

# FDA Fails to Follow the Science on Kratom

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Jane Babin, *Ph.D., Esq.*

*J.D., University of San Diego School of Law*

*Ph.D., Molecular Biology, Purdue University*

## EXECUTIVE SUMMARY

The U.S. Food and Drug Administration (FDA) has an affirmative duty to base all regulatory decisions on the best available scientific information, which must be updated on a continual basis, as well as an obligation to disseminate scientifically accurate and verifiable information on both the benefits and dangers of any substance within its purview, both to the public and to the U.S. Drug Enforcement Agency (DEA) in connection with any scheduling recommendation.

FDA abrogates its responsibilities when selectively choosing which evidence it will or will not accept. As such, the burden is on FDA to demonstrate through credible evidence that uncontaminated and unadulterated whole leaf kratom is a dangerous substance—a claim currently made without scientific integrity.

The FDA has relied on a strategy of manipulating, obscuring, and ignoring science in its inexplicable zeal to impede public access to the natural botanical kratom. The FDA placed an Import Alert on kratom in 2012 (updated in 2014 and 2016); recommended scheduling of kratom in a 3-Factor Analysis submitted to the DEA in 2016; issued a Public Health Advisory in 2017; claiming it was a “narcotics like opioid posing a deadly risk; and has recommended scheduling of kratom in a publicly undisclosed 8-Factor Analysis presented to the DEA in 2017, a recommendation that is currently pending consideration.

The key evidence the FDA has offered on the dangers of kratom as the basis for placing it in Schedule I are case reports on 44 deaths over a nine-year period world-wide associated with the use of kratom. However, the FDA did not independently verify or perform any due diligence on the death reports, and worse, FDA’s own documents indicate that every reported case involved other factors. With no direct investigation by the FDA, and a clearly unprofessional review, those case reports are riddled with significant credibility issues. In addition, there are serious errors and omissions between the source reports and the data entered into the FDA FAERS database by FDA that are either deliberate, or so incredibly unskilled as to call into question the validity of any conclusions made by the FDA. The errors, omissions and mistakes include, but are not limited to:

- Duplication of case reports on the same death, and such poor documentation that there is a high likelihood that many other reports of death the FDA attributes to kratom may be repeats of one another.
- Significant discrepancies between relevant information in the source reports and the case reports actually entered into the FDA FAERS database by FDA staff.
  - Material omissions of data from source documents, e.g., the country of origin of some reports, that impede a fair review of relevant information in the death.
  - Omissions of references to peer-reviewed published source data authored by scientists and analysts that were reported to the FDA and contradicts the FDA claim that kratom is directly associated with the reported deaths.

- Omission of cause of death conclusions by the scientists, medical examiners and healthcare professionals who actually reviewed autopsy, toxicology and investigation reports.

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.

The DEA, CDC, and NIDA have each used their extensive policy and public communication networks to disseminate the FDA misinformation on kratom that resulted in bans on kratom initially being enacted in six states (with additional actions that followed), a number of local jurisdictions, and infusion of a completely unjustified bias against kratom among law enforcement officers, coroners, medical examiners, and state prosecuting attorneys' groups. Furthermore, when NIDA updated its DrugFacts kratom page to make clear that "Kratom by itself is not associated with fatal overdose," FDA apparently intervened to have the statement withdrawn. Equally alarming is the use of the FDA's considerable reputational equity with the public to advance a biased and unwarranted attack on the natural plant kratom.

To restore confidence in the integrity of the policy-making processes of our government with respect to kratom, the following actions demand urgent attention:

- FDA must review the FAERS database to ensure it contains a complete and accurate record of all source documents related to kratom that it intends to rely on.
- FDA must reevaluate its own kratom-related policies and revise the same based on an appraisal of the corrected, accurate scientific evidence.
- The DEA, CDC, and NIDA must update their various policy documents to reflect an accurate and unbiased assessment of the risks of kratom use.
- The DEA must reject the FDA's 8-Factor Analysis and scheduling recommendation and return it to FDA for a full scientific reanalysis of the data and conclusions in that submission. This should include thorough input by NIDA to ensure that FDA's apparent lack of understanding of the neuropharmacology of kratom, its low respiratory depressant effects, and the very low addicting risk of its primary alkaloid mitragynine is taken into consideration, and to ensure that kratom is not mischaracterized as a "narcotics-like opioid," which not surprisingly has been interpreted by the media and many others as a substance like fentanyl, heroin and oxycodone in its risks of addiction respiratory depression and overdose.
- The FDA must also take the following corrective actions:
  - Immediately lift the current Import Alert on kratom;
  - Rescind its November 14, 2017 Public Health Advisory on kratom;

