A Reply to CDC Report on Unintentional Drug Overdose Deaths with Kratom Detected (2019); appropriate regulation of kratom and improved postmortem testing protocols are needed immediately

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The findings of the Centers for Disease Control (CDC) report (Olsen et al.) *(1)* add to the needed public understanding of kratom's actual role in reported overdose deaths. Unfortunately, media outlets have badly misstated the data on kratom's role in the reported deaths. This is evidenced by attention-grabbing headlines such as "Herbal drug kratom linked to almost 100 overdose deaths, CDC says" *(2)*; "More deaths have been associated with kratom than previously known" *(3)*; and "CDC Study Shows Kratom-Linked Overdose Deaths" *(4)*.

In summarizing their assessment of unintentional drug overdose deaths with kratom detected, the CDC report offered two important policy recommendations: (1) the type and number of substances detected in kratom-involved deaths can inform overdose prevention strategies; and (2) documentation of postmortem toxicology testing protocols is needed to further clarify the extent to which kratom contributes to fatal overdoses. Both recommendations should be implemented. The data also strongly argue for an appropriate level of regulation of kratom that is not currently being pursued by the FDA.

A proper understanding of the type and number of substances detected in the postmortem toxicology screens of decedents would allow for the identification of substances that actually cause a death and, importantly, exclude substances that do not. The CDC report showed that in death cases where kratom was found in a toxicology screen, fentanyl and fentanyl analogs were listed as the "cause of death for 65.1% of kratom-positive decedents and 56.0% of kratom-involved decedents." Heroin was the second most frequent substance listed as the cause of death in kratom-positive decedents at 32.9%; benzodiazepines at 22.4%; prescription opioids at 19.7%; and cocaine at 18.4%. Under current protocols, multiple substances can be listed as a cause of death, therefore the substances are not mutually exclusive and a primary cause need not be identified. However, the potentially deadly toxicity profiles of fentanyl, heroin, benzodiazepines, prescription opioids, and cocaine are well-documented in published literature whereas the toxicity of kratom is not.

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The CDC data does not report whether the decedents ingested pure, unadulterated kratom in conjunction with dangerous substances or used an adulterated kratom product. The National Institute on Drug Abuse (NIDA) has documented that polydrug use or adulterated kratom product deaths are properly attributable to the toxicity of the multiplicity of co-consumed drugs or adulterants present whether intentionally consumed as a consequence of an individual's addiction or the result unknowingly using a product adulterated with a toxic dose of a dangerous substance. That is exactly what happened in the case of 9 deaths repeatedly cited by the FDA as kratom-associated deaths despite the peer-reviewed, published Case Report showing all 9 of those deaths were caused by the kratom product (sold as "Krypton" in Sweden) being spiked with a toxic dose of the powerful mu-receptor agonist *O*-desmethyltramadol *(5).*

Absent appropriate FDA interdiction of adulterated kratom products, it is clear that actions by Utah and Georgia in passing the Kratom Consumer Protection Act (KCPA) (similar legislation is actively being considered in many other states) will reduce the deliberate adulteration of kratom products and provide consumers with clear labeling so they know the content of kratom products they purchase as dietary ingredients or herbal supplements. These new laws are based on science, respond to the clear evidence of deaths caused by kratom adulteration, and provide a reasonable regulatory framework to protect consumer access to safe kratom products.

Here are the top-line conclusions that the CDC data actually supports:

- The 91 "kratom-involved" deaths found multiple substances detected in "almost all decedents," with fentanyl and fentanyl analogs as the most frequently identified co-occurring substances. These findings support the NIDA review of the FDA-claimed 44 kratom deaths, which concluded that "most kratom associated deaths appear to have resulted from adulterated products or taking kratom along with other potent substances." The public policy mandate from this data is that the FDA should use its existing statutory authority to interdict manufacturers and marketers who deliberately adulterate kratom products with dangerous substances that cause death.
- Medical examiners and coroners are incorrectly reporting kratom-involved deaths as deaths caused by kratom. The lack of a consistent postmortem testing protocol to accurately pinpoint the extent kratom contributes to a death has exacerbated the grossly inaccurate and overstated FDA public narrative on the potential dangers of kratom. There is a critical need for the publication of standards for postmortem toxicology testing to avoid inaccurate findings by medical examiners and coroners, such as kratom allegedly being the cause of death and comprehensively identify substances that are not detected in routine testing for drugs of abuse.
- The report accurately states that "kratom is not an opioid" and notes that nonopioid substances are included in the State Unintentional Drug Overdose Reporting System (SUDORS), but the system records all substances testing positive on postmortem toxicology testing (including those that did and did not contribute to death). In fact, kratom critically differs from conventional opioids on the two signature features of conventional

> opioids that contribute to the opioid epidemic: It does not cause the powerfully addicting brain rewarding effects or the lethal respiratory depressing effects of conventional "narcotic-like" opioids*" (6) (7).* However, the repeated claims by the FDA that kratom is an opioid and advisories claiming kratom has caused overdose deaths have clearly contributed to incorrect determinations by medical examiners and coroners that the presence of even the tiniest amount of kratom in postmortem toxicology screens was the cause of a death.

In recommending to the Drug Enforcement Administration (DEA) to control two of kratom's alkaloids, mitragynine (MG) and 7-hydroxymitragynine (7-HMG), as Schedule I substances the FDA has failed to meet the evidentiary burden required by the Controlled Substances Act (CSA). FDA's repeated public statements inflating risks associated with kratom use has contributed to inaccurate and, in some cases, clearly incorrect hypotheses now treated as facts that have served to materially mislead coroners, medical examiners, and other public policy makers about the alleged dangers of kratom use.

Clearly, if kratom is adulterated with substances like fentanyl, heroin, benzodiazepines, cocaine, and other prescription opioids as set forth in the CDC report, adulteration can lead to overdose deaths. Those deaths would result if any other common consumer product (coffee, soft drinks, daily vitamins, or health foods) were adulterated with these substances. The only reason we do not see CDC reports on "coffee-involved", "diet coke-involved", or "vitamin-involved" deaths related to drug overdoses is that coroners and medical examiners accept the scientific consensus on the amounts of caffeine and vitamins that are toxic and the effects of those toxicities. Coroners and medical examiners do infer cause of death from the presence of any amount of MG or 7-HMG because the FDA has made repeated scientifically invalid pronouncements that kratom is a potentially deadly opioid whose mere use can cause death.

Kratom, given its centuries-long history of safe consumer use in Southeast Asia where no kratom-caused overdose deaths have been reported, kratom should not be causally linked to a death because it has been used concurrently with other substances, or because it was deliberately adulterated with a toxic dose of a dangerous substance until there is unambiguous toxicological data to indicate causality between kratom-only exposure and a fatality.

It is also clear from the data that polydrug users regularly consume many substances concurrently, and it is only because kratom has been added to the toxicology screens that it is implicated more than other substances also used by those suffering from addictions. Importantly, there is no data that supports the FDA assertion that kratom causes overdose deaths. The NIDA review and the CDC report directly contradict the FDA claims that it does.

The CDC report highlights a critical deficiency in postmortem toxicology testing protocols when they reported that there were 7 deaths where kratom "was the only substance to test positive on postmortem toxicology, although the presence of additional substances cannot be ruled out." To illustrate why no one can responsibly conclude that there were 7 deaths where kratom was the only substance in the bloodstream, the CDC report cites the Gershman et al. commentary published in

the New England Journal of Medicine that looked at 15 deaths that coroners in Colorado had determined included four deaths "reported to involve mitragynine only, and coroners attributed each to mitragynine only.*(8)"* When the investigators looked at those 4 deaths attributed to kratom toxicity alone, they performed a more comprehensive toxicology analysis with tandem mass spectrometry for the 3 cases for which residual blood was available.

