Affidavit of William R. Sawyer, Ph.D., D-ABFM

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Toxicological Review and Health Risk Assessment of Kratom

Docket No. DEA-442W

Withdrawal of Notice of Intent to Temporarily Place *Mitragynine* and *7-Hydroxymitragynine* into Schedule 1; Solicitation of Comments

For comment period ending December 1, 2016

Prepared for Venable LLP

575 7th Street, NW

Washington, DC 20004

November 30, 2016

Contents

AFFIDAVIT OF EXPERT TOXICOLOGIST DR. WILLIAM R. SAWYER

STATE OF FLORIDA '
'
COUNTY OF LEE '

Before me, the undersigned notary, on this day personally appeared WILLIAM R. SAWYER, a person whose identity is known to me. After I administered an oath to him, upon his oath, he said:

A. Identification

Name and Purpose

1. My name is William R. Sawyer, Ph.D. I have been retained as an expert toxicologist to review and assess the potential toxicity and safety of *Mitragyna speciosa Korth*, an herbal product known as kratom.

Qualifications and Training

2. I am a professional toxicologist with a doctorate in toxicology from the Indiana University School of Medicine. I earned an associate degree from the State University of New York Agricultural and Technical College at Morrisville in 1976. I earned a bachelor of science degree in biology from the State University of New York at Geneseo in 1978. I earned a master's degree in cellular and molecular biology, also from the State University of New York at Geneseo, in 1982. I subsequently earned a doctorate in toxicology from the Indiana University School of Medicine in 1988. This required three years of medical school curriculum with three years of course work in toxicology as well as training in the State Department of Toxicology and original, peer-reviewed and published toxicological research.

3. During my training at the Indiana University School of Medicine Department of Toxicology and Pharmacology, I studied under the late Robert B. Forney, Sr., Ph.D. Dr. Forney was the department chairman, the director of the State Department of Toxicology and one of the top researchers in his field and gained international recognition. I received considerable training with respect to toxic exposure evaluations of alcohol, numerous pharmaceuticals, natural products and toxic chemicals. I also worked in the State Department of Toxicology facility at the medical center in Indianapolis, Indiana, performing forensic analyses for poisons (including heavy metals), pharmaceuticals, drugs of abuse and alcohol.

4. I am a diplomate of the American Board of Forensic Medicine and the American Board of Forensic Examiners. I have been previously certified by the State of New York Department of Health as a clinical laboratory director in forensic toxicology (License No. SAWYW1) and as a licensed environmental laboratory director by the states of New York, New Jersey, California and South Carolina. I have previously been trained and certified under OSHA 29 CFR1910.120 for Hazardous Waste Operations and Emergency Response.

5. I am an active member of various professional societies including the American Board of Forensic Medicine, the American Board of Forensic Examiners, Sigma Xi, the Scientific Research Society, the American Academy of Forensic Sciences and the International Association of Forensic Toxicologists.

6. I am presently chief toxicologist at Toxicology Consultants and Assessment Specialists, LLC, in Sanibel, Florida, (also registered to operate in New York). I have served as a peer-reviewer for the journal "*The Forensic Examiner*" and as a member of its editorial board. I was previously an adjunct assistant professor at the Upstate Medical Center in the Department of Medicine at S.U.N.Y. Health Science Center in Syracuse, New York.

7. Subsequent to my training, I served full time in public health as the toxicologist for the Onondaga County Department of Health, Syracuse, New York, from 1988 through 1993. My previous work experience included considerable municipal and civil risk assessment, evaluation of environmental toxic exposures, design and execution of environmental monitoring, health assessment studies, methods to identify and effectively reduce community toxic exposures and assessment of public health matters. During my employment as toxicologist for the health department, I assisted the medical examiner's office with investigations of accidental and intentional poisonings.

8. I have studied the toxicological effects and conducted toxicological assessments of pharmaceuticals, hazardous chemicals, herbal products and alcohol for more than 33 years as part of my training in toxicology and daily work experience as a toxicologist. Specifically, I have studied herbal products and mixed pharmaceuticals with respect to their adverse physiological and neuropsychological impact, behavioral effects, metabolism and impact on operating motor vehicles.

9. I have attached hereto as **Attachment A** my curriculum vitae which accurately reflects my professional standing and experience in the field of toxicology.

10. I have attached hereto as **Attachment B** is a list of relevant toxicological studies, surveys and supporting documents pertaining to kratom and its chemical constituents.

B. Background Information

11. The leaves of the *Mitragyna speciosa Korth* (kratom) plant have been used in traditional herbal medicine in Thailand for centuries. Kratom was first described scientifically in 1839.[1] It is a tree endemic to the Philippines, New Guinea and Southeast Asia.[2,3] Consumption of kratom leaves has a distinctive characteristic in that it can be used as both a mild stimulant (or more correctly, documented antidepressant properties) and a sedative with weak analgesic and antinociceptive activity properties.[4,5] Authoritative reports of kratom use date back to 1836.[6]

12. Peer-reviewed studies indicate that 1 to 5 grams of raw leaf material can produce mild stimulant or, more accurately, antidepressant effects. The substance has been traditionally administered to improve stamina, decrease fatigue in extreme heat, alleviate pain, decrease hypertension, reduce coughing, reduce diarrhea and decrease depression with some slight euphoria. Higher doses of 5 to 15 grams of leaves can produce significant relief from pain (analgesia) with accompanying mild sedation.[7]

Kratom Availability

13. Current use of kratom by U.S. consumers is primarily through ingestion of herbal preparations offered as dietary supplements. Kratom can be purchased in a variety of different types of stores but generally those specializing in herbal products. It can also

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[1] Tao, C. and Taylor, C. "*Mitragyna* Korthals, Observ. Naucl. Indic. 19. 1839, nom. cons., not *Mitragyne* R. Brown (1810)," 2011, Fl. China 19, pgs. 218–220.

[2] Cinosi, E., et al., "Following 'the roots' of kratom (*Mitragyna speciosa*): The Evolution of an Enhancer from a Traditional Use to Increase Work and Productivity in Southeast Asia to a Recreational Psychoactive Drug in Western Countries," 2015, Biomed Research International, Article ID 968786, 11 pages.

[3] Chan et al., "Psychoactive plant abuse: the identification of mitragynine in ketum and in ketum preparations," 2005, Bulletin on Narcotics, Vol. 57 (q and 2,pgs. 249-256; Cinosi, E., et al., "Following 'the roots' of kratom (*Mitragyna speciosa*): The Evolution of an Enhancer from a Traditional Use to Increase Work and Productivity in Southeast Asia to a Recreational Psychoactive Drug in Western Countries," 2015, Biomed Research International, Article ID 968786, 11 pages; Ingsathit, et al., "Prevalence of psychoactive drug use among drivers in Thailand: a roadside survey,:" 2011, Accident Analysis and Prevention, Vol. 41, pgs. 474-478.

[4] Babu, K., McCurdy, C., and Boyer, E., "Opioid receptors and legal highs: *Salvia divinorum* and kratom," 2008, Clinical Toxicology, 46(2), pgs. 146 - 152.