- Undertake a scientific review of the validity of the FAERS database reports to determine which, if any, of the reported deaths is associated solely and causally with the natural plant kratom rather than actually being caused by polydrug use, underlying medical conditions, contraindicated uses of prescription drugs, or adulterated and contaminated kratom products. Simple detection of kratom in the body of a decedent is no more probative than finding water in the same body.
  - The FDA should also immediately commence appropriate enforcement action against companies and individuals who are producing adulterated kratom products that pose a real and present danger to the public.
  - The FDA should engage in a collaboration with kratom product manufacturers and vendors to ensure that appropriate standards are in place as it currently does for other products marketed as foods, natural remedies and dietary supplements, as has been requested by the American Kratom Association and leading kratom product vendors.
  - The FDA should commence enforcement actions against any kratom manufacturer who adulterates any kratom product and/or violates statutes and regulations restricting impermissible health claims.
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## THE FDA CLAIMS OF DEATHS “ASSOCIATED WITH KRATOM” MANIPULATES, OBSCURES, AND IGNORES THE SCIENCE.

*The Import Alerts on kratom are premised on overreaction and misinterpretation if not deliberate obfuscation. In imposing its Import Alert on kratom in 2012 (and subsequent updates in 2014 and 2016; collectively, the “Import Alerts”), the FDA initially reacted to and relied on reports of nine deaths in Sweden that occurred over a twelve-month period. The FDA attributed these deaths to the use of a powdered kratom product marketed on the Internet as “Krypton”, without disclosing that Krypton is not natural kratom, but is an adulterated product contaminated with dangerous levels of O-desmethyltramadol; without citing the Case Report that first brought these deaths to their attention; without giving adequate weight to the conclusions reported in that Case Report; and in direct conflict with the overwhelming lack of evidence associating kratom use with death or harm during hundreds of years of use in Asia<sup>1</sup>. In addition to the Import Alerts, the FDA circulated misleading reports to the DEA, the Centers for Disease Control (CDC), and the National Institutes on Drug Abuse (NIDA), resulting in widespread dissemination and acceptance of false information to state law enforcement agencies, coroners, medical examiners, reference laboratories and prosecuting attorneys’ associations. These false reports led to six states (Alabama, Wisconsin, Arkansas, Tennessee, Indiana, and Vermont) and a number of local*

*jurisdictions, banning the sale of kratom. The FDA misrepresented the nine Swedish deaths in its 3-Factor Analysis recommendation to the DEA in 2016 with the express purpose of triggering the emergency scheduling authority of DEA under the Controlled Substances Act (CSA) to schedule kratom as a Schedule I substance.*

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**FINDINGS:** 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<sup>ii</sup>. That report concluded the deaths were actually the result of adulteration of kratom powder with a toxic dose of *O*-desmethyltramadol.

This Case Report was published prior to the FDA Import Alert and is a part of the publicly available scientific literature the FDA typically relies upon in developing regulatory policies.

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 report<sup>iii</sup> 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.<sup>iv</sup>

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

This 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.

Unfortunately, by the time FDA released the source material in 2017, FDA's fairytales 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.

FDA applies a double standard for consideration of reports on kratom death versus safety.

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***FDA's claim that kratom produces classic opioid-like effects is scientifically unsupported hype.*** *The FDA has repeatedly claimed that the science has conclusively proven that the main active alkaloids mitragynine and 7-hydroxymitragynine pose an "imminent hazard to public safety" because these substances produce dangerous "opioid-like effects." In addition, the FDA falsely cites the classic opioid overdose effect of suppressing the respiratory system as a cause of death related to kratom and claims that kratom is dangerously addictive. At the same time, the FDA refuses to recognize evidence and emerging science that directly contradicts this conclusion.*

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**FINDINGS:** There is no credible scientific evidence showing that kratom produces the deadly effects of classic opioids, and the science cited by the FDA that kratom is an "opioid" or produces dangerous "opioid-like effects" is premised only on the already well-established fact that kratom's alkaloids bind to mu opioid receptors in the brain without acknowledging that that is only the beginning of the inquiry. This ignores critical differences across the many substances that bind to opioid receptors and which vary

widely in their overall effects and risks, ranging from life-saving naloxone to deadly heroin and fentanyl. In fact, as research conducted and supported by NIDA and research out of the United States show, kratom's mitragynines produce little if any of the respiratory depression that is a hallmark sign and cause of death by actual narcotic-like opioids; that its primary alkaloid, mitragynine, is more similar to saline placebo than to morphine in addiction tests; and that its more potentate minor alkaloid, 7-hydroxymitragynine, occurs at such low levels in natural products as to be considered not to be a substantial contributor to the effects of kratom. It also ignores the other neuropharmacology research supported by NIDA that suggests that kratom's mitragynines appear to act as what are termed "biased G-protein coupled signaling pathways" and/or partial agonists, thus greatly limiting their capacity for harm and to cause addiction.

