2019 Regular Session

House Resolution 203

Representative Edward Ted James

Consumer Protection Measures Relative to Kratom

Office of Public Health

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LOUISIANA DEPARTMENT OF HEALTH

Kratom (Mitragyna speciosa)
Quality Control & Consumer Protection

1-HOUSE RESOLUTION NO. 203 BY REPRESENTATIVE JAMES
HLS 19RS-3140 ORIGINAL. 2019 Regular Session

CONSUMERS/PROTECTION: Requests the Louisiana Department of Health to study and make recommendations concerning consumer protection measures relative to kratom.

A RESOLUTION To urge and request the Louisiana Department of Health to study and make recommendations concerning potential consumer protection measures relative to kratom.

WHEREAS, kratom is a preparation made from the leaves of Mitragyna speciosa, an evergreen tree that grows naturally in Southeast Asia, which can be used as either a sedative or a stimulant depending upon the amount consumed; and

WHEREAS, in February of 2019, the Louisiana Department of Health issued a report in response to House Resolution No. 177 of the 2018 Regular Session which discussed several matters relating to kratom, but did not specifically address the issue of protection of consumers from kratom products that are adulterated with dangerous non-kratom substances;

WHEREAS, current Louisiana law, R.S. 40:989.3, prohibits the distribution of any 14 product containing kratom to a minor; however, state law does not provide further for protection of the public from kratom products that are adulterated with dangerous 16 non-kratom substances and sold by retailers.

THEREFORE, BE IT RESOLVED that the House of Representatives of the Legislature of Louisiana does hereby urge and request the Louisiana Department of Health to study and make recommendations concerning potential consumer protection measures relative to kratom.

BE IT FURTHER RESOLVED that the department shall submit a written report of its findings and recommendations resulting from the study called for in this Resolution to the House Committee on Commerce and the House Committee on Health and Welfare not later than 60 days prior to the convening of the 2020 Regular Session of the Legislature of Louisiana.

BE IT FURTHER RESOLVED that a copy of this Resolution be transmitted to the Secretary of the Louisiana Department of Health.

DIGEST: House Legislative Services prepared the digest printed below. It constitutes no part of the legislative instrument. The keyword, one-liner, abstract, and digest do not constitute part of the law or proof or indicia of legislative intent. [R.S. 1:13(B) and 24:177(E)]. HR 203 Original 2019 Regular Session James requests the Louisiana Department of Health to study and make recommendations concerning potential consumer protection measures relative to kratom and to report its findings to the House committees on commerce and health and welfare not later than 60 days prior to the convening of the 2020 R.S.

The following report is a presentation of the issues relate to kratom use.

2-SUMMARY OF THE HR 177 REPORT

This report presents information from scientific articles and information of availability, use and perception from the public, media and users. Any information directly copied from a source is presented in italics.

2.1-Origin and Traditional Use

Mitragyna speciosa Korth is a tropical tree in the coffee family of Rubiaceae. It grows 4 to 16 m high and is originally from Southeast Asia, Philippines and New Guinea. It is now grown in other Southeast Asian countries [1]. In Thailand, the tree and the extracts from its leaves are called kratom. Kratom was first described scientifically in 1839 [2].

In Southeast Asia, kratom has been used for a long time. The leaves, whether fresh or dried up, are chewed or prepared as a tea. They are rarely smoked. Traditionally, doses used were small. A low dose of kratom was used a stimulant by indigenous people to overcome fatigue from working in the fields for long hours. At higher doses, kratom was used as a sedative and narcotic. It was also used by traditional healers and used as a substitute for opium.

The leaves of *Mitragyna speciosa* are oval lanceolate and of deep green color. They can be 15cm long and 10cm wide. Leaves with white stems contain higher levels of alkaloids than

leaves with red stems. The flowers are small yellow balls. The fruit is a capsule that contains numerous small seeds.

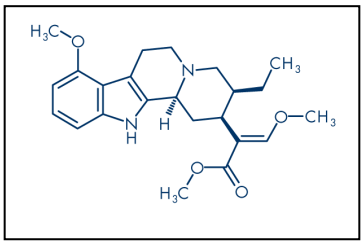
The plant was named *Mitragyna* by a Dutch botanist because of the similarity of the flower with a bishop's hat (miter). Other names for kratom are:

- Kakuam
- Ketum
- Ithang
- Thom
- Biak

In the early 2000s, products labelled as "kratom acetate" or "mitragynine acetate" became available in Europe, although it was found that neither of them contained mitragynine. Caffeine and synthetic O-desmethyltramadol (an active metabolite of tramadol) were found in products under the name "krypton". More recently, products containing kratom have been sold as "incense" for their psychoactive effects, but concentrations of the active components mitragynine and 7-hydroxymitragynine in these products differ depending on the variety of the plant used, the environment and the time of harvesting [1].

2.2-Chemistry

Chemicals isolated from different parts of the plant are comprised of more than 40 structurally related alkaloids, several flavonoids, terpenoides saponines, polyphenols and miscellaneous glycosides.



Formula: $C_{23}H_{30}N_2O_4$
Mitragynine is the most common alkaloid found in the leaves (an alkaloid is any of a class of nitrogenous organic compounds of plant origin that have pronounced physiological actions on humans).

Mitragynine is not soluble in water but dissolves easily in organic solvents such as acetone, alcohols, chloroform. Mitragynine is distilled at 230–240 °C under 5 mm of Hg. Purified, it consists of white crystals that melt at 102–106 °C.

7-hydroxymitragynine is found in small concentrations in kratom leaves. Mitragynine can be used to produce 7-hydroxymitragynine, which is more powerful than simple mitragynine.

2.3-Physical appearance

Kratom is usually sold as leaves, dried and crushed or pulverized into a greenish powder. Powders are sometimes enhanced by leaf extracts. Pasty extracts and a brownish resin are prepared by boiling an aqueous preparation of leaves. Boiling eliminates the water content. Capsules filled up with powder are also available.

Kratom leaves are plucked from trees that are found in tropical swampy areas and rinsed thoroughly with water to remove all traces of dirt. The leaves are boiled for an average of four hours in plain water, resulting in a greenish brown solution that has an extremely bitter taste. The solution is then allowed to cool before it is consumed. Due to its bitterness, the solution is usually gulped rather than sipped at a leisurely pace. Habitual users in Malaysia usually consume kratom juice at least 3 times a day in varying quantities.

2.4-Pharmacology

Traditionally, fresh or dried kratom leaves are chewed, brewed into a tea or smoked. In Malaysia, kratom is usually ingested as a solution or juice while in neighboring Thailand, it is more commonly chewed. In his 1975 Thailand study, Suwanlert reported that regular users initially chew 1 to 3 leaves at one time and repeat this 3 to 10 times per day. The dosage is then increased in varying degrees among individual subjects (10-20 leaves daily [40%]; 21-30 leaves daily [37%]) while the remainder of users increased their daily use to an indefinite number of leaves. An average green kratom leaf weighs approximately 1.7 grams while a dry leaf weighs 0.43 grams. Twenty leaves contain approximately 17 mg of mitragynine [1].

Kratom capsules sold in the U.S. generally contain approximately 80 mg of ground dry kratom leaf. In contrast, chewing 30 dry leaves per day weighing approximately 0.43 grams each results in chewing of 12.9 g of kratom per day, which is equivalent to the amount of kratom in 161 capsules as typically sold in the U.S. In Malaysia, a solution is often prepared by the user or purchased for immediate consumption.

2.5-Health effects

2.5.1-Direct effects

Kratom compounds are comprised of several phytochemicals in different proportions Phytochemicals are non-nutritive plant chemicals that have protective or disease preventive properties. They are non-essential nutrients, meaning that they are not required by the human body for sustaining life. Because of the variability of kratom compounds, pharmacologic evaluation of their properties is complicated. There are few clinical studies in humans that meet strict scientific criteria.

As usual in toxicology, “dose makes the poison”. Small doses cause a stimulating effect while larger doses produces narcotic-sedative effects similar to morphine.

After ingestion of a few grams of dried leaves, the stimulation and euphoria begin within 10 minutes and last one hour to one and a half hour. Consumers are able to work more intensely than usual and become more sociable. In one of the rare experiments in humans, 50 mg of mitragynine caused motor stimulation with vertigo, loss of motor coordination and tremors of face and extremities. The exact mechanism behind the stimulating effect is not well understood.

