Pinney Associates

Leading Edge Kratom Science

Addressing Abuse Potential, Safety, Patterns of Use, Reasons for Use, and New Studies of Mitragynine, 7-hydroxymitragynine, and Other Kratom Alkaloids

September 2, 2021

An annotated update of the 2018 published review article:

The Abuse Potential of Kratom According to the 8 Factors of the Controlled Substances Act:

Implications for Regulation and Research

By

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This report was developed by

Dr. Jack Henningfield and colleagues at PinneyAssociates

For the American Kratom Association to inform and update policy makers, health and regulatory officials, and public health and medical experts on kratom safety and abuse potential

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Acknowledgement and disclosure. This update of the Henningfield et al. 2018 kratom abuse potential assessment review is required to account for the significant number of new research studies that have been completed that collectively adds to the body of scientific evidence about the kratom plant and its constituent alkaloids. The American Kratom Association (AKA) and its affiliate, the Center for Plant Science and Health that funds new research into kratom, have supported an independent assessment of the current research landscape. This update followed a request for partial support of the time and effort for Dr. Henningfield and his colleagues at PinneyAssociates to develop the report. The purpose was to provide a state-of-the-art report to inform policy makers, health and regulatory officials, and public health and medical experts on kratom safety and abuse potential. AKA did not contribute to or influence the conclusions of Dr. Henningfield and colleagues at PinneyAssociates.

Through PinneyAssociates, Dr. Henningfield and his colleagues provide scientific and regulatory consulting to support new drug applications (NDAs) and risk management programs for a broad range of CNS active substances and drug products including psychedelic substances, new chemical entities, and alternative formulations and routes of delivery, as well as dietary ingredient notifications, cannabinoid assessment, and noncombustible tobacco/nicotine products for FDA regulation.

PinneyAssociates scientific experts who contributed to this report include: Rachel Beck, PhD; August Buchhalter, PhD; Yolanda Green; Marilyn Huestis, PhD, HonD; Mark Sembower, MS; and Daniel Wang.

We also acknowledge the thinking embodied in this document by our former colleague and co-author of the 2016 kratom Abuse Potential Assessment submitted to the DEA and FDA and its updated published version in 2018. Dr. Fant died in September 2020, and we miss him dearly. See more about our team and Dr. Fant at www.pinneyassociates.com.

Preface and Main Findings

Background: The 2018 Henningfield, Fant & Wang kratom abuse potential assessment was based on a 2016 assessment developed by Dr. Henningfield and colleagues at PinneyAssociates to inform the United States (US) Drug Enforcement Administration (DEA) and Food and Drug Administration (FDA) in their assessment as to the most appropriate regulatory approach to kratom and whether listing kratom (specifically, its alkaloids mitragynine [MG] and 7-hydroxymitragynine [7-OH-MG]) in Schedule I of the Controlled Substances Act (CSA) was warranted and in the interests of public health.

In brief, we concluded there was no evidence of an imminent threat to public health (a requirement for temporary or emergency scheduling) and that kratom was not like opioids in its safety and addiction risks. Furthermore, there was evidence that millions of people were using kratom for reasons associated with health and well-being, including in place of opioids they had been using for pain and/or addiction, and that thousands of people would be at risk of relapse to opioids and overdose if sale of kratom were banned and possession considered a narcotic criminal offense. We also concluded that banning kratom would foreseeably lead to the emergence of a deadly illicit market that would worsen what appeared to be the main problems with kratom, namely contaminated, adulterated, and inappropriately marketed products. We concluded that these problems could be addressed by continuing to allow legal sale of kratom but with FDA oversight providing standards for product quality, labeling, and other issues that FDA routinely addresses.

Overview of main findings: This update reaffirms all of the conclusions of the 2018 report. The more than 100 new peer-reviewed published studies by researchers worldwide and many laboratory studies in the US with funding from the National Institute on Drug Abuse (NIDA), sustain those earlier findings. These studies provide a much fuller characterization of how kratom works and how it provides the benefits that many people report as their reason for use, but without narcotic-like addiction and overdose risks. The studies include the state-of-the-art types of animal abuse and physical dependence/withdrawal studies that FDA requires for new medicines and which DEA relies on for drug scheduling decisions. New clinical studies in humans provide initial assessments of kratom's physiological health and safety related effects on liver, kidney, and cardiovascular function, as well as brain function, using magnetic resonance imaging techniques.

Conclusions based on new studies since January 1, 2018

- *Since the Henningfield, Fant & Wang (2018) 8-FA, there have been over 100 new published scientific studies, reviews, and commentaries by leading kratom experts, and an accelerating research pipeline funded in part by the US National Institutes of Health (NIH), National Institute on Drug Abuse (NIDA). These studies provide an increasingly strong evidence base for regulation and policy.*

- *Nature got it right. There is a convergence of studies showing that the main natural constituent of kratom that accounts for the reasons people use kratom is MG, which carries relatively low abuse and health risks (See below). 7-OH-MG naturally occurs at*

very low levels and product standards should prevent marketing of products with levels higher than those that appear to carry little risk.

- *Evidence does not support the conclusion that kratom is an imminent public health threat or that it is fueling the opioid and drug overdose epidemic that led to more than 93,000 deaths in 2020. Rather, the evidence supports the conclusion that for many people kratom is a path away from opioids and other drugs to help self-manage craving and withdrawal for people who find kratom more effective, accessible, acceptable, tolerable, and/or prefer natural products.*

- *Animal drug self-administration, physical dependence, and withdrawal studies show low abuse potential and withdrawal risks of kratom relative to opioids. Furthermore, these studies also show that MG administration can reduce self-administration of morphine and heroin as well as withdrawal from morphine. These findings are consistent with human surveys and studies showing that addiction risks for kratom are overall low as compared to opioids.*

- *Numerous surveys and field studies of kratom users have been conducted in the US and Malaysia. These new studies largely confirm the earlier large US survey on kratom consumer usage patterns published by Dr. Grundmann (2017). Most US kratom users are 30-50 years old, employed, have some college education, and have health insurance. Leading reasons for use are to self-manage pain, depression, anxiety, to increase focus and alertness analogous to caffeinated beverage use, and to self-manage opioid and other substance use disorders to relieve craving and withdrawal and often the pain that motivates such drug use.*

- *Surveys also show that users fear a kratom ban and the risks of resumption of opioid and other drug use, and/or turning to illicitly marketed kratom. This makes it foreseeable that thousands of people would be at risk of opioid overdose and other mortality risks associated with illicit drug use, injection drug use, and adulterated kratom products.*

- *Studies of kratom's alkaloids support the conclusion that that MG and other alkaloids are not appropriately categorized as opioids, as they are diverse in their activity, effects, and mechanisms of action. Moreover, the primary active constituent of kratom, MG, does not produce the signature powerfully rewarding and lethal respiratory depressant effects that characterize morphine-like opioids.*

- *Kratom PK and safety studies include examination of the pharmacokinetics (PK) and pharmacodynamics (PD) in rats and dogs by oral and intravenous administration of many kratom alkaloids in addition to MG. MG, at human dose equivalents many times higher than humans take, are without acute serious adverse effects and there is little evidence of a respiratory depressant effect.*

- *Six clinical studies evaluated the effects of long term kratom use on a variety of physiological parameters including kidney and liver function, hematological parameters, cognition, and brain function by magnetic resonance imaging. Although these were*

relatively small studies, none suggest serious adverse consequences of long term kratom use. It is important to note that these are not definitive safety studies and cannot be used to claim that kratom has no adverse effects on any of the studied physiological domains and limitations of each study were noted in the publications. Nonetheless, the findings are encouraging and should facilitate the conduct of more comprehensive follow-up studies.

- *New medicine innovation efforts are developing new molecules as analogs of MG and other kratom alkaloids as possible safer and/or more effective treatments for pain, addiction, depression, and other disorders, due to the promising findings with kratom and its naturally occurring alkaloids. These efforts are also contributing to knowledge about kratom safety and effects; however, New Drug Applications (NDAs) typically require a decade or more of research at costs often exceeding one billion dollars before they can be submitted for review and potential approval by the FDA.*

- *The pipeline of research and new science has been enhanced in quantity and quality not only by funding from the US National Institutes of Health (NIH) and other organizations but as well by regular scientific conferences that are fostering global collaboration and cooperation in an exciting new frontier in search of safer and more effective ways to manage health and well-being. Such efforts are working and should be expanded.*

- *These scientific findings taken together have implications for consideration of kratom regulation by the Controlled Substances Act (CSA). The CSA is intended to protect the public health from substances that pose as imminent threat to public health, and in the case of medicines with a potential for abuse to ensure that they are appropriately regulated if the science supports placement in the CSA. Kratom is not a new drug but rather is a naturally occurring substance with decades of history of use in the US and much longer in Southeast Asia where it grows in abundance and is used by many more people. The scientific evidence does not indicate a profile of meaningful abuse potential or physiological dependence potential of its primary active constituent, mitragynine. This review supports the key findings and action by Assistant Secretary of Health, Dr. Brett Giroir (Giroir, 2018) to rescind the 2017 recommendation (FDA, 2017a) to place MG and 7-OH-MG in Schedule I of the CSA. Specifically, it supports the conclusions that "mitragynine does not satisfy the first of the three statutory requisites for Schedule I", and that "there is a significant risk of immediate adverse public health consequences for potentially millions of users if kratom or its components are included in Schedule I" and that the very research that all parties agree is needed would be severely stifled by CSA scheduling.*

- *Kratom regulation would be better informed by scientific and public health information exchange and active collaboration among CDC, DEA, FDA, NIDA, and the Substance Abuse and Mental Health Services Administration. Kratom science should be accelerated by increased kratom research funding to NIDA, as well as to support increased surveillance that is specific to kratom. As in other areas of science and public health, progress and process would likely be improved if federally funded kratom*

research had input and possibly oversight by a multi-agency task force and with an annual report developed with updates on the state of kratom science and annual surveillance, perhaps led by NIDA.

- *An important development that relates to overall safety, health benefits and risks of kratom use is a regulatory and policy update and is not included in the science updates: at the time of this writing, five states, Arizona, Georgia, Nevada, Utah, and Oklahoma, have enacted laws referenced as the Kratom Consumer Protection Act (KCPA). The KCPA establishes a regulatory framework to protect consumers from unsafe and adulterated kratom products that by requiring manufacturers strict adherence to good manufacturing standards (GMP) to ensure purity; requires testing for contaminants; prohibits adding any dangerous substances to kratom products; forbids boosting the alkaloid levels of MG and 7-OH-MG over those present in the natural kratom plant; bars synthesizing any of the alkaloids; requires registration and product testing; prohibits any therapeutic health claims; and forbids sales to minors. These KCPA laws provide needed consumer protections for consumers. To illustrate the kratom regulatory framework for the Utah KCPA, the Utah Department of Agriculture rule on kratom can be found at https://ag.utah.gov/businesses/regulatory-services/kratom/ . For updates on the status of KCPA legislation in other states, visit the American Kratom Association website at https://www.americankratom.org/advocacy/aka-in-your-state.html .*

Contents

1 Introduction

This is a scientific update to “The abuse potential of kratom according to the 8 factors of the Controlled Substances Act: implications for regulation and research”, by Jack Henningfield, Reginald Fant, and Daniel Wang (Henningfield, Fant & Wang, 2018). Primarily findings and conclusions quoted directly from kratom-related scientific research since December 2017 are included.

Seven of the eight factors of the Controlled Substances Act were affected by new research and survey data. The eighth factor did not change, as neither kratom nor any of the constituents in kratom or its alkaloids are controlled substances, nor are they immediate precursors of controlled substances.

This update includes several new studies employing a variety of state-of-the-art animal models of abuse potential, physical dependence, and withdrawal potential as compared to opioids and other classic drugs of abuse. The understanding of kratom’s mechanisms of action and its safety profile help explain not only why it differs from opioids with respect to safety but also its relatively low potential for abuse and dependence.

1.1 Comments on Efficacy, Risk, and Drug Scheduling According to the Controlled Substances Act

Therapeutic efficacy standard by FDA. This research update includes additional evidence that the major reasons for kratom use for millions of people in the US are for health and well-being including for self-management of pain, addiction, depression, and other disorders. The evidence includes peer reviewed surveys and field studies in the US and Southeast Asia (SEA), some clinical studies, and many animal studies that show that the mechanisms of action of MG are consistent with such effects. Moreover, several animal models used to predict efficacy for treating opioid use disorder, opioid withdrawal, and pain, demonstrated efficacy.

However, none of this research meets FDA’s standard for therapeutic efficacy which is typically determined by evaluation of a New Drug Application (NDA) (whether NDA is based on a new chemical entity or botanical substance). The NDA must be supported by “substantial evidence of effectiveness,” and is defined as “evidence consisting of adequate and well-controlled investigations” (Dabrowska & Thaul, 2018; Katz, 2004). The time and cost to develop and achieve FDA approval of a product as therapeutically effective and acceptably safe varies widely but is often approximately ten years and 1 billion dollars (DiMasi, Grabowski & Hansen, 2016; Wouters, McKee & Luyten, 2020). Only two botanical substances have been developed as drug products consistent with FDA’s Botanical Drug Guidance (FDA, 2016).

Thus, by FDA’s standard for efficacy, no kratom product or kratom alkaloid or derivative is recognized as therapeutically efficacious or “safe and effective”. This report does not endorse or recommend therapeutic use. However, terms such as therapeutic use are used in many of the articles cited and by many consumers of kratom who report using it for and obtaining therapeutic benefits. Denial of this would not be consistent with the science regardless of whether it meets the FDA standard. Neither should it be denied that studies estimate that over ten million people in the US (AKA, 2019; Henningfield, Grundmann, Garcia-Romeu & Swogger, 2021) use kratom products and find them acceptable, and sometimes preferred over

other products. For this population, kratom is perceived as effective, accessible, tolerable, and preferable as a natural product compared to conventional medicines.

1.1.1 Comment on Risk

Risk is a relative concept. This report discusses many risks and benefits of kratom, particularly as compared to morphine-like opioids which carry far greater risks of addiction and overdose death as discussed in the report (see also Henningfield, Grundmann, Babin, et al., 2019). This research does not suggest that kratom consumption is without risk. It is also important to recognize that kratom is not approved for therapeutic use by the FDA. Therefore, surveys showing that individuals use kratom to improve personal health and wellbeing, and for self-management of disease should not be taken as endorsements of such use or that use is without risk.

1.1.2 Comment on Drug Scheduling

Drug scheduling in the US is guided by the Controlled Substances Act (CSA). For new drugs, scheduling recommendations are developed by FDA, with input from NIDA and transmitted to DEA by the Assistant Secretary of Health (ASH) to the Administrator of the DEA (FDA, 2017a; Giroir, 2018). The same process can be applied to substances that are not approved as drugs and this process was followed for the 2017 FDA recommendation that MG and 7-OH-MG be permanently placed in Schedule I of the CSA, although it was concluded in a critique of the FDA recommendation that there was no evidence of actual NIDA input into the FDA 8-Factor Analysis (FDA 2017a; Henningfield, Babin, Boyer, et al. 2018).

By law and in practice, following FDA's 2017 Guidance (FDA, 2017b), scheduling decisions are guided by analysis of the eight factors of the CSA, which include three factors (nos. 4, 5 and 6) that address public health implications of scheduling including whether it is in the interest of public health to schedule a substance and, if so, which schedule is most appropriate. Regardless of the actual level of abuse potential and public health risk, if it is determined that a substance warrants CSA scheduling and it is not approved for therapeutic use by FDA (i.e., as an approved drug), only Schedule I (C-I) is an option. If the substance or product is approved for therapeutic use and is recommended for CSA scheduling then it will be placed in Schedule II, III, IV or V, in which V is least restrictive (e.g., lacosamide, pregabalin, and low dose codeine plus acetaminophen) and Schedule II is most restrictive (e.g., amphetamine, fentanyl, morphine) supported by the 8-factor analysis. For discussions and examples of the process and how public health considerations including risks and benefits related to scheduling are considered, see FDA's 2017 Guidance and review articles (Belouin & Henningfield, 2018; FDA, 2017b; Giroir, 2018: Johnson, Griffiths, Hendricks & Henningfield, 2018; Spillane & McAllister, 2003).

The science update supports the conclusion that kratom is providing a public health benefit by enabling millions of people in the US to self-manage their health and well-being and that it is foreseeable that banning sales and criminalizing those who possess kratom could lead to thousands of opioid overdose deaths among people who reverted to opioid use. We believe that individuals and public health would be better served by regulations that ensure that lawfully marketed products are pure, uncontaminated, and unadulterated by other harmful substances, drugs, or unnaturally high levels of kratom's naturally occurring alkaloids, and that

kratom products are appropriately marketed, packaged, and labeled and unsubstantiated health claims are not made.

1.2 Approach

This update is based on a review of studies published primarily since January 1, 2018 to update the science cited in the Henningfield, et al. (2018) 8-Factor Analysis which was completed and accepted for publication in December 2017.

Published literature was obtained by internet searches and a direct request for the most recent published and "accepted for publication" studies of more than twenty of the leading kratom research centers and research leaders worldwide. Conclusions were also influenced by the several national and international meetings in which new kratom research findings were presented and discussed each year (including virtual meetings from March 2020 to the present).

We do not represent this as a consensus report but have made every effort to reflect the thinking of other leading kratom science and policy experts. The approach to our study summaries is to rely heavily on direct quotes from the authors of articles or brief summaries that we feel accurately represented the articles. We provide the references and will make available the library of the more than 100 articles on request. It is our intent that this transparent process will also facilitate efforts to contact researchers for more information about their research and thinking.

A review of this body of evidence strengthens the conclusions of the 2018 8-FA that the public health benefits of continued access to kratom (ideally, with a regulatory framework developed by FDA with input from stakeholders and experts and other agencies including NIDA) outweigh the risks.