**Respiratory Depression.** The FDA has deliberately excluded numerous peer-reviewed research papers and studies that directly dispute its errant representation that kratom's primary alkaloids produce "opioid-like effects" that result in death. The deadly "opioid-like effect" of a classic opioid is to suppress the autonomic nervous system which controls breathing in the opioid user under which suppression an individual stops breathing and literally suffocates. Numerous research reports document that kratom has no measurable effect on a user's respiratory system<sup>v</sup>, and this is consistent with its biased G-protein/partial agonist mechanism of action. There are even questions surrounding the cause of death observed in animal studies measuring the incredibly high LD<sub>50</sub> values for purified kratom alkaloids and heterogeneous alkaloid preparations.<sup>vi</sup>

Moreover, the most recent, cutting edge research has elucidated at least one mechanism by which kratom alkaloids mitragynine and 7-hydroxymitragynine effect analgesia without classical opioid side-effects, particularly respiratory depression. Unlike morphine, heroin and fentanyl, kratom alkaloids do not recruit  $\beta$ -arrestin 2 upon binding to mu opioid receptors.<sup>vii</sup> This mechanism has long been suspected, but efforts to design new synthetic drugs directed to "biased agonists" such as Trevena's Oliceridine have been long and frustrating. After more than 10 years, untold hundreds of millions of dollars, granting by FDA of "Breakthrough Status" and encouraging results in Phase I and II clinical trials, the final Phase III of the clinical trial process failed to meet expectations for side effect reduction at higher doses. More recent developments in biased opioid receptor agonist research have yielded more promising candidates that surpass Oliceridine in side-by-side pre-clinical testing<sup>viii</sup>, and unsurprisingly demonstrate exactly how unpredictable FDA's 3-D docking method is for predicting receptor binding activity: Stanford investigators reported screening over 3 million candidate compounds before arriving at only 23 that fulfilled their selection criteria and thereafter the top leads required further refinement by synthesis of 500 additional analogues before arriving at the single compound they plan to commercialize.

FDA should note that their most promising biased agonist, PZM21, was discovered paradoxically by docking the *inactive* mu opioid receptor structure and has no structural similarity to previously identified opioids. In another ground-breaking report, Scripps Research Institute scientists<sup>ix</sup> demonstrated a strong correlation between the relative  $\beta$ -arrestin bias of opioid agonists and respiratory depression, both in existing opioids, such as morphine and fentanyl, and potent

experimental opioid compounds. Moreover, biased G protein signaling (the opposite effect from  $\beta$ -arrestin bias) broadened the therapeutic window in these studies, thereby allowing high potency antinociception in the absence of respiratory depression. Only individuals so deeply entrenched in their own faulty dogma as to be blinded to scientific discovery would refuse to recognize that kratom today satisfies goals that these preeminent scientists have been working decades to achieve.

## Addiction and Abuse

In peer-reviewed research on the “Abuse liability and therapeutic potential of *Mitragyna speciosa* (kratom) alkaloids mitragynine and 7-hydroxymitragynine,” scientists concluded that “MG (mitragynine) does not have abuse potential.”<sup>x</sup> Specifically, this study used rats to investigate how these two compounds affect the brain, using FDA-approved protocols that allowed the rats to self-administer each of the compounds tested. The lead researcher, Scott Hemby, observed that the rats were completely uninterested in the mitragynine, even after they increased the dosage several times. “It just wasn’t working. It was almost like it (mitragynine) was innocuous.”<sup>xi</sup> Hemby also commented that mitragynine was not only not addictive, it “appeared to have the opposite effect.”

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.<sup>xii</sup> Also, consistent with human reports, pretreatment 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.”

The FDA has since shifted its focus to a second significant alkaloid in kratom, 7-hydroxymitragynine (7-HMG), which constitutes less than 2% of the alkaloid content of kratom. The Hemby study pointed out that some kratom products are adulterated and contaminated with dangerous substances; purified extracts of 7-HMG in high concentrations are sometimes used as an adulterant in contaminated kratom products, which can potentially pose a danger to consumers. The FDA currently has ample authority to seize and destroy these and any other adulterated kratom products, but it is disingenuous to confuse consumers and authorities by suggesting that the natural and unprocessed presence of 7-hydroxymitragynine poses a danger.

Moreover, Hemby notes that even though 7-HMG demonstrated addictive potential, the investigators observed that in contrast to morphine and other classical opioids “no overt withdrawal symptoms were observed” from 7-HMG. Hemby further stated in a MedScape interview that 7-HMG is about 2% of the alkaloid compound of the plant, whereas MG is about 60%. That’s about a 30 -fold difference between these two alkaloids.... [suggesting] that it probably won’t be reinforcing if kratom were taken as a whole plant with all the alkaloids and everything else in it.”<sup>xiii</sup>



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***The FDA claims of 44 deaths associated with the use of kratom is scientific misconduct.*** *The FDA has premised its major policy decisions related to kratom on inaccurate data representing a direct association between the use of kratom and 44 deaths. These include the FDA’s 2012, 2014, and 2016 Import Alerts; numerous public safety alerts and communications to the DEA, CDC, and NIDA; recommendation to the DEA for emergency scheduling in 2016; a Public Health Advisory in 2017; and the FDA’s current recommendation for scheduling of kratom as a Schedule I substance.*