Heavy users of kratom lose weight and become tired and constipated. Facial redness is noticeable. Repeated doses of 10g to 25g of dried leaves cause perspiration, dizziness, nausea, dysphoria (state of unease or generalized dissatisfaction with life, opposite of euphoria), which become quickly replaced by a calm, euphoric and dreaming state which may last up to 6 hours. Miosis (pupil contraction) is common.

Mitragynine and 7-hydroxymitragynine, which are the main active ingredients of kratom, are selective agonists of the opioid receptor type μ (MOR Receptor). Activation of the μ-opioid receptor by an agonist such as mitragynine causes analgesia, sedation, slightly reduced blood pressure, itching, nausea, euphoria, decreased respiration, miosis and decreased bowel motility often leading to constipation. Some of these effects, such as analgesia, sedation, euphoria, itching and decreased respiration, tend to lessen with continued use as tolerance develops. Miosis and reduced bowel motility tend to persist; little tolerance develops to these effects. Alpha2-adrenergic post-synaptic receptors and the calcium channels are also involved in the pharmacologic activity of mitragynine uronic. The agonist effect of mitragynine is inhibited by naloxone.

In animals, mitragynine has antitussive effects similar to codeine. In mice, 7-OH mitragynine is an analgesic more potent than morphine, even in oral administration. Toxicity in animals is generally milder than in humans. Long-term treatment causes tolerance, which is also applicable to morphine.

Nausea
Vomiting
Constipation
Dry mouth
Loss of appetite
Sweating
Increased urination
Seizures
Hallucinations
Psychotic symptoms

A rodent study published in 2018 found that mitragynine had little abuse potential and actually reduced self-administration of heroin in rats. Another recent rat study found the same result: mitragynine did not have abuse potential and reduced morphine intake, whereas 7- hydroxymitragynine did have high abuse potential. Despite these opposing effects, about 60 percent of the alkaloids in kratom leaves are mitragynine — only 2 percent are 7- hydroxymitragynine [3].

2.5.2-Addiction, dependency

Humans can become dependent on mitragynine after long-term consumption. Weaning symptoms are usually mild and tend to diminish in about one week. Hunger, lethargy, anxiety, hyper-excitability, rhinorrhea, nausea, perspiration, myalgia, tremors, involuntary gestures, sleepiness disorders and hallucinations may occur.

Most cases that researchers have documented portray withdrawals as manageable, with pain and trouble sleeping described as the most unbearable symptoms. One study published this year in the Journal of Psychoactive Drugs noted, "These effects appeared to be relatively mild, since the majority of the participants did not seek treatment for their pain and sleep problems and, in fact, the withdrawal effects only lasted between one and three days.

A case description of kratom usage is reported in Boyer et al.'s "Self-treatment of opioid withdrawal using kratom (Mitragynia speciosa korth)":

"A patient who had abruptly ceased injection hydromorphone abuse self-managed opioid withdrawal and chronic pain using kratom. After co-administering the herb with modafinil he experienced a tonic-clonic seizure, but he reported only modest abstinence once kratom administration stopped. We confirmed the identity of the plant matter he ingested as kratom and identified no contaminants or adulterants. We also conducted high-throughput molecular screening and the binding affinity at mu, delta and kappa receptors of mitragynine."

*"One striking finding of this report is the extent to which kratom attenuates potentially severe opioid withdrawal, yet cessation of kratom administration itself appears to be associated with modest abstinence symptoms. The pharmacological bases underlying this effect are uncertain. For example, mitragynine is theorized to stimulate contributions from adrenergic and serotonergic pathways that augment analgesia, but formal binding data have been obtained only for mu-, delta- and kappa-opioid receptors (*Takayama et al, 2002; Matsumoto et al, 1996*). To delineate more clearly the in vitro pharmacology of kratom, we conducted high-throughput molecular screening of mitragynine activity at central nervous system receptors (Novascreen Biosciences Corp., Hanover, MD, USA); these studies identified that mitragynine extensively inhibits radioligand binding at several central nervous system receptor systems. The clinical implication of these results is that mu-opioid agonism may avert withdrawal symptoms, while kappa agonism attenuates reinforcement and produces aversion (*Narita et al, 2001*). In addition, mitragynine, through its putative alpha-2 adrenergic agonist activity, may mimic adjunctive therapies for opioid withdrawal such as clonidine. Mitragynine, therefore, may exert several convergent pharmacological effects that could attenuate opioid withdrawal symptoms and blunt cravings".*

"We report the self-treatment of chronic pain and opioid withdrawal with kratom. The predominant alkaloid of kratom, mitragynine, binds mu- and kappa-opioid receptors, but has

additional receptor affinities that might augment its effectiveness at mitigating opioid withdrawal. The natural history of kratom use, including its clinical pharmacology and toxicology, are poorly understood." [4]

2.5.3-Absence of respiratory depression, the *β*-arrestin connection

Kratom is virtually incapable of causing respiratory depression or many of the other negative effects of other opioids. Although mitragynine agonizes μ-opioid receptors, respiratory depression, coma, pulmonary edema and death have not been associated with human kratom ingestion.

"To understand what makes these two drugs unique, we need to talk about true opioids. When you take a drug like morphine, it interacts with μ-opioid receptors and brings in, or recruits, a protein called β-arrestin. This sends out chemical signals that can cause side effects like respiratory failure, which leads to deadly overdose.

Most opioids, including fentanyl, recruit β-arrestin, but MG and 7-OHMG do not, meaning there is evidence that kratom has fewer associated risks than opioids, including fatal overdose.

In other words, kratom may be slightly addictive, and it may have opioid-like effects, but based on the available science, it does not seem like kratom is as dangerous as heroin — or even close. However, without human clinical trials, which have yet to be done, it is difficult to truly say." [5]

2.6-Interactions

Consumption of kratom and other drugs could cause very severe health effects. Interactions have been identified in humans between kratom tea and

- Carisoprodol (Soma®, a centrally acting skeletal muscle relaxant of the carbamate class),
- Modafinil (Provigil ®, used to treat excessive sleepiness caused by certain sleep disorders. This includes narcolepsy, sleep apnea, and shift work sleep disorder),
- Propylhexedrine (Benzedrex ®, Obesin®, used as a nasal decongestant, appetite suppressant, and psychostimulant medication, analogue of methamphetamine)
- *Datura stramonium* (jimsonweed or devil's snare, used in traditional medicine to relieve asthma symptoms. It is also a powerful hallucinogen and deliriant, used for the intense visions it produces)

Fatalities in the US were caused by a mixture of kratom, fentanyl, diphenhydramine, caffeine and morphine.

2.7-Addiction

Muscle aches Insomnia Irritability Hostility Aggression Emotional changes Runny nose Jerky movements

Like other drugs with opioid-like effects, kratom might cause dependence, which means users will feel physical withdrawal symptoms when they stop taking the drug. Many reports state that kratom has a relatively minimal capacity to cause dependency.

There are no specific medical treatments for kratom addiction. Some people seeking treatment have found behavioral therapy to be helpful. Scientists need more research to determine how effective this treatment option is.

2.8-Deaths

Data that was reviewed included academic research, poison control data, medical examiner reports, social science research and adverse event reports. Findings indicate there were potentially 44 to 47 reported deaths associated with the use of kratom. This is an increase since a November 2017 advisory, which noted 36 deaths associated with these products [6]. Some reports show the number of deaths (as of October 2018) attributed to kratom as 47. In 2017, the Food and Drug Agency (FDA) began issuing warnings about kratom and identified 44 deaths related to its use, with at least one case being investigated as possible use of pure kratom. [7] The CDC released an April 2019 Morbidity and Mortality Weekly Report that identified kratom as a cause of death in 91 (59.9%) of 152 kratom-positive overdose deaths that occurred during July 2016–December 2017, including seven for whom kratom was the only substance to test positive on postmortem toxicology, though other substances could not be ruled out [8].

Most kratom associated deaths appear to have resulted from adulterated products (other drugs mixed in with the kratom) or taking kratom with other potent substances, including illicit drugs, opioids, benzodiazepines, alcohol, gabapentin, and over-the-counter medications, such as cough syrup. In addition, there have been some reports of kratom packaged as herbal supplements or dietary ingredients that were laced with other compounds that caused deaths.