[5] Hassan, Z., Muzaimi, M., Navaratnam, V., Yusoff, N., Suhaimi, F., Vadivelu, R., Vicknasingam, B., Amato, D., von Hörsten, S., Ismail, N., Jayabalan, N., Hazim, A., Mansor, S., and Müller, C. From "Kratom to mitragynine and its derivatives: Physiological and behavioural effects related to use, abuse, and addiction," 2013, Neuroscience and Biobehavioral Reviews, 37, pgs. 138–151.

[6] Jansen and Prast, "Ethnopharmacology of kratom and *mitragyna* alkaloids," 1988, Journal of Ethnopharmacology, Vol. 23, pgs. 115-119.

[7] Kamal, et al., "Acute toxicity of standardized *Mitragyna speciosa* Korth aqueous extract in Sprague Dawley rats," 2012, Journal of Plant Studies, Vol.1 (2), pgs. 120-129.

be shipped directly to consumers when ordered via the Internet, telephone or other means. Kratom can be consumed in a number of ways including steeped as tea, taken in powder or capsule form (e.g., 80 mg ground leaf capsules).

Kratom Use Outside the U.S.

14. In Thailand, regular users have their own trees hidden in their rubber plantations, rice fields, fruit gardens, yards, ditches or near fishing ponds.[8] Occasional users tend to use kratom in the context of a social occasion with friends at the village shop or when attending a funeral ceremony or a local party or sports tournament. In their 2006 study of kratom users in Thailand, Assanangkornchai, et al., found that most users obtain kratom leaves from neighbors for free or from a kratom tree grown on their own property while a few buy the leaves from neighbors or from shops in the village.[9]

15. In Malaysia, some users cultivate their own *Mitragyna speciosa* trees; however, most obtain their kratom supply from familiar suppliers or local coffee shops where it is sold openly, despite the ban.[10] Coffee shops sell a prepared solution which is ready for immediate consumption.[11] (Note that in both Thailand and Malaysia, the quality of the product is known as are the sources of supply and the suppliers).[12]

16. Kratom leaf preparations in Malaysia have been used to overcome opiate drug addiction as well as an opium substitute.[13] A study by Chan, et al., also indicates that traditional herbal medicine healers have used kratom to wean users from heroin addiction, cure diarrhea, as a de-wormer, to improve blood circulation and treat

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[8] Singh, D., "Traditional and non-traditional uses of *mitragynine* (kratom): A survey of the literature," 2016, Brain Research Bulletin.

[9] Assanangkornchai, S., "The use of *mitragynine specisoa* (kratom), an addictive plant, in Thailand," 2006, Substance Use and Misuse, Vol. 42 pgs. 2145-2157.

[10] Vicknasingam, B., et al., "The informal use of kratom (*mitragyna speciosa)* for opioid withdrawal in the northern state of peninsular Malaysia and implications for drug substitution therapy," 2010, International Journal of Drug Policy, Vol. 21, pgs. 283-288.

[11] Id.

[12] Singh D., "Traditional and non-traditional uses of *mitragynine* (kratom): A survey of the literature," 2016, Brain Research Bulletin. Note: Persons familiar to the users were the main sources of supply; 46% of subjects obtained kratom in this manner. Local coffee shops were the next widely most used source (34%). The sale of kratom is open and quite freely conducted in rural areas, despite it being a banned substance in Malaysia since 2003. Interestingly, 15% of the subjects were cultivating their own trees.

[13] Id.

diabetes.[14] Kratom leaves have also been used for their medicinal value in treating common, mild medical problems such as fever and as a wound poultice.[15]

17. It is unknown when kratom was first used as it has been a part of Thailand's tradition for centuries.[16] Kratom has many uses in Thailand from its use in religious ceremonies[17] to its use by laborers to help tolerate the discomfort of working in the hot sun as well as coping with the physical stress of manual labor – thus, increasing productivity.[18,19,20]

18. In its traditional use, fresh or dried kratom leaves are chewed or made into a tea to obtain the benefits from the alkaloids naturally present.[21,22] Kratom leaves contain approximately 20 different alkaloids amongst other phytochemicals.[23] The most abundant compound, consisting of 66 percent of the total phytochemicals in kratom, is *mitragynine* which is a psychoactive compound of importance that is unique to kratom.[24]

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[14] National Library of Medicine (NLM), "*Mitragyna* CASRN: 4098-40-2," 2012, TOXNET (Toxicology Data Network).

[15] Cinosi, E., et al., "Following 'the roots' of kratom (*Mitragyna speciosa*): The Evolution of an Enhancer from a Traditional Use to Increase Work and Productivity in Southeast Asia to a Recreational Psychoactive Drug in Western Countries," 2015, Biomed Research International, Article ID 968786, 11 pages; Hassan Z., Muzaimi, M., Navaratnam, V., Yusoff, N., Suhaimi, F., Vadivelu, R., Vicknasingam, B., Amato, D., von Hörsten, S., Ismail, N., Jayabalan, N., Hazim, A., Mansor, S., and Müller, C. From "Kratom to mitragynine and its derivatives: Physiological and behavioural effects related to use, abuse, and addiction," 2013, Neuroscience and Biobehavioral Reviews, 37, pgs. 138–151; Jansen and Prast, "Ethnopharmacology of kratom and *mitragyna* alkaloids," 1988, Journal of Ethnopharmacology, Vol. 23, pgs. 115-119.

[16] Suwanlert, S., "A Study of Kratom Eaters in Thailand," 1975, Bulletin on Narcotics, Vol 27(3), pgs. 21-27.

[17] Cinosi, E., et al., "Following 'the roots' of kratom (*Mitragyna speciosa*): The Evolution of an Enhancer from a Traditional Use to Increase Work and Productivity in Southeast Asia to a Recreational Psychoactive Drug in Western Countries," 2015, Biomed Research International, Article ID 968786, 11 pages.

[18] Jansen, K. and Prast, C., "Ethnopharmacology of kratom and *mitragyna* alkaloids," 1988, Journal of Ethnopharmacology, Vol. 23, pgs. 115-119.

[19] Suwanlert, S., "A Study of Kratom Eaters in Thailand," 1975, Bulletin on Narcotics, Vol 27(3), pgs. 21-27.

[20] Tanguay, P., "Kratom in Thailand: decriminalization and community control," 2011, Series on Legislative Reform of Drug Policies, NR. 13; Vicknasingam, B., et al., "The informal use of kratom (*mitragyna speciosa)* for opioid withdrawal in the northern state of peninsular Malaysia and implications for drug substitution therapy," 2010, International Journal of Drug Policy, Vol. 21, pgs. 283-288.

[21] Cinosi, E., et al., "Following 'the roots' of kratom (*Mitragyna speciosa*): The Evolution of an Enhancer from a Traditional Use to Increase Work and Productivity in Southeast Asia to a Recreational Psychoactive Drug in Western Countries," 2015, Biomed Research International, Article ID 968786, 11 pages.

[22]Alkaloids are complex, naturally-produced, nitrogen-containing organic molecules that can exhibit a physiological effect on humans and animals.

[23] Cinosi, E., "Following 'the roots' of kratom (*Mitragyna speciosa*): The Evolution of an Enhancer from a Traditional Use to Increase Work and Productivity in Southeast Asia to a Recreational Psychoactive Drug in Western Countries," 2015, Biomed Research International, Article ID 968786, 11 pages.

[24] Id.