These investigators concluded that of all 15 kratom-related deaths, 14 deaths "clearly involved multiple drugs." For the remaining case, residual blood was not available for confirmatory testing to determine if there were other substances involved in that death. That is the reason the CDC report correctly concludes that documentation of postmortem toxicology testing protocols is needed to clarify the extent to which kratom contributes to fatal overdoses and the extent to which other substances are unequivocally excluded.

This is a very important issue in the context of FDA reports of kratom associated deaths where the FDA has and continues to use such incomplete and inaccurate data to inappropriately inflame the public view of kratom in furtherance of their agenda to have the DEA classify kratom as a Schedule I drug. Given that currently available peer-reviewed and published research demonstrates that kratom is not a candidate for scheduling under the CSA criteria, public safety would be better served by the FDA appropriately regulating kratom under the current framework for dietary ingredients and herbal supplements.

This ongoing and inaccurate FDA narrative on the threats posed by kratom has materially misled public policy makers in 6 states to ban kratom and is fueling kratom ban proposals in other states and local jurisdictions throughout the country. The regulatory framework for kratom must be grounded in accurate scientific evidence, consistent with statutory constraints for regulating dietary ingredients and herbal supplements. This can and should be the primary role of FDA with respect to regulating kratom so as to better serve the public health *(9) (10).*

The need for appropriate regulation on kratom was highlighted in the "*Commentary: Why We Should Regulate Kratom*" in U.S. News and World Report (11) in March 2019 observing that "[w]henever products like kratom are not regulated, there is a risk for adulteration and contamination. There have been some instances of products being sold as kratom that are adulterated with potentially dangerous substances in order to artificially increase quantity and weight." It is also true that some adulterations are made simply to enhance the psychotropic effects of kratom to give the user a "high" that is not achieved by consuming the natural kratom plant – all to increase sales and enrich themselves at a significant cost to public safety.

CONCLUSIONS

Overdose prevention strategies are a critical national health priority that must be premised on scientific evidence. NIDA has demonstrated its commitment to identifying non-addictive pain management options to reduce opioid use by funding studies on the potential for kratom to treat opioid misuse and physical dependence *(12).* The FDA's unjustified scheduling recommendation

for kratom will impede necessary research, and the proposed scheduling would increase the risk of more opioid-related deaths. A ban on kratom would force current kratom users to consider more dangerous options, including dangerously addictive and potentially deadly opioids or equally deadly adulterated kratom products that are freely available on the Internet.

Postmortem toxicology testing protocols must be standardized to provide accurate and actionable reports on the contribution of substances, including kratom, to a death. The consequences of inaccurate data on kratom-associated deaths clearly has contributed to the FDA's persistent attacks on kratom; the decisions of 6 states who have banned kratom; the decision by some local jurisdictions to impose local bans on kratom; and the rampant misinformation disseminated to the public about the alleged risks of kratom use.

The provisions of the Kratom Consumer Protection Act presently enacted in Utah and Georgia (with more states likely to follow) should be considered by the U.S. Congress because it provides protections for consumers from adulterated kratom products and requires labeling to ensure disclosures of the contents of kratom products available to purchase by consumers.

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DISCLOSURES

Jack E. Henningfield provides consulting support through PinneyAssociates, on the development of abuse potential assessments and eight factor analyses according to the Controlled Substances Act pertaining to the development and regulation of new medicines and formulations for pain, addiction, epilepsy, and other central nervous system disorders, and also to the dietary industry including the American Kratom Association (see more at www.pinneyassociates.com).

Jane Babin is a California Attorney, registered to practice before the U.S. Patent Office, who represents clients in the biotechnology, pharmaceutical, chemical and other industries in patent, trademark and licensing matters. She has counseled the American Kratom Association on a variety of legal and scientific issues, with and without compensation. The views expressed in this letter are her own and she has received no compensation for her contributions to this letter.

Oliver Grundmann: The views expressed in this document by Dr. Oliver Grundmann do represent his personal and professional views and not the views of his employer, the University of Florida. He did not receive any funding for contributing to this document.

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