As stated in the FDA's "Statement from FDA Commissioner Scott Gottlieb, M.D., on the agency's scientific evidence on the presence of opioid compounds in kratom, underscoring its potential for abuse":

"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 toxicological evidence of opioid use, except for kratom. The investigation is on-going In addition, a few assessable cases with fatal outcomes raise concern that kratom is being used in combination with other drugs that affect the brain, including illicit drugs, prescription opioids, benzodiazepines and over-the-counter medications, like the anti-diarrheal medicine, loperamide. Cases of mixing kratom, other opioids, and other types of medication is extremely troubling because the activity of kratom at opioid receptors indicates there may be similar risks of combining kratom with certain drugs, just as there are with FDA-approved opioids.

However, unlike kratom, FDA-approved drugs have undergone extensive review for safety and efficacy, and the agency continuously tracks safety data for emerging safety risks that were previously unknown. So we have better information about the risks associated with these products; and can better inform the public of new safety concerns. For example, in August 2016, the FDA required a class-wide change to drug labeling to help inform health care providers and patients of the serious risks (including respiratory depression, coma and death) associated with the combined use of certain opioid medications and benzodiazepines. "

"Taken in total, the scientific evidence evaluated about kratom provides a clear picture of the biologic effect of this substance. Kratom should not be used to treat medical conditions, nor should it be used as an alternative to prescription opioids. There is no evidence to indicate that kratom is safe or effective for any medical use. And claiming that kratom is benign because it's "just a plant" is shortsighted and dangerous. After all, heroin is an illegal, dangerous, and highly-addictive substance containing the opioid morphine, derived from the seed pod of the various opium poppy plants.

Further, as the scientific data and adverse event reports have clearly revealed, compounds in kratom make it so it isn't just a plant – it's an opioid. And it's an opioid that's associated with novel risks because of the variability in how it's being formulated, sold and used recreationally and by those who are seeking to self-medicate for pain or who use kratom to treat opioid withdrawal symptoms. We recognize that many people have unmet needs when it comes to treating pain or addiction disorders. For individuals seeking treatment for opioid addiction who are being told that kratom can be an effective treatment, I urge you to seek help from a health care provider. There are safe and effective, FDA-approved medical therapies available for the treatment of opioid addiction. Combined with psychosocial support, these treatments are effective. Importantly, there are three drugs (buprenorphine, methadone, and naltrexone) approved by the FDA for the treatment of opioid addiction, and the agency is committed to promoting more widespread innovation and access to these treatments to help those suffering from an opioid use disorder transition to lives of sobriety. There are also safer, non-opioid options to treat pain. We recognize that some patients have tried available therapies, and still have unmet medical needs. We're deeply committed to these patients, and to advancing new, safe and effective options for those suffering from these conditions."[7]

In spite of all the assertions made about kratom deaths, it appears that the FDA does not point to any clear correlation between a known property of the botanical and the manner a person died.

"In the case of the statements made by the FDA concerning kratom, it is my scientific opinion that they do not have appropriate evidence to support the conclusions," says Paula Brown, the director of natural products research at British Columbia Institute of Technology. She has conducted a review of the botany, chemistry and ethnomedicinal uses of plants in the genus Mitragyna, as well as undertaken industry-funded research. Brown says in an email that she does not believe the drug should be criminalized. "The import ban and negative commentary has forced this botanical into a gray or illicit market, where responsible procurement of material and manufacture is not seemingly a top priority."[5]

2.9-Lack of sound scientific information

A 2015 study by Cinosi, et. al. stated that the relevant pharmacological data and peer-reviewed toxicological information was insufficient to reach definitive assessment of the safety in using kratom.

"*Kratom pharmacology is complex and requires future research. This compound, in fact, acts on opioid as well as on dopaminergic, serotonergic, GABAergic and adrenergic systems. Therefore, subjective effects are very peculiar and range from psychostimulant to sedativenarcotic. Pharmacological mechanisms responsible for several of its alkaloids' activity deserve to be clearly established in future studies. ... On the other hand, online reports about kratom seem genuine and many users illustrate their detailed experiences as proper experiments on themselves. Thus, in the lack of relevant peer-reviewed data, the online monitoring seems to be indeed a very useful method to obtain preliminary information about new and emergent phenomena. Further, as demonstrated by the outcomes of this study, a better international collaboration is necessary to tackle this rapidly growing drug trend.*" [9]

2.10-Preparation

The dry leaves being sold in shops or in the web come from the Mitragyna speciosa tree cultured in Southeast Asia, a lot of it from Bali in Indonesia. Bali kratom is not controlled. Fresh or dried up leaves are ground or prepared as a tea. Lemon juice is often added to the tea to facilitate the extraction of the alkaloids. Sugar and honey can be added to modify the taste of the tea. Rarely, dry leaves are smoked.

Consumers often chew on two or three leaves at the same time and only swallow the chewed up leaves while spitting out the stems and veins. After eating, consumers often drink some hot water, coffee, tea or a lam sugar syrup.

In South Thailand, icy cocktails are made and have become popular among young people. Cocktails are prepared with kratom leaves, bubbly water with caffeine and sometimes an antitussive syrup with codeine or diphenylhydramine and ice cubes.

2.10.1-Analysis and purity

The analytic methods available to check the composition and quality of kratom products are chromatographic and spectroscopic. DNA phylogenetic studies are helpful in identifying sources of kratom.

Alkaloids and their metabolites can be quantified in urine samples. Urine concentration of a regular kratom user can be typically around 160 ng/mL. Cases with high consumption (15 to 20 grams/day) may have blood levels up to 20 pg/mL. (1 milligram = 1,000 nanograms = 1,000,000 picograms)

The chemical composition of commercially available kratom is not systematically evaluated. It depends on a series of factors: specific strain and age of the plant, environment and harvesting time. The total concentration in alkaloids may vary from 0.5 to 1.5%. In the Thai samples, mitragynine is the most common alkaloid (up to 66%) 7-hydroxymitragynine is only 2% of the total alkaloid content. In samples from Malaysia, mitragynine is in lower proportion (12% of all

alkaloids). Concentration in dry leaves or powder from Malaysia tested in Japan showed levels of mitragynine 12 to 21 mg/g and 0.10 to 0.40 mg/g of 7-hydroxymitragynine. Kratom resins would contain 35 to 60 mg/g of mitragynine and 0.10 to 0.40 mg/g of 7-hydroxymitragynine.

An analysis of a fresh drink from Malaysia prepared from boiling fresh leaves in water contained 25mg of mitragynine for 250mL. Three glasses are deemed sufficient to alleviate withdrawal symptoms from opioids [10].

Some kratom is mixed with other chemicals. Krypton is supposedly a preparation of kratom which does not contain any mitragynine. Instead, it contains caffeine and O-desmethyltramadol (a metabolic derivative of tramadol (synthetic opioid)).

2.11-Medical Use

There are ten species of Mitragyna (6 in SE Asia and 4 in Africa) known to be used in traditional medicine. Only Mytragyna speciosa has these stimulating/sedative effects. In Southeast AsiaAsia, kratom is used as an anti-diarrheic, antitussive, antidiabetic, anti-helminthic drug, cure for heroin users and poultice for wounds. Outside of Southeast AsiaAsia, it is used to treat chronic pain or alleviate opioid user withdrawal syndrome.

Mytragynine has no indication in modern western medicine. In recent years, some people have used kratom as an herbal alternative to medical treatment in attempts to control withdrawal symptoms and cravings caused by addiction to opioids or to other addictive substances such as alcohol. There is no scientific evidence that kratom is effective or safe for this purpose; further research is needed.

One concern is that if banned, use of kratom will be driven underground and no scientific study will be possible [5].

2.11.1-FDA Statement on adverse events and scientific analysis

The following italicized text is from the Statement from FDA Commissioner Scott Gottlieb, M.D., on the agency's scientific evidence on the presence of opioid compounds in kratom, underscoring its potential for abuse available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm595622.htm

" Over the past several months, there have been many questions raised about the botanical substance known as kratom. Our concerns related to this product, and the actions we've taken, are rooted in sound science and are in the interest of protecting public health. However, we recognize that there is still much that is unknown about kratom, which is why we've taken some significant steps to advance the scientific understanding of this product and how it works in the body. Today, we're providing details of some of the important scientific tools, data and research that have contributed to the FDA's concerns about kratom's potential for abuse, addiction, and serious health consequences; including death.