Prevalence of Kratom

19. Due to possible adverse health effects and reported financial/political pressure, the government of Thailand passed a law (Kratom Act 2486) which was enforced beginning on August 3, 1943. The law forbade planting of *M. speciosa* trees and existing trees were ordered to be cut down. Kratom is also prohibited under legislation in Australia, Burma, Malaysia, South Korea and Vietnam. However, herbal medicinal plants are generally viewed more favorably than synthetic drugs, particularly in Southeast Asia. A survey performed in 2007 found that kratom was still the most commonly used controlled substance in Thailand. It was estimated that 1,078,100 people had used kratom at some point in their lifetime and 264,522 people had used kratom within the last thirty days of the survey.[25]

Use of Kratom in Southeast Asia

20. As stated above, growing and possessing kratom has been illegal in Thailand since 1943. In Malaysia, its use was permitted until 2003 at which time it became illegal to sell kratom leaves or preparations. Despite the legal sanctions, kratom sale and use remains open and widespread in both southern Thailand and the northern states of Malaysia, mostly because it continues to be viewed locally as a traditional remedy for many common maladies.[26] No stigma is attached to its consumption because of the long history of use in these areas.[27] Male manual laborers, such as farmers, rubber-tappers, fishermen and machine operators commonly ingest kratom leaves during work.[28]

21. Kratom is currently widely available in many Asian countries and is the most widely used illicit substance (exceeding cannabis) in Thailand despite being officially

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[25] Assanangkornchai, S., "Current situation of substance-related problems in Thailand," 2008, Journal of Psychiatric Association, Thailand, Vol. 53, pg. 25S – 36S.

[26] Vicknasingham, B., et al., "The informal use of kratom (*mitragyna speciosa)* for opioid withdrawal in the northern state of peninsular Malaysia and implications for drug substitution therapy," 2010, International Journal of Drug Policy, Vol. 21, pgs. 283-288.

[27] Id.; Suwanlert, S., "A Study of Kratom Eaters in Thailand," 1975, Bulletin on Narcotics, Vol 27(3), pgs. 21-27; Cinosi, E., et al., "Following 'the Roots' of kratom (*mitragyna speciosa*): The Evolution of an Enhancer from a Traditional Use to Increase Work and Productivity in Southeast Asia to a Recreational Psychoactive Drug in Western Countries," 2015, Biomed Research International, Article ID 968786, 11 pages.2015.

[28] Tanguay, P., "Kratom in Thailand: decriminalization and community control," 2011, Series on Legislative Reform of Drug Policies, NR. 13011; Suwanlert, S., "A Study of Kratom Eaters in Thailand," 1975, Bulletin on Narcotics, Vol 27(3), pgs. 21-27; Assanangkornchai et al., "The use of mitragynine speciose (kratom), an addictive plant, in Thailand," 2006, Substance Use & Misuse, Vol. 42, pgs. 2145-2157; Vicknasingam, B., et al., "The informal use of kratom (*mitragyna speciosa)* for opioid withdrawal in the northern state of peninsular Malaysia and implications for drug substitution therapy," 2010, International Journal of Drug Policy, Vol. 21, pgs. 283-288.

prohibited in Thailand since 1943.[29] The 2007 Thailand survey previously noted cited kratom use in 26,633 people aged 12 to 65 years with a lifetime prevalence of 2.32%, a past-year prevalence of 0.81%, and a past-30 day prevalence of 0.57%.[30] Kratom is generally part of a way of life in southern Thailand, closely embedded in traditions and customs such as local ceremonies, traditional cultural performances and teashops as well as in agricultural and manual labor.[31]

Use of Kratom in Japan and Sweden

22. In 2009, Maruyama, et al., reported that kratom has been sold in street shops or on the Internet in Japan. The Maruyama study revealed that most of the commercial kratoms available in the Japanese markets are derived from *M. speciosa* or closely related plants.[32]

23. In Sweden, kratom has been mixed with a potentially lethal substance known as "Krypton" with resulting accidental deaths. Aside from the leaves and extracts from kratom, Krypton has been found to contain a synthetic opioid called *O-Desmethyltramadol*. This is a tramadol-related substance which is prescribed in moderation to alleviate severe pain. When taken as Krypton, it is metabolized into tramadol in the liver with increased potential of respiratory depression and death at high doses. This is due to the high potency of the transformed *O-Desmethyltramadol* which can lead to respiratory paralysis. Conversely, kratom alone has not been demonstrated to cause human deaths.

Consumption Techniques in Southeast Asia

24. Traditionally, fresh or dried kratom leaves are chewed, brewed into a tea or smoked.[33] In Malaysia, kratom is usually ingested as a solution or juice while in neighboring Thailand, it is more commonly chewed.[34] In his 1975 Thailand study, Suwanlert

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[29] Cinosi, E., et al., "Following 'the Roots' of kratom (*mitragyna speciosa*): The Evolution of an Enhancer from a Traditional Use to Increase Work and Productivity in Southeast Asia to a Recreational Psychoactive Drug in Western Countries," 2015, Biomed Research International, Article ID 968786, 11 pages.

[30] Id.

[31] Tanguay, P., "Kratom in Thailand: decriminalization and community control," 2011, Series on Legislative Reform of Drug Policies, NR 13.

[32] Maruyama, T., "The botanical origin of kratom (*mitragyna speciose*; runiaceae) available as abused drugs in the Japanese markets," 2009, Journal of Natural Medicine, Vol. 63, pg. 340-344.

[33] Jansen & Prast, C., "Ethnopharmacology of kratom and mitragyna alkaloids," 1988, Journal of Ethnopharmacology, Vol. 23, pgs. 115-119; Suwanlert, S., "A Study of Kratom Eaters in Thailand," 1975, Bulletin on Narcotics, Vol 27(3), pgs. 21-27; Ward, J., et al., "Herbal medicines for the management of opioid addiction," 2011, CNS Drugs, Vol. 25(12), pgs. 999-1007.

[34] Vicknasingam, B., et al., "The informal use of kratom (*mitragyna speciosa)* for opioid withdrawal in the northern state of peninsular Malaysia and implications for drug substitution therapy," 2010, International

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 [36.6%]) 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.[35]

25. 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 12,900 mg of kratom per day which is equivalent to the amount of kratom in 161 capsules as typically sold in the U.S.

26. In Malaysia, a solution is often prepared by the user or purchased for immediate consumption. Kratom leaves are plucked from trees that are found in the tropical swampy areas and rinsed thoroughly with water to remove all traces of dirt. The leaves are then 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.[36] Habitual users in Malaysia usually consume kratom juice at least 3 times a day in varying quantities.[37]

Current Use of Kratom in the U.S. and Europe

27. Kratom, with a well-established use pattern in Thailand, has seen a rapid infusion into Western countries in recent years. Here it is viewed as a natural pain and stress reliever and a safer alternative to drugs of abuse. Kratom is sold online as a less expensive alternative to traditional opioid pain relievers for chronic pain and as an anti-anxiety treatment. Kratom is now widely available on the Internet and in street shops across the United States and Europe.[38] In the U.S., kratom is typically ingested in

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Journal of Drug Policy, Vol. 21, pgs. 283-288; Singh, D., "Traditional and non-traditional uses of *mitragynine* (kratom): A survey of the literature," 2016, Brain Research Bulletin.

