associates, a health consulting firm. “It shows that the major naturally occurring constituent responsible for the health-related effects of kratom, mitragynine, is of very low abuse potential. A second substance, 7-HMG, which naturally occurs at such low levels in kratom that it might be of minimal health consequence, has higher abuse potential. This has at least two regulatory implications. First, the findings do not support the FDA’s claim that kratom is a narcotic-like opioid. Second, in regulating kratom products, the FDA could set standards to ensure that no kratom product contain levels of 7-HMG exceeding those that are commonly present in kratom leaves and products.”⁴

**HEMBY STUDY:
MG NOT
DANGEROUSLY
ADDICTIVE**

The Hemby study protocol is important because it is the first to use animal data to address the addiction potential of kratom’s alkaloids. “We stood on our heads to get them to self-administer,” Hemby said, adding that his team tried upping the doses of MG several times. “It just wasn’t working. It was almost like it was innocuous.”⁵ The concern about the addiction potential for 7-HMG was found to be mitigated by the low levels of that alkaloid that are present in the natural kratom plant.

However, the study concluded that 7-HMG’s threat to public health is present in the “purified extracts of 7-HMG [that] are available on the internet and consumed for their euphoric effects.”⁶

² Ibid.

³ Hemby *et al.* “Abuse liability and therapeutic potential of the *Mitragyna speciosa* (kratom) alkaloids mitragynine and 7-hydroxymitragynine,” *Addiction Biology*, 27 June 2018, doi: 10.1111/adb.12639.

⁴ High Point University, *Professor’s Research Shows Therapeutic Potential for Kratom*, June 29, 2018, <http://www.highpoint.edu/blog/2018/06/professors-research-shows-therapeutic-potential-for-kratom/>

⁵ Business Insider, *A mysterious supplement has a viral following of people who take it for addiction — and researchers say it’s too compelling to ignore*, Erin Brodwin, July 2, 2018, <https://www.businessinsider.com/kratom-research-opioid-addiction-2018-6>

⁶ Hemby *et al.* “Abuse liability and therapeutic potential of the *Mitragyna speciosa* (kratom) alkaloids mitragynine and 7-hydroxymitragynine,” *Addiction Biology*, 27 June 2018, doi: 10.1111/adb.12639.

The FDA regulates both finished dietary supplement products and dietary ingredients under the Dietary Supplement Health and Education Act of 1994 (DSHEA). Under this statute, manufacturers and distributors of dietary supplements and dietary ingredients are prohibited from marketing products that are adulterated or misbranded. FDA is responsible for taking action against any adulterated or misbranded dietary supplement product after it reaches the market. The FDA can take action against a firm manufacturing an adulterated dietary supplement by demonstrating that it presents a “significant or unreasonable risk of illness or injury.”⁷

The clear scientific conclusion is that MG is not dangerously addictive, and 7-HMG occurs at such a low level that it has no significant activity that would justify a scheduling decision. Any purification, concentration, or chemical alteration of 7-HMG would render that product adulterated and thereby be subject to FDA regulatory action.

A second study conducted by NIDA’s own intramural research program compared mitragynine to heroin, methamphetamine, and placebo saline and found that it most closely resembled saline in this gold-standard animal model of abuse potential. This research concluded the results “**suggest a limited abuse liability of mitragynine . . .**”⁸ (emphasis added)

Also, consistent with human reports, pre-treatment of animals who were self-administering heroin in addictive-like patterns reduced the heroin seeking. The authors concluded: “With the current prevalence of opioid abuse and its consequent and multiple impacts on public health, it appears at present that mitragynine is deserving of more extensive exploration for the development of a therapeutic use for treating opioid abuse.”

**FDA: KRATOM
USED AS OPIOID
WITHDRAWAL
DRUG**

The FDA focuses a large part of its concerns about the use of kratom as an alternative pain management option for acute or chronic pain, or as a step-down therapy from opioid addiction. There is no doubt that a manufacturer is not permitted to make claims about any therapeutic or health claim, but the decisions by individuals on substances they choose to use in the management of their own health and well-being, including addressing acute or chronic pain, does not violate any statute.

FDA Commissioner Scott Gottlieb emphasized his concerns about the use of kratom as an opioid withdrawal treatment in a statement issued on February 6, 2018.

“We have been especially concerned about the use of kratom to treat opioid withdrawal symptoms, as there is no reliable evidence to support the use of kratom as a treatment for opioid use disorder and significant safety issues exist.”⁹

⁷ 21 U.S.C. § 342(f).

⁸ Yue K, Kopajtic, Katz, Abuse liability of mitragynine assessed with a self-administration procedure in rats, *Psychopharmacology*, 2018, <https://www.ncbi.nlm.nih.gov/pubmed/30039246>

⁹ U.S. Food and Drug Administration, *Statement from FDA Commissioner Scott Gottlieb, M.D., on the agency’s scientific evidence on the presence of opioid compounds in kratom, underscoring its potential for abuse*, February 6, 2018.

Nine leading scientists, in a February 8, 2018 letter to Kellyanne Conway, the Counselor to the President on the Opioid Crisis, and Robert W. Patterson, Acting Administrator of the DEA, issued a chilling warning about the consequences of scheduling kratom as proposed by the FDA.

“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, whether their prior opioid use was for relief of pain or due to opioid addiction. This opinion is supported by four national surveys conducted in the past two years, as well as decades of studies in the US and in Southeast Asia, where kratom has been used as a safer alternative to opioids for more than a century. Failure to evaluate this potential outcome of any proposed scheduling of kratom would directly contradict the expressed purpose of the enactment of the CSA by the U.S. Congress, to protect the safety of consumers. Perversely, it is foreseeable that such an action may lead to the deaths of people and worsen the opioid crisis, not mitigate it.”

In addition, there are a number of peer-reviewed published studies that directly contradict Commissioner Gottlieb’s view on kratom and its potential role in the opioid crisis. In research published in *Drug and Alcohol Dependence* in December 2017 researchers found kratom has “potential as a harm reduction tool, most notably as a substitute for opioids among people who are addicted.”¹⁰

Research published more than a decade ago in *Addiction* concluded that kratom “is recognized increasingly as a remedy for opioid withdrawal by individuals who self-treat chronic pain.”¹¹ A 2010 study published in the *International Journal of Drug Policy* reported that “Ketum (*Mitragynine speciosa*) was described as affordable, easily available and having no serious side effects despite prolonged use. It also permitted self-treatment that avoids stigmatization as a drug dependent. The claims of so many subjects on the benefits of ketum merits serious scientific investigation.”¹²

In a related study, research published in the *Journal of Psychoactive Drugs* reported that “findings showed that regular kratom users do not experience major impairments in their social functioning, despite being dependent on kratom for prolonged periods. Our findings suggest that chronic kratom administration does not significantly impair social functioning of users in a natural context in Malaysia.”¹³

¹⁰ Marc T. Swogger, Zach Walsh, *Kratom use and mental health: A systematic review*, *Drug and Alcohol Dependence*, December 2017, <https://doi.org/10.1016/j.drugalcdep.2017.10.012>

¹¹ Edward W. Boyer, et. al., *Self-treatment of opioid withdrawal using kratom (*Mitragynia speciosa korth*)*, *Addiction*, June 2008, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3670991/>

¹² Vicknasingam, Narayanan, Beng, Mansor, *The informal use of ketum (*Mitragyna speciosa*) for opioid withdrawal in the northern states of peninsular Malaysia and implications for drug substitution therapy*, <https://www.ncbi.nlm.nih.gov/pubmed/20092998#>

¹³ Darshan Singh, Christian P. Müller, Balasingam K. Vicknasingam & Sharif M. Mansor (2015) Social Functioning of Kratom (*Mitragyna speciosa*) Users in Malaysia, *Journal of Psychoactive Drugs*, 47:2, 125-131, DOI: [10.1080/02791072.2015.1012610](https://doi.org/10.1080/02791072.2015.1012610)

If kratom were banned, these scientists argue kratom users who use kratom as an alternative pain management option, or as a way to reduce classic opioid use, would be put at far greater safety risk. The use of over-the-counter non-steroidal anti-inflammatory drugs (NSAIDS) have significant adverse health impacts, including serious liver toxicity issues, and the use of classic opioids puts users at significant risk for dangerous addiction and potential death. The following data was extracted from the FAERS database for the same time period used by the FDA to report the 44 kratom associated deaths.