Notably, we recently conducted a novel scientific analysis using a computational model developed by agency scientists, which provided even stronger evidence of kratom compounds' opioid properties. These kinds of models have become an advanced, common and reliable tool for understanding the behavior of drugs in the body. We also have learned more about deaths that

involved kratom use, and have identified additional adverse events related to this product. This new data adds to our body of substantial scientific evidence supporting our concerns about the safety and abuse potential of kratom.

We have been especially concerned about the use of kratom to treat opioid withdrawal symptoms, as there is no reliable evidence to support the use of kratom as a treatment for opioid use disorder and significant safety issues exist. We recognize the need and desire for alternative treatments for both the treatment of opioid addiction, as well as the treatment of chronic pain. The FDA stands ready to evaluate evidence that could demonstrate a medicinal purpose for kratom. However, to date, we have received no such submissions and are not aware of any evidence that would meet the agency's standard for approval."

"Federal agencies need to act quickly to evaluate the abuse potential of newly identified designer street drugs for which limited or no pharmacological data are yet available. This is why the FDA developed the Public Health Assessment via Structural Evaluation (PHASE) methodology – a tool to help us simulate, using 3-D computer technology, how the chemical constituents of a substance (such as the compounds /alkaloids found in kratom) are structured at a molecular level, how they may behave inside the body, and how they can potentially affect the brain. In effect, PHASE uses the molecular structure of a substance to predict its biological function in the body. For example, the modelling platform can simulate how a substance will affect various receptors in the brain based on a product's chemical structure and its similarity to controlled substances for which data are already available." [7]

2.11.2--Structural similarities with opioids

The following italicized text from the Statement from FDA Commissioner Scott Gottlieb, M.D describes structural similarities between kratom and opioids:

"Using this computational model, scientists at the FDA first analyzed the chemical structures of the 25 most prevalent compounds in kratom. From this analysis, the agency concluded that all of the compounds share the most structural similarities with controlled opioid analgesics, such as morphine derivatives.

Next, our scientists analyzed the chemical structure of these kratom compounds against the software to determine its likely biologic targets. The model predicted that 22 (including mitragynine) of the 25 compounds in kratom bind to mu-opioid receptors. This model, together with previously available experimental data, confirmed that two of the top five most prevalent compounds (including mitragynine) are known to activate opioid receptors ("opioid agonists").

The new data provides even stronger evidence of kratom compounds' opioid properties.

The computational model also predicted that some of the kratom compounds may bind to the receptors in the brain that may contribute to stress responses that impact neurologic and cardiovascular function. The agency has previously warned of the serious side effects associated with kratom including seizures and respiratory depression." [7]

2.11.3-3D Imaging

The following italicized text from the Statement from FDA Commissioner Scott Gottlieb, M.D discusses 3-D imaging of kratom:

"The third aspect of the model is the 3-D image we generate to look at not just where these compounds bind, but how strongly they bind to their biological targets. We found that kratom has a strong bind to mu-opioid receptors, comparable to scheduled opioid drugs.

So what does this body of scientific evidence mean? The FDA relies on this kind of sophisticated model and simulation to supplement its data on how patients react to drugs; often as a way to fully elucidate the biological activity of a new substance. The data from the PHASE model shows us that kratom compounds are predicted to affect the body just like opioids. Based on the scientific information in the literature and further supported by our computational modeling and the reports of its adverse effects in humans, we feel confident in calling compounds found in kratom, opioids.

Furthermore, this highlights the power of our computational model-based approach to rapidly assess any newly identified natural or synthetic opioids to respond to a public health emergency." [7]

Some suggest that although modelling is a very useful tool, one should not have any misconceptions because a model is still only a model. Models do not replace actual scientific observation of health effects.

2.12-Bacteriologic purity

2.12.1-Outbreak of Salmonella among Kratom consumers

Investigation of Salmonella outbreak among kratom users is reported at CDC's Salmonella website:

"CDC, public health and regulatory officials in several states, and the U.S. Food and Drug Administration (FDA) investigated this multistate outbreak of Salmonella infections.

Public health investigators used the PulseNet system to identify illnesses that were part of this outbreak. PulseNet is the national subtyping network of public health and food regulatory agency laboratories coordinated by CDC. DNA fingerprinting was performed on Salmonella bacteria isolated from ill people by using techniques called pulsed-field gel electrophoresis (PFGE) and whole genome sequencing (WGS). CDC PulseNet manages a national database of these DNA fingerprints to identify possible outbreaks. WGS gives a more detailed DNA fingerprint than PFGE.

As of May 24, 2018, 199 people infected with the outbreak strains of Salmonella were reported from 41 states."

"Illnesses started on dates ranging from January 11, 2017 to May 8, 2018. Ill people ranged in age from less than 1 to 75 years, with a median age of 38. Among ill people, 52% were male. Of 132 people with available information, 50 (38%) were hospitalized. No deaths were reported.

Whole genome sequencing analysis did not identify any predicted antibiotic resistance in isolates from 111 ill people and 61 kratom samples. Testing of 17 clinical isolates using standard antibiotic susceptibility testing methods by CDC's National Antimicrobial Resistance Monitoring System (NARMS) laboratory also did not show any antibiotic resistance."

"Epidemiologic and laboratory evidence indicated that kratom was the likely source of this multistate outbreak. Kratom is a plant consumed for its stimulant effects and as an opioid substitute.

State and local health officials interviewed ill people to ask about the foods they ate and other exposures before they became ill. Seventy-six (74%) of 103 people interviewed reported consuming kratom in pills, powder, or tea. Most people reported consuming the powder form of kratom. People who reported consuming kratom purchased it from retail locations in several states and from various online retailers.

This outbreak was detected when a cluster of people infected with Salmonella. It was identified by CDC PulseNet. During the investigation, health and regulatory officials in several states and the FDA collected various leftover and unopened kratom products to test for Salmonella contamination. As additional strains of Salmonella were identified in kratom products, a search of the CDC PulseNet database identified ill people infected with some of these strains, including Salmonella Heidelberg, Salmonella Javiana, Salmonella Okatie, Salmonella Weltevreden, and Salmonella Thompson. These ill people were added to the outbreak investigation. Eighty-five different DNA fingerprints of Salmonella bacteria were identified in samples of kratom products. The FDA website has a list of contaminated kratom products, which were from several retail locations and online retailers. Several companies issued recalls of kratom products. A list of the recalled kratom products is also available on the FDA website.

This outbreak investigation is over. However, some kratom products that were contaminated with Salmonella have not yet been recalled and may still be available for purchase or in people's homes. People who are at risk of severe Salmonella infection should avoid consuming kratom to prevent infection."

"Several companies recalled kratom products because they might be contaminated with Salmonella. The list of recalled kratom products is available on the U.S. Food and Drug Administration website." [11]

"People should not consume recalled kratom products. Consumers who bought recalled kratom products online can contact the website where it was purchased for a refund." [12]

2.12.2-Advice to Consumers

From the CDC Salmonella Homepage's Recalls and Advice to Consumers website:

"People should be aware that kratom could be contaminated with Salmonella and could make them sick.

Contaminated products may still be available for purchase because the outbreak investigation was not able to identify a single, common source of contaminated kratom.

Salmonella was identified in multiple kratom products. The U.S. Food and Drug Administration website has a list of these contaminated products. Some of these products have not yet been recalled and may still be available for purchase or in people's homes.

People who are at risk of severe Salmonella infection should avoid consuming kratom to prevent infection. People in the following groups are more likely to get a severe Salmonella infection:

- *People with weakened immune systems, including people who are receiving chemotherapy or have HIV*
- *Pregnant women*
- *Children younger than 5 years*
- *Older adults*

If you are considering using kratom, talk to your health care provider first, especially if you are in a group more likely to get a severe Salmonella infection.

If you choose to consume kratom, take steps to prevent spreading Salmonella germs to other people in your home.

Wash your hands thoroughly with soap and water after preparing kratom in any form. Wash and sanitize countertops, utensils, and other preparation surfaces after preparing kratom in any form. If you are sick, wash your hands thoroughly with soap and water, especially after using the restroom. Don't prepare food or drinks for other people while you are sick.

Contact a healthcare provider if you think you got sick from consuming kratom. Most people infected with Salmonella develop the following signs and symptoms 12-72 hours after being exposed to the bacteria:

- *Diarrhea*
- *Fever*
- *Abdominal cramps*

Know your options." [11]

2.13-Epidemiology

2.13.1-Prevalence

Since this drug was recently introduced to the international market, there is little data on its use except in the countries of origin.