[35] Amattayakul, T., "The kratom leaves," 1960, Journal of Department of Medical Sciences, Vol. 2(2), pgs. 104-108.

[36] Vicknasingam, B., et al., "The informal use of kratom (*mitragyna speciosa)* for opioid withdrawal in the northern state of peninsular Malaysia and implications for drug substitution therapy," 2010, International Journal of Drug Policy, Vol. 21, pgs. 283-288.

[37] Suwanlert, S., "A Study of Kratom Eaters in Thailand," 1975, Bulletin on Narcotics, Vol 27(3), pgs. 21-27; Vicknasingam, B., et al., "The informal use of kratom (*mitragyna speciosa)* for opioid withdrawal in the northern state of peninsular Malaysia and implications for drug substitution therapy," 2010, International Journal of Drug Policy, Vol. 21, pgs. 283-288.

[38] Prozialeck, Jivan, and Andurkar, "Pharmacology of kratom: An emerging botanical agent with stimulant, analgesic and opioid-like effects," 2012, The Journal of the American Osteopathic Association, Vol. 112(12), pgs. 792-799; Maruyama, T., "The botanical origin of kratom (*mitragyna speciose*; runiaceae)

capsules or, less often, brewed into a tea, chewed or smoked. It is available as ground, dry leaves in capsules and in powder, extract, pellet and gum forms.

28. Kratom is usually marketed as a dietary supplement[39] to treat chronic pain. It has rapidly become viewed as an economical alternative to self-treat pain from prescription opioid withdrawal as well.[40]

29. 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.[41]

30. In the U.S., powdered kratom leaves can be purchased at shops, kava bars and via the internet. The largest volume of sales appears to be via the internet (Babu, et al., 2008; Rosenbaum, et al., 2012).

31. 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.[42] 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.

32. By comparison, exposures involving analgesics accounted for nearly 300,000 calls in 2014 while cosmetics and personal care products, cleaning solutions, antidepressants

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available as abused drugs in the Japanese markets," 2009, Journal of Natural Medicine, Vol. 63, pg. 340-344.

[39] Boyer, E., et al. "Self-treatment of opioid withdrawal using kratom (*mitragynia speciose* korth)," 2008, Addiction, Vol. 103(6), pgs. 1048-1050.

[40] Boyer et al., 2007, 2008; McWhirther and Morris, 2010; Nelsen et al., 2010; Neerman et al.,2013; McIntyre et al., 2015 in Singh, D., "Traditional and non-traditional uses of *mitragynine* (kratom): A survey of the literature," 2016, Brain Research Bulletin.

[41] Forrester, A, et al., "Kratom exposures reported to Texas Poison Centers," 2013, Journal of Addictive Diseases, Vol. 32(4), pgs. 396-400.

[42] Anwar, M., et al., "Kratom (*mitragyna speciosa*) exposures reported to poison centers, U.S., 2010-2015," 2016, US Department of Health and Human Services/CDC, MMWR, Vol. 65(29), pgs. 748-749. 2016

and antihistamines each accounted for more than 100,000.[43] 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.

C. Kratom Alkaloids and Pharmacokinetics

33. Unlike drugs of abuse which contain a single component responsible for the desired effect, kratom is an herbal product with a unique combination of alkaloids, including *mitragynine*. Thus, kratom has very different properties compared to mitragynine on its own. This fact adds complexity to any assessment of the beneficial properties of kratom vs. its potential toxicity.

34. The biochemical effects of *M. speciosa* are obtained by consuming the leaves of the plant. The leaves of Kratom are ingested by chewing, drinking and infusion made from its leaves, or smoking.[44] The phytochemical alkaloid composition of kratom leaves are documented in **Table 1**.

35. Recent research has led to the discovery of more than 20 alkaloids associated with kratom. *Mitragynine* and, to a lesser extent, *7-hydroxymitragynine*, *speciogynine* and *paynantheine* are considered to be the major alkaloids.[45]

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[43] Sullum, J., "The DEA's Crazy Kratom Ban Dresses Pharmacological Phobia In Scientific Garb," 2016, Forbes.com, Retrieved from: http://www.forbes.com/sites/jacobsullum/2016/09/01/the-deas-crazy-kratom-ban-dresses-pharmacological-phobias-in-scientific-garb/#44adc8244f86

[44] Jansen, K. and Prast, C., Ethnopharmacology of kratom and the *mitragyna* alkaloids," 1988, Journal of Ethnopharmacology, Vol. 23, pgs. 115-119.

[45] Hassan Z., et al., From "Kratom to mitragynine and its derivatives: Physiological and behavioral effects related to use, abuse, and addiction," 2013, Neuroscience and Biobehavioral Reviews, 37, pgs. 138–151.

Table 1

Alkaloid profile of kratom leaves and phytochemicals as a percentage of total alkaloid extract and the known pharmacological effects of each phytochemical (*Source, Hassan et al., 2013*)[46]

Alkaloid	Percentage	Effect
Mitragynine	66%	Analgesic, antitussive, antidiarrheal, adrenergic, antimalarial
Paynantheine	9%	Smooth muscle relaxer
Speciogynine	7%	Smooth muscle relaxer
7-Hydroxymitragynine	2%	Analgesic, antitussive, antidiarrheal
Speciociliatine	1%	Weak opioid agonist
Mitraphylline	<1%	Vasodilator, anti-hypertensive, muscle relaxer, diuretic, anti-amnesic, immunostimulant, antileukemic
Isomitraphylline	<1%	Immunostimulant, antileukemic
Speciophylline	<1%	Antileukemic
Rhynchophylline	<1%	Vasodilator, antihypertensive, calcium channel blocker, antiaggregant (decreased platelet aggregation and inhibit thrombus formation), anti-inflammatory, antipyretic, anti-arrhythmic, antithelmintic
Isorhynchophylline	<1%	Immunostimulant
Ajmalicine	<1%	Cerebrocirculant, antiaggregant, anti-adrenergic, sedative, anticonvulsant, smooth muscle relaxer
Corynantheidine	<1%	Opioid agonist
Corynoxine A	<1%	Calcium channel blocker, anti-locomotive
Corynoxine B	<1%	Anti-locomotive
Mitrafoline	<1%	
Isomitrafoline	<1%	
Oxindole A	<1%	
Oxindole B	<1%	
Speciofoline	<1%	Analgesic, antitussive
Isospeciofoline	<1%	
Ciliaphylline	<1%	Analgesic, antitussive
Mitraciliatine	<1%	
Mitragynaline	<1%	
Mitragynalinic acid	<1%	
Corynantheidalinic acid	<1%	

36. Kratom contains multiple active alkaloids with various individual pharmacological properties. Most studies have focused almost solely on the pharmacological activity

[46] Id.

and toxicity of *mitragynine* in an attempt to evaluate the toxicity of kratom.[47] However, with more than 20 known different alkaloids[48] present in kratom (*mitragynine* being the most prominent), there is a wide scope of possible interactions - some of which may, in fact, be beneficial. Thus, basing an objective evaluation of toxicity solely on *mitragynine* is confounded by kratom's chemical complexity.