Kratom and its primary alkaloid, mitragynine, is not without risks or devoid of abuse potential; however, those risks are overall relatively small as compared to the serious risks of a kratom ban. The abuse potential of kratom and mitragynine do not rise to the level of abuse potential or risk that would be effectively or appropriately mitigated by placement in the CSA. This takes into consideration the overall public health impact, as required by consideration of factors 4, 5 and 6.

Thus, this update does not fundamentally change the following conclusion of the 2018 8-FA:

> "The overarching public health and policy question is not could kratom be regulated as a controlled substance but rather should kratom be so regulated. From a pharmacological perspective, this review suggests, as concluded by Henningfield (2015) and Pinney Associates (2016) that a case could be made to place kratom in the CSA. In fact, if MG, for example, was a newly discovered active chemical entity in a medicine submitted for approval by FDA, and hence without decades of use in the community, it would certainly be evaluated for potential scheduling according to the CSA and FDA's guidance (FDA 2017b), and it might be recommended for scheduling following its approval as a therapeutic medicine." (Henningfield, Fant & Wang, 2018, p. 585)

1.3 Comment on Current State of Research

There have been extensive new scientific advances since 2018 on the impact of kratom on substance use disorders and rehabilitation. This includes many thoughtful integrative reviews. We provide an example of one of these that we think provides a useful framing from this report.

Drs. Veltri and Grundmann (2019) concluded as follows:

> "Throughout its history of use, Kratom has been known to exert stimulant- and opioid-like effects that is raising concerns with regulatory agencies and resulted in scheduling actions in various countries. Although knowledge from clinical studies is limited, epidemiological data obtained from Southeast Asia, Europe, and the United States indicate that Kratom has a distinct user profile and presents with discrete effects from other stimulants or opioids. A substance-dependent opioid user does not prefer Kratom over another opioid but instead would utilize Kratom as a harm reduction or mitigation agent. This has been the conclusion from studies in Malaysia and the United States although the current information is preliminary in scope based on the small sample sizes and regional limitation of the surveys. The findings do align with preclinical observations in rodents that report a reduction in morphine self-administration with the use of mitragynine. This current knowledge points to a potential for further development of mitragynine or use of Kratom as a harm reduction agent similar to methadone or buprenorphine….While a majority of regular Kratom users in Southeast Asia and the West alike do not experience acute or chronic adverse effects, the incidence of unwanted side effects remains unknown and can include both stimulant and opioid-like sedative effects….a direct causative link between the fatalities in which Kratom was detected cannot be drawn because nearly all of them involved poly-drug exposures. The toxicity of Kratom in various animal species is variable and has not been determined for most of them following acute and chronic exposure. The only clinical pharmacokinetic study in humans that provides blood concentrations of mitragynine does not correlate with post-mortem blood mitragynine concentrations thus not allowing for the determination of a toxic or lethal cut-off level…. Reports and studies of the dependence potential to Kratom are of serious concern given the current opioid crisis in the United States and rising abuse of opioids in other countries. It appears that most Kratom-dependent users had a prior substance use disorder or were seeking relief from a chronic pain condition but wanted to avoid opioid use. The severity of Kratom dependence symptoms appears to be milder compared to opioid use disorder…" (pg. 29)

Note that research is rapidly expanding in the US and SEA, especially at the Center for Drug Research (CDR), Universiti Sains Malaysia, in part due to increased support of kratom related research by NIDA. For nearly a decade, NIDA has supported research into potentially safer and less abusable medicines for pain and treatments derived from kratom alkaloids for opioid use disorder. This is among the more rapidly expanding areas of research providing new facts and insights to characterize the benefits and risks of kratom use and how appropriate regulation could minimize risks.

Along with this accelerated research, NIDA has also supported conferences in the US and internationally which have been important in the facilitation of research sharing. This has also fostered global collaborative efforts that are evident in many of the published articles in this update in which authorship represents multiple research centers, sometimes from three or four countries.

Two conferences in particular are important to note for their important research stimulating effects. The first was the 2018 NIDA International Forum: Building International Collaborative Research on Drug Abuse, June 8–11, as a satellite meeting of the annual College on Problems of Drug Dependence meeting, which itself included a major kratom symposium and several individual presentations by researchers whose work is included in this update.[1,2]

The second major international meeting that accelerated research and fruitful cross disciplinary, global collaborations was the NIDA supported Second International Kratom Symposium convened by the University of Florida Clinical and Translational Science Institute and the Department of Pharmacodynamics from February 8-10,2019.[3] See more about their program and efforts to accelerate kratom science at the University of Florida Kratom Resource page[4].

An additional influence on the conclusions of the present report were policy efforts that involved more than a dozen kratom and substance abuse research leaders developing three reports in the form of open letters to update FDA, DEA, NIDA, the White House, and Congressional leaders[5,6,7] . These reports were also developed with support from the AKA. Each of these reports were co-authored and signed by nine or more contributors with eight contributing to all of them.

As the safety and effects of kratom and its primary active alkaloid MG have become increasingly studied over the past 5-10 years there have been a growing number of articles and scientific meetings exploring the diverse potential public health and therapeutic benefits of kratom that are already evident (Grundmann, Brown, Henningfield, et al., 2018; Prozialeck et al., 2020; Sharma & McCurdy, 2021). All of these articles recognized that the FDA standard for therapeutic benefit, which is generally approval of a new drug application (NDA) for therapeutic use, has not been met.

To date, there has not been an NDA submission to FDA for a kratom product and it is not clear that there ever will be. However, kratom-related potential new drug development efforts are already underway as some companies have announced on their websites (e.g., Kures

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[1] https://www.drugabuse.gov/international/2018-nida-international-forum-building-international-collaborative-research-drug-abuse
[2] https://www.drugabuse.gov/international/kratom-research-presented-nida-international-forum-promotes-international-cooperation
[3] https://www.leg.state.nv.us/App/NELIS/REL/80th2019/ExhibitDocument/OpenExhibitDocument?exhibitId=41965&fileDownloadName=0403ab303c_gasr_symposium.pdf
[4] https://pd.pharmacy.ufl.edu/research/kratom/
[5] February 2018 Letter to White House and DEA at http://www.americankratom.org/images/file/Document%2019%20Science%20Letter%20on%20Kratom%20Sent%20to%20WH%20and%20DEA%20Feb%208%202018.pdf
[6] June 2018 Letter to Leaders of Congress at https://www.americankratom.org/images/16_Kratom_Scientist_Letter_to_Congressional_Leaders_June_21_2018_FINAL.pdf
[7] November 2018 letter to DHHS, FDA, DEA, and NIDA critiquing the FDA's kratom 8 Factor Analysis at https://www.americankratom.org/images/file/Scientists-Response-to-FDA-Kratom-8FA--28-Nov-2018-FINAL.pdf

Therapeutics, Inc[8] and Sparian Biosciences[9]). The foregoing efforts include scientists on their teams who have been researching kratom alkaloids, with support from NIDA, as part of NIDA's efforts to foster research to stimulate the development of new medicines to treat substance use disorders as well as medicines for other disorders for which the present leading medicines carry addiction and safety risks.

2 Summary of Findings

For each factor, this report will begin with a short summary of the main finding of the 2018 8-Factor Analysis (8-FA), followed by key scientific updates, and finally conclusions. Mitragynine is abbreviated "MG" and 7-hydroxy-mitragynine "7-OH-MG". Unless specified, "opioids" means morphine, heroin, oxycodone and fentanyl, and other full opioid agonists, and not opioid antagonists such as naloxone (Narcan®) or naltrexone, or the partial opioid agonist buprenorphine.

2.1 Factor 1 – Actual or Relative Potential for Abuse

2.1.1 Summary of 2018 Findings

Henningfield, Fant & Wang (2018) did not have the benefit of classic animal self-administration and withdrawal studies of kratom's alkaloids; however, other data suggested relatively low abuse potential as compared to opioids and other drugs of abuse. Survey data from the US and field studies in SEA observed most kratom use was for health-related benefits, including management of drug dependence and drug withdrawal, primarily for opioid related dependencies but also for alcohol and stimulant use disorders. Initial drug discrimination and conditioned place preference (CPP) studies with rats suggested weak opioid-like discriminative effects and weak rewarding effects at extremely high human dose equivalents that might not be tolerable in humans. Taken together, the 2018 Factor 1 evidence suggested that kratom was not without abuse potential but that its potential for individual and societal harm was relatively low as compared to opioids and other drugs of abuse.

2.1.2 Factor 1 Science Updates

2.1.2.1 Intravenous (IV) Self-administration Studies of Abuse Potential

Two 2018 studies provided assessment of kratom's abuse potential in the IV rat self-administration model, the most predictive animal model for reinforcing effects and abuse potential (FDA, 2017b). In addition, MG's brain rewarding effects were evaluated in the intracranial self-stimulation model and the CPP procedure.

Hemby, MacIntosh, Leon, et al. (2019) summarized the reinforcing effects of MG and 7-OH-MG compared to morphine, and also evaluated pretreatment of animals with MG or 7-OH-MG on morphine self-administration:

> "The present findings indicate that MG does not have abuse potential and reduces morphine intake, desired characteristics of candidate pharmacotherapies for opiate

[8] https://www.kures.life/
[9] https://www.sparianbiosciences.com/

addiction and withdrawal, whereas 7-HMG should be considered a kratom constituent with high abuse potential that may also increase the intake of other opiates." (p. 1)

It is important to note that the reinforcing human dose equivalents of 7-OH-MG in the rat were many times higher than would be tolerable for humans, and that 7-OH-MG is present at or near de minimis levels in kratom leaves and most marketed products. Their findings support recommendations that marketed kratom products should not contain more than 1-2% 7-OH-MG, the highest concentration found naturally in plants and that does not provide reinforcing or harmful effects. This is the approach adopted by states that passed Kratom Consumer Protection Act laws to regulate kratom.[10]

Yue, Kopajtic and Katz (2018) compared MG's reinforcing effects to heroin and methamphetamine and evaluated MG pretreatment of animals prior to the opportunity to self-administer heroin or methamphetamine. Their conclusions:

> "In rats trained to self-administer methamphetamine, saline substitutions significantly decreased the number of responses, whereas different doses of methamphetamine (0.002–0.068 mg/kg/injection) or heroin (0.001–0.03 mg/kg/injection) maintained self-administration with maximal responding at 0.022 or 0.01 mg/kg/injection, respectively. In contrast, no dose of mitragynine maintained response rates greater than those obtained with saline. Presession mitragynine treatment (0.1 to 3.0 mg/kg) decreased response rates maintained by heroin but had little effect on responding maintained by methamphetamine across the same range of doses. These results suggest limited abuse liability of mitragynine and the potential for 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." (p. 2823)

2.1.2.2 Intracranial Self-Stimulation (ICSS) Study of Abuse Potential

Another classic model for assessing the brain rewarding effects and drug abuse potential is the intracranial self-stimulation (ICSS) model. In the ICSS model, rats are equipped with electrodes in brain regions that lead animals to press a lever to self-deliver rewarding electrical brain stimulation (Negus & Miller, 2014). Opioids, amphetamine-like stimulants, cocaine, and other classic drugs of abuse reduce the threshold of stimulation and increase the strength of the rewarding effect of brain stimulation that delivers small electrical stimulations.

Behnood-Rod, Chellian, Wilson, et al. (2020) compared the potential brain rewarding effects of MG to morphine and found that morphine robustly and dose-dependently decreased the stimulation threshold consistent with other opioids, cocaine, amphetamine, and other drugs with high abuse potential (see also, Negus & Miller, 2014). In contrast, MG produced only a weak reduction in threshold with higher doses increasing the threshold. 7-OHMG did not reduce thresholds. Behnood-Rod, et al. (2020) concluded:

[10] https://www.americankratom.org/media/attachments/2021/01/25/kcpastates.pdf

> "These initial findings indicate that mitragynine and 7-hydroxymitragynine are not rewarding in the ICSS procedure. The present results suggest that these kratom alkaloids do not have abuse potential." (p. 7)

2.1.2.3 Conditioned Place Preference Studies of Abuse Potential

Four studies employing various preparations of MG on CPP observed mixed effects across studies and some evidence suggestive of abuse potential at high doses. Japarin, Yusoff, Hassan, et al. (2021) evaluated cross-reinstatement of MG and morphine place preference in rats.

Another study found that baclofen pretreatment could prevent the acquisition and expression of MG-induced CPP (Yusoff, Mansor, Müller et al., 2018).

CPP also was demonstrated in mice but at high doses of a methanolic extract of kratom leaves (Vijeepallam, Pandy, Murugan, et al., 2019). The relevance of the high dose CPP studies to humans is not clear but is an example of the importance of diverse scientific approaches to better profile the overall safety including abuse potential of substances.

In the fourth study, described in greater detail I Factor 2, Wilson, Harris, Eans, et al. (2020) evaluated lyophilized (freeze-dried) kratom tea (LKT) as a potential treatment for pain and opioid dependence in a mouse model in which mice (referred to as knockout mice) were absent various drug receptors. The effects of oral LKT were examined in a warm water tail assay for nociception (pain relief), locomotor effects, respiratory depression, conditioned place preference, and to determine if it would reduce withdrawal signs in mice that were made physically dependent to on morphine by chronic morphine administration.

LKT did not induce conditioned place preference. See Factor 2 for summary of results on other measures.

Taken together these seven studies found no evidence of rewarding effects of MG in the IV self-administration and ICSS models, and weak evidence of potential reward in the CPP procedure.

2.1.2.4 Physical Dependence and Withdrawal Studies

The CDR at University Sains, Malaysia is actively evaluating MG's potential to produce physical dependence and withdrawal, as well as how its effects differ from those of classic opioids in animal physical dependence models evaluating substances under development as potential new medicines.

Harun, Johari, Mansor & Shoaib (2020) performed a series of studies comparing withdrawal following chronic MG and chronic morphine administration. Physical dependence with naloxone challenge tests and MG's effectiveness at reducing morphine withdrawal were evaluated. These studies found little evidence of physical dependence or withdrawal as compared to morphine and evidence of potential therapeutic benefits of MG for treating opioid withdrawal, consistent with human reports. Harun et al. (2020) concluded:

> "…the discontinuation of MG was not associated with the disruption of schedule-controlled behaviour in rats. This suggests that MG or analogs might be further investigated as potential therapeutic drugs for treating OUD and opioid withdrawal…The findings from this study suggest that discontinuation of MG is not associated with overt withdrawal effects, a finding that supports published studies using other behavioural models. For example, Hemby et al. (2019) and Yue et al. (2018) found that MG administration reduced IV morphine self-administration in rats but that MG itself did not maintain self-administration. The findings may suggest that MG possesses the desired characteristics of candidate pharmacotherapies for opioid dependence and withdrawal…. Although mitragynine may possess some addictive properties on its own, it may, in low-medium doses, in which humans voluntarily use it, help to manage opiate addiction." (p. 864)

In a follow-up study to Harun, et al. 2020, Johari, Harun, Sofian & Shoaib (2021) compared mitragynine to morphine withdrawal using the pentylenetetrazol (PTZ) discrimination mode for evaluating anxiogenic signs in rats. Although there are qualitative similarities in kratom withdrawal signs with opioid withdrawal signs, they are not only weaker for kratom but also may be distinct in several respects and this model can be helpful in characterizing the profile. The administration of PTZ produces a rodent model of anxiety that is used in pharmaceutical development. Morphine dependent rats press levers associated with PTZ administration when withdrawal is precipitated by naloxone administration. A recent study showed that MG withdrawal was not associated with such a response.

Twenty rats were treated with either MG at doses known to produce some physical dependence and withdrawal in rats and morphine. Then they were challenged with naloxone. Johari, et al. (2021) concluded as follows:

> "Unlike morphine that produced dose-related PTZ-like stimulus, MG at 3, 10, 30 and 45 mg/kg doses showed no substitution to the PTZ discriminative stimulus. In contrast to morphine which produced a time-dependent generalization to the PTZ stimulus, naloxone did not precipitate withdrawal effects in MG-treated rats as they selected the vehicle lever at three withdrawal time points. These results demonstrate that MG produces a very different response to morphine withdrawal that is not associated with anxiogenic-like subjective symptoms. These characteristics of MG may provide further support for use as a novel pharmacotherapeutic intervention for managing opioid use disorder." (p. 1)

Hassan, Pike See, Sreenlivasan, et al. (2020) compared the efficacy of MG to methadone for treating morphine withdrawal in a rat model of physical dependence and withdrawal. Hassan, et al. (2020) concluded:

> "…the morphine withdrawal model induced withdrawal signs for 16 days in rats. Four-day replacement treatment with mitragynine attenuated the withdrawal symptoms significantly, suggesting that mitragynine is able to reduce morphine withdrawal symptoms similar to methadone and buprenorphine. ...The present study suggests that mitragynine may serve as an alternative treatment for opiate withdrawal effects as they occur in opiate addiction. Although mitragynine may possess some addictive properties

on its own, it may, in low-medium doses, in which humans voluntarily use it, help to manage opiate addiction. The current report details the efficacy in comparison to methadone and buprenorphine. While mitragynine is equally effective in reducing opiate withdrawal effects in rats, it may be the safer drug with less undesired side-effects." (p. 9-10)

Although withdrawal signs in rats are weak as compared to morphine withdrawal, there does appear to be evidence of some degree of physical dependence. Other studies have explored brain proteins that might serve as more sensitive biomarkers for physiological dependence in rats (Hassan, Othman, Mansor, et al., 2021). Another study examined the attenuation of MG withdrawal signs in rats with clonidine (Hassan, Sreenivasan, Müller et al., 2021). Another study examined potential signs of naloxone precipitated withdrawal in rats (Harun, Johari, Japarin, et al., 2021a). Overall, such research is consistent with human reports that kratom withdrawal is generally more modest and more readily self-manageable than that produced by opioids.