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**FINDINGS:** FDA reports that associate kratom use with 44 deaths are so poorly documented they could not pass basic standards for publication in any credible scientific journal, even as a letter or comment. Still, the FDA persists in basing major public policy recommendations and actions on this poorly documented and even misleading information. In fact, a scientific review of the FDA death reports revealed the following glaring deficiencies in the data used to demonize kratom:

**DUPLICATION OF REPORTED DEATHS.** At least two of the claimed deaths in the documents FDA released are clearly the same death, reported twice (FAERS ID No. 14449343 and FAERS ID No. 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 ID No. 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 ID No. 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.”

There can be no valid reason for the Commissioner to implicitly sign-off on such a glaring duplication of the same case. Perhaps it relates to the fact that the front pages of the two reports differ in immediately recognizable ways. ID No. 14449343 lists six substances found in the decedent’s body: 1. Bupropion HCl XL; 2. Dextromethorphan; 3. Diphenhydramine; 4. Ethanol; 5. *Mitragyna speciosa*, korthals; and 6. U-47700. In contrast, ID No. 14254346 lists only four substances: 1. Bupropion; 2. Dextromethorphan; 3. Ethanol; and 4. *Mitragyna Speciosa* (*Mitragynine*). The first case does in fact mention the additional substances Diphenhydramine and U-47700, but on the second page, along with toxicology measurements of 4 of the 6 substances. However, it appears that the FDA’s review of these cases didn’t extend beyond a cursory glance and counting of the number of substances listed on first page.

The documentation on numerous other reports is so shoddy and incomplete it is impossible to determine if there are additional duplicate reports in FAERS. There is a high likelihood of additional duplications because the FAERS database accepts reports from consumers, family members of decedents, health care professionals and various public health reporting agencies.

More importantly, FAERS relies on FDA staff to triage and enter the reported data into the relevant database fields.

- **EXCLUSION OF TOXIC DRUGS IN FAERS THAT DISTORTS THE DATA.** The FDA FAERS database entries for kratom-associated deaths excludes critical information available in the source data with the apparent intent of enhancing the illusion that kratom was involved in a fatality, e.g. the primary cause of death in FAERS ID No. 14449343 that the reporter, Endo Pharmaceuticals, gleaned from a published report from the American Association of Poison Control Centers<sup>xiv</sup> listed U-47700 (“PINK”) as the primary cause of death. The FDA completely omitted U-47700 in the FAERS Database entry for ID No. 1424346 among the substances detected in the decedent, despite PINK being listed by GlaxoSmithKline in the source report as the primary cause of that death determined by the authors of the same publication from which both source reports were derived. It is impossible to determine if this omission was made to deliberately make it more difficult to recognize the duplication of report 14449343, or if the purpose was to remove reference to the substance deemed to be the primary cause of death to enhance the role of kratom in the death. Either explanation is a serious breach of ethical responsibilities of the FDA.
  
- **DATA FROM SOURCE DOCUMENTS IS MANIPULATED, MISCHARACTERIZED OR COMPLETELY OMITTED IN FAERS.** There are repeated instances where FDA staff have altered the source report data, or completely omitted relevant data, in an apparent effort to support the FDA narrative that kratom is dangerous.
  - **FDA STRIPS CRITICALLY IMPORTANT SOURCE DATA OUT OF THE FAERS DATA.** IN FAERS ID No. 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 report<sup>xv</sup> 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.
  
  - **DEATHS FROM LOPERAMIDE ABUSE ATTRIBUTED TO KRATOM.** Two allegedly “kratom-associated” deaths (FAERS ID Nos. 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.<sup>xvi</sup> The evidence implicating loperamide as the primary cause of death included supertherapeutic 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 CNS 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.

