Kratom Science Brief to Help Inform Maryland Legislation Pertaining to SB0147 (Sen. Young) and HB0283 (Del. Kerr)

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I would like to provide some background on the current state of kratom science and its place in public health, with a focus on implications for Maryland in the context of the opioid epidemic. I'd also like to review how our current knowledge can help determine the most appropriate way to regulate kratom in order to minimize risks to kratom consumers, while contributing to their health and wellbeing, as well as to serve public health.

By way of background and disclosure, I have been involved in the science, regulation, and public health policy, related to a broad range of substances and products since the early 1970s and these include alcohol, caffeine, cannabis, opioids and many other drugs of abuse, as well as medicines that have abuse related issues and/or are used as treatments for substance abuse and addiction.

During the 1980s and 1990s I headed the Clinical Pharmacology laboratory of the National Institute on Drug Abuse (NIDA) and led research across a wide range of substances including opioids, cannabis, cocaine and other stimulants, and a myriad of other drugs. I also worked NIDA, FDA and DEA on drug scheduling issues. I have published nearly 450 papers on these topics and contribute to numerous federal and international reports.

I consult on pharmaceutical development and have contributed to the research and/or approval of for most treatments approved for drug, alcohol and nicotine addiction since the 1980s and have advised NIDA, CDC, FDA, the World Health Organization, and other organizations since then. I advise the American Kratom Association on kratom science. That began as a pro bono effort when DEA proposed placing kratom in Schedule I in 2016.

My efforts with respect to kratom were focused on setting the record straight because my colleagues and I at PinneyAssociates (a team with extensive opioid and other drug experience) believed that DEA and FDA were wrong on the science and policy, and worse, that banning kratom would result in the quick establishment of a deadly kratom black market. We were frankly surprised, but thankful that then DEA Administrator Chuck Rosenberg withdrew the proposal. I discussed this with senior DEA staff who said that the comments from the public and scientists along with other information indicated that many people were using kratom to abstain from opioids and they did not want to risk sending them back to opioids. Surprisingly, a year later FDA again requested DEA to Schedule Kratom. Thankfully, and unusually, DEA has not acted on FDA's request.

First, please allow me to provide a few basic kratom facts:

- Kratom is in the coffee family, not the opium poppy family – it is not an opioid by nature, chemical structure, or listing in the US Controlled Substances Act or the major United Nations international drug control conventions.
- It produces caffeine like stimulation and many users report using kratom as a morning pick-me-up and to help maintain alertness, focus and productivity in the workplace – these are not typical uses of opioids.
- Most kratom consumers do not use kratom for its opioid like effects but rather for one or more other effects including its use as a morning pick-me-up in place of caffeinated beverages, increased focus and work enhancing effects, modulation of feelings of anxiety and depression, relaxing effects and

sometimes aid to getting to sleep, however, its use in place of opioids by about 1/3 or more kratom consumers gives special urgency to appropriate regulation.

- Kratom, like coffee contains many alkaloids, most of which have little pharmacological or toxicological activity. Its primary alkaloid, common to most kratom products is mitragynine. Mitragynine is not an opioid by nature, chemical structure, or overall profile of effects.
- Mitragynine mimics some of caffeine's alerting effects and also mimics some opioid effects like reducing pain and diarrhea, **BUT** with little of the signature powerful brain rewarding addictive effects and lethal respiratory depressing effects of heroin-like opioids.
- Kratom does provide some of the pain relieving and constipating effects of opioids and can help relieve opioid withdrawal but it is not approved for this or any therapeutic use by FDA.
- It is possible to develop some dependence on kratom and this is reported by some heavy kratom users, however, such people surveyed in the US and in studies in South East Asia report that it is generally far milder than opioid dependence and that unlike opioids, kratom helps them function in the workplace and home. In this sense it is more analogous to caffeine than to opioids.
- NIDA is supporting research on mitragynine analogs as potential future medicines for pain, addiction and other disorders. But potential medicines are likely a decade or more away.
- There are an estimated 10-16 million kratom users in the US. Surveys indicate that the population of kratom users is dominated by adults aged 30-50 with lower rates of use among younger and older persons. Their demographics indicate that most have at least some college education, are married or in monogamous relationships, and have health care.
- These respondents report that they use kratom for health and well-being and that for them, kratom is either more effective, better tolerated with respect to side-effects, and/or more affordable than available pharmaceuticals. For many people, kratom is a path away from opioids, whether for managing pain or addiction.
- The surveys indicate a compelling argument for regulation rather than a ban because kratom consumers are rightly terrified that a ban that would leave them only with black market products or a return to opioid use and risk of overdose. Mortality data show that the overdose risk of opioids is at least one thousand times greater than for kratom.
- **The opioid crisis has hit Maryland particularly hard:** 2nd or 3rd among all states in per capita fentanyl deaths in the past few years, and 6th, 7th or 8th in per capita other opioid overdose and all opioids combined for a total of approximately 2000 opioid overdose deaths in 2017 (CDC and NIDA reports).
- **Kratom is an informal asset in addressing the opioid epidemic and it is helping people who find formal treatment ineffective, inaccessible or unacceptable.** I estimate that Maryland's population of approximately 6 million likely includes approximately 180,000 adult kratom users of which surveys suggest that 20-30% or 36-54 thousand, are at reduced risk of opioid overdose due to their use of kratom in place of opioids. These are estimates based on import and sales data and four national internet surveys as we do not have valid state or nationally projectable data.
- **Two misconceptions that are often reported in the general media.**
    - **Headline: "CDC reported 91 kratom over dose deaths"** In actual fact, CDC stated that this is what medical examiners stated and then CDC pointed out that most of the deaths for which there were data involved other drug use, and the few that did not find other drug use might have missed other drugs because they did not properly test for them. The CDC made no conclusion about how many deaths (if any) in which kratom was reported by medical examiners could actually be attributed primarily if at all to kratom. From CDC report: "Kratom was determined to be a cause of death (i.e., kratom-involved) by a medical examiner or coroner for 91 (59.9%) of the 152 kratom-positive decedents, including seven for whom kratom was the only substance to test positive on postmortem toxicology, although the presence of additional substances cannot be ruled out (4). In approximately 80% of kratom-positive and kratom-involved deaths in this analysis, the decedents had a history of substance