2.1.2.5 Real World Evidence of Abuse and Dependence

As reported in 2018, there is kratom recreational use; however, all surveys in the US and SEA indicate that its euphoriant effects are relatively low as compared to opioids and other recreational drugs. Also, for opioids, stimulants, and other drug use there is a strong tendency to increase euphoria by smoking, injecting, and/or insufflating the drug. Electronic vaping devices can also be employed. This is notably less common for kratom, as raising the dose produces little increase in euphoria and increases undesirable effects including nausea. These factors limit kratom doses, as reported by kratom users in public hearings and internet discussion groups and may contribute to kratom's overall safety profile. Rapid delivery of high doses by non-oral routes contributes to the morbidity and mortality of opioids, stimulants, and other recreational drugs.

Several new surveys from the US and SEA and conclusions from leading kratom researchers worldwide in consensus-type review articles support the conclusions of the 2018 8-FA. The new survey data are summarized in Factors 4, 5 and 6. Several reviews and studies confirm that chronic high daily intake can lead to kratom dependence and withdrawal in some kratom users, but these are substantially less likely to interfere with family, social and occupational life and commitments as compared to opioid dependence. Moreover, kratom is widely viewed as a healthier and less life-impairing substance to replace opioids and other drugs including alcohol and stimulants (Galbis-Reig, 2016; Prozialeck, et al., 2019; Singh, et al., 2014; Swogger & Walsh, 2018).

A variety of reports confirm kratom use to self-manage opioid withdrawal and also that abstinence from high chronic kratom use is typically associated with milder symptomatology than abstinence from classical opioids as documented in surveys and discussed on the internet in websites and discussion groups such as Erowid and Reddit (See survey and internet discussion data in the following: Coe, et al., 2019; Prozialeck, et al., 2019; Singh, et al., 2014; Singh, et al., 2016; Singh, Narayanan, Müller, et al., 2018; Grundmann, et al., 2017 Garcia-Romeu, et al., 2020; Henningfield, et al., 2020; Smith, et al., 2017; Swogger, et al., 2015; Veltri & Grundmann, 2019).

The conclusions by Prozialeck, et al. (2020) and Grundmann, et al. (2018) were further strengthened by two published US surveys, which found that the overwhelming majority of kratom consumers use for health benefits and not to get high or for other recreational purposes (Coe, et al., 2019; Garcia-Romeu, et al., 2020). A third survey of over 12,000 kratom consumers presented at the 2020 annual meeting of the American College of Neuropsychopharmacology by Henningfield, Barr, Wang & Huestis (2020) showed that approximately 8300 respondents were using kratom to manage some "ailment" other than a substance use related disorder and approximately 3800 (32%) respondents were using kratom to manage "drug" withdrawal.

These three surveys were generally consistent with the Grundmann (2017) survey that reported most US kratom users were approximately 30-50 years old, had some college education and healthcare, were employed and consumed kratom for health and well-being. Leading reasons for use were pain, self-management of opioid and other substance use disorders and withdrawal, and mood disorders including depression, anxiety, and post-traumatic stress disorder. Dependence and withdrawal can occur but are generally reported as more tolerable, less disruptive to work and social function, and more readily self-manageable than opioid and other classic drugs of abuse, dependence, and withdrawal.

While this update on science related to the abuse potential and regulatory status was under development by Dr. Henningfield and colleagues at PinneyAssociates, several of the world's leading kratom researchers, Drs. Harun, Johari, Japarin, Suhaimi, Hassan, & Shoaib (2021b), published a new review article addressing similar scientific issues and reached generally similar conclusions. Harun, et al. (2021b) also described needed research, particularly for development of MG and/or analogs for submission for FDA regulatory approval as new drugs.

2.1.3 Factor 1 Updated Conclusions

Two rat intravenous self-administration studies showed no evidence of morphine or heroin like abuse potential by MG (Hemby et al. 2018 and Yue et al. 2018). Those same studies showed that MG pretreatment of animals reduced subsequent self-administration of morphine (Hemby et al., 2018) and heroin (Yue et al., 2018). These findings are consistent with human reports that kratom is useful in the management of opioid craving and withdrawal and to support opioid abstinence (Grundmann et al., 2018; Prozialeck et al., 2020; Coe et al., 2019; Garcia-Romeu et al., 2020).

Taken together, the new research suggests an overall abuse potential that is relatively low as compared to morphine and morphine-like opioids. Several models revealed little abuse potential, whereas the CPP model suggested weak but not zero abuse potential. This contrasts with opioids, stimulants and other classic drugs of abuse that demonstrate robust rewarding effects across all such abuse potential models. Similarly, MG's potential to produce physical dependence and withdrawal appears relatively low, but not absent, as compared to opioids in animal models. It is worth noting that the animal self-administration studies were published during the summer of 2018 when the Department of Health and Human Services was reviewing the FDA's 2017 recommendation (FDA, 2017a) that DEA permanently list MG and 7-OH-MG as CSA Schedule I drugs (see discussion below in Factors 4, 5 & 6) and one of the studies was cited as a new finding supporting the decision to withdraw the scheduling recommendation (Giroir, 2018).

The relevance and importance of such animal model data are well established, and in the case of kratom, was recognized in the formal FDA rescission of the kratom scheduling request submitted to the DEA in which Assistant Secretary Giroir stated:

> "One recently published peer reviewed animal study indicated that mitragynine does not have abuse potential and actually reduced morphine intake. As such, these new data suggest that mitragynine does not satisfy the first of the three statutory requisites for Schedule I, irrespective of broader considerations of public health."

These animal model findings are generally consistent with human reports that MG has a relatively low abuse potential as compared to Schedule II opioids but can reduce opioid self-administration and withdrawal. Surveys indicate that reducing opioid self-administration and withdrawal are among the most common reasons for kratom use in the US.

Not discussed above because they are not published articles are the tens of thousands of comments by kratom users and others interested in kratom policy to the DEA (approximately 20,300 in 2016) discussed in the Henningfield, Fant & Wang (2018) 8-FA, and many more in public hearings by FDA and NIDA (April, 2018), and public hearings convened by cities and states across the nation since 2018, in which kratom regulatory laws and policies were under consideration. These comments largely focused on the reasons that people use kratom which primarily fall into the category of health and well-being consistent with the surveys discussed in Factors 4, 5, and 6, and relatively rare reports of use to get high, or reporting addiction or serious harm.

2.2 Factor 2 – Scientific Evidence of its Pharmacological Effect

2.2.1 Summary of 2018 Findings:

"More research is clearly needed to elucidate receptor binding profiles and the diverse and probably complex mechanisms of action of the kratom alkaloids singly, in combination, and as commonly occurs in marketed products and brewed extracts." (Henningfield, Fant & Wang, 2018, p. 589).

2.2.2 Factor 2 Science Updates

Since 2018, pharmacological research characterizing kratom's effects and the mechanisms of action of its alkaloids rapidly advanced. For example, as discussed in Factor 1, the impact of drugs such as methadone, buprenorphine, and clonidine on rats that show evidence of MG withdrawal was studied (Hassan, Sreenivasan, Müller et al., 2021). This research documents the lower mortality risks of kratom compared to opioids based upon its mechanisms of action including its biased partial agonist effects that are lower in beta-arrestin recruitment, and thus also relatively low in producing physical dependence and respiratory depression.

There were also rapid advances in characterizing many of kratom's alkaloids in addition to MG and 7-OH-MG. Although most were insufficiently abundant in kratom leaves to contribute to its effects, some may be model analogs for potentially more effective and safe medicines for a variety of medical disorders. Whereas new medicines based on kratom's alkaloids may be ten years in the future, they are attracting increasing attention from leading researchers and pharmaceutical developers.

An important international clinical study collaboration between researchers at Yale School of Medicine and the Center for Drug Research Malaysia investigated kratom efficacy and safety for the treatment of pain (Vicknasingam, Chooi, Rahim, et al., 2020). As reported in 2018, animal models demonstrated MG's analgesic antinociceptive effects consistent with kratom's widespread use globally to self-manage pain; however, clinical evidence was lacking. The Vicknasingam et al. (2020 study employed the classic cold pressor task to evaluate the effects of kratom concoctions on pain tolerance by assessing how long research participants could tolerate the pain of inserting their hands into an ice water bath. Kratom produced significantly increased tolerance for pain as compared to placebo in long term daily kratom users, an important advancement in understanding kratom's therapeutic potential. The authors concluded:

> "These study findings provide the first objectively measured evidence obtained in controlled research with human subjects that are preliminarily supporting or confirming previously published reports of kratom pain relieving properties based on self-reports collected in observational studies." (p. 235-236).

In a study mentioned in Factor 2, Wilson, Harris, Eans, et al. (2020) evaluated lyophilized (freeze-dried) kratom tea (LKT) as a potential treatment for pain and opioid dependence in a mouse model in which mice (referred to as knockout mice) were absent various drug receptors. The effects of oral LKT were examined in a warm water tail assay for nociception (pain relief), locomotor effects, respiratory depression, conditioned place preference, and to determine if it would reduce withdrawal signs in mice that were made physically dependent on morphine by chronic morphine administration. Wilson, et al. (2020) reported the following results:

> "Oral administration of LKT resulted in dose-dependent antinociception (pain relief) in mice lacking the mu-opioid receptor (MOR) and reduced in mice lacking the kappa-opioid receptor. These doses of LKT did not alter coordinated locomotion or induce conditioned place preference, and only briefly reduced respiration. Repeated administration of LKT did not produce physical dependence, but significantly decreased naloxone-precipitated withdrawal in morphine dependent mice. The present study confirms the MOR agonist activity and therapeutic effect of LKT for the treatment of pain and opioid physical dependence." (p. 1)

Obeng, Wilkerson, Leon, et al. (2021) compared MG and 7-OH-MG in in vitro receptor binding affinity studies and in vivo studies of morphine discrimination, antinociception in the model pain "heated plate" test, and naloxone challenge tests to understand the role of endogenous morphine opioid receptors. This series of studies concluded:

> "At human m-opioid receptor (MOR) in vitro, mitragynine has low affinity and is an antagonist, whereas 7-hydroxymitragynine has 9-fold higher affinity than mitragynine and is an MOR partial agonist. In rats, intraperitoneal mitragynine exhibits a complex pharmacology including MOR agonism; 7-hydroxymitragynine has higher MOR potency and efficacy than mitragynine. These results are consistent with 7-hydroxymitragynine being a highly selective MOR agonist and with mitragynine having a complex

pharmacology that combines low efficacy MOR agonism with activity at nonopioid receptors." (p. 412)

Todd, Kellogg, Wallace, et al. (2020) investigated the functional selectivity of MG and 7-OH-MG to produce biased G-protein signaling, with little recruitment of β-arrestin. They concluded:

> "…To evaluate the biological relevance of variable speciofoline levels in kratom, we compared the opioid receptor binding activity of speciofoline, mitragynine, and 7-hydroxymitragynine. Mitragynine and 7-hydroxymitragynine function as partial agonists of the human μ-opioid receptor, while speciofoline does not exhibit measurable binding affinity at the μ-, δ-, or ƙ-opioid receptors. Importantly, mitragynine and 7-hydroxymitragynine demonstrate functional selectivity for G-protein signaling, with no measurable recruitment of β-arrestin. Overall, the study demonstrates the unique binding and functional profiles of the kratom alkaloids, suggesting potential utility for managing pain, but further studies are needed to follow up on these in vitro findings. All three kratom alkaloids tested inhibited select cytochrome P450 enzymes, suggesting a potential risk for adverse interactions when kratom is co-consumed with drugs metabolized by these enzymes." (p.1)

Kruegel, Uprety, Grinell, et al. (2019) examined this possibility in a series of studies and concluded:

> "…preliminary research has provided some evidence that mitragynine and related compounds may act as atypical opioid agonists, inducing therapeutic effects such as analgesia, while limiting the negative side effects typical of classical opioids. Here we report evidence that an active metabolite plays an important role in mediating the analgesic effects of mitragynine. We find that mitragynine is converted in vitro in both mouse and human liver preparations to the much more potent mu-opioid receptor agonist 7-hydroxymitragynine and that this conversion is mediated by cytochrome P450 3A isoforms. Further, we show that 7-hydroxymitragynine is formed from mitragynine in mice and that brain concentrations of this metabolite are sufficient to explain most or all of the opioid-receptor-mediated analgesic activity of mitragynine. At the same time, mitragynine is found in the brains of mice at very high concentrations relative to its opioid receptor binding affinity, suggesting that it does not directly activate opioid receptors". (p. 1)
>
> "Further, it suggests a possible explanation for the seemingly improved safety profile of mitragynine compared to classical opioid agonists. However, the critical involvement of hepatic metabolism also complicates our understanding of mitragynine's pharmacology and introduces the possibility of interindividual variability in the compound's potential therapeutic effects and side effects. We believe mitragynine and related compounds have great potential as future therapeutics, but metabolic processes must be carefully considered as the field continues to advance". (p. 7)

The Kruegel et al. studies provided the foundation for their new pharmaceutical company to develop new kratom derived molecular entities for the treatment of pain, depression, and substance use and other disorders[11].

Reeve, Obeng, Oyola, et al. (2020) evaluated the discriminative stimulus properties of MG in a series of studies to determine the pathway that primarily mediates these effects since it only partially generalizes to opioids. They found full generalization to lofexidine and phenylephrine suggesting that its discriminative effects are primarily mediated by adrenergic and not opioid receptors.

Hiranita, Sharma, Oyola, et al. (2020) investigated the hypothesis that MG exerts opioid agonist activity, in part, through metabolic conversion to 7-OH-MG. The authors concluded:

> "Though the conversion rate of 7-hydroxymitragynine from p.o. mitragynine is low, 7-hydroxymitragynine is a more potent and efficacious μ-opioid receptor agonist than mitragynine, suggesting that conversion to this metabolite may contribute to the in vivo μ-opioid activity of mitragynine." (p. 1)

Multiple investigators' research characterizing MG alkaloids receptor binding profiles and pharmacologic activities also supports pursuit of kratom alkaloid-based substances for the treatment of alcohol use disorder, pain, opioid withdrawal, and other disorders (Chakraborty, Uprety, Daibani, et al., 2021; Gutridge, Robins, Cassell, et al., 2020). Chakraborty, Uprety, Daibani, et al. (2021) concluded:

> "In conclusion, we report a thorough and complete in vitro pharmacological characterization of five kratom based minor alkaloids. Given their low abundance, it seems unlikely that these alkaloids play a major mediating role in the biological actions of kratom consumed by humans. However, these alkaloids represent novel starting points for optimizing probes to better understand opioid receptor function.
>
> There are three major findings from this present work. First, we identify three new templates present in kratom with antinociceptive activity in mice, with corynoxine being equipotent to morphine. Second, we identify ligands with an array of pharmacological profiles, ranging from the partial opioid agonism displayed by corynantheidine and mitraciliatine and full agonism of corynoxine and KOR agonism with isopaynantheine. Finally, we identify corynoxine and mitraciliatine to be structurally unique natural products with safer, MOR dependent antinociception, and we identify isopaynantheine as the first kratom alkaloid with KOR mediated antinociceptive actions." (p. 11)

Animal models are also employed to assess potential cognitive effects of kratom. Although kratom is commonly taken to enhance occupational performance and as a coffee substitute for energy at low doses, it would not be surprising to see performance decrements at high doses. Indeed, in an animal model of special learning and memory, high doses impaired memory in this model (Hassan, Suhaimi, Ramanathan, et al., 2019). The relevance of the results to

[11] https://www.kures.life/

humans cannot be assessed based on this study but it suggests that more research is warranted.

Suhaimi, Hassan, Mansor & Müller (2021) studied brain electroencephalogram (EEG) activity after acute and chronic exposure to chronic MG in rats. Suhaimi, et al. (2021) summarized their findings as follows:

> "… the changes in brain electroencephalogram (EEG) activity after acute and chronic exposure to mitragynine in freely moving rats. Vehicle, morphine (5 mg/kg) or mitragynine (1, 5 and 10 mg/kg) were administered for 28 days, and EEG activity was repeatedly recorded from the frontal cortex, neocortex and hippocampus. Repeated exposure to mitragynine increased delta, but decreased alpha powers in both cortical regions. It further decreased delta power in the hippocampus. These findings suggest that acute and chronic mitragynine can have profound effects on EEG activity, which may underlie effects on behavioral activity and cognition, particularly learning and memory function." (p. 1)

Gutridge, Robins, Cassell, et al. (2020) pharmacologically characterized kratom extracts, kratom alkaloids, and synthetic carfentanil-amide opioids interactions with G proteins and beta-arrestin at mu, delta and kappa opioid receptors *in vitro* and assessed the degree to which opioids reduced alcohol intake and whether they had rewarding properties. The authors stated:

> "In conclusion, we found that kratom alkaloids do not recruit β-arrestin 2 at the μOP, δOP and κOP and can significantly reduce both moderate and binge alcohol intake in male and female mice. This pharmacological profile and effect on alcohol intake in rodents may explain why some find kratom useful to self-medicate for alcohol use disorder. Yet, as we observed that kratom extract and 7-hydroxymitragynine exhibited reinforcing properties, our study also highlights the risks associated with kratom use. Our results indicate that δOPs contributed to the efficacy of the kratom alkaloids to reduce alcohol intake, whereas the lack of efficacy for the G protein-biased μOP agonist TRV130 to decrease alcohol intake argued against a major role for the μOP in this behavioral response. The ability of MP102, a synthetic G protein-biased opioid with a preference for δOP, to reduce alcohol intake without affecting general locomotion or inducing (δOP-mediated) CPP provides support for future efforts to produce G protein-selective, δOP-selective opioids for the treatment of alcohol use disorder, some of which could be plant-derived still as well". (p. 1510)

Hiranita, Leon, Felix, et al. (2019) compared the effects of MG to morphine in behavioral and antinocioception assays in rat models. They wrote:

> "Morphine and mitragynine dose-dependently decreased schedule-controlled responding; the ED50 values were 7.3 and 31.5 mg/kg, respectively. Both drugs increased thermal antinociception (the ED50 value for morphine was 18.3). Further, doses of naltrexone that antagonized morphine did not antagonize mitragynine. Mitragynine (17.8 mg/kg) did not alter the rate-decreasing or antinociceptive effects of morphine. …The antinociceptive effects of mitragynine and morphine occur at doses larger than those that disrupt learned behavior. Opioid receptors do not appear to mediate the disruptive effects of mitragynine on learned behavior. Mitragynine had

lesser antinociceptive effects than morphine, and these did not appear to be mediated by opioid receptors. The pharmacology of mitragynine includes a substantial non-opioid mechanism." (p. 1)

2.2.2.1 Studies of Kratom Minor Alkaloids and their Metabolites

While kratom contains many alkaloids (more than 50 identified to date and more likely to be discovered), only one or a few of these account for most of the effects produced in humans. This is a trait also found in other psychoactive plants, such as coffee, tea, and cannabis.