- **A SUICIDE WITH NO KRATOM ASSOCIATION.** In a case reported in FAERS ID No. 14554565, a 53-year-old woman died several days after presenting to the ER with fulminant liver failure. Both the Emergency Room physician records and the American Association of Poison Control Centers’ published report <sup>xvii</sup> determined the primary cause of death was an apparent suicide from the intentional abuse of acetaminophen, with the report only noting only the possible consumption of both alcohol and kratom as no toxicology on these substances or autopsy was performed. There is no basis whatsoever for a conclusion that kratom had any role in this death.
- **A HOMICIDE WITH NO KRATOM ASSOCIATION – AND A DELIBERATE MANIPULATION OF THE REPORT.** The FDA includes a death report (FAERS ID No. 12639316) that consists only of 14 pages of completely redacted information with only the case number visible at the top of each page that the FDA claims is associated with kratom. Research conducted by Huffington Post’s Senior Reporter, Nick Wing, found the actual report on this fatality in another FDA database that revealed that the death was actually a homicide due to a gunshot wound to the chest. <sup>xviii</sup> The FDA clearly hid the details on this death in its release of the documentation on the 44 kratom associated deaths even though the information was publicly available on a separate database maintained by the FDA. The FDA provided no explanation on why they released a completely redacted death report to the public claiming it to be a kratom-associated without disclosing that it had been ruled a homicide from a gunshot wound to the chest, particularly when a full report on the homicide was available on another FDA database.
- **INCONSISTENT REPORTS BY FAMILY ON KRATOM USE WITH NO KRATOM IN TOXICOLOGY SCREEN.** In a death case report characterized as “voluntary” in FAERS ID No. 174035, the husband of the decedent reported his wife was using kratom. The medical reports showed the patient was “also known to have a history of heroin abuse and supposedly did not use heroin for 1-2 years.” The report specifically noted that it was unknown if the kratom product being used had been adulterated in any way, and, critically important, “the husband’s information on the patient was not consistent throughout the hospital stay.” Yet, the FDA reports this poorly-documented fatality as a kratom associated death. There is no toxicology data provided in this report that shows kratom was in the decedent’s bloodstream at the time of death, and it only took the word of the husband that his wife must have died from kratom use.

- **A DEATH FROM TOXIC CHEMICAL USED TO MAKE OPIOID TRAMADOL NOT ASSOCIATED WITH KRATOM.** In FAERS ID No. 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.
  
- **SUICIDE BY HANGING BY DECEDENT WITH LIFE-LONG BI-POLAR DISORDER.** In FAERS ID No. 12639556, the autopsy report revealed the cause of death was ligature hanging, and the manner of death as suicide. Prior to taking his own life, the decedent sent a suicide note to a friend. The medical record of the decedent showed he had suffered from bipolar affective disorder, depression, anxiety, insomnia, and multiple psychiatric hospitalizations. The decedent had also begun cutting himself and sought help from his family, who then had him admitted to an inpatient psychiatric hospitalization due to suicidal ideations, about one-week prior to his death. When he was released, the young man hung himself from a tree. The toxicology report showed eight different substances, including alcohol, benzodiazepines, Zolpidem, 7-Aminoclonazepam, Nordiazepam, Zolpidem, mitragynine, and Quetiapine present at the time of his suicide.
  
- **DEATH FROM DEEP VEIN THROMBOSIS AND CHRONIC POLYSUBSTANCE ABUSE.** In FAERS ID No. 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 vein thrombosis, with obesity; dilated cardiomyopathy and chronic polysubstance abuse were listed as contributing conditions.
  
- **DEATH IN GERMANY FROM INJURIES SUSTAINED IN FALL FROM A WINDOW.** FAERS ID No. 1342166 involves a death in Germany where a man fell from a window and sustained serious injuries but refused medical treatment. The toxicology report showed the decedent had ten substances in his blood, including both toxic and contraindicated drugs. The subject later lost consciousness and died of aspiration. The toxicology screen simply noted the presence of mitragynine as one of those ten substances.
  
- **NINE SWEDEN DEATHS FROM KRATOM ADULTERATED WITH O-DESMETHYLTRAMADOL.** Eight of the 44 deaths reported by the FDA to be associated with kratom are the Krypton deaths in Sweden in 2009. The FDA again failed to offer any clear reference to the 2011 Case Report that nine deaths actually were caused by a toxic

dose of *O*-desmethyltramadol in the adulterated kratom powder product. The FDA does not publicly acknowledge the role of the toxic dose of *O*-desmethyltramadol in these deaths.

- Source documents released for FAERS ID Nos. 8121551, 8121559, 8121566, 8124388 8124494, 8132531, 8083892, and 8121536 all specifically referenced the presence of the adulterant *O*-desmethyltramadol.
  - None of the FAERS data for these deaths lists *O*-desmethyltramadol.
  - None of the FAERS data for these deaths lists Sweden as the country where the deaths occurred, nor is there a reference to the literature source despite the citations to the Kronstrand, et.al., Case Report on the nine deaths being attributable to a toxic dose of *O*-desmethyltramadol.
  - It would have been virtually impossible for anyone with even the most basic knowledge of pharmacology **not** to conclude that the primary if not sole cause of death in each of these cases was *O*-desmethyltramadol if they had read either the source report(s) or the Kronstrand reference cited prominently in each of the reporters' submissions.
  - Yet the FAERS database summaries substituted tramadol for *O*-desmethyltramadol, not just once, but in each of the cases entered into database.
- **None of the FDA reported 44 deaths document any specific cause that is consistent amongst the cases or that can be linked specifically to kratom; a vast majority of the cases document polydrug use by the decedent and, in a few cases, the possible use of adulterated kratom products. In most cases, the cumulative contributions of multiple drugs and interactions between drugs are not even considered by FDA.**

The FDA cannot legitimately base any scientifically valid conclusion of a causal relationship between kratom consumption and death on opinion and speculation. The FAERS database records of kratom deaths shows numerous reports from grieving family members implicating kratom. No matter how strong their convictions, these individuals lack the objectivity to consider the totality of circumstances surrounding a death and most frequently lack the training and knowledge of the decedents' complete medical history and post mortem findings to make such a determination. While such reports should not be dismissed out of hand, it is incumbent upon the FDA to obtain independent investigative, medical, autopsy and toxicology reports before it disseminates critical information to the public or makes a scheduling recommendation to the DEA.