37. *Mitragynine* binds to specific receptors in the central nervous system (supraspinal opioid mu- and delta-receptors). However, it is important to note that many reports and studies do not exemplify all known kratom alkaloids working in tandem at various receptor sites. For example, studies which dose human subjects or animals only with *mitragynine* (an indole alkaloid found in and extracted from kratom in concentrated form) greatly inflate or exaggerate toxicity and/or undesirable effects to scientifically establish the dose-response characteristics of the substance.

38. Of the alkaloid phytochemicals identified, *Mitragynine* (66%) and *7-hydroxymitragynine* (2%) were found to exhibit opioid effects. *7-Hydroxymitragynine* produced the most potent opioid effects and is structurally related to *mitragynine* (see **Figure 1**).[49,50] *Mitragynine* can constitute as much as 6 percent of the total weight of the dried plant.[51] Consequently, *mitragynine* has been the primary focus with respect to its pharmacological and toxicological properties and is "presumed" to be the chemical responsible for the overall biochemical effects of the plant.

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[47] Yusoff, et al., "Abuse potential and adverse cognitive effects of *mitragynine* (kratom)," 2016, Addict Biol., Vol. 21(1), pgs. 98-110.

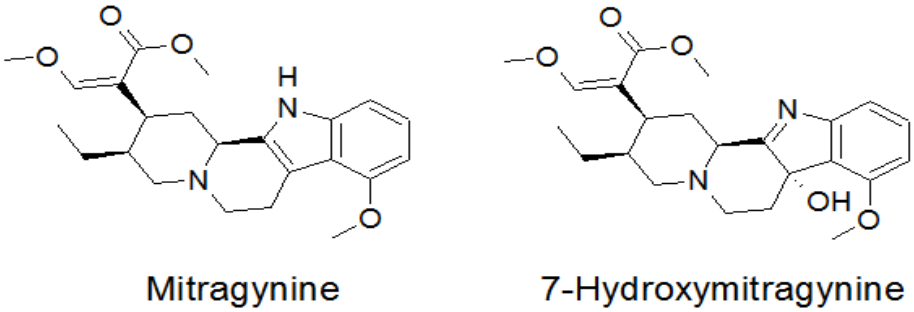
[48] National Library of Medicine (NLM) "*Mitragyna* CASRN: 4098-40-2," 2012, TOXNET (Toxicology Data Network).

[49] Horie, et al., "Indole Akaloids of a Thai Medicinal Herb, *Mitragyna speciosa*, that has Opioid Agnostic Effect in Guinea Pig Ileum," 2005, Planta Med., Vol. 71(30), pgs. 231-236.

[50] Raffa, R., et al., "Chapter 2: Short Overview of *Mitragynines*," in Raffa, "Kratom and other Mitragynines - The Chemistry and Pharmacology of Opioids from a Non-Opium Source," 2015, CRC Press, Taylor and Francis Co.

[51] Id.

Figure 1: Chemical Structure of Mitragynine and 7-Hydroxymitragynine



39. Horie, et al., (2005)[52] evaluated the effect of the different components of *M. speciosa* leaf alkaloids on the twitch contraction induced by electrical stimulation of the ileum of Guinea pigs. The opioid effect of reducing muscle contraction was found in the crude extract of kratom, and five alkaloids were isolated and tested. A determination of the agonist potency value from the *mitragynine* concentration required to produce 50% of the maximum response compared to morphine was measured. **Table 2** shows the most prominent alkaloid profile of kratom as published by Horie, et al., 2005.

Table 2
Alkaloid profile of kratom leaf extract and its opioid agonistic activity in Guinea pig ileum. (Source, Horie, et al., 2005)[53]

Chemical Compound	Percentage of total alkaloids extracted from *M. speciosa* (Korth)	Relative potency compared to morphine at 100%	Agonist potency value compared to morphine at 7.5	Relative inhibitory activity
Kratom crude extract	100%	0.8%	5.05	49%
Mitragynine	66%	58%	6.91	96%
Paynantheine	8.9%	1%	4.99	86%
Speciogynine	6.6 %	3%	5.61	86%
7-Hydroxymitragynine	2%	1698%	8.38	99%
Speciociliatine	0.8%	3%	5.55	99%

[52] Horie, et al., "Indole Akaloids of a Thai Medicinal Herb, *Mitragyna speciosa*, that has Opioid Agnostic Effect in Guinea -Pig Ileum," 2005, Planta Med, Vol 71(30), pg. 231 -236.

[53] Id.

40. As can be seen in **Table 2**, the most potent alkaloid providing the opioid effect is *7-hydroxymitragynine* with a potency 17 fold greater than morphine (although it is only 2% of the overall alkaloid profile). Other alkaloids from kratom leaves are less potent but all displayed strong inhibitory activity to the nerve contraction reaction in the Guinea pig ileum (> 86%) as compared to the crude extract at 49%. This means that the other minor alkaloids most likely have an inhibitory effect on overall opioid response.

41. Recent studies carried out by Kruegel, et al., (2016)[54] reveal that the alkaloids of kratom, represented by the prototypical member *mitragynine*, are an unusual class of opioid receptor modulators with distinct pharmacological properties. Kruegel, et al., has examined the first receptor-level functional characterization of *mitragynine* and related natural alkaloids of kratom at the human mu-, kappa- and delta-opioid receptors. The study revealed that *mitragynine* and the oxidized analogue, *7-hydroxymitragynine*, are partial agonists of the human mu-opioid receptor and competitive antagonists at the kappa- and delta-opioid receptors. Kruegel, et al., have also demonstrated that *mitragynine* and *7-hydroxymitragynine* are G-protein-biased agonists of the mu-opioid receptor, which do not recruit β-arrestin following receptor activation. This is important in that kratom alkaloids are unique, functionally-biased opioid modulators "*which may exhibit improved therapeutic profiles."*

    Within the Kruegel, et al., study, several significant studies are cited that also provide consistent findings. For example, "*an early study with mitragynine indicated that the behavioral effects in cats and analgesic effects in rats were not reversed by treatment with nalorphine, an opioid antagonist, while at the same time, mitragynine was found to produce markedly less respiratory depression than codeine*." Additionally, the Kruegel study referenced studies in which *mitragynine* was shown to bind in some degree to several non-opioid central nervous system (CNS) receptors including alpha-2 adrenergic receptor (α2R), adenosine (A2a), dopamine (D2) and the serotonin receptors 5-HT2C and 5-HT7 and that "*mitragynine analgesia has also been shown to be inhibited by the α2R antagonist idazoxan and by the nonspecific serotonin antagonist cyproheptadine*." Thus, the profile of the 20 known kratom alkaloids provides a very different mode of action (MOA) than that of morphine or other opiates and differential toxicological profiles as well as clinical pharmacological effects.