Most of these alkaloids are likely at what may be de minimis levels with respect to the human experience, effects, and safety. However, it is also possible that while the majority of the effects produced by natural plant-based preparations are mediated by MG, one or more of these minor alkaloids may also play a minor role. This may account for possible differences in strains of kratom products. Increasingly, it appears that 7-OH-MG, long considered a substance of potentially greater concern than MG from a safety perspective may occur naturally at functionally de minimis levels (Chear, Leon, Sharma, et al., 2021; Kruegel, Uprety, Grinell, et al., 2019).

These molecules are also of interest as potential new drug candidates or as templates for novel synthesized molecules. It has been estimated that up to one third to one half of FDA approved medicines are based on natural plant product substances that provided the novel structures utilized in development of the final approved medicines or which at least were critical in the drug development process (Newman & Cragg, 2016; Domnic, Narayanan, Mohana-Kumaran & Singh, 2021).

Chear, et al. (2021) reported the results of an extensive study in which:

> "Ten indole and oxindole alkaloids were isolated from the freshly collected leaves of Malaysian Mitragyna speciosa (Kratom). The chemical structures of these compounds were established on the basis of extensive 1D and 2D NMR and HRMS data analysis. The spectroscopic data of mitragynine oxindole B (4) are reported herein for the first time. The spatial configuration of mitragynine oxindole B (4) was confirmed by single-crystal X-ray diffraction. Simultaneous quantification of the isolated alkaloids in the M. speciosa leaf specimens collected from different locations in the northern region of Peninsular Malaysia was also performed using UPLC-MS/MS. The oxindole alkaloids (1−4) and the indole alkaloid (10) were assessed for binding affinity at opioid receptors. Corynoxine (1) showed high binding affinity to μ-opioid receptors with a Ki value of 16.4 nM. Further, corynoxine (1) was 1.8-fold more potent than morphine in rats subjected to a nociceptive hot plate assay. These findings have important implications for evaluating the combined effects of the minor oxindole alkaloids in the overall therapeutic activity of *M. speciosa*." (p. 1).

Domnic, Chear, Rahman, et al. (2021) showed that combinations of kratom alkaloids may inhibit cell proliferation and migration of nasopharyngeal carcinoma cells suggesting potential for the development of the substances themselves or possibly new analogs as new treatments for cancer. As discussed by the authors, these are early-stage findings but certainly findings that merit further study. Regarding 7-OH-MG, they also reported that 7-OH-MG was only

present at very low levels in all samples, supporting other reports which suggest that it is a postharvest artifact resulting from MG.

Kruegel, et al. (2019) has also suggested that the effects of kratom are not produced by exogenously ingested 7-OH-MG but that the metabolism of MG to small amounts of 7-OH-MG may modulate and contribute to some of the desired effects such as pain relief.

Sharma, Kamble, Leon, et al. (2019) employed a method to simultaneously quantify ten key kratom alkaloids in kratom leaf extracts and commercial products using ultra-performance liquid chromatography–tandem mass spectrometry. They summarized their results as follows:

> "…an ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) method was developed and validated for the quantification of ten key alkaloids, namely: corynantheidine, corynoxine, corynoxine B, 7-hydroxymitragynine, isocorynantheidine, mitragynine, mitraphylline, paynantheine, speciociliatine, and speciogynine… After successful validation, the method was applied for the quantification of kratom alkaloids in alkaloid-rich fractions, ethanolic extracts, lyophilized teas, and commercial products. Mitragynine (0.7%–38.7% w/w), paynantheine (0.3%–12.8% w/w), speciociliatine (0.4%–12.3% w/w), and speciogynine (0.1%–5.3% w/w) were the major alkaloids in the analyzed kratom products/extracts. Minor kratom alkaloids (corynantheidine, corynoxine, corynoxine B, 7-hydroxymitragynine, isocorynantheidine) were also quantified (0.01%–2.8% w/w) in the analyzed products; however mitraphylline was below the lower limit of quantification in all analyses." (p. 1)

Kamble, Berthold, King, et al. (2021) developed and validated a bioanalytical method for the simultaneous quantification of 11 kratom alkaloids in rats following oral administration of lyophilized kratom tea (LKT) and a marketed kratom product, Optimized Plant Mediated Solutions (OPMS). The authors concluded:

> "In the present study, OPMS liquid showed an extended exposure of kratom alkaloids as compared to LKT. Among the tested alkaloids, only MTG, 7-HMG [7-OH-MG], COR, and SPC showed measurable systemic exposure following an oral dose. Having an understanding of the pharmacokinetics of individual kratom alkaloids following the oral administration of kratom products in preclinical species will facilitate the design of clinical trials evaluating kratom products. Additionally, the developed bioanalytical method can be implemented for the analysis of plasma samples obtained from a variety of animal species including humans using standardized kratom products". (p. 6)

Bhowmik, Galeta, Havel, et al. (2021) mapped the neuropharmacology of Mitragyna alkaloids. The authors concluded

> "In summary, we describe a systematic examination of late-stage functionalization of kratom alkaloids, which provided efficient access to MG analogs and identified 11-F-7OH (22) as an important lead compound for further investigations". (p.11)

2.2.2.2 MG Metabolism and Metabolite Profiling.

Another rapidly advancing area of research is understanding the metabolic pathways and modulating enzymes including profiling of MG's metabolites, and identification of enzymes modulating MG metabolism.

Kamble, Sharma, King, et al. (2019) included the following summary in their abstract:

> "Metabolic pathways of MG were identified in human liver microsomes (HLM) and S9 fractions. A total of thirteen metabolites were identified, four oxidative metabolites and a metabolite formed by demethylation at the 9-methoxy group were the major metabolites of MG. 3. The cytochrome P450 enzymes involved in the metabolism of MG were identified using selective chemical inhibitors of HLM and recombinant cytochrome P450. The metabolism of MG was predominantly carried out through the CYP3A4 with minor contributions by CYP2D6 and CYP2C9. The formation of five oxidative metabolites (Met2, Met4, Met6, Met8 and Met11) was catalyzed by the CYP3A4. 4. In summary, MG was extensively metabolized in HLM primarily to O-demethylated and monooxidative metabolites. The CYP3A4 enzyme plays a predominant role in the metabolic clearance of MG and also in the formation of 7-hydroxyMG (Met2), a known active minor alkaloid identified in the leaf material." (p. 1)

Another study by Kamble, Sharma, King, et al. (2020) examined the potential interactions in metabolism of MG and other alkaloids that may occur with other substances including pharmaceutic products. This is also early work but fundamental in understanding potential interactions that could increase risk of use and may thereby at some point be included in warning labels for kratom and/or future potential kratom based drug products.

A systematic metabolic study evaluated how metabolism alters opioid mediated effects, possibly without increasing harmful respiratory effects. Kamble, León, King, et al. (2020) reported:

> "…in human plasma 7-HMG is converted to mitragynine pseudoindoxyl, an opioid that is even more potent than either mitragynine or 7-HMG. This novel metabolite is formed in human plasma to a much greater extent than in the preclinical species tested (mouse, rat, dog, and cynomolgus monkey) and due to its μ-opioid potency may substantially contribute to the pharmacology of kratom in humans to a greater extent than in other tested species." (p. 1)

Such research may explain potential human effects and benefits that may not be predicted in animal studies alone.

2.2.3 Factor 2 Updated Conclusions

Scientific advances in understanding the pharmacology and mechanisms of action of kratom's primary active alkaloid, MG, as well as 7-OH-MG, and increasingly the minor alkaloids that appear to contribute relatively little to the effects of kratom in kratom consumers may ultimately contribute to safer and more effective new medicines for a variety of disorders as well as for general health and well-being. Development and approval of such products may be a decade or more in the future, but in the meantime, this rapidly advancing science is helping to explain

how kratom works, and why its pain relieving and other benefits occur with relatively low levels of abuse, dependence, and harmful decreases in respiration as compared to opioids.

2.3 Factor 3 – The State of Current Scientific Knowledge Regarding the Drug

2.3.1 Summary of 2018 Findings:

The 2018 8-FA highlighted kratom's pharmacodynamic effects described in earlier investigations and reviews (e.g., Prozialeck, et al., 2012; Warner, et al., 2016). In one PK study involving oral MG administration to ten healthy male volunteers, a two-compartment model best described MG's pharmacokinetics (Trakulsrichai, et al., 2015). Preclinical and clinical pharmacokinetic data are limited, with significant variability within and between species. There was little clinical study of human physiological effects and health parameters to draw on.

2.3.2 Factor 3 Science Updates

Several new preclinical pharmacokinetic studies also provide important safety data, as animals were closely monitored over 12 h or more for adverse events associated with MG and 7-OH-MG plasma concentrations.

2.3.2.1 Pharmacokinetics and Pharmacodynamics Findings Related to Safety (MG and 7-OH-MG)

Most human consumption in the US and SEA is in traditional tea-like decoctions containing 0.5-1 mg/kg MG per serving; however, more intense users managing chronic pain or suffering from opioid use disorder may consume four or more servings per day and in some cases, larger serving sizes, totaling 20 mg/kg/day.

Avery, Boddu, Sharma, et al. (2019) studied the pharmacokinetics of mitragynine in rats following oral administration of a variety of preparations. One of the many important findings was summarized as follows:

> "The results provide evidence that an equivalent oral dose of the traditional preparation (lyophilized kratom tea) and formulated/manufactured products (organic fraction) of kratom leaves provide better systemic exposure of mitragynine than that of mitragynine dosed alone." (p. 1)

Maxwell, King, Kamble, et al. (2020) evaluated MG's safety and pharmacokinetics in beagle dogs following 5 mg/kg oral MG (equivalent to approximately 3 mg/kg in humans) and 0.1 mg IV MG. The authors summarized:

> "The dose of 7-HMG used in this study was well tolerated with no adverse events or major abnormalities in clinical parameters…Derived pharmacokinetic parameters of 7-HMG from this study can be scaled allometrically along with the pharmacokinetic parameters of mitragynine to predict the dose of mitragynine while designing the first in human study." (p. 462)

No life threatening or serious adverse events were reported.

The Hiranita, Sharma, Oyola, et al. (2020) study discussed in Factor 2 also evaluated the pharmacokinetics of 55 mg/kg oral MG in rats. As reported:

> "Following p.o. administration of mitragynine (HCl salt, 55 mg/kg), the Cmax value of 7-hydroxymitragynine (85 ng/mL) was 14-fold less than that of mitragynine. The Tmax values of 7-hydroxymitragynine and mitragynine were 30 and 84 minutes, respectively… drug discrimination was used as a pharmacologically selective measure of μ-opioid receptor agonism *in vivo*. In rats discriminating morphine (3.2 mg/kg, i.p.) from vehicle, the discriminative stimulus effects of mitragynine were assessed 90 minutes after p.o. administration to correspond to its Tmax. Mitragynine (up to 178 mg/kg) produced 76% morphine-lever responding (ED50=51 mg/kg). Though the conversion rate of 7-hydroxymitragynine from p.o. mitragynine is low, 7-hydroxymitragynine is a more potent and efficacious μ-opioid receptor agonist than mitragynine, suggesting that conversion to this metabolite may contribute to the *in vivo* μ-opioid activity of MG." (p. 1)

2.3.2.2 Pharmacokinetic and Pharmacodynamic Findings Related to Safety (Minor Alkaloids)

In addition to studies of MG and 7-OH-MG pharmacokinetics, there is increasing attention to the pharmacokinetics and other effects of other alkaloids from traditional kratom tea decoctions and commercial products.

Kamble, Berthold, King, et al. (2021) characterized the pharmacokinetics of eleven alkaloids given orally to rats. As described by the authors, they:

> "…developed and validated a bioanalytical method for the simultaneous quantitation of 11 kratom alkaloids (mitragynine, 7-hydroxymitragynine, corynantheidine, speciogynine, speciociliatine, paynantheine, corynoxine, corynoxine-B, mitraphylline, ajmalicine, and isospeciofoline) in rat plasma. The validated method was used to analyze oral pharmacokinetic study samples of lyophilized kratom tea (LKT) and a marketed product, OPMS liquid shot, in rats. Among the 11 alkaloids, only mitragynine, 7-hydroxymitragynine, speciociliatine, and corynantheidine showed systemic exposure 8 h post dose, and the dose-normalized systemic exposure of these four alkaloids was higher (1.6−2.4-fold) following the administration of the commercial OPMS liquid. Paynantheine and speciogynine levels were quantifiable up to 1 h post dose, whereas none of the other alkaloids were detected. In summary, the method was successfully applied to quantify the exposure of individual kratom alkaloids after an oral dose of traditional or commercial products. This information will contribute to understanding the role of each alkaloid in the overall pharmacology of kratom and elucidating the pharmacokinetic differences between traditional and commercial kratom products." (p. 1)

Berthold, Kamble, Raju, et al. (2021) studied the pharmacokinetics of the minor indole kratom alkaloid, speciociliatine. They summarized:

> "An ultra-performance liquid chromatography tandem mass spectrometry method was developed and validated to quantify speciociliatine in rat plasma. The quantitation range

was 3−600 ng/mL. The validated method was applied to a preclinical pharmacokinetic study in male Sprague-Dawley rats after 2.5 mg/kg intravenous (I.V.) and 20 mg/kg oral (P.O.) dosing. The plasma was analyzed to obtain concentration-time profiles and results were subjected to non-compartmental analysis to determine pharmacokinetic parameters including volume of distribution (6.2 ± 2.3 L/kg I.V.), clearance (0.7 ± 0.2 L/h/kg), and absolute oral bioavailability (20.7%). Speciociliatine had higher systemic exposure and lower clearance compared to the other kratom alkaloids mitragynine and corynantheidine. The speciociliatine pharmacokinetic parameters described here will help to better understand the overall effects reported with kratom product use." (p. 1)

These data suggest why natural kratom leaf based kratom products, extracts, and tea-like decoctions might differ in the effects experienced by kratom users from more refined extracts, as explained by the authors:

> "Interestingly, the exposure of mitragynine when it is dosed orally in rats as lyophilized kratom tea or the organic fraction obtained from lyophilized kratom tea increases by 1.5- and 1.8-fold, respectively [18]. The lyophilized kratom tea and organic fraction contains all the alkaloids that would be present in the plant, including speciociliatine. These results indicate that the presence of other alkaloids found in the traditional preparation have influence on the pharmacokinetics of mitragynine. Similarly, the pharmacokinetic parameters of speciociliatine, when dosed in combination with the other naturally occurring alkaloids, may be altered. Further research into the pharmacokinetics of minor indole alkaloids after administration of a lyophilized kratom tea product must be investigated to determine which alkaloids' parameters are affected by the presence of other compounds." (p. 2)

This is not to imply that chewing kratom leaves, kratom tea like decoctions or more simplified extracts are more beneficial or safer than other MG products, but that they may differ in the effects that users seek, desired and undesired. It supports the conclusion that since none were demonstrated to be more beneficial or harmful than others, with the exception of adulterated products in which other substances are added or possibly an individual alkaloid's concentration is boosted to unnaturally high levels (e.g., 7-OH-MG), that there is yet no safety basis for banning such products from the marketplace.

A published abstract by Jagabalan, Zainal, Ganaby, et al. (2019) reported:

> "Estimated typical clearance (CL/F) value was 2.21 L/hr, absorption rate (Ka) of 0.82/hr, and volume of distribution (Vd) of 30.8L. . . . Based on the single dosing experimental rat data, the model [2-compartment distribution with 1st order absorption] provides a useful tool to quantify the pharmacokinetic parameters to propose an optimal dosing regimen in rats. Subsequently, the pharmacokinetics parameter can be modeled to the pharmacodynamics of MG for extrapolation into human use." (p. 1)

King, Sharma, Kamble, et al. (2020) developed bioanalytic methods to study the PK of corynanthidine, which is a minor kratom alkaloid that binds to opioid receptors and acts as a functional opioid antagonist (e.g., with some naloxone-like properties). This study was important both for its methods development as well as characterization of the PK of corynanthidine given intravenously and orally to rats.

2.3.2.3 Safety Assessments from Preclinical and Clinical Studies

Currently, there are no validated assessments of the lethal dose for humans or animals, mainly due to the unreliability and difficulty in studies that have attempted to determine lethal doses in animals, and the fact that most human deaths in which kratom use was verified were more likely caused by other substances (e.g., Olsen et al. 2019; Henningfield, Grundmann, Babin, et al. 2018, Babin, 2019).

Smith et al., 2019 conducted a study comparing oral and intravenous MG and 7-OH-MG to establish the lethal doses (LD_{50} doses) in mice. They were able to produce death by an oral dose of 547.7 mg/kg MG, though were unable to produce death by oral 7-OH-MG administration. Large intravenous doses of MG (27.8mg/kg), 7-OH-MG (24.7 mg/kg), and heroin (23.7 mg/kg) were also lethal. Some of their observations are inconsistent with those from other laboratories (e.g., Kruegel, Gassaway, Kapoor et al., 2016 and see also Kruegel et al., 2019), though not consistent with rat toxicity study data summarized in Henningfield, Fant & Wang, 2018; thus, this study awaits replication.