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## THE FDA USE OF FAERS DATA TO RECOMMEND SCHEDULING IS “JUNK SCIENCE” AND SHOULD BE REJECTED.

The FDA FAERS database cites a number of disclaimers warning about how the data cannot be relied upon for any scientific conclusions, including:

1. **“Duplicate and incomplete reports are in the system:** There are many instances of duplicative reports and some reports do not contain all the necessary information.”
2. **“Existence of a report does not establish causation:** For any given report, there is no certainty that a suspected drug caused the reaction. While consumers and healthcare professionals are encouraged to report adverse events, the reaction may have been related to the underlying disease being treated, or caused by some other drug being taken concurrently, or occurred for other reasons. The information in these reports reflects only the reporter's observations and opinions.”
3. **Information in reports has not been verified:** Submission of a report does not mean that the information included in it has been medically confirmed nor it is an admission from the reporter that the drug caused or contributed the event.
4. **Rates of occurrence cannot be established with reports:** The information in these reports cannot be used to estimate the incidence (occurrence rates) of the reactions reported.

In the DEA’s August 31, 2016 Notice for the “Temporary Placement of Mitragynine and 7-Hydroxymitragynine into Schedule I,” reference is made to “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.”<sup>xix</sup>

In FDA Commissioner Scott Gottlieb’s statement on November 14, 2017 announcing a Public Health Advisory on kratom and referencing 36 deaths associated with kratom, Dr. Gottlieb made the following statement:<sup>xx</sup>

The FDA is aware of reports of 36 deaths associated with the use of kratom-containing products. There have been reports of kratom being laced with other opioids like hydrocodone. The use of kratom is also associated with serious side effects like seizures, liver damage and withdrawal symptoms.

None of the FAERS disclaimers was referenced in the statement by Dr. Gottlieb, and the statement clearly is intended to alarm the public – and the audience of public policy makers at the federal, state, and local level. On its face, those claimed “36 deaths” associated with kratom are little more than uncorroborated, undocumented, and duplicative reports that have no place in determining any important Public Health Advisory to the American people, which should be based on reliable and verified science.

A review of the FDA FAERS data on the referenced death reports the FDA relied upon in issuing the Public Health Advisory on kratom confirmed that all of the disclaimers warning of the deficiencies in the accuracy of the data were applicable in every single one of the claimed kratom associated deaths. There are no credible conclusions that can or should be drawn from these uncorroborated reports unless and until a full investigation using accepted scientific methods to verify the association that is alleged in these deaths.

Yet, Dr. Gottlieb doubled-down on promoting his “Junk Science” on kratom in his February 6, 2018 statement when he increased the number of reported deaths to a total of 44.<sup>xxi</sup>

Now, I’d like to share more information about the tragic reports we have received of additional deaths involving the use of kratom. Looking at the information we have received – including academic research, poison control data, medical examiner reports, social science research and adverse event reports – we now have 44 reported deaths associated with the use of kratom. This is an increase since our November advisory, which noted 36 deaths associated with these products. We’re continuing to review the newly received reports and will release those soon. But it’s important to note that these new reports include information consistent with the previous reports.

The only part of Dr. Gottlieb’s statement about the new reports that can be verified is his claim that “these new reports include information consistent with the previous reports.” However, the common consistency is that the reports are equally unreliable in validating any scientific conclusions about kratom being dangerous.

Dr. Gottlieb attempted to address the deficiencies in the FAERS data by disclosing the lack of specific information in “many of the cases,” but his statement opened up a whole new set of questions about why the FDA is selectively investigating some deaths and not others.

Today, we’re releasing the reports of the 36 deaths we referenced in November. These reports underscore the serious and sometimes deadly risks of using kratom and the potential interactions associated with this drug. 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.

On one hand, Dr. Gottlieb acknowledges that many of the reports could not be fully assessed because of the limited information provided, but he then cites a new case where, according to the report, one death had “no known historical or toxicological evidence of opioid use, except for kratom.” Dr. Gottlieb indicated the FDA was continuing to investigate that report, but it ignores the fact that none of the other death reports was being investigated by the FDA to verify the accuracy of the report.

Indeed, in many cases that had previously been reported in the published scientific literature following evaluation of the available facts and circumstances, including toxicology, autopsy and investigative reports, the FDA simply dismissed the fact-finders' expert analysis and conclusions on cause of death and inserted their own conclusion of kratom causation without so much as a footnote.