*Analysis of Adverse Events Reported on the FAERS Public Dashboard
From 2008 – 2017 for Pain Management Therapies¹⁴*

<i>Product</i>	Total Cases	Serious Cases (including deaths)	Deaths
<i>Myragynine/herbal</i>	64	44	44
<i>Ibuprofen</i>	46,209	26,910	4,068
<i>OxyContin</i>	16,940	11,666	2,250
<i>Tramadol</i>	10,703	9,183	3,301
<i>Fentanyl</i>	47,925	25,753	8,233

The only option left for an individual using kratom as an alternative pain management option who does not want to use NSAIDS or a classic opioid, would be to turn to the black market for kratom that is well-documented to be rife with adulterated kratom products. The FDA and NIDA have documented that adulterated kratom products that have been spiked with synthetic chemicals or highly-toxic classic opioid medicines can be and often are deadly.

THE SAFETY PROFILE OF KRATOM

There is a long history of centuries of safe use of kratom in Southeast Asia (SEA), and there are no overdose deaths associated with kratom use in SEA or the United States. In an analysis published in the *American Chemical Society Medicinal Chemistry Letters* in 2017, where a discussion observing that withdrawal from kratom is milder than withdrawal from opiates, the “most significant advantage of kratom is that it has not caused any overdose deaths.¹⁵

¹⁴ <https://fis.fda.gov/sense/app/777e9f4d-0cf8-448e-8068-f564c31baa25/sheet/45beeb74-30ab-46be-8267-5756582633b4/state/analysis>

¹⁵ Genevieve M. Halpenny, *Mitragyna speciosa: Balancing Potential Medical Benefits and Abuse*, American Chemical Society Medicinal Chemistry Letters, 2017.

**THE 44
“KRATOM
ASSOCIATED
DEATHS”**

Despite the clear record of safe use, the FDA claims there are 44 deaths globally that they characterize as “kratom associated deaths.” The data supporting this claim, in an independent analysis conducted by Jane Babin, Ph.D., Esq., was found to be filled with exaggerated claims, discredited research, and distorted data that fails to meet the evidentiary standard for placing kratom as a Schedule I controlled substance.

“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.”¹⁶

Any deaths alleged to be associated to the use of kratom merely document the possible use of kratom products at the time of the occurrence of a death caused by other specific factors, i.e., where the cause of death is related to a gunshot wound; a suicide related to mental health issues; physical injuries that caused ancillary medical issues resulting in a fatality; use of an illegal drug; polydrug use of prescription and/or illegal drugs as toxic dose levels; and deaths that are related to other unrelated medical conditions that have no relationship to kratom use, i.e., a death from deep vein thrombosis.

Of the 44 claimed deaths, the FDA identifies only a single death as being kratom-related involving an individual who “had no known historical or toxicologic evidence of opioid use, except for kratom.” The FDA refuses to release any additional information on the death other than the subject’s age and ethnicity and provides no information on how kratom was determined to have contributed to the death.

The science is extremely important to resolve the claims by the FDA about deaths being associated with kratom. If kratom is not the primary causative substance in the death report, the fact that a decedent used kratom along with some other substance at the time of the death is not a sufficient basis to seek a scheduling recommendation for kratom. The CSA was enacted to remove truly dangerous substances from the market. There are important reasons why kratom does not cause overdose deaths, and the evaluation of the science should be the determinative factor in any scheduling decision.

First, as demonstrated through numerous studies in animals, kratom has very low toxicity. In such studies, even extremely high doses—doses that, when adjusted for humans, would be difficult to consume—do not cause death or significant toxic effects.¹⁷

¹⁶ American Kratom Association, *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*, Jane Babin, Ph.D., Esq., March 2018.

¹⁷ See, e.g., M.S.A. Kamal et al., *Acute toxicity study of standardized *Mitragyna speciosa* Korth aqueous extract in Sprague Dawley rats*, J. PLANT STUD. 2012;1(2):120-129; A. Sabetghadam et al., *Subchronic exposure to Mitragynine, the principal alkaloid of *Mitragyna speciosa*, in rats*, J. ETHNOPHARMACOL. 2013 Apr. 19;146(3):815-23; Henningfield at 4 (citing studies).

Second, kratom's unique pharmacology distinguishes it from classic opioids such as codeine, fentanyl, and morphine. Although mitragynine binds to the mu-opioid receptors, several of the other major alkaloids in kratom demonstrate competing antagonist activity at the opioid receptors.¹⁸ For example, kappa agonism "seems to attenuate reinforcement and produce aversion." This distinct pharmacological behavior limits any possible "high" that can be achieved through kratom use and significantly reduces any potential for abuse.¹⁹

Third, kratom exhibits very low bioavailability—only about 3% when taken orally. For comparison, oral morphine shows bioavailability between 20 and 25%,²⁰ fentanyl ranges from 50% to almost 70%,²¹ and oral codeine is approximately 90% bioavailable.²² Kratom's low bioavailability also reduces the extent to which any effect, positive or negative, can be achieved, and substantially reduces the possibility of overdose because a user would need to ingest an overly large (and likely aversive) amount to achieve a euphoric "high."

As described by Walter C. Prozialeck, a professor of pharmacology at Midwestern University who has studied kratom extensively, "[T]he amount [of kratom] that a person has to take in to get any severe effects is ridiculously high. You're talking 10 to 15 grams of raw leaf. Most people who are using kratom for pain management don't take that much. Most people can't take that much."²³ Indeed, an intoxicating effect can be achieved with lower doses of dextromethorphan or nutmeg.²⁴

Finally, unlike potent opioid substances, kratom does not carry a high risk of respiratory depression, which is generally the cause of death in cases of opioid overdose.²⁵ The "[r]espiratory depressant effects appear substantially lower than those produced by opioids and this would be consistent with the absence of verified kratom caused overdose death."²⁶ Moreover, because kratom does not produce the euphoric "high" that drives addiction to opioids and other drugs, it is less likely to be abused at high doses, also lessening the risk of respiratory depression.

¹⁸ Kruegel at 6754, 6762.

¹⁹ *Id.* at 6762.

²⁰ P.J. Hoskin et al., *The Bioavailability and Pharmacokinetics of Morphine after Intravenous, Oral and Buccal Administration in Healthy Volunteers*, 27 *J. Clin. Pharmacol.* 499 (1989).

²¹ Abstral Clinical Pharmacology Review, NDA 22510 (Mar. 11, 2010); *see also* M. Darwish et al., *Absolute and Relative Bioavailability of Fentanyl Buccal Tablet and Oral Transmucosal Fentanyl Citrate*, 47 *J. Clin. Pharmacol.* 343 (2007).

²² *See, e.g.*, Clinical Pharmacology and Biopharmaceutics Review at 5, NDA 202245, Codeine Sulfate oral solution (Dec. 6, 2010).

²³ Nick Wing, *Some Say Kratom Is A Solution to Opioid Addiction. Not If Drug Warriors Ban It First*, Huffington Post, updated Sept. 7, 2016, 8:38 am, http://www.huffingtonpost.com/entry/kratom-ban-drugpolicy_us_56c38a87e4b0c3c55052ee3f.

²⁴ Henningfield at 6.

²⁵ *See* Kruegel at 6754-55 ("Unfortunately, acute [mu-opioid receptor] activation is also associated with serious side effects, including respiratory depression, constipation, sedation, nausea, and itching. At sufficiently high doses, the evoked respiratory depression may be fatal.").

²⁶ Henningfield at 6.

**THE 9
“KRYPTON
DEATHS” IN
SWEDEN**

The pharmacology on how kratom works directly refutes the FDA claim that kratom is an opioid, or it has classic opioid effects. The DEA certainly should not have a high degree of confidence in FDA meeting its evidentiary burden to justify any scheduling of kratom.

The FDA failed to adequately disclose and account for material facts from the peer-reviewed Case Report of nine deaths in Sweden that were published in 2011 in the *Journal of Analytical Toxicology*.²⁷ That Case Report concluded the deaths were actually the result of adulteration of kratom powder with a toxic dose of *O*-desmethyltramadol rather than being associated with the use of kratom, other than the kratom powder being the product adulterated by a bad actor seeking to market a product for economic gain to those seeking a recreational high.