It should be noted that human use of kratom alkaloids by intravenous injection is not practiced for several reasons. First, rapid administration (e.g. smoking) does not produce as pleasurable effects or desired effects compared to oral use (Henningfield, Fant and Wang, 2018). Additionally, MG and 7-OH-MG are not soluble in water and must be prepared using specialized laboratory preparations involving a tween/DMSO based vehicle (as used in Smith et al., 2019). Thus, this study represents another line of research that will be important to continue but its relevance to real world kratom safety and toxicity is not clear.

To better understand potential health and safety related effects related to kratom use, Leong Bin Abdullah, Tan, Mohd, et al. (2020) studied the lipid profiles, liver function and other parameters in 100 chronic kratom users compared to 100 healthy nonusers in Malaysia. Although the study was acknowledged by the authors to be relatively small and exploratory, their preliminary findings will be useful in the design of future studies. They found:

> "The liver parameters of the study participants were within normal range. The serum total cholesterol and LDL of kratom users were significantly lower than those of healthy subjects who do not use kratom. There were no significant differences in the serum triglyceride and HDL levels. However, higher average daily frequency of kratom use and increasing age were associated with increased serum total cholesterol among kratom users. Other kratom use characteristics such as age of first kratom intake, duration of kratom use, and quantity of daily kratom intake were not associated with increased serum triglyceride, total cholesterol, LDL, and HDL levels. Our findings suggest regular kratom consumption was not linked to elevated serum lipids, except when there is a higher frequency of daily kratom intake. However, the study was limited by the small sample size, and hence a more comprehensive study with larger sample size is warranted to confirm the findings." (p. 1)

A preliminary study of the impact of kratom use on brain function (as assessed by brain magnetic resonance imaging) among chronic kratom users in Malaysia was conducted by Singh, Chye, Suo, et al. (2018). In brief, they reported:

> "A total of 14 subjects (7 regular kratom users and 7 non-kratom users) voluntarily participated in this cross-sectional study…. There were no significant differences (p>0.05) in the intracranial volume (ICV), cortical volumes (frontal, parietal, temporal, occipital, or cingulate lobe), or subcortical volumes (striatum, hippocampus, or amygdala), as well as in the diffusion tensor imaging (DTI) metrics, fractional anisotropy (FA) and mean diffusivity (MD) between kratom users and the controls.
>
> Conclusion: This preliminary study showed long-term consumption of kratom decoction is not significantly associated with altered brain structures in regular kratom users in traditional settings. However, further study is needed to establish more data for kratom use and its effects." (p. 1)

Singh, Müller, Murugaiyah, et al. (2018) studied various hematological and clinical-chemistry parameters of kratom users in Malaysia. In brief, Singh, et al. (2018) summarized their results as follows:

> "A total of 77 subjects (n=58 regular kratom users, and n=19 healthy controls) participated in this cross-sectional study. All the surveys were conducted through face-to-face interview to elicit subject's sociodemographic characteristics and kratom use history. A full-blood test was also administered. Laboratory analysis was conducted using GC-MS to determine mitragynine content in the acquired kratom samples in order to relate mitragynine consumption with possible alterations in the blood parameters of kratom users. Findings showed that there were no significant differences in the hematological and clinical-chemistry parameters of traditional kratom users and healthy controls, except for HDL and LDL cholesterol values; these were found to be above the normal reference range for the former. Similarly, long-term kratom consumption (> 5 years), and quantity of daily kratom use (≥3 ½ glasses; mitragynine content 76.3–114.8 mg) did not appear to alter the hematological and biochemical parameters of kratom users. These data suggest that even long-term and heavy kratom consumption did not significantly alter the hematological and clinical-chemistry parameters of kratom users in a traditional setting." (p. 1)

Singh, Narayanan, Grundmann, et al. (2020), studied the long-term effects of kratom use in thirteen people in Malaysia who had used kratom longer than 20 years in a cross-sectional pilot study. They summarized their results as follows:

> "Respondents were required to undergo a blood-test and laboratory analysis was conducted to determine the mitragynine content in an acquired street sample of kratom. The regular, long-term consumption of brewed kratom decoction did not cause any significant alterations in haematological, kidney, liver, thyroid, inflammatory and gastrointestinal analytes in a cohort of kratom users who had no history of substance misuse. However, those who had a higher intake (>3 glasses per day) of kratom exhibited higher lipid values (except for HDL-cholesterol), and a moderate elevation of homocysteine level. Long-term (>20 years with a daily intake of ≥87.54mg of mitragynine) kratom consumption was not associated with altered biochemical levels, although prolonged and heavy use (>3 glasses daily) may result in cardiovascular risks. The latter finding, however, requires further investigation." (pg. 1)

Singh, Narayanan, Müller et al. (2019) studied potential long-term cognitive effects associated with kratom use in kratom uses in Malaysia. Singh, et al. (2019) summarized their results as follows:

> "We assessed the cognitive function of 70 regular kratom users and 25 control participants using the Cambridge Neuropsychological Test Automated Battery. Participants performed six neuropsychological tasks that assessed motor, learning and memory, attention and executive function. Relative to control participants, higher consumption (>3 glasses daily or mitragynine doses between 72.5 mg and 74.9 mg) of kratom tea was selectively associated with impaired performance on the Paired Associates Learning task, reflecting deficits in visual episodic memory and new learning. Overall, the performance of kratom users compared to control participants, and the performance of high (>3 glasses per day) as well as low (≤3 glasses per day) kratom using groups, were comparable on all neuropsychological domains. Higher intake of kratom juice (>3 glasses daily) did not appear to impair motor, memory, attention or executive function of regular kratom users." (p. 1)

Increasing attention to safety related signals is evident in much ongoing kratom research. For example, Leong Abdullah, Tan, Narayanan, et al. (2021) studied the prevalence of ECG abnormalities and QTc intervals in kratom users without histories of illicit drug use. They found:

> "…the odds of having ECG abnormalities did not differ between kratom users and non-kratom-using control subjects, except for higher odds of sinus tachycardia in kratom users. Torsades de pointes was not reported among kratom users, but greater age at first kratom use, longer duration of kratom use, the higher daily quantity of kratom use, and intake of kratom less than 3 h before an assessment could increase the QTc interval with an estimated daily mitragynine intake of 434.28 mg (7.06 mg/kg/day). Hence, we found that regular daily kratom consumption led to borderline QTc intervals, but it was not associated with prolonged QTc intervals. However, further controlled clinical studies are needed to confirm our findings." (p. 1)

2.3.3 Factor 3 Updated Conclusions

Among the most important data in assessing product safety is investigation of the patterns of exposure and associated safety in pharmacokinetics and other studies. As described, the science advanced considerably in this domain. It shows that over a broad range of doses, dosage form and within two species (rat and dog) MG can be safely given. This includes oral doses that are many multiples of those consumed by humans.

Additionally, six clinical studies evaluated the effects of long-term kratom use on a variety of physiological parameters including kidney and liver function, blood chemistry hematological parameters, cognition, cardiac parameters including ECG, and on brain function by brain magnetic resonance imaging. Although these were relatively small studies, none suggest serious adverse consequences of use. It is important to note that these are not definitive safety studies and cannot be used to claim that kratom has no adverse effects on any of the studied physiological domains and limitations of each study were noted in the publications. Nonetheless, the findings are encouraging and should facilitate the conduct of more comprehensive follow-up studies.

2.4 Factors 4, 5, and 6 – History and Current Patterns of Abuse; The Scope, Significance and Duration of abuse; What, if any, Risk is there to the Public Health

Note that for this update, Factors 4, 5 and 6 are considered together because they all contribute to understanding nonmedical use, recreational use and abuse, and public health impact, relying on some of the same surveys across factors.

These factors address public health considerations which include the impact of various regulatory approaches on individual and public health risks and benefits of CSA scheduling versus not scheduling, as well as the most appropriate schedule if the substance or product is approved for therapeutic use. Substances that are considered to merit control in the CSA but which are not approved for therapeutic use can only be placed in Schedule I regardless of their actual abuse potential.

For temporary scheduling (also known as “emergency” scheduling) only factors 4, 5, and 6 must be considered. Temporary scheduling lasts for two years and can be recommended by the FDA or conducted by DEA without recommendation from FDA.

The key conclusion of analysis of Factors 4, 5 and 6 that must be drawn to support temporary scheduling is that the substance poses an imminent risk to public health related to its abuse. For poisons and toxins not used for psychoactive and abuse related effects, such as contaminated food products, etc. public health interventions and sometimes regulations other than the CSA are employed as appropriate.

2.4.1 Summary of 2018 Findings:

Survey and public health data are the most important sources of information to determine if a substance merits temporary scheduling. Only Factors 4, 5 and 6 must be considered for temporary scheduling. If these factors together support the conclusion that a substance poses imminent risk to public health related to its abuse and apparently addictive use, then the substance or product can be placed in the CSA. Schedule I is the only option if there is no FDA approved therapeutic use (i.e., approval as a medicine). Note for poisons and toxins that are not used for psychoactive and abuse related effects, the CSA is not considered the appropriate regulatory tool to protect public health.

Factors 4, 5 and 6 of the 2018 8-FA documented several decades of kratom use in the US that began before the 1980s. In contrast to opioids, kratom use in SEA and the US was almost exclusively by the oral route with use primarily for health and well-being including self-management of pain, opioids and other addictions, improvement of mood in people with depression and anxiety disorders, and for many people as an alternative or complement to coffee to improve occupational performance. Use for recreational purposes, e.g., to get “high” was not a major category of use. Major US federal surveys including the Drug Abuse Warning Network (DAWN) (until 2011 when it was discontinued), the Monitoring the Future Survey (MTFS), Treatment Episodes Data Set (TEDS), and the National Survey on Drug Use and Health (NSDUH) showed little evidence of kratom use, abuse, addiction or harm.

Although the DEA’s National Forensic Laboratory Information System (NFLIS) began detecting MG use and reporting it in 2010 as a potential emerging trend, overall reports remained low (less than 200 of 1,549,313) in 2015, and apparently below the threshold for continued

reporting when the 2018 8-FA was written. The Henningfield, Fant & Wang (2018) 8-FA summarized Factor 4 as follows

> "As confirmed by NFLIS, kratom is available to persons who have been found with substances of abuse, yet kratom has not emerged as a substance of abuse by any of the federal surveillance systems. Nonetheless, as MG identifications were a new category, the DEA placed MG on its "watch list," meaning essentially that laboratories and investigators are encouraged to be alert for products potentially containing MG and to be testing for MG....The relative absence of apparent abuse of kratom as measured by national surveys does not mean there is no abuse, but certainly the signal is very weak compared to many other substances that people seek help for to achieve abstinence.…As mentioned earlier, the very low risk of overdose poisoning and serious adverse events does not mean that they have not and will not occur. However, given the two decades during which consumption has increased to an estimated two or more million consumers in the US, in addition to far more extensive consumption in SE Asia, this is a substance and category of product with a remarkable safety record." (p. 580)

2.4.2 Factor 4, 5, and 6 Science Updates

2.4.2.1 Prevalence of Kratom Use in the US

One of the most important questions in public health assessments relevant to a drug's health risks and benefits is the number of users. The surveys and more than 20,000 comments to the DEA in 2016 define the demographics of kratom users and their reasons for use. Although estimates vary across surveys, together they suggest that most kratom users are 30-50 years of age, more male than female, with some college education, employed, have health care, and are a diverse ethnic/racial mix with somewhat more kratom users identifying as White than other ethnicities (Coe et al., 2019; Covvey, Vogel, Peckham, et al., 2020; Garcia-Romeu, et al., 2020; US DHHS, 2020; Palamar et al., 2021). Surveys that focused on kratom use and opioids (e.g., Coe, et al., 2019; Garcia-Romeu, et al., 2020) or kratom use and pain find high rates of opioid use motivated in large part to replace opioids. The Grundmann (2017) survey found that most kratom users were not opioid users, and similarly the survey presented by Henningfield et al. at the American College of Neuropsychopharmacology meeting with more than 14,000 respondents found that most people used for reasons that were not related to opioids or addiction (Henningfield, et al., 2020).

But there still is no reliable estimate of the actual number of kratom users and surveys vary widely in their estimates, as shown in Table 5 below. There is consensus from 2014 that the American Botanical Education Alliance estimate of 3-5 million was credible and consistent with kratom suppliers and marketers estimates, and that kratom sales and use steadily increased. Thus, the American Kratom Association estimate of approximately 10-15 million based on Indonesian kratom export data, and with input from US marketers appears plausible.

The Covvey, et al. (2020) nationally representative online survey estimated past year use to be approximately 10.5 million kratom consumers. Informal marketer estimates suggest that kratom consumption also increased during the COVID-19 epidemic, which is not surprising due to frequent use of kratom to self-manage opioid use disorder, anxiety, stress, and depression.

2.4.2.1.1 National Survey on Drug Use and Health (NSDUH)

Prior to 2019, NSDUH did not include kratom/MG-specific items. From 2010 through 2018, there were a total of nine (9) lifetime kratom mentions (unweighted – not nationally representative), although five of those were in the last two years (2017 and 2018). By contrast, and over the same time frame, lifetime mentions (unweighted) of oxycodone, heroin, cocaine, amphetamine, marijuana, and other prototypic substances of abuse were in the many thousands. Lifetime aspirin mentions ranged from 7 to 23 per year, while lifetime diphenhydramine mentions ranged from 11 to 46 per year. See Table 1.

Table 1: Number of Unweighted Lifetime Cases of Kratom, Aspirin, Diphenhydramine, and Other Substances Reported to the National Survey on Drug Use and Health (2010-2018)

	NSDUH – Lifetime Number of Unweighted Cases								
	2010	*2011*	*2012*	*2013*	*2014*	*2015*	*2016*	*2017*	*2018*
Kratom/Mitragynine†	1	0	0	0	1	1	1	3	2
Oxycodone§	2,068	2,097	2,017	1,877	1,835	*	*	*	*
Heroin§	771	826	829	842	946	956	961	1,029	962
Cocaine§	6,464	6,260	6,009	5,653	6,636	6,740	6,580	6,748	6,646
Amphetamine§	3,916	4,136	4,113	4,171	4,179	*	*	*	*
Marijuana§	22,842	22,994	22,238	22,163	23,462	24,302	23,789	24,225	24,280
Aspirin†	17	22	18	18	19	7	7	18	23
Diphenhydramine†	29	21	19	20	12	18	11	21	46

† Unweighted non-medical/illicit use case mentions from open-ended response items only
§ Unweighted non-medical/illicit use case mentions from drug-specific and open-ended response items
** Estimate suppressed by SAMHSA*

In 2019, NSDUH added a series of kratom-related items to the survey, allowing for nationally representative estimates of lifetime, past-year, and past-month kratom use vs. comparators. In 2019, an estimated 3.9 million (1.4%) Americans aged 12 and older had used kratom in their lifetime, with 1.9 million (0.7%) using in the past year and 0.8 million (0.3%) using in the past month. In comparison, 4.5 million (1.6%) had misused prescription amphetamine products and 3.2 million (1.2%) had misused oxycodone in the past year, while illicit drugs such as marijuana (48.2 million [17.5%]) and cocaine (5.5 million [2.0%]) were also used more frequently than kratom. As shown in Table 2, the majority of kratom use is kratom only or kratom with alcohol which is different from the “polypharmacy” that is increasingly normal in recreational drug users; the exception is the common use of kratom by users of opioids, alcohol, stimulants, and other drugs as an aid to reducing and/or stopping use of those drugs and/or managing withdrawal when use of those drugs was discontinued.

Table 2: Lifetime, Past Year, and Past Month Use of Kratom vs. Misuse or Illicit Use of Comparators (Numbers in 1,000s), NSDUH (2019)

	Use / Misuse / Illicit Use N in 1,000s (%)		
	Lifetime	*Past Year*	*Past Month*
Kratom/Mitragynine	3,909 (1.4%)	1,919 (0.7%)	825 (0.3%)
Oxycodone†	*	3,185 (1.2%)	N/A
Heroin§	5,696 (2.1%)	745 (0.3%)	431 (0.2%)
Cocaine§	41,445 (15.1%)	5,468 (2.0%)	1,998 (0.7%)
Amphetamine†	*	4,486 (1.6%)	N/A
Marijuana§	127,139 (46.2%)	48,242 (17.5%)	31,606 (11.5%)

All estimates (N and %) are weighted to be nationally representative
N/A Data not collected by NSDUH
† Misuse of prescription or OTC product
§ Illicit use
** Estimate suppressed by SAMHSA*

Past month kratom use alone and in combination with other substances are presented in Table 3 below.

Table 3: Past Month Kratom Use Among Adults 18+: Overall, Kratom Only Use, and In Combination with Misuse or Use of Other Substances, NSDUH (2019)

	Past Month Kratom Use	
	% of US Adults 18 Years of Age or Older	*% of Adult Past Month Kratom Users*
Overall	0.32%	100.00%
Kratom and Pain Reliever Misuse	0.02%	7.04%
Kratom and Sedative Misuse	<0.01%	1.05%
Kratom and Alcohol	0.23%	71.87%
Kratom and Stimulant Misuse or Cocaine Use	0.04%	12.38%
Kratom Only	0.08%	24.41%

** All estimates are weighted to be nationally representative*
***Categories are not mutually exclusive (e.g., Kratom and Pain Relievers includes all respondents using both kratom and pain relievers, regardless of whether they were using other substances listed here)*
****The Kratom Only category excludes only those substances listed in this table. A respondent using Kratom and a substance not included in this table would be considered a kratom only user for the purposes of this analysis*

However, the NSDUH survey appears to greatly underestimate kratom use (see estimates in **Error! Reference source not found.**), just as it apparently does for many new psychoactive s ubstances (NPS). This deficiency was discussed by Palamar et al. (2015), who called for “new survey methods to prevent underreporting”. Similarly, the RADARS survey (Schimmel, et al., 2021) may have similar deficiencies. Both of these surveys include large panels who are interviewed, and it is possible that panel selection and/or interview approaches that provide realistic assessments of traditional recreationally used drugs and prescription opioids may underestimate use of novel products, and products taken for health and well-being and not for recreational purposes. These hypotheses require examination as the answers are not clear; however, kratom experts and marketers agree that that the NSDUH and RADARS surveys substantially underestimate the number of kratom users in the US.