42. **Figure 2** shows the similarity in the chemical structures of the major alkaloid components of kratom leaf extracts. Close examination of these chemical structures reveals similarities that are quite remarkable. In some cases, there is only a single minor variation in chemical structure; nevertheless, the pharmacokinetic effects of each

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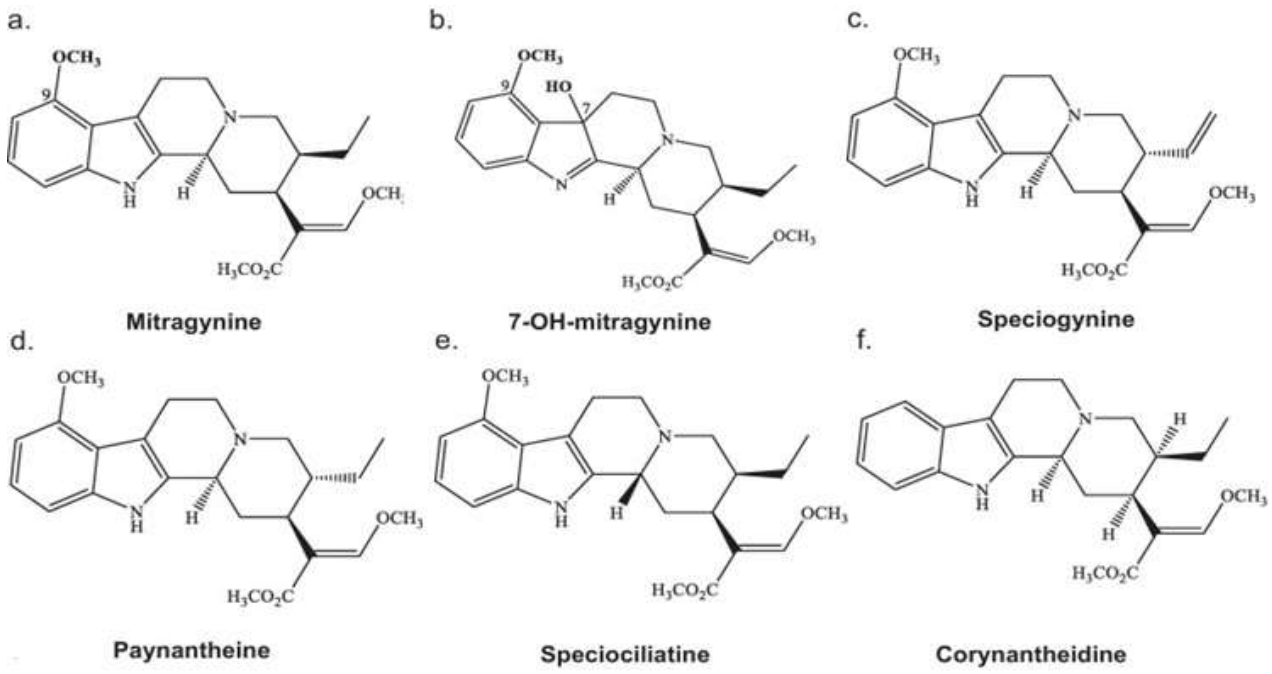
[54] Kruegel, Andrew C. et al., "Synthetic and receptor signaling explorations of the *Mitragyna* alkaloids: *Mitragynin*e as an atypical molecular framework for opioid receptor modulators," J. Am. Chem. Soc. 2016, 138, pg. 6754−6764.

component are radically different. Such similarity of chemical structures might explain why there is similar inhibitory activity.[55]

Figure 2: Chemical Structures of Major Alkaloid Components in Kratom Leaf Extracts



[55] Hassan, Z., et al., From "Kratom to mitragynine and its derivatives: Physiological and behavioural effects related to use, abuse, and addiction," 2013, Neuroscience and Biobehavioral Reviews, 37, pgs. 138–151.

Pharmacokinetics

43. *Mitragynine* is absorbed into the blood through the mucosa of the digestive system and the intestinal epithelial layer through passive diffusion.[56] One of the few studies on the distribution of *mitragynine* was performed in a rat model.[57] The study described *mitragynine's* absorption from oral ingestion as "poor, slow, prolonged and incomplete." The oral bioavailability *(*i.e*.,* the percentage of *mitragynine* absorbed) was 3%. Peak plasma concentration was demonstrated to occur between 1.26 – 4.5 hours depending on dosage (higher doses required longer to reach peak plasma concentration).[58] In humans, peak plasma concentration occurred at approximately 0.83 hour.[59] *Mitragynine* bioavailability from inhalation has not been studied.[60]

44. *Mitragynine* is lipophilic and exhibits a two compartment model of distribution (i.e., first rapidly into the blood and extracellular fluid and subsequently deep into tissues from which it can transfer back into the blood). [61,62] *Mitragynine* is eventually metabolized in the liver in two phases. The first phase of its metabolism is mediated primarily by cytochrome P450 enzymes – CYP2C9, CYP2D6 and CYP3A4.[63]

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[56] Cronin, A., et al., "Chapter 12: The ADME of *Mitragynine* and Analogs," 2015, in Raffa, "Kratom and other Mitragynines - The Chemistry and Pharmacology of Opioids from a Non-Opium Source," 2015, CRC Press, Taylor and Francis Co. 2015.

[57] Parthasarathy, S., et al., "Determination of *mitragynine* in plasma with solid-phase extraction and rapid HPLC–UV analysis and its application to a pharmacokinetic study in rat," 2010, Anal Bioanal Chem, Vol. 397, pg. 2023–2030.

[58] Cronin, A., et al., "Chapter 12: The ADME of *Mitragynine* and Analogs," 2015, in Raffa, "Kratom and other Mitragynines - The Chemistry and Pharmacology of Opioids from a Non-Opium Source," 2015, CRC Press, Taylor and Francis Co. 2015.

[59] Trakulsrichai, S., et al., "Pharmacokinetics of *Mitragynine* in Man," 2015, Dove Medical Press, Vol. 2015(9) pg. 2421-2429.

[60] Id.

[61] Parthasarathy, S., et al., "Determination of *mitragynine* in plasma with solid-phase extraction and rapid HPLC–UV analysis and its application to a pharmacokinetic study in rat," 2010, Anal Bioanal Chem, Vol. 397, pg. 2023–2030.

[62] Trakulsrichai, S. et al., "Pharmacokinetics of *Mitragynine* in Man," 2015, Dove Medical Press, Vol. 2015(9) pg. 2421-2429.

[63] Hanapi, N., et al., "Evaluation of Selected Malaysian Medicinal Plants on Phase I Drug Metabolizing Enzymes, CYP2C9, CYP2D6, and CYP3A4 Activities in vitro," 2010, Int. J. Pharm. 6(4), pgs. 494-499.

Pharmacologic Effects

45. Hanapi, et al., (2013) demonstrated that *mitragynine* had a non-competitive inhibitory effect on CYP2C9 and CYP2D6 (in that order of increasing degree). Theoretically, *mitragynine* may extend metabolism of drugs that utilize the same metabolic pathway;[64] however, kratom has not been demonstrated to do so. *Mitragynine* metabolites from the phase 1 process undergo further modification in the phase 2 stage[65] mediated by glutathione transferases (GST).[66]

46. Phase 2 metabolism often results in loss of chemical activity of the compound and increases its water solubility thus facilitating its excretion.[67] None of the seven phase 1 metabolites and six phase 2 metabolites of mitragynine were active except for 7-hydroxymitragynine.[68] Thus far, there is no evidence that any of the metabolic products of mitragynine have active biological pharmacologic effects.[69]

47. Metabolites of *mitragynine* are eliminated from the body primarily in urine.[70] Very little unmetabolized *mitragynine* was present in the urine (approximately 0.14%) with most

[64] Hanapi, N, et a., "Inhibitory effect of *mitragynine* on human cytochrome P450 enzyme activities," 2013, Pharmacognosy Res., Vol. 5(4), pg. 241-246.