The FDA became aware of the Case Report at least as early as August 2, 2011 when, in fulfillment of its adverse effects reporting requirements, Schering Plough (now part of pharmaceutical giant Merck) filed a report²⁸ on one of the Swedish deaths that was associated with one or more products it manufactured. Actavis (now Allergan PLC, a subsidiary of Israeli generic drug maker, Teva Pharmaceuticals), filed similar reports on August 8, 2011 related to seven additional deaths discussed in the Kronstrand Case Reports for which it had reporting responsibility.²⁹

The reports submitted to FDA clearly identify the Kronstrand Case Report by authors' names, title, journal, issue and publication date; the presence of *O*-desmethyltramadol; and the country of origin (foreign; Sweden). However, the FAERS database entries altered this critical information by replacing *O*-desmethyltramadol in the “Suspect Product Active Ingredients” field with Tramadol Hydrochloride; omitting the literature citation from the appropriate field; and indicating “Country where Event occurred” as unspecified.

It would be virtually impossible to read the reports submitted to FDA and the Kronstrand Case Report and not appreciate these key details that were omitted. Indeed, report 8083892 submitted by Schering Plough states unequivocally on page 6 “NO TRAMADOL IN BLOOD” -- yet the FAERS entry lists tramadol as a “suspect product”. The significance of this finding (that the nine decedents consumed a synthetic version of *O*-desmethyltramadol rather than tramadol that was then changed by the body to the *O*-desmethyl metabolite) is discussed extensively in both the Kronstrand publication and the reports filed by Schering Plough and Actavis.

These omissions and alterations suggest that FDA deliberately excluded important and clarifying information on the actual causation of the nine deaths in Sweden. To include evidence of *O*-desmethyltramadol adulteration would contradict the narrative FDA adopted on the dangers of kratom. Failure to recognize the scientifically documented causes of these deaths served to materially mislead the DEA, CDC, NIDA, and many state and local

²⁷ Kronstrand *et al.*, “Unintentional Fatal Intoxications with Mitragnine and *O*-Desmethyltramadol from the Herbal Blend *Krypton*”, *J Anal Toxicol* 35: 242-47 (2011).

²⁸ See Public Database entry for FAERS ID No. 808389 viewed by querying the FAERS Public Dashboard at <https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adversedrugeffects/ucm070093.htm>.

²⁹ *Ibid.*

governments in the publication of their respective alerts on kratom because the alleged kratom-caused deaths, if credible, required public action by these agencies.

**USING
UNRELIABLE
FAERS DATA AS
SCIENTIFIC FACT**

The import of these errors and omissions cannot be overstated. FAERS database entries are the primary source of information for anyone wishing to query the massive amount of adverse effects data in FDA's possession and control, not only related to kratom, but to all drugs and substances reported to FDA. Until 2017 when FDA released a limited number of source documents upon which kratom-associated death determinations had been made, the FAERS database was the only source of information from FDA on many of the alleged kratom-associated deaths.

Omission of the literature citation included in reports submitted by both Schering Plough and Actavis, which were reviewed by FDA on different days in August 2011 three weeks apart, precluded independent evaluation of the circumstances leading to deaths identified in FAERS by anyone other than FDA and the reporters, Schering Plough and Actavis. As the word of these deaths spread throughout the scientific world, the identification of Sweden as the country of origin would have been a dead giveaway to their identity and these cases would have immediately been linked to the Kronstrand Case Report. It seems highly unlikely that these errors and omissions were merely inadvertent typos.

There are two important priorities in the FDA's handling of the FAERS data. The first involves the value of allowing the public to report adverse events. The purpose is to allow access of FAERS data to the general public to search for information related to human adverse events reported to the FDA by the pharmaceutical industry, healthcare providers and consumers.³⁰ The FDA warns of the inherent flaws in the unverified data with a detailed set of disclaimers that warn those accessing the database, including:

- Duplicate and incomplete reports are in the system.
- Existence of a report does not establish causation.
- Information in reports has not been verified.
- Rates of occurrence cannot be established with reports.³¹

The second priority relates to the use of the FAERS data to identify safety signals and selecting particular products for further investigation. An investigation into multiple adverse event reports on a substance allows the FDA to gather additional data to better characterize the risk. When multiple reports create a safety signal alert, that substance is added to the Potential Signals of Serious Risks Quarterly Report and is tracked until the FDA has either determined there is no regulatory action required or the FDA has taken a regulatory action to address the issue.³² Importantly, once a serious risk is identified, it will continue to be tracked until a resolution is completed.

³⁰ U.S. Food and Drug Administration, FDA Adverse Event Reporting System (FAERS) Public Dashboard, <https://www.fda.gov/drugs/guidancecompliance regulatoryinformation/surveillance/adversedrugs effects/ucm070093.htm>

³¹ Ibid.

³² U.S. Food and Drug Administration, *Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Event Reporting System (FAERS)*, <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082196.htm>

“A new report will be made available each quarter showing newly identified potential signals of serious risks/new safety information identified from the FAERS database during the previous quarter. Information from previous quarters with updates will remain available on the website until an FDA regulatory action has been taken. FDA actions may include a determination either that a) the drug is not associated with the risk and therefore no regulatory action is required, or b) the drug may be associated with the risk, and one of the following is required: a modification to the product labeling; development of a REMS; marketing suspension or withdrawal; **or gathering additional data to characterize the risk.** After FDA has determined that either no regulatory action is required or has taken a regulatory action for each issue on a quarterly report, no further updates will be made and the quarterly report will be archived.”³³ (emphasis added)

Interestingly, despite the FDA targeting kratom for significant regulatory action, a search of the archived potential safety risks from 2009 – 2017 does not record any listing by the FDA to add mitragynine or 7-hydroxymitragynine to the Serious Risks/New Safety Information Quarterly Report. It is not an inconsequential omission given that FDA is required to post these reports under Title IX, Section 921 of the Food and Drug Administration Amendments Act of 2007.

“This section in FDAAA, among other things, **directs FDA to "conduct regular, bi-weekly screening of the Adverse Event Reporting System [AERS] database and post a quarterly report on the Adverse Event Reporting System Web site of any new safety information or potential signal of a serious risk identified by Adverse Event Reporting System within the last quarter."** When a potential signal of a serious risk is identified from AERS data, it will be posted in the required report in the quarter in which it is first identified. A potential signal of a serious risk may in some cases constitute new safety information as defined in FDAAA (newly created section 505-1(b)(3) of the FDCA) which includes, among other things, information derived from adverse event reports about a serious risk associated with use of a drug that FDA has become aware of since the drug was approved or, for drugs that have REMS, since the REMS was required or last assessed. FDA will post each potential signal of a serious risk in the quarter in which it is first identified. If additional new safety information is developed concerning a potential signal that has already been posted, it will be addressed by FDA in new safety communications, but will not appear again as a new quarterly posting.”³⁴ (emphasis added)

Yet, despite no recorded entry on the Serious Risks/New Safety Information Quarterly Reports for the kratom alkaloids, the FDA imposed an Import Alert on kratom as an unapproved drug, and then imposed a second Import Alert in February 2014 regarding kratom-containing dietary supplements and bulk dietary ingredients.³⁵

³³ Ibid.

³⁴ Title IX, Section 921 of the Food and Drug Administration Amendments Act 2007 (FDAAA) (121 Stat. 962) amends the Federal Food, Drug and Cosmetic Act (FDCA) to add a new subsection (k)(5) to section 505 (21 U.S.C. 355).

³⁵ U.S. Food and Drug Administration, FDA and Kratom, <https://www.fda.gov/newsevents/publichealthfocus/ucm584952.htm>

Prior to the imposition of the first Import Alert, there were 11 serious adverse events. From 2012 to 2014, there was one additional serious adverse event reported, for a total of only 12 serious adverse events.³⁶ It appears the only significant kratom-related event that triggered the FDA interest was the report of the 9 deaths in Sweden in 2009, and despite the peer-reviewed published report on the true cause of the deaths being attributable to a toxic dose of an adulterant, *O*-desmethyltramadol, the FDA persisted in its biased regulatory actions against kratom.

The FDA also made no effort to investigate, verify, or validate any of the adverse event data submitted to FAERS on kratom, the reports were deliberately manipulated to create a false safety signal to justify additional regulatory actions. Unfortunately, by the time FDA released the source material in 2017, FDA's claims about kratom-associated deaths had become deeply entrenched in FDA's web of influence, which extends well beyond the scope of FDA's direct authority.

The DEA's Drugs of Abuse report, CDC's Morbidity and Mortality Weekly Report, and NIDA's DrugFacts publications resulting from FDA's false and misleading reports are widely relied upon by law enforcement agencies, coroners and medical examiners, and prosecuting attorneys' groups across the country in seeking legislation and regulatory policies in their individual states and local jurisdictions. The FDA's failure to provide accurate and critically relevant data biased the narrative on the alleged deaths associated with kratom, amounting to a viral event that infected wide ranging opinions, and produced deeply flawed public policy at federal, state, and local levels.