Table 4: Kratom use prevalence estimates across studies in the United States

Year	Source	Method	Prevalence
2019	NSDUH 2020	• US Federal survey by SAMHSA (N=67,625) • Nationally representative multi-stage probability sample with face-to-face interviews • % estimates of US population aged 12+ (18+ presented in this slide)	Lifetime: 1.5% Past year: 0.7% Past month: 0.3% Past year adult users estimate: 1,790,000
2018-2019	Schimmel et al. 2020	• US survey by RADARS System panel (N=59,714) • Non-probability sample with online self-administration • % estimates of US population aged 18+	Lifetime: 1.3% Past year: 0.8% Past year adult users estimate: 2,040,000
2019	Covvey et al. 2020	• US survey via Qualtrics Panels (N=1,842) • Non-probability sample with online self-administration • % estimates of US population aged 18–59	Lifetime: 6.1% Past year: 4.1% Past month: 3.5% Past year adult users estimate: 10,500,000
2019	American Kratom Association	• Southeast Asian survey of commercial kratom exporters • Average monthly volume of kratom exported to US ÷ average volume of kratom used by US kratom consumer = approximate number of US kratom consumers	estimated US kratom consumers: 15,600,244
2014-2016	Botanical Education Alliance	• US survey of kratom venders	Estimated 3–5 million kratom consumers

2.4.2.1.2 Treatment Episode Datasets (TEDS) and Monitoring the Future (MTF)

There are no updates to the TEDS and MTF data sets since the 2018 report. Note that the lack of reports does not mean there were no instances of treatment seeking or recreational use by young people. In fact, there are internet and media reports that suggest some recreational use by youth, and there are self-reports of addiction in some kratom users on internet discussion groups and in internet surveys of adults. However, the signals from TEDS and MTF are apparently small enough not to warrant reporting.

2.4.2.1.3 Drug Abuse Warning Network (DAWN)

A new iteration of DAWN began collecting data from a sample of hospitals in April 2019. While some preliminary data were released (April 2019-October 2020), data related to kratom are not yet available.

2.4.2.1.4 American Association of Poison Control Centers' National Poison Data System (AAPCC-NPDS)

From 2011-2017, a total of 1,807 exposures involving kratom were reported to AAPCC, with about two-thirds of those occurring in 2016-2017 (Post, Spiller Chounthirath & Smith, 2018). *Kratom* is listed as a separate product in the AAPCC annual reports since 2016; however,

Plants-Mitragyna and *Mitragyna speciosa korthals* are not listed separately in the reports (they are included in broader categories). Thus, only the generic-coded *Kratom* cases are available when using the AAPCC annual reports as a data source. Table 5 below shows those calls listed under the generic *Kratom* code, as well as widely used substances that are readily available without prescription as comparators, for the years 2016-2019. Nicotine gum, lozenge and patch and the lessor used prescription nicotine nasal spray and oral inhaler all carry dependence potential, are used off-label by some people, and can sustain dependence. Abrupt discontinuation is not recommended due to the possibility of a withdrawal syndrome, but these comparators are not listed in the Controlled Substances Act because their abuse potential is lower than the products they replace (namely cigarettes) and it was considered in the interest of public health to make them more readily available (FDA, 1995, 1996).

Table 5: Exposure Cases by Product, (AAPCC-NPDS, 2016-2019)

	2016	2017	2018	2019
Kratom	1	372	1,146	1,357
Diphenhydramine*	55,740	55,075	53,842	53,121
Aspirin**	17,882	18,089	17,380	16,317
Nicotine Pharmaceuticals***	1,571	1,582	1,741	1,809

*Diphenhydramine alone or in combine
**Aspirin only; does not include combination products
***Nicotine gum, patch, and lozenge

2.4.2.1.5 National Forensic Laboratory Information System (NFLIS)

There are no updates to the NFLIS data set since the 2018 report.

2.4.2.2 Reports of Overdose and Death

In FDA's February 6, 2018 report by Commissioner Scott Gottlieb[12], in which FDA stated that it had documented 44 kratom associated deaths (worldwide over nearly ten years), it included the following acknowledgement:

> "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."

About six months later, the Assistant Secretary of Health of the US Department of Health and Human Services (DHHS) reviewed the FDA-prepared 8-FA submitted to the US Drug Enforcement Administration (DEA) in October of 2017 with a recommendation to Schedule MG and 7-OH-MG as Schedule I drugs in the CSA (thus, effectively banning legal sales and possession of kratom). The Secretary discovered that the death highlighted in Commissioner

[12] https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-agencys-scientific-evidence-presence-opioid-compounds

Gottlieb's report due to the apparent absence of other substances was caused by an automobile crash, and there was no evidence that kratom use was a contributing factor.

Babin (2018) evaluated all deaths reported by the FDA as potentially related to kratom. She concluded:

> "None of the case reports released to date support the evidentiary standard required by the CSA to prove there is a risk to the public health that relies primarily on the FDA claim of numerous deaths associated with kratom.
>
> In fact, the data show only that a relatively small number of individuals died from a variety of actual causes related to underlying health issues, abuse of prescription or illicit drugs either at toxic doses or taken in combination when contraindicated. The use of kratom by these individuals has no medical or statistical significance in assessing the safety signal required for scheduling." (p. 8).

Olsen, O'Donnell, Mattson, et al. (2019) commented on 152 unintentional drug overdose deaths listed as associated with kratom, out of 27,338 deaths listed in the State Unintentional Drug Overdose Reporting System (SUDORS). The authors included the following statements supporting their concerns about potential kratom risks, as well as uncertainties about the actual contribution of kratom to deaths reported by medical examiners as "kratom caused" and/or "kratom associated":

> "Data on 27,338 overdose deaths that occurred during July 2016–December 2017 were entered into SUDORS, and 152 (0.56%) of these decedents tested positive for kratom on postmortem toxicology (kratom-positive). Postmortem toxicology testing protocols were not documented and varied among and within states. 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)." (p. 1)

Gershman, Timm, Frank, et al. (2019) reviewed autopsy reports and performed additional analyses on available blood samples from 15 death cases that mentioned kratom from 1999 to 2017. They reported:

> "Autopsy reports were reviewed for all 15 deaths, which included 13 men and 2 women, with a median age of 28 years (range, 24 to 53). On the basis of toxicology testing, 11 cases involved multidrug ingestion (two to six drugs), and 8 persons had positive test results for other opioids. Four deaths were reported to involve mitragynine only, and coroners attributed each to mitragynine toxicity. We further investigated the 4 deaths that appeared to be due to mitragynine only, reviewing police investigation records for all 4 and performing comprehensive toxicology screening with high-performance liquid chromatography with tandem mass spectrometry for the 3 cases for which residual blood was available (Table 1). In our investigation of all 15 kratom-related deaths, we determined that 14 deaths clearly involved multiple drugs. Mitragynine levels varied widely, from 16 to 4800 ng per milliliter. Residual blood was not available for confirmatory testing in the remaining kratom-related death." (p. 1)

The Olsen, et al. (2019) and Gershman, et al. (2019) reports are consistent with the evaluation of Dr. Babin (2018) and the position of NIDA (2019) on its website that suggests that in the vast majority of kratom associated deaths, it cannot be ruled out that other substances or conditions were contributing, if not the primary, cause of death.

NIDA's Kratom Facts webpage states:

> "Can a person overdose on kratom? There have been multiple reports of deaths in people who had ingested kratom, but most have involved other substances. A 2019 paper analyzing data from the National Poison Data System found that between 2011-2017 there were 11 deaths associated with kratom exposure. Nine of the 11 deaths involved kratom plus other drugs and medicines, such as diphenhydramine (an antihistamine), alcohol, caffeine, benzodiazepines, fentanyl, and cocaine. Two deaths were reported following exposure to kratom alone with no other reported substances, but the extent of toxicological testing is unknown.* In 2017, the FDA identified at least 44 deaths related to kratom, with at least one case investigated as possible use of pure kratom. The FDA reports note that many of the kratom-associated deaths resulted from intake of adulterated products or taking kratom with other potent substances, including illicit drugs, opioids, benzodiazepines, alcohol, gabapentin, and over-the-counter medications, such as cough syrup. Also, there are reports of kratom packaged as dietary supplements or dietary ingredients laced with other compounds that caused deaths. People should check with their health care providers about the safety of mixing kratom with other medicines." (NIDA, 2019)

NIDA's position is consistent with the conclusion drawn by Assistant Secretary of Health Brett P. Giroir, MD, ADM who stated:

> "There is still debate among reputable scientists over whether kratom by itself is associated with fatal overdoses" (Giroir, 2018).

Palamar (2021) examined data from the 2019 National Survey on Drug Use and Health that included 56,136 respondents. The author concluded:

> "Kratom use is particularly prevalent among those with opioid use disorder but is also prevalent among people who use other drugs. Use has been associated with numerous adverse events, although most have involved use of other drugs." (p. 5)

Gershman, Timm, Frank, et al. (2019) reviewed autopsy reports and performed additional analyses on available blood samples from 15 death cases that mentioned kratom from 1999 to 2017. They reported:

> "Autopsy reports were reviewed for all 15 deaths, which included 13 men and 2 women, with a median age of 28 years (range, 24 to 53). On the basis of toxicology testing, 11 cases involved multidrug ingestion (two to six drugs), and 8 persons had positive test results for other opioids. Four deaths were reported to involve mitragynine only, and coroners attributed each to mitragynine toxicity. We further investigated the 4 deaths that appeared to be due to mitragynine only, reviewing police investigation records for all 4 and performing comprehensive toxicology screening with high-performance liquid chromatography with tandem mass spectrometry for the 3 cases for which residual

blood was available (Table 1). In our investigation of all 15 kratom-related deaths, we determined that 14 deaths clearly involved multiple drugs. Mitragynine levels varied widely, from 16 to 4800 ng per milliliter. Residual blood was not available for confirmatory testing in the remaining kratom-related death." (p. 1)

Henningfield, Grundmann, Babin, et al. (2019) summarized animal toxicology data, surveys and mortality data associated with opioids and kratom to provide a basis for estimating relative mortality risk. Related to safety, the authors concluded:

> "Kratom is not without risk, but the risk estimates as calculated by any of the approaches used, relative to opioids, suggest that morphine-like opioids carry an overdose risk of a thousand or more times greater than kratom. This conclusion has the limitation that some kratom users inherently carry or assume factors that might greatly increase the risk of kratom-associated mortality, e.g., use in combination with opioids, sedatives, alcohol or other drugs, or some preexisting disease states that may make kratom use especially risky. The fact that deaths associated with kratom use varied widely and included liver disease, homicide, suicide, trauma, and overdose with clearly lethal other drug concentrations (Babin, 2018; Henningfield et al., 2018b), cannot form the basis for concluding that co-existing conditions make kratom use more or less risky compared to opioids."
>
> "In fact, while the contribution of kratom to death in some cases cannot be ruled out, there has yet to be an overdose death from kratom alone in either the US or South East Asia where heavy kratom use is common (Prozialeck et al., 2019)."
>
> "Because many deaths possibly involving kratom appear to have also involved opioids and other drugs that are known to carry a high risk of overdose death, a regulatory approach that establishes standards for kratom product purity, packaging, labeling, and alkaloid content is urgently needed to reduce the risks for persons who purchase lawfully marketed products." (p. 2-3)

2.4.2.3 US and International Survey Data

In all of the surveys reporting reasons for use, despite descriptions by some authors with terms such as "therapeutic use", it is important to note that reasons for kratom use provide some basis for establishing benefits, though these do not imply FDA approved therapeutic claims.

Leong Abdullah, Tan, Narayanan, et al. (2021) conducted an analytical cross-sectional study of 200 participants (100 kratom users and 100 control subjects) in Malaysia, where kratom grows in abundance, leaves and marketed products are widely available, and use is widespread despite its illegality. The authors cardiovascular safety conclusions were:

> "The odds of having ECG abnormalities did not differ between kratom users and non-kratom-using control subjects, except for higher odds of sinus tachycardia in kratom users." (p. 7-8)

Leong Bin Abdullah, Yuvashnee & Singh (2021) conducted a cross-sectional study including data from 200 respondents (100 subjects who use kratom and 100 healthy controls) in Malaysia. The authors concluded:

> "The results of this study have some clinical implications to healthcare professionals. People who use kratom may experience some impairment of physical health, psychological, and environment QoL. Longer duration of kratom use may impair the physical health QoL, whereas greater severity of kratom dependence may impair all domains of QoL except for social relationship QoL. Hence, it is necessary to adequately treat kratom dependence in order to achieve better QoL in people who use kratom." (p. 5)

Garcia-Romeu, Cox, Smith, et al. (2020) conducted a MG survey of 2798 respondents. Related to safety, the authors concluded:

> "This study supports the results of previous studies (Coe et al., 2019; Grundmann, 2017; Smith and Lawson, 2017; Swogger et al., 2015) by suggesting that kratom has a relatively benign risk profile compared to typical opioids, with only a minority of respondents endorsing kratom related adverse effects, withdrawal symptoms, or problematic use. Adverse effects reported here were most commonly rated as mild and lasted ≤1 day, and less than 1% of the total sample found the effects of kratom to be severe enough to seek medical treatment. Adverse effects of kratom use were related to a number of demographic, health, and drug use variables including age, sex, education, income, depression, pain severity, and past 12-month alcohol and opioid use. Therefore, younger individuals or people with depression or more severe pain may experience more kratom-related adverse effects, potentially related to co-use with alcohol or other opioids. However, daily kratom users among the current sample were unlikely to meet criteria for a kratom related SUD, or report substantial problems or concerns related to their kratom use. Logistic regression models additionally found that greater kratom-related SUD symptoms predicted negative effects of kratom use, kratom withdrawal, and seeking treatment for kratom use, but not kratom use for the purposes of opioid reduction. Thus, kratom may differ in important respects from typical opioids, and may have significant therapeutic potential in light of the present opioid crisis." (p. 6)

Smith, Rogers, Schriefer, et al. (2021) analyzed 280 kratom subreddit posts and concluded:

> "Ultimately, kratom subreddit posts contained complicated narratives that do not make for simple characterizations. For some, kratom was lifesaving and for others it was ruinous, or yet another substance to which they had become beholden. Like other findings, the (provisional) takeaway is that it is premature to laud kratom as a cure-all and equally premature to demonize it as a dangerous substance with risk that outweighs benefit. At base, this stems from insufficient information, but also from the fact that "kratom" in the US constitutes many different products with variability in alkaloid content, composition, and purity, some of which is an artifact of factors related to the geographic region of the tree, kratom harvesting, post-harvesting handling, or other agricultural or horticultural conditions and practices (Fowble and Musah, 2019; Griffin et al., 2016; Mudge and Brown, 2017; Zhang et al., 2020). Findings here reinforce current scientific consensus, which is that kratom is a highly varied psychoactive substance being used in different doses and for different reasons among a diverse group of people that we are only beginning to understand." (p. 7)

Swogger & Walsh (2018) conducted a systematic review of kratom use and mental health including 13 studies addressing kratom use in the US, SEA, and other countries and regions of the world. Most mental health related uses were for harm reduction as a substitute for less desirable substances including opioids, alcohol, and other drugs, or for modulation of mood including energizing effects to counteract fatigue and self-management of mood disorders including anxiety, depression, and posttraumatic stress. The authors stated:

> "In conclusion, kratom use appears to have several important mental health benefits that warrant further study. Kratom dependence is a risk for some people, though the dependence syndrome appears to be mild in its psychosocial and physiological effects relative to that of opioids." (p. 139)

The Garcia-Romeu, et al. (2020) survey mentioned earlier concluded:

> "Most respondents endorsed using kratom for pain relief (91.3%), and/or to treat mood-related issues such as anxiety (67.2%), and depression (64.5%). Among these, the majority said they would recommend kratom for pain relief (98.7%), and mood-related issues (96.7%). Mean (SD) efficacy ratings of kratom for treating pain on a scale from 0 (not at all) to 100 (extremely) were 83.3 (18.5); for anxiety were 76.7 (24.3); and for depression were 76.5 (25.4). Subgroups also reported using kratom for post-traumatic stress (29.6%) or bipolar mood (24.6%), with mean (SD) efficacy ratings of 60.2 (38.2), and 51.4 (39.9), respectively." (p. 3-4)

Covvey, et al. (2020) conducted an online cross-sectional survey including data from 1,842 respondents, of which 112 (6.1%) reported lifetime kratom use. The authors concluded:

> "Similar to existing data, the presence of emotional and mental health conditions, including concurrent substance use, was ubiquitous for individuals reporting kratom use compared to others. Anxiety, depression, and chronic pain were the most reported medical conditions among both groups, with significantly higher rates among respondents reporting kratom use. Previous surveys of individuals who use kratom cite treatment of pain and mental health conditions as the primary motivations for use. Coe and colleagues identified treatment of pain (48%) or mental health conditions (21.5%) as the most common reasons for use, while Grundmann identified even higher percentages reporting use for pain (68%) or mental health (66%) conditions. While the present study was not able to directly ascertain reasons underlying the use of kratom, these conditions were found with higher frequency among individuals reporting kratom use, suggesting a possible connection." (p. 5)

Singh, Grundmann, Murugaiyah, et al. (2020) conducted a field face-to-face survey including data from 92 respondents (long-term male kratom users). The authors stated:

> "Seventy-two participants (78%) reported using kratom to enhance sexual performance, and 71 of them (71/72, 99%) reported experiencing improved sexual performance. Of those who reported not using kratom to enhance sexual performance, 7/20 (35%) also experienced improved sexual performance after kratom use. The reported enhancements of sexual performance included: more energy during sex (75/92), delayed ejaculation (71/92), help to maintain erection (70/92), longer climax (51/92),

increased sexual desire (44/92), and reduced sex organ sensitivity (43/92). The mean (SD) Mal-BMSFI score was 33.9 (7.1) and 78/92 (85%) reported overall high satisfaction with their sex life in the past 30 days." (p. 1)

Singh, Narayanan, Müller, Swogger, et al. (2019) studied the motives for using kratom among regular kratom users in Malaysia. Singh, et al. (2019) summarized their results as follows:

> "A total of 116 regular kratom users were recruited for this cross-sectional survey. The Drinking Motives Questionnaire (DMQ) was administered to measure kratom use motives. Our results indicate that heavy (> 3 glasses daily, each glass contains 48.24–50.4 mg of mitragynine) kratom use was associated with coping ($t87.09 = 3.544$, $p < 0.001$), and enhancement ($t114 = 2.180$, $p=003$). Single subjects had higher mean scores on the coping domain, relative to married subjects ($t113.89 = 3.029$, $p < 0.003$), while those earning more than RM1500 per month had higher mean scores on the enhancement domain, compared to those earning less than RM1500 per month ($t107 = 2.151$, $p < 0.034$). Higher scores on the coping domain were significantly associated with higher (> 3 glasses daily) kratom consumption ($p < 0.0045$). Coping was associated with high (> 3 glasses daily) kratom consumption among regular kratom users in traditional, rural settings." (p.1)

Singh, Chear, Narayanan, et al. (2020) studied patterns of use and reasons for use by current and former opioid poly-drug users in Malaysia. They summarized their findings as follows:

> "A total of 204 opioid poly-drug users (142 current users vs. 62 former users) with current kratom use history were enrolled into this cross-sectional study. A validated UPLC-MS/MS method was used to evaluate the alkaloid content of a kratom street sample. Results from Chi-square analysis showed that there were no significant differences in demographic characteristics between current and former opioid poly-drug users except with respect to marital status. Current users had higher odds of being single. Similarly, there were no significant differences in the duration, daily quantity, or frequency of kratom use between current and former opioid poly-drug users. While both current and former opioid users reported using kratom to ameliorate opioid withdrawal, current users had significantly higher likelihood of using kratom for that purpose. In contrast, former opioid users were more likely to be using kratom for its euphoric (mood elevating) effects. Results from the UPLC-MS/MS analysis indicated the major alkaloids present in the representative kratom street sample (of approximately 300 mL of brewed kratom) were mitragynine, followed by paynantheine, speciociliatine and speciogynine, as well as low levels of 7-hydroxymitragynine. Both current and former opioid poly-drug users regularly used kratom (three glasses or about 900 mL daily or the equivalent of 170.19 mg of mitragynine) to overcome opioid poly-drug use problems." (p. 1)

2.4.2.4 Public Health and Individual Benefits of Kratom.

In a systematic review of the global mental health effects of kratom, Swogger & Walsh (2018) stated:

> "In conclusion, kratom use appears to have several important mental health benefits that warrant further study. Kratom dependence is a risk for some people, though the dependence syndrome appears to be mild in its psychosocial and physiological effects

relative to that of opioids. More and better research, including well-controlled, prospective studies is necessary to further elucidate kratom's potential for good and harm and the moderators of its effects." (p. 139)

2.4.2.4.1 Kratom Use for Pain Management and Managing Opioid Use/Withdrawal

Coe, Henningfield, Pillitteri, et al. (2019) conducted an anonymous online survey of 3,024 kratom users (2867 current users and 157 former users). The authors wrote:

> "Kratom was used primarily to relieve pain (endorsed by 48% of respondents), for anxiety, PTSD, or depression (22%), to increase energy or focus (10%) and to help cut down on opioid use and/or relieve withdrawal (10%). Over 90% of respondents who used it in place of opioids indicated that it was helpful to relieve pain, reduce opioid use, and relieve withdrawal." (p. 24)
>
> "In contrast to the well-documented and serious risks associated with opioids (Baldini et al., 2012; Benyamin et al., 2008), respondents reported kratom effects as relatively minor, with few requiring medical attention. The rates and severity of "bad reactions" were generally similar to those reported previously (Grundmann, 2017), occurring in approximately 13% of respondents. The reported incidence of bad adverse reactions was 13%, and reactions were overwhelmingly mild and self-managed." (p.24)
>
> "The findings from this survey indicate that many individuals are taking kratom for conditions that often involve the prescribing of or self-medication with opioids (i.e., pain, withdrawal relief). Survey respondents overwhelmingly reported that kratom was helpful for these conditions and that bad effects from kratom, including those leading them to seek medical care, were uncommon." (p. 29).
>
> "Results of this survey and others (Grundmann, 2017) suggest that kratom may be a useful alternative to opioids for some persons with pain, and this would be consistent with what is known about kratom pharmacology (Kruegel et al., 2016; Raffa et al., 2018; Takayama et al., 2002)." (p. 29)
>
> "Although severity and relatedness of the bad reactions to kratom were not assessed, only 0.8% of respondents stopped using kratom because of a bad reaction or because they didn't like the way it made them feel." (p. 30)
>
> "The rates and severity of "bad reactions" were generally similar to those reported previously (Grundmann, 2017), occurring in approximately 13% of respondents." (p. 30)
>
> Müller, Hillemacher & Müller (2020) illustrates the realities of pain management that are typical in the real world. In this case, illustrated by a patient who benefited at times satisfactorily and at others less so. A summarized by the authors:
>
> "We present the case of a 26-year-old man in Substitol-assisted treatment of excessive Kratom and Tilidin use expressing the wish for a drug-free management of a chronic pain condition. After an accidental calcaneus impression fracture, the patient was suffering from severe chronic pain and anxiety of further accidents. This was managed initially with Tilidin. Resulting from the wish to self-manage the pain condition in a way that permitted continuation of a job, the patient searched for a 'natural' treatment

> alternative obtained from an Internet vendor. He successfully instrumentalized Kratom for 3 years with daily consumption intermixed with occasional Tilidin for pain management. However, the dose of Kratom was increased considerably up to a level of effect reversal, when no analgesic and behaviorally activating effects occurred any more, but only intense drowsiness. The patient was treatment seeking and subsequently detoxified from Kratom and Tilidin. Pain management was shifted to retarded morphine." (p. 1)

Note that in the foregoing report by Müller et al. (2020) (and another below by Müller et al., 2021), as in some other studies from the Malaysia Center for Drug Research reviewed by Henningfield, Fant & Wang (2018), the term "instrumentalized" and "instrumentalization" or "instrumental use" elsewhere, is approximately interchangeable with terms such a "therapeutic" and "beneficial" used in other studies and reviews.

Although the surveys indicate that a major reason for kratom use is the self-management of pain, it is also important to understand that kratom, like other pain management approaches, whether FDA-approved medicines or any other therapeutic approach, is not a panacea for all types of pain, people or pain sufferers (see Henningfield, Ashworth, Gerlach, et al., 2019; Kroenke, Alford, Argoff, et al., 2019).

A harm reduction benefit of replacing opioids and other drugs with kratom is the absence of opioid-like respiratory depressant effects and substantially lower overdose potential of kratom as compared to opioids. Considering the more than 93,000 drug overdose deaths in 2020, the majority of which are due to opioid intoxications, kratom use provides an alternative to opioid use and withdrawal (CDC, 2021). Kratom also has a low risk of inducing psychopathological states or aggression. Swogger & Walsh (2018) concluded:

> "Apart from kratom dependence, available studies give no indication that kratom causes psychopathology…. We searched for scientific information on kratom use and self-and-other directed aggression. Although few studies directly assessed aggression, reports of this outcome were notably absent from studies that indirectly enabled such reporting (e.g., Anwar et al., 2016; Saingam et al., 2012; Swogger et al., 2015; Trakulsrichai et al., 2013). No studies indicated increased self-or-other directed aggression following acute kratom ingestion. Approximately 1% of Malaysian interviewees indicated being aggressive or experiencing hostility while in kratom withdrawal (Ahmad and Aziz, 2012)." (p. 5)

An international consortium of leading kratom researchers (Prozialeck, Avery, Boyer et al., 2019) conducted a scientific and policy analysis of kratom and concluded:

> "The many positive user comments on Erowid.org (Erowid, 2016), SageWisdom.org (Wisdom, 2016), Reddit.com/r/kratom (Reddit, 2018) and Speciosa.org (speciosa.org, 2016) comprise an extensive collection of anecdotal data documenting kratom use. Scientific analyses of such user reports clearly indicate that the therapeutic potential of kratom is too large to be ignored (Swogger et al., 2015). The 23,000+ comments submitted to the federal register in response to the DEA's proposed scheduling action also provide a vast collection of anecdotal data suggesting profound therapeutic benefits for kratom (DEA, 2016a). Another piece of evidence suggesting that kratom

may have significant therapeutic potential is that US patents have been issued for companies and individuals who are interested in developing kratom-based drugs (Heyworth, 1964; Takayama, Kitajima, Matsumoto, & Horie, 2008). Together, these observations provide evidence that kratom may have potentially useful therapeutic effects, and that well-controlled clinical trials are urgently needed to evaluate the safety and efficacy of kratom and its principal alkaloid mitragynine." (p. X)

2.4.2.4.2 Kratom Use During the COVID-19 Pandemic

Müller, Hillemacher & Müller (2021) published a case history of the use of kratom to self-manage anxiety and depression during the COVID-19 pandemic. They reported:

> "Altogether, the present report may add evidence for long-term instrumentalization of Kratom for self-management of major depression and general anxiety disorder and Morbus Meniere. It also evidences the boundaries of drug instrumentalization when environmental conditions change, such as during increased psychological stress in the COVID-19 pandemic." (p. 3)

In the first half-year of the COVID-19 pandemic, Singh, Brown, Cinosi, et al. (2020) discussed how the pandemic may have affected kratom supply and use drawing on observations from researchers globally as well as kratom suppliers and marketers from the SEA region. Their observations included the following:

> "The widespread use of kratom and consistent reports of its benefits or therapeutic value that are important to users raises the question: would sudden decreases in the availability of the plant have negative impacts on kratom users? Various internet studies found that some kratom users are concerned about the possibility of relapsing to opioids and/or seeking alternative, possibly questionable, sources of kratom if products become less readily available. This is a serious concern as kratom, not currently regulated as a dietary supplement, may be adulterated by unscrupulous traders and cause users to relapse to opioid use and inevitably experience a significant increase in overdose risk (7, 9, 14–17). Indeed, there is evidence to suggest that the COVID-19 pandemic has been associated with increased drug overdose deaths and that the reduced access to conventional treatment, as well as mutual-aid groups, is a plausible contributing factor (18), though it is unknown whether diminished access to kratom has explicitly contributed to any overdose deaths." (p. 1)

Note that similar concerns as expressed above were also discussed by US DHHS, Assistant Secretary of Health Dr. Giroir in his August 2018 formal rescission of the October 2017 recommendation developed by the FDA to permanently list MG and 7-OH-MG as Schedule I drugs, which would have abruptly banned legal consumer sales and possession (see below).

As of 2021, it has already been estimated by the US Centers for Disease Control and Prevention (CDC) that total drug overdose deaths rose nearly 30% in 2020 to more than 93,000 in the US (Ahmad, Rossen & Sutton, 2021). The actual impact on kratom use and supply related to the COVID-19 pandemic may not be understood for a year or more to come but would seem to merit further study. Given that a major use of kratom is as a less harmful substitute for opioids and the absence of evidence suggesting that it has contributed to the opioid epidemic (see Factors 4, 5 and 6 and Henningfield, Raffa, Garcia-Romeu & Doshi,

2018), it is hypothesized that kratom access may have prevented many deaths. Regardless of the actual and probably complex relationship, this merits study.

2.4.2.4.3 Potential Effects of Inappropriate Regulation

Public health risks of regulation, including decisions as to where public health is better served by scheduling or not scheduling substances and products, must consider the risks and benefits of decisions. For example, the leading nicotine replacement medicines (gum, lozenge and patch) were not listed in the CSA despite meeting all criteria for CSA control and other risks. Additionally, they were converted to over-the-counter status due to their lower abuse potential and addiction risk and better safety profile than cigarettes (FDA, 1995, 1996; Henningfield, 2011). Similarly, common cough, cold and allergy products (e.g., diphenhydramine and dextromethorphan and caffeine), substances that lead to dependence and withdrawal, are not scheduled in the US or globally. This illustrates the point that drug scheduling and control actions in the US and internationally consider the public health risks and benefits of scheduling actions in the determination of whether drugs are scheduled or not and if they are controlled, which schedule they are placed in (Spillane & McAllister, 2003)

Survey findings and internet monitoring provided no compelling evidence that kratom was fueling the opioid epidemic but provided substantial evidence that kratom offered a life-saving path away from opioids. It appeared that DEA shared similar concerns and that US DHHS agreed. Although DEA proposed scheduling kratom in August 2016, within approximately one month they withdrew the proposal inviting public comment and FDA input (DEA, 2016). This was in response to thousands of comments from kratom consumers describing kratom's health benefits, its use as an opioid replacement, and fear of a relapse to opioids if kratom was scheduled. The DEA Administrator, Chuck Rosenberg, explained that withdrawing kratom from the market could pose risks to people who used kratom to abstain from opioids and a relapse could put them at risk of an overdose death. Assistant Secretary of DHHS, Dr. Giroir, in his MG and 7-OH-MG scheduling rescission letter stated:

> "Furthermore, there is a significant risk of immediate adverse public health consequences for potentially millions of users if kratom or its components are included in Schedule I, such as:
>
> - Suffering with intractable pain;
> - Kratom users switching to highly lethal opioids, including potent and deadly prescription opioids, heroin, and/or fentanyl, risking thousands of deaths from overdoses and infectious diseases associated with IV drug use;
> - Inhibition of patients discussing kratom use with their primary care physicians leading to more harm, and enhancement of stigma thereby decreasing desire for treatment, because of individual users now being guilty of a crime by virtue of their possession or use of kratom;
> - The stifling effect of classification in Schedule I on critical research needed on the complex and potentially useful chemistry of components of kratom."

Assistant Secretary Giroir also noted:

> "I am also concerned about the impact of scheduling kratom on our ability to conduct research, especially survey research and our current inability to routinely test for kratom in those brought into an emergency room as a result of a possible overdose."

Concerns about these foreseeable risks if kratom was banned for sale and criminalized for consumer possession were expanded in several published articles (e.g., Grundmann, Babin, Henningfield, et al., 2021; Grundmann, Brown, Henningfield, et al., 2018), and joint expert report/letters to the DEA, DHHS, FDA, NIDA, White House and Congressional leaders (Henningfield, Swogger, Walsh, Kruegel, et al., 2018a, 2018b). A critique of FDA's own 8-FA (FDA, 2017a) by kratom and substance abuse experts and those experienced in drug scheduling was also published (Henningfield, Babin, Boyer, et al., 2018). These analyses raised concerns in addition to those raised by Assistant Secretary Giroir. These included the foreseeable consequence of a rapidly developing kratom black market increasing the problems of product adulteration and quality, instead of gaining the benefits of legally regulated kratom with standards for purity, packaging, labeling, marketing, and claims.

2.4.2.5 Factor 4, 5, and 6 Updated Conclusions

The most important finding from substantially more survey evidence in the US is that the surveys do not support the conclusion that kratom products and kratom's primary active alkaloid, MG, pose a "serious imminent threat to public health". This extensive survey update supports the Henningfield, Fant & Wang (2018) conclusion:

> "There has been no documented threat to public health that would appear to warrant emergency scheduling of the products and placement in Schedule I of the CSA carries risks of creating serious public health problems…. Although kratom appears to have pharmacological properties that support some level of scheduling, if it was an approved drug, placing it into Schedule I, thus banning it, risks creating public health problems that do not presently exist".

Conversely, the evidence is affirmative that millions of people in the US purchase and use kratom products for the health benefits they provide and are preferred to FDA approved medicines because for them, kratom products are more effective, accessible, and tolerable. Furthermore, many prefer managing health problems with natural products.

For those using kratom products in place of opioids, which appears to be approximately 1/3 of all kratom users, it is foreseeable that removing kratom from the legal marketplace would put many at risk of returning to opioid use and risking opioid overdose death. This was clearly stated in comments to the DEA and public hearings as reported in the 2018 8-FA, and in surveys. As stated by Assistant Secretary Dr. Giroir, as noted earlier:

> "Furthermore, there is a significant risk of immediate adverse public health consequences for potentially millions of users if kratom or its components are included in Schedule I, such as: … Kratom users switching to highly lethal opioids, including potent and deadly prescription opioids, heroin, and/or fentanyl, risking thousands of deaths from overdoses and infectious diseases associated with IV drug use…" (Giroir, 2018).

As noted in Factor 1, the survey data are consistent with comments by kratoms users to DEA[13,14,15,16] and FDA[17],[18] that were summarized in the Henningfield, Fant & Wang, 2018 kratom 8-FA, as well as with comments in public hearings in cities and states that have been considering, and in many cases, implementing kratom regulations, to ensure access to kratom and provide some regulatory oversight over products and marketing. Although some commentors describe addiction to kratom, the most common themes are used for health and well-being, including to stay off opioids. Although not scientific surveys, these comments from real world kratom users provide an important complement to the scientific findings.