[65] Philipp,A., et al. "Studies on the metabolism of *mitragynine*, the main alkaloid of the herbal drug, kratom, in rat and human urine using liquid chromatography-linear ion trapmass spectrometry," 2009, J. Mass. Spectrometry., Vol. 44, pgs. 1249–1261.

[66] Azizi, J., et al., "In Vitro and in Vivo Effects of Three Different *Mitragyna speciosa* Korth Leaf Extracts on Phase II Drug Metabolizing Enzymes—Glutathione Transferases (GSTs)," 2010, Molecules, Vol. 15, pgs. 432-441.

[67] Cronin, A., et al., "Chapter 12: The ADME of *Mitragynine* and Analogs," 2015, in Raffa, "Kratom and other *Mitragynines* - The Chemistry and Pharmacology of Opioids from a Non-Opium Source," 2015, CRC Press, Taylor and Francis Co. 2015.

[68] Philipp,A., et al., "Studies on the metabolism of *mitragynine*, the main alkaloid of the herbal drug, kratom, in rat and human urine using liquid chromatography-linear ion trapmass spectrometry," 2009, J. Mass. Spectrometry., Vol. 44, pgs. 1249–1261.

[69] Raffa, R., et al., "Chapter 2: Short Overview of *Mitragynines*," 2015, in Raffa, "Kratom and other *Mitragynines* - The Chemistry and Pharmacology of Opioids from a Non-Opium Source," 2015, CRC Press, Taylor and Francis Co. 2015.

[70] Philipp, A., et al. "Studies on the metabolism of *mitragynine*, the main alkaloid of the herbal drug, kratom, in rat and human urine using liquid chromatography-linear ion trapmass spectrometry," 2009, J. Mass. Spectrometry., Vol. 44, pgs. 1249–1261.

of it undergoing hepatic metabolism.[71] The elimination half-life ranged from 3.85 to 9.43 hours,[72] taking about 24 hours before *mitragynine* was undetectable in blood.[73,74]

Clinical Pharmacology

Traditional Medicine

48. The rubiaceae family to which kratom (*M. speciosa* Korth*)* belongs includes such plants as coffee, rubia, gardenia and cinchona species.[75] The rubiaceae family is an invaluable source of medicinal plant compounds (alkaloids) such as caffeine from coffee and quinine from cinchona species (used as an antimalarial) and has been used to treat and cure fevers for more than 350 years.[76] As another medicinal plant from the rubiaceae family, kratom has a history of beneficial use dating back centuries in the medicinal traditions of Thailand.[77] Kratom has a long history in folk medicine for the treatment of asthma and cough, for deworming, and gastrointestinal (stomach) problems[78] Kratom extracts have also shown in the laboratory setting to have antitussive (cough), antinociceptive (pain blocking), anti-inflammatory and antidiarrheal properties.[79]

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[71] Trakulsrichai S., et al., "Pharmacokinetics of *Mitragynine* in Man," 2015, Dove Medical Press, Vol. 9, pgs. 2421-2429.

[72] Cronin, A., et al., "Chapter 12: The ADME of *Mitragynine* and Analogs," 2015, in Raffa, "Kratom and other *Mitragynines* - The Chemistry and Pharmacology of Opioids from a Non-Opium Source," 2015, CRC Press, Taylor and Francis Co. 2015.

[73] Parthasarathy, et al., "Determination of *mitragynine* in plasma with solid-phase extraction and rapid HPLC–UV analysis and its application to a pharmacokinetic study in rat," 2010, Anal Bioanalytical Chem., Vol. 397, pgs. 2023–2030.

[74] Trakulsrichai S., et al., "Pharmacokinetics of *Mitragynine* in Man," 2015, Dove Medical Press, Vol. 9, pgs. 2421-2429.

[75] Prozialeck, et al., "Pharmacology of Kratom: An Emerging Botanical Agent with Stimulant, Analgesic and Opioid-Like Effects," 2012, The Journal of the American Osteopathic Association, Vol 112(12), pgs. 792-799.

[76] Andrade-Neto, V., et al., "Antimalarial activity of Cinchona-like plants used to treat fever and malaria in Brazil," 2003, Journal of Ethnopharmacology, Vol. 87, pg. 253 -256.

[77] Jansen, K. and Prast,C., "Ethnopharmacology of kratom and the *mitragyna* alkaloids," 1988, Journal of Ethnopharmacology, Vol. 23, pgs. 115-119.

[78] Mossadeq, et al., "Anti-Inflammatory and Antinociceptive Effects of *Mitragyna speciosa* Korth Methanolic Extract.,"2009, Medical Principles and Practice, Vol. 18, pgs. 378–384.

[79] Id.

49. The complex, naturally-produced, nitrogen-containing organic molecules that can exhibit a physiological effect on humans and animals are known as alkaloids.[80] These alkaloids are responsible for the positive health benefits and are frequently attributed to herbs and some other natural remedies. *M. speciosa* (kratom) leaves have been found to contain over 25 known alkaloids as shown in **Table 1**.[81]

50. The clinical pharmacological effects of kratom have been studied and ranked based upon the relative abundance of each alkaloid. Approximately, up to 66% of the alkaloids extracted from kratom leaves include *mitragynine*. Various analogues of *mitragynine* are also found in kratom leaves including *paynantheine* at 9% and *speciogynine* at 7% and are the second and third most abundant alkaloids in kratom leaves respectively. Kratom leaves also contain 7-hydroxymitragynine (2%) while other alkaloids were found at concentrations of 1% or lower (see **Table 1**).[82] Although the percentage composition of these alkaloids can vary depending on the region/location where kratom is grown, [83] *mitragynine* remains the most abundant alkaloid in kratom leaves.[84]

Human Clinical Pharmacology

51. Kratom has also been observed and reported as a potential treatment for opioid withdrawal. One of the first scientific documentations of this was by Boyer, et al., (2008). The study outlined the case history of a 43 year old man who suffered chronic pain caused by thoracic outlet syndrome (a condition where the blood vessels and nerves in the space between the collarbone and first rib are compressed). He had developed a high tolerance for hydromorphone (Dilaudid) and would inject the crushed pills subcutaneously. The subject reported that during periods when he could not obtain hydromorphone, he managed his hydromorphone withdrawal by drinking a tea made from kratom. When he decided to quit abusing hydromorphone abruptly, he again averted opioid withdrawal by consuming kratom tea which he reported helped to manage his chronic pain and improve his alertness. He also reported not experiencing the drowsiness brought on by opioid use. However, after three years of uneventful kratom use, he tried to improve his alertness by taking Provigil® (modafinil) which binds to the dopamine transporter and inhibits dopamine reuptake. The introduction of

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[80] Henry, T. A., "Introduction: The Plant Alkaloids," 1913, London J. & A. Churchill, Great Marlborough Street, London at https://www.forgottenbooks.com/en/books/ThePlantAlkaloids_10312948

[81] Hassan Z., et al., From "Kratom to *mitragynine* and its derivatives: Physiological and behavioural effects related to use, abuse, and addiction," 2013, Neuroscience and Biobehavioral Reviews, Vol. 37, pgs. 138–151.