In his February 6, 2018 statement, Commissioner Gottlieb makes two significant admissions about the problems with the FDA analysis of the potential risks of kratom use.

“Overall, many of the cases received could not be fully assessed because of limited information provided; however, one new report of death was of particular concern. This individual had no known historical or toxicologic evidence of opioid use, except for kratom. We’re continuing to investigate this report, but the information we have so far reinforces our concerns about the use of kratom. In addition, a few assessable cases with fatal outcomes raise concern that kratom is being used in combination with other drugs that affect the brain, including illicit drugs, prescription opioids, benzodiazepines and over-the-counter medications, like the anti-diarrheal medicine, loperamide. Cases of mixing kratom, other opioids, and other types of medication is extremely troubling because the activity of kratom at opioid receptors indicates there may be similar risks of combining kratom with certain drugs, just as there are with FDA-approved opioids.”³⁷ (emphasis added)

First, Commissioner Gottlieb admits the death data used by FDA to recommend scheduling of kratom “could not be fully assessed,” but the FDA clearly did not provide such disclaimers to the DEA in the submission of the 3-

³⁶ U.S. Food and Drug Administration, FAERS Public Dashboard, <https://fis.fda.gov/sense/app/d10be6bb-494e-4cd2-82e4-0135608ddc13/sheet/45beeb74-30ab-46be-8267-5756582633b4/state/analysis>

³⁷ U.S. Food and Drug Administration, *Statement from FDA Commissioner Scott Gottlieb, M.D., on the agency's scientific evidence on the presence of opioid compounds in kratom, underscoring its potential for abuse*, February 6, 2018.

Factor Analysis supporting its scheduling recommendation. There are no disclaimers included in the Federal Register Notice of Intent for the Temporary Placement of Mitragynine and 7-Hydroxymitragynine Into Schedule I.³⁸

Second, Gottlieb states that one of the concerns of the FDA about kratom is that it is being used in combination or mixed with “other opioids” that “indicates there may be similar risks of combining kratom with certain drugs, just as there are with FDA-approved opioids.” Scheduling any substance under the CSA has nothing to do with the mixing that substance with other drugs because that is an issue that is addressed under FDA’s existing regulatory authority.

**FDA VIOLATES
THE
INFORMATION
QUALITY ACT**

The deliberate withholding of peer-reviewed and published scientific analysis by the FDA and using uncorroborated and unverified adverse reaction reports as the basis for recommending a scheduling decision on kratom, violates the requirements of the Information Quality Act (IQA) in several important ways. Passed as an amendment to the Paperwork Reduction Act, 44 U.S.C. § 3501, the IQA requires administrative agencies to devise guidelines to ensure the “quality, objectivity, utility, and integrity of information” they disseminate.”³⁹

Additionally, where the agency is responsible for disseminating “influential” scientific or statistical information, the FDA has a higher duty under the Act to ensure that such disseminated information is reproducible and accurate. HHS has affirmed its commitment to “disseminating information that meets the standards of quality set forth in OMB and in the guidelines discussed in this document.”⁴⁰ HHS states it is its goal to ensure and maximize the quality, objectivity, utility, and integrity of information that it disseminates to the public and strives to provide information that is accurate, reliable, clear, complete, unbiased, and useful.

The IQA is clear in its intent to prevent exactly what occurred with the FDA deliberately excluding information that undermined its claims that the nine deaths in Sweden were attributable to kratom consumption. The claim that these deaths were caused by kratom is neither reproducible or accurate.

There is another deeply troubling issue relating to the quality of the information used by the FDA in the data submitted to the DEA to support a recommendation to schedule kratom as a Schedule I substance, thereby denying the nearly 5 million kratom users’ access to safe kratom products. The FDA submitted data on kratom associated deaths drawn from the FDA Adverse Event Reporting System (FAERS) but did nothing to verify or validate the data when it was used to recommend to the DEA the scheduling of kratom.

The FDA prominently displays disclaimers on the inherent limitations of data submitted to the FAERS database that require users to affirmatively acknowledge as they sign in to the website.

³⁸ Federal Register Volume 81, Number 169, Wednesday, August 31, 2016, Proposed Rules, Pages 59929-59934.

³⁹ 44 U.S.C. § 3516, Statutory and Historical Notes.

⁴⁰ HHS Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated to the Public, 10/1/2002.

“First, there is no certainty that the reported event (adverse event or medication error) was actually 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. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.”⁴¹

However, the FDA then took that data with all of its embedded deficiencies and presented it to the DEA as a part of the official transmittal of its recommendation to schedule kratom. The evidence of the utilization of this inaccurate and uncorroborated data is found in the Federal Register Notice for the Temporary Placement of Mitragynine and 7-Hydroxymitragynine Into Schedule I where reference is made to the “deaths related to kratom exposure have been reported in the scientific literature beginning in 2009-2010, with a cluster of nine deaths in Sweden from use of the kratom product ‘Krypton’.”⁴² No disclaimers were offered or published, and this flawed data contributed to the transparent effort to influence the actions of the Congress, state legislatures, and local governments to support bans on kratom using a perverse regulation by database strategy.

If the FDA chooses to use any database as a part of a submission to support a scheduling recommendation on any substance, the data must be accurate, truthful, and objective. The data used by the FDA from the FAERS database on kratom, that it openly characterizes as not being reliable as a basis for any conclusion by the public reading the information, as the basis for a major public policy scheduling decision undermines the integrity of the CSA rulemaking process for such scheduling decisions.

In an analysis done by Jane Babin, Ph.D., Esq. on the FDA’s use of the unverified and deliberately manipulated FAERS data to support its recommendation to the DEA to schedule kratom, the conclusions are scathing.

“The FDA has also misled the DEA, the Centers for Disease Control (CDC), and the National Institute on Drug Abuse (NIDA) with incomplete, inaccurate, extrapolated, and distorted information on adverse events and deaths allegedly associated with the use of kratom to encourage unwarranted legislative and regulatory restrictions on kratom at the federal, state, and local government levels. Any public policy decision-maker (or staff) or media reporter, seeking to validate the FDA claims in policy deliberations will encounter a massively manipulated and sloppily documented public record.”⁴³

The FDA used the Krypton death data, despite knowing of the research that discredited their claim that the deaths were caused by the kratom powder product, as the basis for imposing its Import Alert on kratom in 2012.

⁴¹ FDA, FAERS, General Questions, Does FAERS data have limitations?, https://fis.fda.gov/extensions/fpdwidgets/2e01da82-13fe-40e0-8c38-4da505737e36.html#_Toc493751926

⁴² Federal Register Volume 81, Number 169, Wednesday, August 31, 2016, Proposed Rules, Pages 59929-59934.

⁴³ Jane Babin, Ph.D., Esq., *FDA Fails to Follow the Science on Kratom*, August 2018.

The imposition of the Import Alert, combined with the dissemination of biased and inaccurate information by the FDA to federal and state agencies and policy makers, led to the bans on kratom in 6 states.

Lawmakers responded to the wide dissemination of FDA and DEA alerts on the purported threat posed by kratom, and Alabama, Arkansas, Indiana, Wisconsin, Vermont, and Tennessee (since repealed) passed laws banning kratom in one form or another. In addition, based on that same biased information, the Director of the Rhode Island Department of Health added kratom to its banned substances list, and a number of local jurisdictions have also enacted bans.

The data-quality requirements of the IQA are not satisfied with transposing uncorroborated and unverified FAERS data into a policy recommendation document. The FDA has a substantial staff assigned to produce such recommendations, but it is clear there was no effort to ensure the data used in its recommendation for the scheduling of kratom was validated in any way.

The IQA applies to all executive departments and to any independent regulatory agency⁴⁴ and the “utility” of the information refers to the usefulness of the information to the public or any intended user.⁴⁵ In this case, the DEA has been misled in its prior review of the 3-FA in 2016 when the FDA recommended emergency scheduling of kratom, and in the current review of the 8-FA submitted by the FDA; Congress has been misled in the development of legislation to deal with the opioid crisis; and state and local governments have been misled in enacting kratom bans.

Separately, the IQA requires “influential scientific information” to be reproducible to demonstrate its objectivity because it has a clear and substantial impact on important public policy decisions.⁴⁶ In addition to deliberately excluding peer-reviewed and published scientific literature that disputes the conclusion of the FDA on the safety of kratom, the use of poorly-documented and unverified information as the basis for a scheduling recommendation is a major public policy decision that the IQA was enacted to protect against.