The FDA has an army of scientists, investigators, analysts, and lab technicians who are fully capable of conducting a rigorous scientific review of each of the alleged deaths associated with kratom. Such an effort may not be necessary if the FDA simply intended for the public to make their own assessment of risks of using kratom by reviewing the data on the FAERS database, but when the FDA determines to use the FAERS information to formally issue a Public Health Alert, and uses that same deeply-flawed data as the basis for recommending the scheduling kratom as a Schedule I substance under the CSA, removing kratom from the marketplace and essentially criminalizing any future use, the FDA has a clear obligation to base that recommendation on real science, not an amalgamation of duplicative, uncorroborated, and woefully deficient records of those deaths.

While mistakes in data entry into the FAERS database may be attributed to clerical error, and the lengthy disclaimer cautions against drawing conclusions on causation, incidence or frequency of association between a drug or substance reported in conjunction with an adverse effect in FAERS, the Commissioner's personal statements that FDA had received reports of 36 and subsequently 44 deaths associated with kratom, and the implication that such reports were credible, must be held to a higher standard. It should rightfully be expected that allegations from the leader of the agency that includes the most highly regarded expertise on food and drugs in world would have been thoroughly vetted, analyzed and evaluated before they were disseminated through public address and press release. Those expectations have not been fulfilled. Instead, the documents released by FDA and relied upon by the Commissioner, are riddled with inconsistencies and direct contradictions to the position espoused by the Commissioner and summarized in the FAERS database. Instead of documenting relevant relationships between 44 reported deaths and consumption of kratom, the documents reveal a lack of honesty and a complete disregard for objective scientific inquiry. We can but hope that Dr. Gottlieb failed to bring his A team to the meeting on kratom.

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## **THE FDA USE OF THE SWEDISH DEATH REPORTS ON KRYTON TO IMPOSE IMPORT ALERTS IS DECEPTIVE**

The FDA has targeted kratom for prohibition and has repeatedly circulated reports that can at best be described as incomplete, in an effort to associate nine deaths that occurred in Sweden over a 12-month period beginning in 2009 as its bedrock evidence of kratom's threat to public safety. The FDA's first Import Alert on kratom in 2012 (#54-15), and subsequent import alerts in 2014 (#54-15) and 2015 (#66-41) <sup>xxii</sup>, included the justification that "scientific literature disclosed serious concerns regarding toxicity of



kratom in multiple organ systems.” Yet FDA did not disclose the scientific literature it relied on to reach that conclusion.

The Dietary Supplement Health and Education Act of 1994 (DSHEA) places the burden on FDA to demonstrate that a dietary supplement is unsafe before it can remove a product from the marketplace. In a perverse twist, when FDA invoked its authority to impose an Import Alert on kratom, it shifted the burden to the importer to demonstrate safety. FDA can impose an Import Alert and a “Detention Without Physical Examination” order with a much lower evidentiary burden than required for demonstrating that dietary supplements in the market are unsafe. Import Alerts identify companies, which are placed on an FDA “Red List”. If a company is placed on the FDA’s Red List, it cannot be removed until sufficient evidence is produced by the company to demonstrate that the imported product(s) meets FDA requirements. A simple allusion to scant scientific associations, allegations and suggestions is sufficient to Red List kratom importers, but a much higher level of proof is required by the importer to have their product released.

However, when FDA issues an Import Alert through misrepresentation, deception and willful disregard of relevant evidence that is inconsistent with its established narrative, the exercise of that authority is illegitimate and must be voided.

Despite its statutory obligation to ensure and maximize the quality, objectivity, utility, and integrity of the information it disseminates<sup>xxiii</sup>, the FDA has either ignored or deliberately withheld material scientific information that contradicts the conclusion that the nine deaths in Sweden resulted from the use of kratom.

- The FDA relied on autopsy and toxicology information from the nine Swedish deaths in its 2012 Import Alert on kratom and subsequent updates.
- The FDA perpetuated half-truths and mischaracterizations of the Swedish deaths in the report provided to the Drug Enforcement Administration to justify its own desire to schedule the two primary alkaloids of the botanical plant kratom, mitragynine and 7-hydroxymitragynine, as Schedule I substances under the Controlled Substances Act (CSA) in its initial recommendation to the DEA.
- The FDA included Swedish deaths amongst the group of 36 deaths allegedly “associated with the use of kratom” in issuing its Public Health Advisory on kratom on November 14, 2017. Based on statements to media by FDA Commissioner Scott Gottlieb the inaccurate representation of these deaths was included in the FDA’s recommendation for DEA to publish a **new** Notice of Intent to place kratom and/or its constituent alkaloids into Schedule I substance under the CSA.