misuse, and approximately 90% had no evidence that they were currently receiving medically supervised treatment for pain. Postmortem toxicology testing detected multiple substances for almost all decedents." (see CDC. O'Malley Olsen et al, 2019, report at: https://www.cdc.gov/mmwr/volumes/68/wr/mm6814a2.htm). This does not mean kratom has not contributed to any drug overdose deaths but the media reports misrepresent the CDC article and there is no question that the risk of kratom is far lower than carried by opioids and other drugs that it is substituted for by many people.

- **Headline: "Kratom-related liver injuries on the rise in the US"** Some articles based on Navarro et al abstract, 2019 titled: "Increasing episodes of hepatotoxicity in the drug induced liver injury network associated with kratom, a botanical product with opioid-like activity" state that kratom carries liver disease risk as though this was an established fact. In actual fact, we do not know if pure kratom leaf material or any of its mitragynines carry risk of liver disease, but we can't rule it out either. Two of the problems with reports, such as that by Navarro et al. are that first, because of restrictions on kratom access in some states, and the lack of regulation to ensure pure kratom in most other states, some kratom is contaminated or adulterated by substances that might contribute to liver disease and other health risks. Secondly, and in my opinion, most importantly, is that many kratom users, especially heavier users, use kratom because of pain and other conditions that led to their likely heavy use and sometime decades long use (as reported in comments to DEA and public testimony) of acetaminophen and other drugs that are known to carry serious risks of liver disease. Sorting out the actual risk, if any, of kratom and is so what should be mentioned in the labeling of regulated kratom will take actual evidence as we have with acetaminophen and which can then be appropriately communicated to consumers.

Kratom regulation has potential to serve Maryland's kratom consumers and contribute to public health whereas Schedule I placement seems more likely to adversely affect public health. I believe that at the national level, the foregoing were considerations by DEA in its 2016 withdrawal of its proposed Schedule I listing of mitragynine and 7-hydroxymitragynine, and its inaction on FDA's October, 2017 recommendation to schedule these alkaloids.

Schedule I banning is predicted by surveys and more than 20,000 public comments to the Drug Enforcement Administration (see below – Coe et al., 2019; Grundmann, 2017, Garcia et al. 2020, Henningfield, et al., 2018) to drive some people using kratom in place of opioids back to the far deadlier opioids, and to create a kratom black market that is likely to include kratom products adulterated with fentanyl and other substances. I believe Maryland's residents would be best served by efforts to ensure adult use but with a regulatory framework to discourage inappropriate use including use by young people and to address kratom's main health risks which are related to impure and adulterated products.

Efforts like a minimum age of purchase of 21 should contribute to discouraging use by young people but would have little impact on people who use kratom for health and well being because the vast majority of kratom consumers are at older than 21.

Conversely a ban on kratom, would predictably result in the emergence of a black market. This is predicted by surveys that have asked adult kratom users what they would do if kratom was banned. Many said they would find other sources because they prefer it to convention medicines either because for them it works better or has fewer side-effects of concern. This include adults with chronic pain who are desperate to get off opioids as well as people with chronic pain for whom opioids were beneficial but can not longer get opioid prescriptions. For people with opioid use disorder, kratom reaches many people who find conventional treatments ineffective, inaccessible, or unacceptable. They are rightly terrified of a kratom ban and deadly black market.

I can provide scientific articles including recent peer-review publications as sources of these facts. I will be pleased to do whatever I can to provide science and regulatory perspective to help you find a path to protect kratom consumers in Maryland, address the opioid epidemic, and minimize unintended consequences of kratom availability.

Thank you for the opportunity to provide this information.

Key publications relevant to these opinions – available by internet or from myself upon requests.

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Swogger, M.T. and Walsh, Z., Kratom use and mental health: A systematic review. Drug and Alcohol Depend, 2018. 183: p. 134-140.

Yue, K., Kopajtic, T.A., and Katz, J.L., Abuse liability of mitragynine assessed with a self-administration procedure in rats. Psychopharmacology (Berl), 2018. 235(10): p. 2823-2829.