**ADULTERATION
OF KRATOM IS
THE CAUSE OF
DEATHS**

That is precisely why NIDA’s restatement of its DrugFacts publication on kratom made on September 20, 2018 affirms the deeply flawed logic of the FDA in attributing deaths related to other causations as “kratom associated deaths.” NIDA initially updated its information on kratom overdose deaths in July 2019 stating “kratom by itself is not associated with fatal overdose, but some forms of the drug packaged as dietary supplements or dietary ingredients can be laced with other compounds that have caused deaths.”

This dramatic change on NIDA’s website generated controversy, and the statement was removed, and NIDA reported it was collaborating with the FDA to verify the data on kratom’s role in any substance overdose. After

⁴⁴ 44 U.S.C. § 3502.

⁴⁵ 67 F.R. at 8659

⁴⁶ 67 F.R. at 8460.

conducting a two-month review of its previous kratom description, NIDA offered the following correction in its DrugFacts webpage on kratom⁴⁷:

“In 2017, the Food and Drug Administration (FDA) began issuing a series of warnings about kratom and now identifies at least 44 deaths related to its use, with at least one case being investigated as possible use of pure kratom. Most kratom associated deaths appear **to have resulted from adulterated products (other drugs mixed in with the kratom) or taking kratom along with other potent substances, including illicit drugs, opioids, benzodiazepines, alcohol, gabapentin, and over-the-counter medications, such as cough syrup.** Also, there have been some reports of kratom packaged as dietary supplements or dietary ingredients that were **laced with other compounds that caused deaths.**” (emphasis added)

There is no dispute that adulterated kratom products that have been spiked with dangerous and toxic doses of opioids or other toxic substances can cause deaths. If the same concentration of *O*-desmethyltramadol as was added to the powdered kratom product in Sweden were added to a cup of coffee, a Diet Coke, or an iced tea drink, the consumer would die. That would not result in FDA or any other responsible petitioner to initiate a scheduling recommendation for coffee, Diet Coke, or iced tea, but rather the FDA would be tasked to remove the adulterated product from the market, and to identify and prosecute the individual or company that produced and distributed these adulterated consumer products.

There is not a single instance in the history of DEA scheduling where a substance was banned because it had been deliberately adulterated with a separate deadly drug or substance. An exhaustive review of the regulatory record has failed to document any instance where the DEA acted to publish an intent to schedule any adulterated substance. Congress never intended for the Controlled Substances Act (CSA) to be used to ban substances that were deliberately adulterated with other toxic or deadly drugs that cause deaths, and nothing in the statute or the legislative history permits this abuse of discretion in the scheduling recommendation initiated by the FDA.

NIDA reports the FDA claims that there is at least one case reported by the FDA that is “being investigated as possible use of pure kratom.” However, the FDA made that statement on its investigation into a “pure kratom death” on February 6, 2018, and now more than 7 months later there is not any corroborating evidence produced by the FDA to validate that claim. The investigation of this single referenced death associated with kratom will not be determinative but speaks to the overall lack of credible information to justify any conclusion that kratom use has resulted in a safety signal that requires its being scheduled.

Any adulterated kratom products are subject to FDA regulatory action for seizure, recalls, and prosecution of the individuals or companies involved in the supply chain of such dangerous products to consumers. The FDA has sufficient statutory authority and existing regulations for food and dietary supplement products to ensure the safety of natural plant kratom products, and extracts of them using acceptable methods approved by the FDA, by removing adulterated kratom products from the market.

⁴⁷ National Institute on Drug Abuse, DrugFacts, revised September 2018, *What is kratom?*, <https://www.drugabuse.gov/publications/drugfacts/kratom>

KRATOM'S BINDING AFFINITY TO THE MU-OPIOID RECEPTOR AND SUBSEQUENT EFFECTS

The FDA has made repeated claims that it has strong evidence of kratom's compounds opioid properties and cited the development of a "novel scientific analysis using a computational model developed by agency scientists" as the tool that validates these assertions.

"This is why the FDA developed the Public Health Assessment via Structural Evaluation (PHASE) methodology – a tool to help us simulate, using 3-D computer technology, how the chemical constituents of a substance (such as the compounds/alkaloids found in kratom) are structured at a molecular level, how they may behave inside the body, and how they can potentially affect the brain. In effect, PHASE uses the molecular structure of a substance to predict its biological function in the body. For example, the modelling platform can simulate how a substance will affect various receptors in the brain based on a product's chemical structure and its similarity to controlled substances for which data are already available."⁴⁸

The scientific community reacted swiftly with skepticism on the validity of the FDA PHASE modeling to predict kratom's pharmacologic activity. According to Andrew Kruegel, a research chemist at Columbia University, the FDA's use of computer modeling is significantly less rigorous than the methods used in previous kratom studies. Furthermore, according to Kruegel, the FDA's claim that kratom has risks comparable to morphine is akin to "saying that all opioid agonists have the same effect, which is not true based on what we've learned about these compounds." Instead of lumping kratom in with classic opioids such as morphine and heroin, Kruegel prefers to call it an atypical opioid because it may have different effects, and a preferable side-effect profile, compared to classic opioids.⁴⁹

KRATOM IS NOT A CLASSIC OPIOID

According to University of Florida clinical toxicologist Oliver Grundmann, the interaction of mitragynine and 7-hydroxymitragynine with opioid receptors "is distinctly different from classical opioids."⁵⁰ This is critically important because the FDA is alleging that kratom has the same effects on the brain and respiratory system of a user as classic opioids do, and its scheduling recommendation is largely premised on this theory.

Commissioner Gottlieb reported that FDA scientists had analyzed the chemical structure of kratom compounds using the PHASE computational methodology and concluded that "22 (including mitragynine) of the 25 compounds in kratom bind to mu-opioid receptors. This model, together with previously available experimental

⁴⁸ U.S. Food and Drug Administration, *Statement from FDA Commissioner Scott Gottlieb, M.D., on the agency's scientific evidence on the presence of opioid compounds in kratom, underscoring its potential for abuse*, February 6, 2018.

⁴⁹ Journal of the American Chemical Society, *Synthetic and Receptor Signaling Explorations of the Mitragyna Alkaloids: Mitragynine as an Atypical Molecular Framework for Opioid Receptor Modulators*, Andrew C. Kruegel, June 1, 2016.

⁵⁰ The Scientist, *FDA Declares Kratom an Opioid. We're Here to Explain What It Does*, Jim Daley, February 7, 2018, <https://www.the-scientist.com/news-analysis/fda-declares-kratom-an-opioid-were-here-to-explain-what-it-does-30306>

data, confirmed that two of the top five most prevalent compounds (including mitragynine) are known to activate opioid receptors (“opioid agonists”).⁵¹

If kratom binds to the mu-opioid receptor in the brain but does not have the same or similar effects in suppressing the user’s respiratory system, then the basis for the FDA to argue for scheduling is substantially diminished. This research directly negates the PHASE computer model being relied upon by the FDA.

“On the molecular level, what we know in terms of interaction with the different opioid receptors is that yes, they bind to the opioid receptor. . . . But how they interact with the opioid receptor is distinctly different from classical opioids. If you look at morphine or at something like fentanyl . . . what we usually look at when we classically look at opioid receptors, these are G-protein-coupled receptors, where basically the morphine or another binding agent binds from the outside to the receptor and then you have a kind of second-messenger cascade that happens inside the cell.”⁵²

The fact is, the PHASE modeling system has significant limitations in simulating drug binding. The pharmacologic effects of a substance depend on a number of factors other than protein binding affinity, including its means and rate of absorption, the speed at which it is metabolized, and how readily it crossed the blood-brain barrier. Each of these factors are more difficult to predict than binding affinity. Critically, the “data produced by binding simulations are simply predictions of physiologic activity, and drug protein binding is only one piece of an elaborate puzzle.”⁵³

The evidentiary standard for classifying a substance as being an opioid based on its binding affinity to the mu-opioid receptor is a dangerous path to promote a scheduling decision that will have significant public policy impacts. For example, naloxone (the antidote for an opioid overdose) also binds to the mu-opioid receptors in the brain, just as kratom’s alkaloids do, but naloxone also has no effect on the respiratory system of the user.

There are also a number of other well-known substances that similarly bind to those same receptors, but we do not seek to schedule them, i.e., Chamomile, St. John’s Wort, and nutmeg. The important issue is that a scheduling decision must be based on reliable and replicable science to avoid stifling needed additional research that would benefit the public, and the use of suspect evidence has potentially harmful results.