2.5 Factor 7 – The Psychic or Physiological Dependence Liability

2.5.1 Summary of 2018 Findings:

Psychic dependence has been commonly referred to in recent years simply as "dependence" (APA, 1994; WHO, 1994) or by the 5th edition of the APA's Diagnostic and Statistical Manual as "substance use disorder" and more commonly as "addiction" though definitions of addiction vary widely. Physiological dependence is often used interchangeably with the most common measure of physiological dependence, namely "withdrawal" which is also considered a clinical disorder (APA, 2013). In the 2018 8-FA, Henningfield, Fant & Wang (2018) concluded:

> "There have not been laboratory studies of physical or psychological dependence or abuse potential in humans caused by kratom." Nor had classic animal studies of employing the drug self-administration and physical dependence/withdrawal model been conducted as have been conduct since 2018 (see Factor 2 in this report)." (p. 584)

Nonetheless, the real-world evidence in the published literature supported the following conclusions:

> "…abrupt discontinuation [of kratom use] may be accompanied by withdrawal symptoms that are qualitatively similar but generally weaker than those observed following discontinuation of opioids. However, such reports make it difficult to disentangle the emergence of preexisting symptoms that had been mitigated by kratom use from those

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[13] See 22,232 comments to the DEA in 2016 at https://www.regulations.gov/document/DEA-2016-0015-0006/comment

[14] An Excel file of the comments is available at https://www.dropbox.com/s/6txmv91536oujhq/DOCKET_DEA-2016-0015.xlsx?dl=0

[15] An analysis of the comments where a comment ID allowed for a classification of the source of the comment (conducted on 19,419 of the comments) is available at https://www.dropbox.com/s/h1b4qz36lzqm1d5/KratomCommentProject_DataSet%20-%20STATISTICS_VERIFIABLE_DATA.pdf?dl=0

[16] A general summary news release of the foregoing analysis is available at https://www.prnewswire.com/news-releases/review-of-dea-kratom-public-comments-shows-strong-support-among-vets-doctors-cops-and-seniors-for-coffee-like-herb-300401575.html

[17] Public comments concerning the benefits of kratom as life-saving assets with respect to the opioid epidemic were also made orally and in written submissions to the FDA and NIDA April 17, 2018 Public Meeting on Patient-Focused Drug Development for Opioid Use Disorder at https://www.fda.gov/industry/prescription-drug-user-fee-amendments/public-meeting-patient-focused-drug-development-opioid-use-disorder.

[18] Written comments for the docket are at https://www.regulations.gov/document/FDA-2018-N-0987-0001/comment

that occur as a physiological rebound accompanying the abrupt discontinuation of kratom use in kratom-dependent people. More studies of kratom's potential to produce physical dependence, tolerance, and withdrawal are needed to characterize the nature and severity, and determinants of abstinence-associated symptoms." (p.584)

2.5.2 Factor 7 Science Updates:

There have been new research findings, a systematic review, and a review by an international consortium of kratom experts that contribute to a significant advance in knowledge on the psychic and physiological dependence potential of kratom.

The systematic review of kratom use and mental health discussed earlier in Factors 4, 5 and 6 by Swogger & Walsh (2018) provided additional perspectives related to kratom's potential to produce dependence or addiction (also referred to as a substance use disorder, APA, 2013), and physical dependence and withdrawal. The researchers concluded:

> "Kratom withdrawal symptoms resemble the opioid withdrawal syndrome (Miranda and Taca, 2017). Extant data suggest that kratom's withdrawal syndrome is uncomfortable, but generally milder and of shorter duration than is characteristic of opioid withdrawal (Singh et al., 2015; Swogger et al., 2015)." (p. 137).

Regarding dependence, Swogger & Walsh (2018) concluded:

> "There is good evidence that kratom dependence is typically less severe than opioid dependence, with which kratom shares some mechanisms of action (Hassan et al., 2013). Moreover, unlike opioids, kratom use does not appear to result in significant respiratory depression (Kruegel et al., 2016) and is thus far less likely to cause fatal overdose. The perception that kratom is a milder and less dangerous opioid-like psychoactive substance is supported by the uptake of kratom use as an opiate substitute (Vicknasingam et al., 2010) and is consistent with data on the unimpaired social functioning of regular kratom users (Singh et al., 2015). For future research on the effects of heavy kratom use, a scale designed to measure kratom dependence has shown good preliminary reliability and validity (Scale; Saingam et al., 2014)." (p. 138)

The international consortium of leading kratom researchers mentioned earlier in Factors 4, 5 and 6 also assessed dependence and withdrawal associated with kratom use. According to Prozialeck, et al., 2019):

> "Regular use of kratom, particularly at higher doses, can lead to tolerance and dependence (Galbis-Reig, 2016; Singh et al., 2014; Swogger & Walsh, 2018; Yusoff, et al., 2016)." (p. 73)

However, available human reports suggest that abstinence from kratom is typically associated with milder symptomatology than abstinence from classical opioids (Erowid, 2017; Henningfield, et al., 2020; Singh, et al., 2014, Singh, et al., 2016; Singh, Narayanan, Müller, et al., 2018; Swogger, et al., 2015). At the same time, although these reports indicate that the effects of kratom can, in some ways, resemble those of opioids, many individuals report that the subjective effects of kratom are quite different from those of opioids. As noted previously, low to moderate doses of kratom tend to be somewhat stimulating, rather than sedating, and

do not produce the “high” or strong euphoric effects associated with opioids, although some users have reported intoxication and euphoria after using higher doses (Erowid, 2017; Henningfield, et al., 2020; Singh, et al., 2016; Swogger, et al., 2015). This distinct spectrum of effects, including attenuated euphoria and abuse potential, is supported by two recent preclinical studies, which found that mitragynine is not self-administered by rats (Hemby, McIntosh, Leon, Cutler & McCurdy, 2019; Yue, Kopajtic & Katz, 2018). Further, even at high doses, kratom does not appear to severely depress respiration as do classical opioids (Singh, et al., 2014, 2016). Thus, even though kratom has some potential for abuse and dependence, several investigators have concluded that kratom has both less abuse liability and much lower risk of fatal overdose than traditional opioids and that the potential benefits of kratom in the treatment of OUD may outweigh these risks (Henningfield, Fant & Wang, 2018; Singh, et al., 2014, 2015, 2016; Swogger, et al., 2015). This does not mean that kratom is not sometimes used by people to get high and/or intoxicated because such use has been documented (Swogger, et al., 2015). Such findings were also considered by Henningfield, Fant & Wang (2018).

The Vicknasingam, et al. (2020) study included in Factor 2 that evaluated kratom’s effects on pain tolerance in a clinical trial also assessed potential withdrawal signs using the Clinical Opiate Withdrawal Scale (COWS) comparing scores on days that the participants were administered placebo to days that participants were administered a kratom concoction (Vicknasingam, et al., 2020). Although this study was not designed to be a definitive withdrawal assessment study, and did not include an opioid comparator, it would have been likely that people who were using opioids multiple times per day for many years would have experienced pronounced withdrawal symptoms. In this study the authors concluded as follows:

> “None of the participants reported withdrawal symptoms either using spontaneous self-report or had significant withdrawal symptoms based on the COWS scores. All urine toxicology screens conducted at the end of the testing day were negative.” (p. 236)
>
> “All participants reported long histories of daily kratom consumption, with high frequency of daily consumption and substantial amounts consumed. It is not possible to quantify these reports into markers that could be used to approximate amounts of plant material or active ingredients consumed. However, despite the reported long duration and high levels of daily kratom consumption, during documented kratom discontinuation lasting from 10 to 20 hours, no participant reported or displayed discomfort, symptoms, or signs of potential withdrawal symptoms.” (p. 236)

Leong Bin Abdullah, Yuvashnee & Singh (2021) studied kratom users in Malaysia to assess potential symptoms related to kratom dependence and withdrawal. They concluded:

> “In the context of regular kratom use, most people with kratom use experience some anxiety and depressive symptoms during kratom withdrawal. . .
>
> Greater Kratom Dependence Scale (KDS) score and longer duration of kratom use were significant predictors of physical health Quality of Life (QoL), while only greater KDS score significantly predicted psychological and environment QoL scores. Prolonged kratom use and kratom dependence may negatively impact the QoL of people who use kratom, hence kratom addiction has to be treated adequately.” (p. 1)

Garcia-Romeu, Cox, Smith, et al. (2020) conducted a survey that specifically asked questions about potential withdrawal symptoms associated with discontinuation of kratom use. They concluded as follows

> "Kratom-related withdrawal symptoms were reported by 9.5 % of respondents with another 17.5 % reporting possible kratom-related withdrawal." (p. 4)
>
> "This study supports the results of previous studies (Coe et al., 2019; Grundmann, 2017; Smith and Lawson, 2017; Swogger et al., 2015) by suggesting that kratom has a relatively benign risk profile compared to typical opioids, with only a minority of respondents endorsing kratom-related adverse effects, withdrawal symptoms, or problematic use." (p. 6)

The survey by Coe, Henningfield, Pillitteri, et al. (2019) also asked questions related to potential kratom use associated dependence and discontinuation related withdrawal. They concluded as follows:

> "The survey did not address whether respondents experienced any physical dependence or craving as a result of kratom use, but it appears likely that chronic kratom use is associated with physical dependence and withdrawal, albeit both are reportedly milder and more readily self-managed compared to opioid dependence and withdrawal (Singh et al., 2014, 2016; 2018). Furthermore, kratom use and dependence reportedly do not interfere with social, family, and occupational functioning (Singh et al., 2014, 2016; Swogger and Walsh, 2018; Vicknasingam et al., 2010) to the extent that conventional opioids do." (p. 30) This conclusion is similar to Grundmann's (2017) findings.
>
> The foregoing conclusions are also consistent with those of Grundmann, Babin, Henningfield, et al. (2021) who stated as follows "Some user reports suggest that regular kratom consumption carries risks of dependency and addiction, though with generally self-manageable withdrawal (12)." (p. 1)

Another study employed widely used psychiatric instruments (Beck Depression Inventory and Beck Anxiety Inventory) to assess potential symptoms of anxiety and depression that may accompany abrupt discontinuation of kratom use in chronic kratom consumers in Malaysia. (Singh, Narayanan, Müller et al., 2018). Singh, et al. (2018) concluded:

> "Most respondents (70%) experienced symptoms of mild anxiety, while 81% experienced symptoms of mild depression during kratom cessation. Those who consumed higher quantities of kratom tea daily (≥4 glasses) had higher odds of reporting longer duration of kratom use history…, higher frequency of daily kratom use (≥4 times) …, and were more likely to experience moderate symptoms of depression during kratom cessation than those who consumed between one and three glasses of kratom tea per day. Cessation from regular and long-term kratom tea consumption was not associated with symptoms of high anxiety or depression." (p.1)

Nonetheless, it is evident that some fraction of chronic heavy kratom users exhibit strong dependence or use disorder, albeit with generally moderate withdrawal symptoms (Singh, Narayanan, Müller et al., 2018). In many such cases, the people had preexisting opioid or

other substance use disorders and/or were using kratom to self-manage chronic pain. It is not known what fraction of kratom users experience what might be termed a kratom use disorder (even though this term is not an APA, 2013 recognized term). Surveys by Grundmann (2017), Coe, et al. (2019), and Garcia-Romeu, et al. (2020) suggest that 5-10% of kratom users report some level of dependence with evidence suggesting that it is tolerable, manageable and not disruptive to life demand for most people. However, as noted in the 2018 scheduling recission letter by Assistant Secretary of Health Giroir, the number is not known and is important to know, particularly before any effort to substantially restrict kratom access.

Swogger & Walsh (2018) concluded as follows "In conclusion, kratom use appears to have several important mental health benefits that warrant further study. Kratom dependence is a risk for some people, though the dependence syndrome appears to be mild in its psychosocial and physiological effects relative to that of opioids." (p. 139)

2.5.3 Factor 7 Updated Conclusions

Several surveys in the US, field studies in Malaysia, and a clinical trial of pain relief efficacy that included assessment of withdrawal support the conclusions of the 2018 8-FA. The main findings are that some people report dependence/addiction and/or withdrawal. The likelihood is generally related to higher levels of chronic daily consumption. In general, it is more readily self-managed and less likely to interfere with occupational, social and family activities and responsibilities as dependencies to opioids, alcohol, stimulants and other drugs of abuse. Many users had histories of opioids and/or other addictive drug use and so the degree to which their addiction to kratom is a new addiction cannot readily be ascertained.

For some people for whom kratom use is considered by themselves and/or others to be a serious problem, they should have the same access to treatment as anyone else with a substance use disorder. Many addiction treatment providers already advertise and offer kratom use disorder treatment assistance. Use of opioids such as methadone and buprenorphine should be used judiciously with people seeing help to manage their kratom use disorder and/or withdrawal. If they were formerly and perhaps still using opioids, then the possibility of treatment with buprenorphine or methadone may be more helpful and appropriate if kratom is not satisfactory. However, for people without prior histories of recreational opioid use and dependence, using buprenorphine or methadone as a treatment may be introducing them to opioids and may not be the best option. For some people that might be like treating unwanted caffeine dependence with amphetamine to replace the caffeine.

3 Conclusions Based on New Studies since January 1, 2018

- *Since the Henningfield, Fant & Wang (2018) 8-FA, there have been over 100 new published scientific studies, reviews and commentaries by leading kratom experts, and an accelerating research pipeline funded in part by the US National Institutes of Health (NIH), National Institute on Drug Abuse (NIDA). These studies provide an increasingly strong evidence base for regulation and policy.*

- *Nature got it right. There is a convergence of studies showing that the main natural constituent of kratom that accounts for the reasons people use kratom is MG which carries relatively low abuse and health risks. 7-OH-MG naturally occurs at very low*

levels and product standards should prevent marketing of products with levels higher than those that appear to carry little risk.

- *Evidence does not support the conclusion that kratom is an imminent public health threat or that it is fueling the opioid and drug overdose epidemic that led to more than 93,000 deaths in 2020. Rather, the evidence supports the conclusion that for many people, kratom is a path away from opioids and other drugs to help self-manage craving and withdrawal for people who find kratom more effective, accessible, acceptable, tolerable, and/or prefer natural products.*

- *Animal drug self-administration and physical dependence/withdrawal studies show low abuse potential and withdrawal risks of kratom relative to opioids. Furthermore, these studies also show that MG administration can reduce self-administration of morphine and heroin as well as withdrawal from morphine. These findings are consistent with human surveys and studies showing that addiction risks for kratom are overall low as compared to opioids.*

- *Numerous surveys and field studies of kratom users have been conducted in the US and Malaysia. These studies largely confirm the large US survey published by Dr. Grundmann (2017). Most US kratom users are 30-50 years old, employed and have some college education and healthcare. Leading reasons for use are to self-manage pain, depression, anxiety, to increase focus and alertness analogous to caffeinated beverage use and to self-manage opioid and other substance use disorders to relieve craving and withdrawal and often the pain that motivates such drug use.*

- *Surveys also show that users fear a kratom ban and the risks of resumption of opioid and other drug use, and/or turning to illicitly marketed kratom. This makes it foreseeable that thousands of people would be at risk of opioid overdose and other mortality risks associated with illicit drug use, injection drug use, and adulterated kratom products.*

- *Studies of kratom's alkaloids support the conclusion that that MG and other alkaloids are not appropriately categorized as opioids, as they are diverse in their activity, effects, and mechanisms of action. Moreover, the primary active constituent of kratom, MG, does not produce the signature powerfully rewarding and lethal respiratory depressant effects that characterize morphine-like opioids.*

- *Kratom PK and safety studies include examination of the pharmacokinetics (PK) and pharmacodynamics (PD) in rats and dogs by oral and intravenous administration of many kratom alkaloids in addition to MG. MG, at human dose equivalents many times higher than humans take, are without acute serious adverse effects and little evidence of respiratory depressant effect.*

- *Six clinical studies evaluated the effects of long term kratom use on a variety of physiological parameters including kidney and liver function, hematological parameters, cognition, and on brain function by brain magnetic resonance imaging. Although these were relatively small studies, none suggest serious adverse consequences of long term*

kratom use. It is important to note that these are not definitive safety studies and cannot be used to claim that kratom has no adverse effects on any of the studied physiological domains and limitations of each study were noted in the publications. Nonetheless, the findings are encouraging and should facilitate the conduct of more comprehensive follow-up studies.

- *New medicines development efforts are developing new molecules as analogs of MG and other kratom alkaloids as possible safer and/or more effective treatments for pain, addiction, depression and other disorders, due to the promising findings with kratom and its naturally occurring alkaloids. Though, it is likely that it may be a decade or more before they result in New Drug Applications to the FDA.*

- *The pipeline of research and new science has been enhanced in quantity and quality not only by funding from the US National Institutes of Health (NIH) and other organizations but as well by regular scientific conferences that are fostering global collaboration and cooperation in an exciting new frontier in search of safer and more effective ways to manage health and well-being. Such efforts are working and should be expanded.*

- *Kratom regulation would be better informed by scientific and public health conversation by active collaboration among CDC, DEA, FDA, NIDA, and the Substance Abuse and Mental Health Services Administration. Kratom science should be accelerated by increased kratom research funding to NIDA, as well as to support increased surveillance that is specific to kratom. An annual report should be provided by multi-agency committee with updates on the state of kratom science and annual surveillance, perhaps led by NIDA.*

- *An important development that relates to overall safety and health benefits and risks that is a regulatory and policy update and is not included in the science updates: at the time of this writing, five states (Arizona, Georgia, Nevada, Utah, and Oklahoma) have enacted laws referenced as the Kratom Consumer Protection Act (KCPA). The KCPA establishes a regulatory framework to protect consumers from unsafe and adulterated kratom products that require adherence to good manufacturing standards (GMP) to ensure purity; requires testing for contaminants; prohibits adding any dangerous substances to kratom products; forbids boosting the alkaloid levels of MG and 7-OH-MG over those present in the natural kratom plant; bars synthesizing any of the alkaloids; requires registration and product testing; prohibits any therapeutic health claims; and forbids sales to minors. These KCPA laws provide needed consumer protections for consumers. To illustrate the kratom regulatory framework for the Utah KCPA, the Utah Department of Agriculture rule on kratom can be found [at https://ag.utah.gov/businesses/regulatory-services/kratom/](https://ag.utah.gov/businesses/regulatory-services/kratom/) . For updates on the status of KCPA legislation in other states, visit the American Kratom Association website at https://www.americankratom.org/advocacy/aka-in-your-state.html .*

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