In Thailand, a national survey from 2007 (26,633 responses from people age 12 to 65) showed the following prevalence:

- Ever used in lifetime 2.3%
- Used during past year 0.8%
- Used past 30 days 0.6%

The prevalence rates of kratom usage were higher than the prevalence rates for cannabis. Usage. [9]

An estimated five million people use kratom regularly, according to the American Kratom Association (AKA), a pro-kratom lobbyist group:

"In 2016, the AKA and the University of Florida conducted an anonymous online survey of 8000 kratom users and found the majority were white, middle-aged, employed, and married. Two-thirds of respondents used the drug to self-treat pain and emotional or mental conditions. A smaller amount of people have used it to wean off opioids. Some researchers have also suggested kratom could have therapeutic potential, including antidepressant effects. [5]

2.13.2-Poison Control Studies

According to Forrester (2013), 14 kratom exposures were reported to Texas poison centers between 2009 and 2013. (There were no kratom exposures reported from 1998 through 2008). Even though this is a significant increase, it should be noted that during 2012, a total of 474 synthetic cannabinoid (e.g., K2, Spice) and 160 synthetic cathinone (e.g., bath salts) exposures were reported to Texas poison centers. This suggests that, even though the number of reported kratom exposures may have increased in recent years, its impact on poison centers is small compared with new substances of abuse [13].

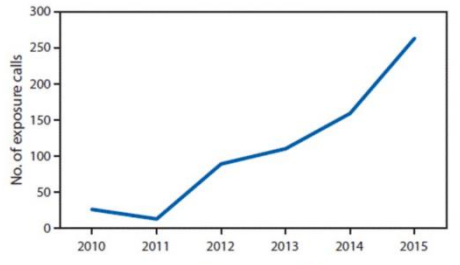
Between January 2010 and December 2015, 660 calls reporting exposure to kratom were received by poison centers and uploaded to the National Poison Data System (NPDS). The NPDS serves all 50 United States, the District of Columbia and Puerto Rico and collects information from call reports made by both the public and health care providers. The number of calls per year between 2010 and 2015 increased tenfold from 26 calls in 2010 to 263 calls in 2015 [L]. There were an average of 110 calls per year, which represents about 0.004 % of the approximately 3 million calls received by poison control centers each year.

By comparison, exposures involving analgesics accounted for nearly 300,000 calls in 2014 while cosmetics and personal care products, cleaning solutions, antidepressants and antihistamines each accounted for more than 100,000. Of the 3 million calls received by poison control centers each year, one death was reported in a person who was exposed to the medications paroxetine (an antidepressant) and lamotrigine (an anticonvulsant and mood stabilizer) in addition to kratom. However, due to multiple substances involved in this matter, there was insufficient toxicological evidence to conclude that kratom played a causative role

2.13.3-Centers for Disease Control study of Poison Control Centers

From the CDC Morbidity and Mortality Weekly Report for July 26, 2016:

"Kratom (Mitragyna speciosa) is a plant consumed throughout the world for its stimulant effects and as an opioid substitute. It is typically brewed into a tea, chewed, smoked, or ingested in capsules. It is also known as Thang, Kakuam, Thom, Ketum, and Biak. The Drug Enforcement Administration includes kratom on its Drugs of Concern list (substances that are not currently regulated by the Controlled Substances Act, but that pose risks to persons who abuse them), and the National Institute of Drug Abuse has identified kratom as an emerging drug of abuse. Published case reports have associated kratom exposure with psychosis, seizures, and deaths. Because deaths have been attributed to kratom in the United States, some jurisdictions have passed or are considering legislation to make kratom use a felony. CDC characterized kratom exposures that were reported to poison centers and uploaded to the National Poison Data System (NPDS) during January 2010–December 2015. The NPDS is a national database of information logged by the country's regional poison centers serving all 50 United States, the District of Columbia, and Puerto Rico and is maintained by the American Association of Poison Control Centers. NPDS case records are the result of call reports made by the public and health care providers.



oison Control Center calls for kratom, 2010-2015. Source: CDC

During the study period, U.S. poison centers received 660 calls about reported exposure to kratom. The number of calls increased tenfold from 26 in 2010 to 263 in 2015. Health care provider reports constituted 496 (75.2%) of calls. Among calls, 487 (73.8%) exposed persons reported intentional exposure, and 595 (90.2%) reported ingestion of the drug. Isolated kratom exposure (single exposure) was reported in 428 (64.8%) cases. Among calls reporting use of kratom in combination with other substances (multiple exposures), the most commonly reported other substances were ethanol, other botanicals, benzodiazepines, narcotics, and acetaminophen. Among 658 (99.7%) calls for which information on sex of the exposed person was available, 472 (71.7%) were male, and among 604 (91.5%) for which information on age was available, the median age was 28 years (range = 2 months–69 years).

Medical outcomes associated with kratom exposure were reported as minor (minimal signs or symptoms, which resolved rapidly with no residual disability) for 162 (24.5%) exposures, moderate (non-life threatening, with no residual disability, but requiring some form of treatment) for 275 (41.7%) exposures, and major (life-threatening signs or symptoms, with some residual disability) for 49 (7.4%) exposures. One death was reported in a person who was exposed to the medications paroxetine (an antidepressant) and lamotrigine (an anticonvulsant and mood stabilizer) in addition to kratom. For 173 (26.2%) exposure calls, no effects were reported, or poison center staff members were unable to follow up again regarding effects. Among exposed persons for whom information on signs and symptoms was available, reported signs and symptoms included tachycardia (n = 165, 25.0%), agitation or irritability (157, 23.8%), drowsiness (128, 19.4%), nausea (97, 14.7%), and hypertension (77, 11.7%). A chi-square test demonstrated a significant association between severity of outcome and multiple versus single exposures ($p<0.001$). Pairwise comparisons (adjusted by the stepdown Bonferroni procedure) indicated a higher likelihood of a report of a severe outcome among persons aged 21–30 years ($p = 0.04$), 31–40 years ($p = 0.02$), and >40 years ($p = 0.02$) compared with persons aged 0–10 years.

Kratom use appears to be increasing in the United States, and the reported medical outcomes and health effects suggest an emerging public health threat. Members of the public and health care providers should be aware that the use of kratom can lead to severe adverse effects, especially when consumed in combination with alcohol or other drugs." [14]

Critics of the CDC Study point out that the report is alarmist since:

--173 of the 660 calls reviewed (26.2%) did not report any effect
--An additional 162 (24.5%) calls were for health effects that resolved rapidly with no residual disability.
--For another 165 calls (25%), the health effects were not life threatening (tachycardia, agitation or irritability, drowsiness, nausea, and hypertension.
--No details are presented for the other 160 cases (24.2%)
--Only one death is reported. This person had taken kratom with other drugs (an antidepressant and an anticonvulsant.

2.13.4-Louisiana Poison Center Opinion

The Louisiana Poison Center seems to have a mitigated view on this topic:

"--Kratom (Mitragyna speciosa) has been on my radar since 2009. There has been much speculation about the opioid effects that mitragynine, the major active substance in the plant has. Mitragynine does bind to the opiate mu receptor but we do not know how powerful the pain relieving activity may be. We have not observed an increase in the use of Kratom that would lead me to believe it acts as a strong pain reliever and that it was being used as a replacement for other known very powerful pain medications.

--At present, only five states have placed Kratom in Schedule I. Several, including LA, have restricted the sale of Kratom by age. One state regulated Kratom as a synthetic drug which is not correct. It is very much a natural product. The DEA has made attempts to regulate Kratom in recent years. They have issued advisories but have yet collected enough data that suggests Kratom is a danger and warrants regulation. The DEA passed the torch to FDA at the end of 2017, thinking that there were greater opportunities to regulate Kratom as a supplement. Kratom continues to be monitored at many levels and if information becomes available that Kratom is a true threat to public health a move to regulate it will be successful.