“The need to discover new treatments is no less important than the need to shield the public from adverse events. As a result, the negative effects of banning a drug prematurely or placing it in Schedule I based on weak evidence, or on the predictions of an undisclosed or untested

⁵¹ U.S. Food and Drug Administration, *Statement from FDA Commissioner Scott Gottlieb, M.D., on the agency’s scientific evidence on the presence of opioid compounds in kratom, underscoring its potential for abuse*, February 6, 2018.

⁵² The Scientist, *FDA Declares Kratom an Opioid. We’re Here to Explain What It Does*, Jim Daley, February 7, 2018, <https://www.the-scientist.com/news-analysis/fda-declares-kratom-an-opioid-were-here-to-explain-what-it-does-30306>

⁵³ Harvard Law, Bill of Health, *Simulated Side Effects: FDA Uses Novel Computer Model to Guide Kratom Policy*, Mason Marks, February 8, 2018, <https://blogs.harvard.edu/billofhealth/2018/02/08/fda-uses-novel-computer-simulation-to-guide-kratom-policy/>

algorithm, could be more harmful to public health than leaving a drug on the market that has not been thoroughly tested.”⁵⁴

The FDA’s insistence that the PHASE modeling system is an important tool in proving kratom is a dangerous substance drew sharp criticism from some of the leading scientists in kratom research, Jack Henningfield, Oliver Grundmann, Paula Brown, Marc Swogger, and Zach Walsh.⁵⁵

“It is our opinion that the evidence does not support such conclusions regarding the risks of kratom. Although using well-defined, validated *in-silico* models in hypothesis development can provide valuable insights, an isolated receptor interaction study does not reflect the complexity of a living organism and has never been considered an acceptable replacement for experimental *in-vivo* data for FDA drug evaluations and approval. The physiological consequences of opioid receptor bindings vary widely, from the deadly effects of fentanyl to the relatively innocuous effects of the non-scheduled dextromethorphan. In the case of mitragynine, whole cell assay research shows binding to mu-opioid receptors without recruitment of beta-arrestin 2, which is linked to many adverse effects associated with classical opioids, such as respiratory depression, euphoria and tolerance development.⁵⁶ **The available scientific evidence indicates that the kratom indole alkaloids mitragynine and 7-hydroxymitragynine are not functionally identical to opioids; their molecular and pharmacodynamic mechanisms of action are distinctly different. This has been shown at the molecular and cellular level, as well as with whole organisms in animal models and observational studies.**”⁵⁷ (emphasis added)

FDA would not rely on a computer model as the basis for final approval on any drug, and they should not rely on a computer model as the primary rationale for a scheduling decision for any substance. The PHASE model accurately shows kratom’s alkaloids bind to the mu-opioid receptors, but the model cannot demonstrate kratom has the same effect as classic opioids on other brain activity or the central nervous system.

NIDA participates in the review of substance scheduling decisions prior to their submission to the Assistant Secretary for Health because of NIDA’s expertise in investigating and evaluating the potential for abuse associated with drug products.⁵⁸ In that context, NIDA’s scientific conclusions on how kratom should be

⁵⁴ Ibid.

⁵⁵ Grundmann, Brown, Henningfield, Swogger, Walsh, *Addiction*, *The therapeutic potential of kratom*, June 27, 2018, <https://onlinelibrary.wiley.com/doi/full/10.1111/add.14371>

⁵⁶ Kruegel A. C., Gassaway M. M., Kapoor A., Varadi A., Majumdar S., Filizola M. *et al.* Synthetic and receptor signaling explorations of the *Mitragyna* alkaloids: mitragynine as an atypical molecular framework for opioid receptor modulators. *J Am Chem Soc* 2016; 138: 6754–6764.

⁵⁷ Henningfield J. E., Fant R. V., Wang D. W. *The abuse potential of kratom according the 8 factors of the controlled substances act: implications for regulation and research.* *Psychopharmacology* (Berl) 2018; 235: 573–589.

⁵⁸ MOU 225-85-8251, Memorandum of Understanding Between the National Institute on Drug Abuse and The Food and Drug Administration, FDA Compliance Policy Guide 7155e.09, <https://www.fda.gov/AboutFDA/PartnershipsCollaborations/MemorandaofUnderstandingMOUs/DomesticMOUs/ucm116365.htm>

characterized are reflected in their description of kratom in their recently revised DrugFacts web page. It is important to note that NIDA likely was consulted on the FDA’s proposed scheduling recommendation on kratom prior to the FDA’s November 14, 2017 announcement. Since then, NIDA researchers have also published data on their own research⁵⁹ that challenges the FDA conclusions with respect to kratom’s addiction potential, that is a key component of the scheduling recommendation to be considered by the DEA.

In its 2016 DrugFacts kratom posting, NIDA characterized kratom as an “opioid drug.” Then, apparently relying on updated science data, NIDA significantly changed the designation of kratom to having “opioid-like effects.” In the context of a scheduling recommendation, this is a substantial change.

2016	2018 (July 2, 2018 Update)
<p>Is kratom addictive?</p> <p>Like other opioid drugs, kratom may cause dependence (feeling physical withdrawal symptoms when not taking the drug), and some users have reported becoming addicted to kratom.</p>	<p>Is kratom addictive?</p> <p>Like other drugs with opioid-like effects, kratom might cause dependence, which means users will feel physical withdrawal symptoms when they stop taking the drug.</p>

Withdrawal symptom assessments from the use of and dependency upon kratom are also appropriately considered in the context of a scheduling recommendation to the DEA. In an article published in *Drug and Alcohol Dependence* in December 2017 directly addressed the severity of kratom withdrawal symptoms.

“Extant data suggest that kratom’s withdrawal syndrome is uncomfortable, but generally milder and of shorter duration than is characteristic of opioid withdrawal.”⁶⁰

The inference by Dr. Gottlieb that kratom mirrors classic opioid withdrawal symptoms requires the DEA to accept the “novel” application of the PHASE computer modeling program and accepting without any reservation the FDA’s claims that kratom is an opioid, a claim that has been debunked by numerous scientists and their research.

It is a completely separate issue as to whether there are kratom users who self-medicate to wean themselves off of opioids. Some users report they have taken kratom as a replacement for opioids as a pain management therapy.

⁵⁹ Yue K, Kopajtic, Katz, Abuse liability of mitragynine assessed with a self-administration procedure in rats, *Psychopharmacology*, 2018, <https://www.ncbi.nlm.nih.gov/pubmed/30039246>

⁶⁰ Marc T. Swogger, Zach Walsh, *Kratom use and mental health: A systematic review*, *Drug and Alcohol Dependence*, December 2017, <https://doi.org/10.1016/j.drugalcdep.2017.10.012>

CONCLUSION

The CSA was enacted in 1970 to allow for the classification of drugs and substances based on their medical value, harmfulness, and potential for abuse or addiction. It was intended that the most harmful substances would be placed in Schedule I, with substances with lower addiction and safety profiles placed in descending order in one of the remaining four schedules based on the data supporting that level of regulation.

In the case of kratom and its alkaloids, the FDA has initiated the recommendation for its control as a Schedule I drug. The CSA provides that when a recommendation is received, the DEA commences its own investigation of the substance or drug that includes a review of the 8-FA provided by HHS that supports the recommendation.

Kratom, because it is available as a dietary supplement/dietary ingredient and has not been the subject of any application to the FDA to receive an FDA approval as a therapeutic drug, can only be listed as a Schedule I substance. If kratom is listed as a Schedule I substance it will make it illegal for any of the nearly 5 million consumers who currently safely use kratom to purchase or use kratom in the United States.

The infringement of the freedom of consumers to make their own decisions on products they use for their health and well-being regimens is a significant public policy decision. Any interested party submitting a petition to the DEA to schedule any substance has the burden of proof for this recommendation. The FDA has initiated the recommendation on the scheduling of kratom to the DEA and given its role as the repository for scientific and adverse event records, FDA would have a higher obligation to present compelling, scientifically valid, and data that is untainted by bias or deliberate manipulation to artificially strengthen the case for designating kratom as a Schedule I substance.

The CSA sets forth eight factors that are required to be considered in whether a substance should be scheduled,⁶¹ which essentially break down to two criteria: (1) What is kratom's actual or relative potential for abuse; and (2) Is kratom safe for consumer use.