The critical science that has been excluded, referenced in passing without proper acknowledgment of its significance, or dismissed entirely as irrelevant was the more detailed analysis of these deaths published in May 2011 in the Journal of Analytical Toxicology.<sup>xxiv</sup> The peer-reviewed Case Report included

important scientific information that should have been disclosed and appropriately considered by the FDA in both its 3-Factor Analysis supporting a recommendation to schedule kratom in 2016, and in the 8-Factor Analysis believed to have been prepared by FDA and submitted to DEA in November 2017 to justify scheduling of kratom.

The Kronstrand Case Report concludes:

“We believe that the addition of the potent mu-receptor agonist *O*-desmethyltramadol to powdered leaves from Kratom contributed to the unintentional death of the nine cases presented. We conclude that intake of the herbal blend ***Krypton*** is not as harmless as it often is described on internet websites, and the large packages sold increase the risk for unintentional overdose.”<sup>xxv</sup> (emphasis added).

Notably, this Case Report detailed the following observations:

1. Each of the nine decedents had toxic or near toxic doses *O*-desmethyltramadol in peripheral blood, suggesting overdose on *O*-desmethyltramadol alone was sufficient to cause death.<sup>xxvi</sup>
2. None of the decedents had unmodified tramadol or *N*-desmethyltramadol in their blood, excluding the possibility that they consumed analgesic medication containing tramadol.<sup>xxvii</sup>
3. Each of the decedents had consumed at least one other psychoactive substance in addition to mitragynine and *O*-desmethyltramadol; as many as six other substances and alcohol were detected in blood from these individuals.<sup>xxviii</sup>
4. Mitragynine was detected, but its contribution to death could not be ascertained due to a lack of reference data on mitragynine blood concentrations at the time.<sup>xxix</sup> Blood concentrations ranged from 0.02 to 0.18 µg/g, with only two exceeding 0.10 µg/g.<sup>xxx</sup>

Significantly, after publication of the Kronstrand Case Note, Trakulsrichai et al. published the first report of blood concentrations of mitragynine in human subjects following consumption of unadulterated kratom tea.<sup>xxxi</sup> In this study, tea prepared from low doses (about 1-3 g/dose) of kratom containing 6.25 to 23 mg mitragynine, resulted in maximal blood concentrations of 0.0185 to 0.105 µg/mL mitragynine in these subjects without serious side effects.<sup>xxxii</sup> Seven of the nine decedents in Kronstrand had blood concentrations within this clearly non-toxic range.

The nine deaths in Sweden that the FDA repeatedly uses as a justification to ban kratom, were actually caused by an adulterated kratom product laced with a toxic dose of *O*-desmethyltramadol. Neither FDA nor DEA has taken any action to schedule *O*-desmethyltramadol.

Kratom consumers advocate for use of pure, unadulterated whole leaf kratom and assistance from the federal government in ensuring that the kratom available for consumption in the U.S. is not contaminated with harmful substances like *O*-desmethyltramadol. The FDA has the authority to provide this needed assistance under the Federal Food Drug and Cosmetic Act (FDCA), which prescribes criminal penalties for the introduction into interstate commerce of adulterated or misbranded foods, drugs, cosmetics, or medical devices; and is an enforcement tool the FDA currently has at its disposal to remove such products from the marketplace.<sup>xxxiii</sup> Instead, FDA has abandoned kratom users and all those who might benefit from kratom, by insisting that kratom itself is deadly, despite mounting evidence to the contrary from its own archives, which it has deliberately hidden from public view.

The FDA, in its self-proclaimed war on kratom, has engaged in a clear pattern of deceit in its public statements to support both its Import Alerts on kratom and its recommendations to the Drug Enforcement Administration (DEA) to schedule the key alkaloids of kratom, mitragynine and 7-hydroxymitragynine, as Schedule I substances under the Controlled Substances Act (CSA). The effect of these misleading and often false public statements by the FDA on kratom has resulted in significant policy decisions that reach into states and local communities across America.

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

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

<sup>iv</sup> See Public Database entries for FAERS ID Nos. 8121536, 8121551, 8121559, 8121566, 8124388, 8124494, and 8132531 viewed by querying the FAERS Public Dashboard at <https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adversedrugs/effects/ucm070093.htm>.

<sup>v</sup> Reviewed in Henningfield *et al.*, “The abuse potential of kratom according the 8 factors of the controlled substances act: implications for regulation and research,” *Psychopharmacology (Berl)*. 23:573-589 (2018).

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- xv Gummins, *supra*.
- xvi Bishop -Freeman et al. “Loperamide-Related Deaths in North Carolina,” *J Anal Toxicol* 40:677-86 (2016).
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- xxv *Id.* at 247.

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<sup>xxvi</sup> See *id.* at Table II; p. 246, right column, first full paragraph under “Discussion” (suggesting 0.5 µg/g peripheral blood is a toxic if not fatal concentration of *O*-desmethyltramadol).

<sup>xxvii</sup> See *id.* at p. 246, right column, second full paragraph.

<sup>xxviii</sup> *Id.*, Table II.

<sup>xxix</sup> *Id.*, paragraph bridging pp. 246-47.

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