*--At the LA Poison Center monitors the records database and **did not show** an increase in cases involving Kratom. In fact, the number of cases is very low and has stayed in the 12-15 number for several years. Severe effects or deaths are observed resulting from Kratom use they will be reported immediately to LDH so that kratom can be moved to immediately to Schedule I. It does not currently rise to that level."* --Louisiana Poison Center (personal communication, October 29, 2018)

2.14-Louisiana Early Events Detection System (LEEDS)

The Louisiana Early Event Detection System (LEEDS) is a web-based reporting system that automatically processes hospital Emergency Department and Urgent Care data to identify visits indicative of specific syndromes tracked by the Louisiana Office of Public Health (OPH). LEEDS

electronically tracks chief complaints from 60 hospital emergency departments which represent 35,000 to 40,000 visits per year. LEEDS tracks numerous syndromes and is used by Infectious Disease Epidemiology for important public health surveillance activities. The program has the ability to track specific keywords.

Out of 35,000 visits, there were only five instances of tracking the word "kratom". These were one allergic reaction, one "kratom withdrawal", one for minor health effects from use of kratom and muscle relaxant, one with a cyanotic reaction after ingesting alcohol and 3 spoonful of kratom. None of these five cases were hospitalized and were discharged from the ED.

2.15-Availability / Marketing

Kratom is heavily advertised on the internet. A google search displays several pages with advertisement on location, price and benefits of kratom use mixed with pages on the dangers of kratom.

Here are a few examples of advertisement / marketing easily viewable on the web. This is shown in this report to show the kind of information being publicly available. Evidently, some of the reader will embrace these statements. Kratom is often advertised as a milder herbal remedy for a whole variety of ailment.

- *Xxx kratom is a magical herb to boost a person's mental health and good news is it is the most affordable herb and kratom box is a place where you will find best versions of Xxx kratom and all the herbal remedies.*
- *It is a favorite brand of many people because of wide variety of strains, which are curing mental health of people effectively, if you are tired of dealing with fatigue, too much stress, depression and anxiety try using Xxx kratom to have a perfect relaxation of the mind and body.*
- *Using heavy drugs to get relief from pain is not a good idea you will ultimately get used to these drugs that they have long term destroying effects on you rather than curing you. On this site, Xxx remedies are introduced so you can cure your health without damaging it further, any person can try these remedies and get high time benefits through them.*
- *These remedies have such a great response from people and they have become very popular among them, they are available in fewer prices and you can get them in just 25 dollars and 250 grams in it.*
- *They have the best shipping time also as it will be delivered to you on the same day you make the order no matter where in the world you are living. Expect the product arrive to your doorstep on time.*

2.16-Media Environment

The kratom issue has attracted a lot of media attention. Here is an example of article published in an October 2016 issue of the Huffington Post:

"After intense backlash, the agency is making an unprecedented move to reconsider prohibition. The U.S. Drug Enforcement Administration appeared to concede Wednesday that it had been too hasty in attempting to ram through a controversial ban on the herbal supplement kratom.

In a notice set to be published in the Federal Register, the DEA said it has formally withdrawn an August announcement that initially outlined plans to place mitragynine and 7-hydroxymitragynine, two active compounds in kratom, in Schedule I. Schedule I drugs include heroin and LSD and are considered to have no known medical benefit and a high potential for abuse.

Citing widespread backlash from kratom users, advocates and other stakeholders, the DEA says it will open an official comment period, set to end on Dec. 1. It is also asking the U.S. Food and Drug Administration for a formal scientific and medical evaluation of the herb, which will be used to make an updated scheduling recommendation.

Kratom is an herb made from the leaves of Mitragyna speciosa, a Southeast Asian tree related to coffee. The alkaloids mitragynine and 7-hydroxymitragynine appear to activate opioid receptors in the brain and reduce pain. In addition, although most opioids have sedative qualities, low to moderate doses of kratom actually serve as a mild stimulant.

All of this has made kratom a popular traditional medicine for millennia in Asia and more recently in the West, where many users tout it not just as an analgesic, but also as a treatment for anxiety, depression and opioid addiction.

However, the DEA has raised concerns about kratom's addictive potential, as well as isolated reports of harm associated with use. The agency's change in course will keep kratom legal for the immediate future, but it is unclear how long the delay will last.

The DEA will take submitted comments and the FDA's findings into consideration as it decides how to proceed. If it determines after Dec. 1 that there is 'substantial evidence of potential for abuse to support' scheduling kratom, the agency can take additional action through the permanent or temporary scheduling process. To ban kratom on a permanent basis, the DEA would need to submit an additional notice of proposed rulemaking, which would allow for further input from the public and lawmakers.

However, if the DEA maintains, as it did in August, that emergency scheduling of kratom is 'necessary to avoid an imminent hazard to the public safety,' it could file a new notice of intent, which would likely go into effect a month later. The agency could also opt to pursue both emergency and permanent scheduling simultaneously, or to leave kratom unregulated.

Still, the DEA's decision to reverse course on banning a drug, even temporarily, is unprecedented. Kratom and drug policy reform advocates who have spent the past month aggressively lobbying against the ban effort were quick to hail the news as a victory.

'This is a truly remarkable moment to see the Drug Enforcement Administration, a law enforcement agency with a long track record of ignoring both science and public opinion, being forced to consider the scientific evidence and public opinion before taking additional steps with respect to kratom,' said Grant Smith, deputy director of national affairs at the Drug Policy Alliance, in a statement. 'People who oppose a federal kratom ban only have about six weeks to tell the federal government that kratom does not belong in our broken drug scheduling system.'

Susan Ash, founder of the American Kratom Association, a nonprofit that works with consumers, credited the effort by kratom users, congressional lawmakers and scientists who have challenged the DEA's unilateral move to expand the drug war.

'We believe kratom should not be scheduled in any way, shape or form,' she said in a statement to The Huffington Post. 'It's been consumed safely for decades in the U.S. and worldwide for millennium, so there is no impetus to make it a controlled substance. We look forward to working cooperatively with the DEA as they conduct their review.'

Earlier this month, two groups of senators wrote acting DEA administrator Chuck Rosenberg asking him to delay the kratom ban. Sen. Cory Booker (D-N.J.) said in a letter that a group of 11 scientists from 'well-respected research institutions in the U.S.' had contacted him to express concern about the agency's crackdown. They pointed out that a number of initial studies on kratom have shown the herb to have therapeutic potential, with relatively few risk factors. Some research has even suggested that kratom could aid in the development of safer, non-opioid painkillers, which are currently contributing to a national epidemic of addiction and overdose.

The Senate letter built on a similar push by a group of 50 House lawmakers, led by Rep. Mark Pocan (D-Wis.), as well as a White House petition that now has more than 140,000 signatures. In a statement to HuffPost on Wednesday, Pocan called the DEA's move toward transparency a good step forward. The next step, he suggested, should be to make the ban's delay permanent.

'I hope the DEA will take a hard look at the federally funded research into the potential health benefits of kratom, especially with regards to curbing opioid abuse and addiction,' said Pocan. 'Concerned citizens across the country have made it clear, they want the DEA to listen to the science when it comes to the potentially life-saving properties of kratom. I hope a more thorough process will reverse their decision, and allow for continued research in this area.' "[15]

2.17-Legal environment

From the Kratom Online article, "Kratom USA: Legal Status, FDA Rulings and State Laws":

"Confusion has abounded on the matter of the legal status of Kratom within the United States. Some sources will tell you that Kratom is a narcotic and should be illegal to buy or use. Others will tell you that Kratom is entirely legal as it is not a controlled substance. This matter is made further complex by the presence of local state laws that may impose different restrictions from those set out by the Federal government. At present, there is an ongoing push for stricter legislation on Kratom by some parties in the US, while others are urgently trying to spread the word on the benefits of this natural herb for health and mental well-being." [16]

2.17.1-Federal Controlled Substance Act

From the Kratom Online article, "Kratom USA: Legal Status, FDA Rulings and State Laws":

"In the USA, the question of whether Kratom is legal is determined by the Federal Controlled Substances Act (CSA). This Act sets out parameters for regulating different drugs and narcotics, categorizing them into several scheduled based on their potential for abuse. Kratom leaves and the alkaloids found in this plant are not currently listed on any of these schedules, nor have they ever been. This means that possession of Kratom is not a crime and you do not need a prescription in order to buy or use it. There are also no laws put in place that would make it illegal to sell this plant or its byproducts under the CSA. In other words, Kratom is legal to buy, sell, possess, use, import, export, process and market in the United States" [16]

2.17.2-Food and Drug Agency

From the Kratom Online article, "Kratom USA: Legal Status, FDA Rulings and State Laws":

"Despite being a legal substance in the US, Mitragyna Speciosa has not been approved by the FDA for human consumption. This means it cannot be sold as a product intended to be ingested by humans. A supplier may not be able to label the product as a health supplement or a natural remedy and they are not allowed to promote the benefits of Kratom plants for energy, mood and relaxation.