What is kratom's actual or relative potential for abuse:

The FDA asserts there is "evidence that certain substances found in kratom are opioids and data suggest that one or more may have a potential for abuse."⁶² The standard set forth in the CSA requires that the actual or relative potential for abuse be proven, and a scheduling decision should not be based on data that "suggest[s]" or that "may" have a potential for abuse.

In his public statement, Dr. Gottlieb relies on the claim kratom is an "opioid" and imputes the same effects of classic opioids, and the predictive capabilities of the PHASE computer modeling program developed by FDA scientists that FDA maintains provides evidence of kratom's high potential for abuse. However, numerous credible scientists directly refute the theory that kratom's alkaloids have the same effects as classic opioids, and

⁶¹ [Section 201 \(c\), \[21 U.S.C. § 811 \(c\)\]](#)

⁶² U.S. Food and Drug Administration, *Statement from FDA Commissioner Scott Gottlieb, M.D., on new warning letters FDA is issuing to companies marketing kratom with unproven medical claims; and the agency's ongoing concerns about kratom*, September 11, 2018.

that the PHASE computer model cannot accurately predict kratom’s effects other than affirming the accepted fact that MG and 7-HMG bind to the mu-opioid receptors.

The Hemby research directly contradicts the FDA assertions in its conclusion that MG “does not have abuse potential and reduces morphine intake . . .”⁶³ This study is particularly credible because it used animal studies to measure the addiction potential of the kratom alkaloids, and the clarity of the findings on MG has no abuse potential cannot be easily dismissed. In the absence of human clinical trials on kratom, animal studies are the most reliable mechanism to assess the behavioral effects of MG and 7-HMG.

The only remaining issue is whether 7-HMG poses a public safety threat because of its potential for abuse, and Hemby was equally clear in concluding that “7-HMG potentially has abuse potential, but only in purified or concentrated adulterants.”⁶⁴ This conclusion demonstrates that kratom is not a “narcotic-like opioid” that is the foundational premise of the FDA recommendation for scheduling of kratom. Importantly, Hemby concludes that 7-HMG occurs at such low levels in the natural plant it has no safety impact unless it is adulterated.

It is also significant that NIDA’s own intramural research concluded MG had a “limited abuse liability.”⁶⁵ This finding is critical to the merit of the FDA recommendation for scheduling given that it directly refutes the FDA claim that kratom is dangerously addictive. The results of this study, while independent of the Hemby research, came to a similar conclusion with respect to the abuse liability of mitragynine.

“These results suggest a limited abuse liability of mitragynine and potential mitragynine treatment to specifically reduce opioid abuse. With the current prevalence of opioid abuse and misuse, it appears currently that mitragynine is deserving of more extensive exploration for its development or that of an analog as a medical treatment for opioid abuse.”⁶⁶

The results of this scientific study affirm that the FDA’s reliance on the PHASE computer modeling on kratom being dangerously addictive demonstrates the weakness of FDA using a predictive modeling tool rather than real-world evidence. It is also ironic that the FDA’s efforts to schedule kratom would interfere and significantly limit any future research into what the NIDA funded research concluded is “deserving of more extensive exploration for its development or that of an analog as a medical treatment for opioid abuse.”

Dr. Gottlieb stated in his November 14, 2017 announcement of the public health advisory on kratom that the FDA had completed its 8-FA for review by the DEA.⁶⁷ Given that the Hemby study and the NIDA research study were reported in June and July of 2018, and that occurred after that the FDA’s submission to the FDA, and given

⁶³ Hemby *et al.* “Abuse liability and therapeutic potential of the *Mitragyna speciosa* (kratom) alkaloids mitragynine and 7-hydroxymitragynine,” *Addiction Biology*, 27 June 2018, doi: 10.1111/adb.12639.

⁶⁴ *Ibid.*

⁶⁵ Yue K, Kopajtic, Katz, Abuse liability of mitragynine assessed with a self-administration procedure in rats, *Psychopharmacology*, 2018, <https://www.ncbi.nlm.nih.gov/pubmed/30039246>

⁶⁶ *Ibid.*

⁶⁷ U.S. Food and Drug Administration, *Statement from FDA Commissioner Scott Gottlieb, M.D. on FDA advisory about deadly risks associated with kratom*, November 14, 2017, <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm584970.htm>

they contradict the FDA assertions on the abuse potential of kratom, it would be appropriate for the DEA to either reject the FDA recommendation, or for the FDA to withdraw it for further research.

The FDA has ample statutory authority to interdict any adulterated kratom product that has been chemically altered or enhanced by purifying or concentrating the 7-HMG alkaloid. It would be a clear abuse of discretion to schedule any product because of the presence of an adulterant in that product.

Is kratom safe for consumer use:

The FDA relies primarily on the raw and unverified adverse event data extracted from the FAERS database to demonstrate that the use of kratom is associated with 44 reported deaths. The FDA released the specific records documenting these alleged “kratom-associated deaths” that were drawn from the FAERS database, and an independent analysis conducted by Dr. Jane Babin⁶⁸ exposed significant flaws in the data presented by the FDA, including:

- The FDA failed to disclose that 9 of the 44 deaths were actually caused by a toxic dose of *O*-desmethyltramadol that was added to the kratom product transforming it into an illegally adulterated substance. These are the 9 deaths reported in Sweden over a 12-month period in 2009 and that were reviewed in the Kronstrand report.⁶⁹
- The FDA failed to report that 29 of the reported deaths involved polydrug use where the decedent had used illegal or prescription medications concurrently, many of which are contraindicated for concurrent use, in a manner that resulted in death. As an illustration, 1 of the reported deaths showed the decedent had 9 illegal or prescription medications that showed on the toxicology report, in addition to mitragynine (FAERS Incident #8121551), where the cause of death was listed as “accidental drug intoxication/overdose.”
- The FDA redacted the information on the true cause of death in the documents showing that 1 of the 44 deaths resulted from a gunshot wound to the chest that was ruled as a homicide (FAERS Incident #12639316), and that a subsequent toxicology screen simply showed the murder victim had consumed kratom (along with 3 other prescription drugs) that had nothing to do with the death.
- The FDA ignored the fact that 1 of the 44 deaths resulted from a suicide where the decedent, who suffered from Bipolar disorder, hung himself (FAERS Incident #12639556). The decedent had alcohol, 6 prescription drugs, and mitragynine that showed on the toxicology report, none of which caused the death.
- The FDA ignored the fact that 1 of the 44 deaths resulted from a hematoma and humerus fracture of the left arm injury sustained from a fall where the decedent refused medical treatment (FAERS Incident #13421666). The decedent had 9 prescription drugs and mitragynine that showed on the toxicology screen, including a finding in the autopsy report that the benzodiazepine in the femoral blood was in a concentration range that was likely to result in toxic effects. The reported cause of death was

⁶⁸ Jane Babin, Ph.D., Esq., *FDA Fails to Follow the Science on Kratom*, August 2018.

⁶⁹ Kronstrand *et al.*, “*Unintentional Fatal Intoxications with Mitragynine and O-Desmethyltramadol from the Herbal Blend Krypton*”, *J Anal Toxicol* 35: 242-47 (2011).

“aspiration of chime” that likely was caused by the victim being impacted by the injuries and the toxic dose of benzodiazepine.

- The FDA duplicated at least 2 of the 44 deaths (FAERS Incident #14449343 and FAERS Incident #14254346). The source documents FDA released demonstrate both the duplication and the variability with which cases are documented in FAERS. On page 2 of FAERS Incident #14449343, second paragraph, the reporter refers to the 27-year-old male as “Case 358 from the 2016 AAPCC toxicology report Table 21. Listing of fatal non-pharmaceutical and pharmaceutical exposures.” A second report of the same 27-year-old male, in Incident #14254346, on page 2, 6th paragraph under the heading “Additional Information” the following statement is found: “This case corresponds to case number 358 in the literature article.”
- The FDA stripped critically important source data out of the FAERS data. In FAERS Incident #14449343, the FDA strips the assessment of the likely cause of deaths contained in the data submitted by Endo Pharmaceuticals Inc -- based on the American Association of Poison Control Centers report⁷⁰ that weights the substances by their probable role in the death. In this case, U-47700 (PINK) is cited as the primary cause of death, with kratom listed as fifth out of six substances in relevance to possible cause of death. Without that important weighting data, kratom appears to have a far greater role in the fatality, despite the weighted data indicating it had a very small probability of causation in any fatality.
- The FDA lists deaths from Loperamide overdose and attributes them to kratom. Two allegedly “kratom-associated” deaths (FAERS Incident #'s 12665823 and 12665824) were of a married couple whose deaths had been investigated extensively by the North Carolina Office of the Chief Medical Examiner and reported in a peer-reviewed journal.⁷¹ The evidence implicating loperamide as the primary cause of death included super-therapeutic levels of loperamide, along with instructions on the couple’s computer for getting high on loperamide by potentiating the CNS opioid effects through concomitant consumption of quinine, which was also detected in the decedents. Kratom consumption was deemed secondary to the desire to potentiate the euphoric effects of loperamide because it had also been reported to increase central nervous system effects of loperamide. The FDA not only ignored these conclusions when releasing the cases as kratom deaths, but also appears to have buried them in FAERS: a search for mitragynine does not bring up either case although searching for loperamide does; mitragynine is listed as concomitant instead of a suspect product; and reference to the journal article was obscured by citing the authors first names “Sandra, Marc & Jennifer” instead of their last names in the FAERS database.
- The FDA misstates the actual cause of death in 1 of the 44 deaths where the cause of death was deep vein thrombosis and chronic polysubstance abuse, not kratom use. In FAERS Incident #12639594, a death was reported in a 5’9” 43-year old male who weighed 298 pounds and who died of pulmonary thromboemboli and deep vein thrombosis. The toxicology report showed a “potentially toxic concentration of morphine” and other drugs (fluoxetine, benzodiazepines, trazodone, and gabapentin). Kratom was also detected. The Medical Examiner concluded that the death was attributable to deep

⁷⁰ Gummin et al. “2016 Annual Report of the American Association of Poison Control Centers’ National Poison Data System (NPDS): 34th Annual Report” *Clinical Toxicology* 55:1072–1254, at p. 1119 (2017).

⁷¹ Bishop -Freeman et al. “Loperamide-Related Deaths in North Carolina,” *J Anal Toxicol* 40:677-86 (2016).

vein thrombosis, with obesity; dilated cardiomyopathy and chronic polysubstance abuse were listed as contributing conditions.

- The FDA ignored the fact that 1 of the 44 deaths resulted from a toxic chemical used to make the opioid Tramadol that is not associated with kratom. In FAERS Incident #191303, a MedWatch Report concluded the subject 27-year-old male “died due to cardiac arrhythmia while swimming.” The coroner confirmed the cause of death as cardiac arrhythmia, with contributing factors of acute mitragynine *and* *O*-desmethyltramadol. Whether the decedent used an adulterated kratom product containing *O*-desmethyltramadol, or used *O*-desmethyltramadol alone, it is well known that *O*-desmethyltramadol is dangerously toxic and has a deadly safety profile. Yet, the FDA persists in its clearly unjustified claim this is a kratom associated death.
- The FDA has openly acknowledged there is only 1 of the 44 reported deaths that “was of particular concern” because of a report the decedent had “no known historical or toxicologic evidence of opioid use, other than kratom.”⁷² Yet, the results of that incident investigation have not been made public and there is no indication it has been submitted to the DEA for review in the intervening 7 months.

The scientific credibility of the FAERS database that was used to justify FDA’s recommendation to the DEA for scheduling of kratom turns on whether any substantive effort was undertaken by the FDA Controlled Substance Staff located in Center for Drug Evaluation and Research’s (CDER) Office of the Center Director⁷³ to validate the data being relied upon by the FDA in its scheduling recommendation.

A glaring example of the lack of credible review of the FAERS data is illustrated in two specific reports on what the FDA claims are deaths associated with kratom use that occurred in Germany; FAERS Incident #13407030 and Incident #1342166, that reference a published article that purportedly supports the FDA claim that these two deaths were associated with the use of kratom. However, the referenced article, *Mitragynine concentrations in two fatalities*, authored by Domingo, Roider, Graw, Misshoff, and Sachs,⁷⁴ actually directly contradicts the FDA conclusion:

“Two cases of fatalities are reported of which the recreational use of *Mitragyna speciosa* (“kratom”) could be confirmed. One of these cases presents with one of the highest postmortem mitragynine concentrations published to date. Our results show that even extremely high mitragynine blood concentrations following the consumption of kratom do not necessarily have to be the direct cause of death in such fatalities as a result of an acute overdose (emphasis added). The two cases are compared with regard to the differences in mitragynine concentrations detected and the role of mitragynine in the death of the subjects. Irrespective of the big differences in mitragynine concentrations in the postmortem blood samples, mitragynine was not the primary cause of death in either of the two cases reported here (emphasis added). Additionally, by rough estimation, a significant difference in ratio of

⁷² U.S. Food and Drug Administration, *Statement from FDA Commissioner Scott Gottlieb, M.D., on the agency’s scientific evidence on the presence of opioid compounds in kratom, underscoring its potential for abuse*, February 6, 2018.

⁷³ U.S. Food and Drug Administration, *Assessment of Abuse Potential of Drugs*, Center for Drug Evaluation and Research (CDER), January 2017.

⁷⁴ Domingo, Roider, Stover, Graw, Mussoff, Sachs, Bicker; *Mytragynine concentrations in two fatalities*, Forensic Science International, 2016, <http://dx.doi.org/10.1016/j.forsciint.2016.12.020>

mitragynine to its diastereomers in the blood and urine samples between the two cases could be seen.”

It is unexplainable why the FDA used this documentation for two deaths they claim to be associated with kratom (unless the FDA analysts only read the title of the article, as opposed to actually reviewing its content), but the inclusion of these two deaths in their list of 44 deaths illustrates the deep flaw in the FDA justification for its argument that kratom is a risk to public health. For reference, the published title of the Domingo Case Report is expressed as follows: “*Mitragynine concentrations in two fatalities.*”⁷⁵

There is no question that the official recommendation of the FDA to the DEA for the scheduling of kratom constitutes the dissemination of influential scientific and statistical information that is “expected to have a genuinely clear and substantial impact at the national level, or on major public and private policy decisions as they relate to federal justice issues.”⁷⁶ The recommendation to schedule kratom as a Schedule I substance will potentially impact the nearly 5 million Americans who currently use kratom products and requires strict adherence to the standards on the quality and credibility of the evidence being used by the FDA to justify its recommendation.

Yet, the FDA clearly expressed the fatal flaw in the submitted data when Dr. Gottlieb stated that “[O]verall, many of the cases received could not be fully assessed because of limited information provided.”⁷⁷ The assessment of the cases falls directly upon the FDA, and that responsibility is delegated to the Controlled Substance Staff located in CDER’s Office of the Center Director.⁷⁸ The raw data files of uncorroborated and unverified incidents appears to have been consolidated from the FAERS database without any effort by the FDA to investigate the incidents prior to its being made public and transmitted to the DEA. That clearly does not meet the statutory requirements under the IQA for data that will have a substantial impact on a national policy decision.⁷⁹

The PHASE computer modeling program is also highly suspect in meeting the data quality standards for such a significant public policy decision, particularly in the face of credible real-world research that directly contradicts its predictive computer algorithms. The more credible *in-vivo* data has always been preferred to predictive computer modeling, and that evidence currently exists with respect to the safety and addiction profile of kratom.

The suspect fatality data the FDA has used in its scheduling recommendation; the reliance upon what the FDA itself acknowledges is a new and “novel” computer modeling algorithm for predicting the effects of kratom alkaloids and characterizing kratom as an opioid; and the failure to adhere to required standards for the quality

⁷⁵ Ibid.

⁷⁶ <https://www.justice.gov/iqpr/information-quality>, at “Standards for Disseminated Information.”

⁷⁷ U.S. Food and Drug Administration, *Statement from FDA Commissioner Scott Gottlieb, M.D., on the agency’s scientific evidence on the presence of opioid compounds in kratom, underscoring its potential for abuse*, February 6, 2018.

⁷⁸ U.S. Food and Drug Administration, *Assessment of Abuse Potential of Drugs*, Center for Drug Evaluation and Research (CDER), January 2017.

⁷⁹ 67 F.R. at 8460.

of data used to justify a major public policy decision are the basis for the DEA to reject the recommendation and return it to the FDA for additional analysis and scientific review.

In addition to the scientific research that existed at the time of the transmittal of the FDA scheduling recommendation to the DEA that should have been factored into the 8-FA prior to it being finalized, there is new compelling and credible scientific research that has been published since the 8-FA transmittal that directly challenges the FDA's position on the safety and addiction profile of kratom.

In addition to the DEA returning the 8-FA to the FDA for additional review, the FDA should immediately commence an appropriate regulatory effort to interdict individuals and corporations who are adulterating kratom products that pose a real threat to public safety.