In order for a supplement, herb or novel food item to be approved for consumption by the FDA, it requires a massive amount of capital and a lengthy trial process. This procedure can cost upwards of $50 million and can take several years before a conclusion is reached. The main problem is that one business may decide to spend the $50 million to push through the approval process, but once it has been given the green light, any number of competitors can jump into the market to start selling their product at a cheaper price and undercut the original sponsor. This set-up makes it very unlikely that one company will choose to shoulder the burden of paying for approval." [16]

2.17.3-Dietary Supplement Health and Education Act of 1994 (DSHEA):

FDA regulates both finished dietary supplement products and dietary ingredients. FDA regulates dietary supplements under a different set of regulations than those covering "conventional" foods and drug products. Under the Dietary Supplement Health and Education Act of 1994 (DSHEA):

Manufacturers and distributors of dietary supplements and dietary ingredients are prohibited from marketing products that are adulterated or misbranded. That means that these firms are responsible for evaluating the safety and labeling of their products before marketing to ensure that they meet all the requirements of DSHEA and FDA regulations.

FDA is responsible for taking action against any adulterated or misbranded dietary supplement product after it reaches the market.

It has been argued that placing kratom under the DSHEA would not be effective because kratom would not qualify as a dietary supplement and supplement manufacturers are not required to demonstrate supplements safety before marketing the supplements. The FDA can only ban a supplement if the FDA finds proof that the supplement is dangerous. This means that unsafe or ineffective supplements can be sold freely, while the FDA has only a limited capacity to monitor adverse reactions from supplements.

2.17.4-Is kratom a drug or an herbal supplement?

The following section is quoted from the American Council on Science and Health's article, "Kratom Is A Drug By Any Measure –Treat It Like One"*:*

"In January, U.S. Marshals, at the request of the FDA, raided Dordoniz Natural Products of South Beloit, Illinois, to seize almost 90,000 bottles of a drug the company called RelaKzpro, valued at around $400,000. What it really was about was kratom, a drug being sold as a supplement, but which slides under the radar because it is a "natural" product derived from the leaves of the Mitragyna Speciosa *tree.*

Kratom is instead, in plain terms, an opioid, like codeine or hydrocodone, plus components of a psychoactive drug. Because Kratom is a drug, whether it is "natural" or not is irrelevant. If some supplement maker crushes up opium poppy seeds to put them in a supplement, that is also completely natural, but it is not allowed to be sold as a supplement, it is still a drug. Kratom is no different. It certainly does not matter how many inexperienced proponents or people educated by publicity reps claim "it is in the coffee family." Supplement lobbyists use "family" to make it sound like kratom could be twins with coffee but there are over 13,000 other species in the Rubiaceae *family. Also in that family is* psychotria viridis, *a key source for ayahuasca, another dangerous psychoactive like kratom.*

It's not a harmless analgesic, as the surge in calls to poison control centers have shown. Kratom is a drug that has been directly linked to psychosis, seizures, and deaths. The U.S. Centers for Disease Control and Prevention reported that from 2010 to 2015 calls to U.S. poison centers related to kratom increased 1,000 percent. Major life threatening instances occurred in over 7 percent of cases. Minimally or hypothetically harmful chemicals like lead and chromium-6 are all

over the news with a minute fraction of that harm and environmental groups scaremonger things like BPA, formaldehyde and parabens, which can't possibly harm anyone, yet media are giving kratom false equivalence with claims this will prevent opioid abuse. Here is what it has done to people, according to the CDC: In those poisoned by this drug, tachycardia - rapid heart rate - occurred in 25 percent, agitation or irritability in almost 24 percent, drowsiness in almost 20 percent, nausea was almost 15 percent and hypertension was in almost 12 percent.

That's a lot of different health effects, none of them good, and it's no surprise. Mitragynine, the major psychotropic alkaloid that gives kratom its properties, binds to numerous receptors, so the medicinal value of kratom is suspect, but it is certainly a drug.

Kratom is not one chemical substance, it is a mixture of more than 40. Twenty-five of them belong to a broad class called alkaloids nitrogen-containing chemicals that are found in plants, many of which are potent poisons."

A poison isn't healthier for you because it's natural. Despite that, some groups are claiming that the Drug Enforcement Agency is being too heavy-handed - basically,- we should wait until there are a pile of dead bodies before they do anything. It misses the point, which is that just about anything can be foisted off on the public as a supplement until it kills people.

Due to concern about the surge in poisonings, the Drug Enforcement Agency published a 'notice of intent' to list kratom as a Schedule I substance in August 2016, putting it right along with heroin and LSD, effective September 30th. Immediately the American Kratom Association began to fight back, convincing politicians on one side of the aisle that this is a free market issue, and those on the other side of the aisle that it should be 'studied' by the U.S. government's alternative medicine group, now called the National Center for Complementary and Integrative Health, rather than being scheduled. They got 51 members of the U.S. House of Representatives to agree that 'consumer access and choice of an internationally recognized herbal supplement' would be hindered by the DEA.

It's not in our mandate to be concerned about what DEA wants to ban, we are actually more worried about what they still allow, and that applies to any number of supplements which are either useless junk or contain dangerous unlabeled chemicals. That's a public health issue and is due to the disastrous Dietary Supplement Health and Education Act of 1994, which was signed by President Bill Clinton (but to be fair, Senators Orrin Hatch and Tom Harkin share blame for shepherding it through) and designed to prevent FDA from tightening regulations regarding supplement labeling. Since then, with scant accountability unless someone dies, the supplements business in the United States has gone out of control.

It is a drug. It should have to undergo clinical trials before it can be sold, the same way pharmaceutical drugs must." [17]

The Drug Enforcement Administration includes kratom on its Drugs of Concern list (substances that are not currently regulated by the Controlled Substances Act, but that pose risks to persons who abuse them). The National Institute of Drug Abuse has identified kratom as an emerging drug of abuse.

2.17.5-Drug Enforcement Administration

In late 2016, out of concern for public safety, the DEA placed a temporary ban on kratom. The Agency's move was followed by a substantial negative reaction from kratom supporters and was quickly rescinded. In August 2016, the DEA announced it would make kratom a Schedule 1 drug -- the same as heroin, LSD, marijuana and ecstasy [18]. The decision was delayed after members of Congress urged the DEA to delay the ban and give the public a chance to comment. As of April 2017, the DEA did not have a timetable for banning or scheduling the drug, though some states have banned it. However, the (DEA) was initially moving to ban its sale as of Sept. 30, 2016, citing an "imminent hazard to public safety."

The DEA has listed Kratom as a "Drug and Chemical of Concern." There is a sense that the law may change in the future and no one is entirely sure what will come of the legal status of Kratom in the USA.

The federal government's moves to ban kratom have already made it difficult to study, as many researchers have protested. At least two human studies were cancelled following the DEA's 2016 intent to ban kratom, and a Schedule I ban would likely make things more difficult to research, not less [19].

2.18-Kratom and the US States and Foreign Countries

The DEA has yet to publish a final decision and the future status of kratom remains unknown. However, the current legality of kratom remains a gray area for many people. Kratom is currently legal in the United States but there are several states who have banned kratom's use, making it illegal.

According to a June 5, 2019 article on the KratomMasters website, kratom is illegal in Alabama, Arkansas, Indiana, Rhode Island, Vermont, and Wisconsin. It is also banned in Florida's Sarasota County, Jerseyville, Illinois and Denver, Colorado [20].

Some of the states' rules have added to the confusion. The Indiana House of Representatives passed a bill that added the alkaloids mitragynine and 7-hydroxymitragynine to the list of Controlled Substances in that state. This law passed in 2012 made them the first state to try to control the use of Kratom. However, because Kratom is a natural plant as opposed to a synthetic substance, this law only prevents the alkaloids from being sold in synthetic formulations. As such, the Kratom plant has not been banned and is still legal in the state of Indiana.

Kratom is not legal in Australia, Finland, Malaysia, Myanmar and Thailand. Kratom was used in Thailand for centuries but is now banned. When the Thai government started levying taxes from users and shops involved in the opium trade many users switched to kratom to manage their withdrawal symptoms.

From the *Discover* web article:

"*In its native Thailand, the plant's leaves have been chewed or sipped as tea for at least 200 years, despite being outlawed by the government in 1943 during the Greater East Asia War.*

Thailand, on the Japanese side, was fighting the U.S., and the war caused the cost of opium to skyrocket. (The region, the so-called Golden Triangle, was long notorious as the world's largest heroin-producing hub, until Afghanistan later usurped the title.) Many Thai users switched from opiates to kratom, which was not taxed, so the government responded with a blanket ban.

Ever since, the Thai government has sent in troops to burn down kratom's natural rainforest habitat, threatening other wildlife as well. More recently, Thailand's president, Pornpetch Wichitcholchai, expressed support for a bill decriminalizing kratom and marijuana for medical research, which passed in early November." [5]

3-Kratom quality testing

This section will address the House of Representatives of the Legislature of Louisiana, which urges and requests the Louisiana Department of Health to study and make recommendations concerning potential consumer protection measures relative to kratom.

3.1-Kratom lab testing importance

It is very crucial that before making a substance public to be consumed by the humans, it should be tested in the labs. The reason is simple. Health effects may result from chemical (heavy metals, other alkaloids) or biological contamination (mostly bacteria or fungi). Kratom testing is not prevalent and there is no proper regulation of Kratom in many parts of the world. Many vendors sell Kratom products without lab testing, which end up causing side effects in their consumers.

3.2-Sampling issues

No two tests should be the same. One should not just look at the lot/batch/harvest number and mitragynine percent results. Those are easy to change with counterfeits. It is necessary to look at the graph itself and the details of the results. All of it must be different for each test. Even with testing, the same exact batch will have some visible differences. The size of the batch/harvest being tested should be considered. If a vendor is applying a single test result to a hundred kilos of kratom or more, that is a problem. The number of samples taken from the batch/harvest to test should be representative of the batch. The timing of collection of test samples and sending to the lab is important. Some suppliers will do testing on their botanicals before they ship to a vendor. Contamination and issues can happen after a supplier does their testing. How a botanical is handled from storage, shipping, to repackaging can create contamination issues. Testing needs to be done at the end once botanicals have arrived to their final destination. The lab should have a stable sample for reference.

3.3-What to test for

3.3.1: Alkaloids:

The alkaloids that are naturally present in kratom should be limited to mitragynine and 7-hydroxymitragynine (7OH).The alkaloids should be tested against a reference that is the standard

value. The amount of mitragynine present in kratom is around 1 to 2% only and 7-hydroxymitragynine is even less. Any kratom company claiming to have more than this content has adulterated their product unless it is an extract or a tincture.

3.3.2: Pathogens:

The most common pathogens in kratom include mold and yeast and sometimes-harmful aerobes and anaerobes including Coliforms, Salmonella and Staph bacteria.

3.3.3-Heavy metals and organic chemicals

Kratom is tested for heavy metals like arsenic, cadmium, lead, and mercury. Kratom should be tested for pesticides. It would be useful to search for pesticides used in the area/country where Kratom is coming from.

3.4-Lab Tests Used To Check Kratom Ingredients

3.4.1- Identification of Botanical Compounds

Some of the product tested for identification and alkaloid percentage is not Mitragyna speciosa at all. Some are another strain, such as Mitragyna javanica, and some are not Kratom leaf at all. Other substances to be tested are THC, opioids, fentanyl.

3.4.2-High-Pressure Liquid Chromatography (HPLC)

There are simple methods to quantify Mytragynine. For example Parthasarathya et al describe in an article from 2013 "A simple HPLC–DAD method for the detection and quantification of psychotropic mitragynine in *Mitragyna speciosa* and its products for the application in forensic investigation" [21]

3.4.3-Gas Chromatography-Mass Spectrometry (GCMS)

An example of these methods is described in Lebel et al's "A rapid, quantitative liquid chromatography-mass spectrometry screening method for 71 active and 11 natural erectile dysfunction ingredients present in potentially adulterated or counterfeit products" [22]

3.4.4-Thin Layer Chromatography (TLC)

Thin-layer chromatography (TLC) is a chromatography technique used to separate non-volatile mixtures. Thin-layer chromatography is performed on a sheet of glass, plastic, or aluminum foil, which is coated with a thin layer of adsorbent material, usually silica gel, aluminum oxide (alumina), or cellulose. This layer of adsorbent is known as the stationary phase.

After the sample has been applied on the plate, a solvent or solvent mixture, (the mobile phase) is drawn up the plate via capillary action. Because different analytes ascend the TLC plate at different rates, separation is achieved. The mobile phase has different properties from the stationary phase. Chemical processes can also be used to visualize spots.

A number of enhancements can be made to the original method to automate the different steps, to increase the resolution achieved with TLC and to allow more accurate quantitative

analysis. This method is referred to as HPTLC or "high-performance TLC". HPTLC typically uses thinner layers of stationary phase and smaller sample volumes, thus reducing the loss of resolution due to diffusion.

3.4.5- Organoleptic Testing

This is the Use of Human Senses for Identification)

Scent: To check aroma of the sample.

Color: To compare it to an accepted standard.

3.4.6- Microbiology Testing

In laboratories with extensive experience, bacterial contamination is common. About 5% of the total material tested comes up positive for pathogens and up to 15% comes up positive for pathogens from some areas.

Testing consists of Total Aerobic plate count/yeast and mold count: this test identifies and counts the microorganisms in the sample.

Testing for E.coli and Salmonella.

3.4.7- Chemical Analysis

Pesticides: Kratom sample should be free from pesticides. Pesticides are widely used in many of countries where Kratom comes from.

For example, a major exporter of rice, rubber, corn, tropical fruit, and cassava, Thailand's farmlands supply many of the world's countries with bulk produce — so much so that it equates to about $10 billion US$ per year. To meet this demand, the Kingdom relies heavily on pesticides to control insect populations and increase the yield of crops. In the past, the country has lost nearly 50% of its produce to insect scourges and other threats. Over the past ten years, Thailand's agricultural exports have risen to make up at least 40% of the country's GDP; therefore, the nation's use of pesticides has exploded exponentially to nearly four times the initial amount.

On average, there were 28 pesticides used, including aldrin, atrazine, captan, carbaryl, carbofuran, carbosulfan, chlormefos, chlorpyrifos, chlorothanlonil, cypermethrin, deltanethrin, diazinon, dichlorvos, dicofol, chlorpyrifos… the list goes on. On average, there were 28 pesticides used, including aldrin, atrazine, captan, carbaryl, carbofuran, carbosulfan, chlormefos, chlorpyrifos, chlorothanlonil, cypermethrin, deltanethrin, diazinon, dichlorvos, dicofol, chlorpyrifos… the list goes on.

Heavy metals: Identify Arsenic and other metallic compound known to occur in the soil of the area where Kratom in coming from. The State of California has very strict limits on how much of these four metals can be in any material intended for consumption:

- Arsenic
- Cadmium
- Lead
- Mercury

3.4.8-Analysis of Physical Properties

-Size of particles: this is checked by maneuvering the sample through a sieve to identify the size of particles.

-Product density.

4. Recommendations for Consumer Protection

While kratom is currently legal at the federal level, the DEA is considering labeling it as a Schedule I drug -- a category that includes heroin, marijuana, LSD, and ecstasy. Kratom is illegal in six states, Washington, D.C., and several cities, according to the American Kratom Association. It is on the DEA's list of drugs and chemicals of concern [23]. Louisianans should heed FDA's warning:

"The U.S. Food and Drug Administration is warning consumers not to use Mitragyna speciosa, commonly known as kratom, a plant which grows naturally in Thailand, Malaysia, Indonesia, and Papua New Guinea. FDA is concerned that kratom, which affects the same opioid brain receptors as morphine, appears to have properties that expose users to the risks of addiction, abuse, and dependence.

There are no FDA-approved uses for kratom, and the agency has received concerning reports about the safety of kratom. FDA is actively evaluating all available scientific information on this issue and continues to warn consumers not to use any products labeled as containing the botanical substance kratom or its psychoactive compounds, mitragynine and 7-hydroxymitragynine. FDA encourages more research to better understand kratom's safety profile, including the use of kratom combined with other drugs."

"While FDA evaluates the available safety information about the effects of kratom, the agency encourages health care professionals and consumers to report any adverse reactions to the FDA's MedWatch program." [24]

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Louisiana Department of Health
628 North Fourth Street, Baton Rouge, Louisiana 70802
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