[82] Id.

[83] Takayama, H., "Chemistry and Pharmacology of Analgesic Indole Alkaloids from the Rubiaceous Plant, m*itragyna speciose*," 2004, Chem. Pharm. Bulletin, Vol. 52(8), pgs. 916—928.

[84] Id.

modafinil resulted in the subject presenting at the hospital with tonic-clonic seizures. The subject reported only mild symptoms after ceasing kratom use.[85]

52. Vicknasingam, et al., (2010) presented the first study to document the use of kratom as a substitute for reducing dependence on other illicit substances including cannabis, morphine and amphetamine-type stimulants and also to suppress opiate withdrawal symptoms outside a treatment setting.[86] Several other studies have reported that users were relying on kratom for these purposes because it was inexpensive and readily available.[87] In addition, in the case of those facing opiate withdrawal symptoms, self-treatment with kratom obviated the need to approach government facilities that might expose their identities. [88] It is not uncommon for drug-addicted subjects to self-treat with kratom and avoid formal rehabilitation with a physician and the stigma of being known as a drug addict.[89]

53. In 1975, a study by Suwanlert of longtime kratom users in Thailand was performed with 29 males and 1 female.[90] Ninety percent of the kratom consumers in the study chewed the fresh leaf or ground fresh or dried leaves. They either ate the ground dried leaf, or steeped the ground leaf in warm water to make a tea. Sometimes salt was added to prevent constipation, and warm water or coffee was often consumed afterwards. [91] Although the dosage in units of mg/day were not reported, chewing fresh leaves while working throughout the day most likely produced substantially higher doses than that of 80 mg capsules typically sold in the U.S. (See paragraph 25 regarding leaf chewing potentially resulting in a kratom dose equivalent to the amount of kratom in 161 capsules per day as typically sold in the U.S.)

54. The participants in the study reported feeling active, strong and happy approximately five minutes after consumption. They also reported increased productivity and feeling a sense of calmness although they preferred to avoid other people. Kratom was also

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[85] Boyer, E., et al. "Self-treatment of opioid withdrawal using kratom (*mitragynia speciose* korth)," 2008, Addiction, Vol. 103(6), pgs. 1048-1050.

[86] Vicknasingam, B., et al., "The informal use of kratom (*mitragyna speciosa)* for opioid withdrawal in the northern state of peninsular Malaysia and implications for drug substitution therapy," 2010, International Journal of Drug Policy, Vol. 21, pgs. 283-288.

[87] Boyer et al., 2008; Boyer et al., 2007; McWhirter and Morris, 2010; Rosenbaum et al., 2012; Vicknasingam et al., 2010

[88] Singh, D., "Traditional and non-traditional uses of *mitragynine* (kratom): A survey of the literature," 2016, Brain Research Bulletin.

[89] Vicknasingham, B., et al., "The informal use of kratom (*mitragyna speciosa)* for opioid withdrawal in the northern state of peninsular Malaysia and implications for drug substitution therapy," 2010, International Journal of Drug Policy, Vol. 21, pgs. 283-288.

[90] Suwanlert, S., "A Study of Kratom Eaters in Thailand," 1975, Bulletin on Narcotics, Vol 27(3), pgs. 21-27.

[91] Id.

reported to have side effects as well as being "addictive." Additionally, while kratom enabled workers to work all day in the hot sun, consumers tended to avoid the rain because they reported that it caused them to develop a cold more readily. About thirty percent experienced reduced sexual desire while approximately seven percent of users reported prolonged sexual intercourse. Weight loss, loss of appetite and insomnia were common among long-term kratom users.

55. Suwanlert (1975) stated that "*Progression to kratom addiction is a gradual process with increases in dosage and frequency of use.*" The study by Suwanlert is one of the first and best known studies about long-term kratom use. It has been cited in at least 87 different published scientific articles on kratom. Suwanlert's article, which is also his only cited publication on the subject and published in the *Bulletin on Narcotics,* Vol. 27, Issue 3 (pages 21 – 27) was titled "*A study of kratom eaters in Thailand*."

56. Using interviews and a thirty question questionnaire, Suwanlert examined the demographic characteristics, method of consumption, onset of addiction and physiological effects of kratom on 1 female and 29 male kratom users from the suburbs of Bangkok, Thailand. He also performed a psychiatric and physical review of five additional cases of kratom users from a psychiatric hospital.

57. According to the study, physiological effects of long-term kratom addiction were loss of weight, skin darkness (particularly on the cheeks), mouth dryness, frequent urination and constipation along with pellet-like black feces. He determined that the withdrawal symptoms from kratom use were hostility, aggression, teary eyes, runny nose, aching muscles and bones, jerky movement of limbs and an inability to work.

58. There are several limitations to Suwanlert's work that call into question some of his results. Suwanlert did not provide any methodology for the selection of the thirty five kratom users he studied. Consequently, it is impossible to rule out bias in the selection of subjects. Also, apart from long-term use, no methodology was provided for Suwanlert's determination that the subjects of the study were indeed "addicted" to Kratom.

59. Suwanlert presents a detailed list of the symptoms of kratom withdrawal without providing any information on the variability surrounding a body's reaction to withdrawal from kratom use. The author stated that only one of the thirty five subjects expressed a desire to stop using kratom and that the study included psychotic patients from a psychiatric facility with a multiple drug use history as participants in the study. It is not clear whether the subjects using opiates or other drugs simultaneously ceased kratom along with the various drug of abuse.

60. Given that 33% of the Suwanlert's subjects were in a lower social class and that the author clearly stated that the majority of kratom eaters interviewed used kratom to help "*overcome the burden of their hard work and meager existence,*" the author fails to state how he determined that some the symptoms of kratom addiction he described

(i.e., anorexia, weight loss, and insomnia) were not simply symptoms of underlying depression.

61. The Suwanlert study ends by describing five cases of psychosis in kratom users selected from out-patients at Srithunya Psychiatric Hospital in Nondhaburi. Of the five cases, one subject had been combining kratom use with alcohol consumption for the past two years while two other subjects had combined their use of kratom with heroin, alcohol and amphetamines. It should be noted that six subjects of the 30 participants in the earlier study had been using kratom long-term for between 26 and 30 years without any psychotic symptoms.

62. Thus, with respect to the results of the Suwanlert study, more information is needed with respect to the author's methodology to draw meaningful conclusions. A larger sample size is also needed to draw conclusions on the effects of kratom "addiction and withdrawal." There is clearly insufficient evidence to support his suspicion of "kratom psychosis" since he selected subjects from a psychiatric center who may have already had underlying psychoses or effects from their use of multiple drugs of abuse.

63. Therefore, from the data presented in the Suwanlert study, it can only be concluded that kratom use may cause adverse health symptoms upon cessation as the study is far from conclusive. It should also be noted, and as previously stated, studies by Amattayakul (1960) reveal that chewing 30 dry leaves per day weighing approximately 0.43 grams each results in chewing of 12,900 mg of kratom per day - equivalent to the amount of kratom in 161 capsules per day as sold in the U.S.[92] Thus, the Suwanlert (1975) study very likely represents the extreme high-end use of kratom since Suwanlert identified many of the subjects as farmers of low social and economic means who used kratom to enable them to work all day in the hot sun.

64. There is some debate in the scientific community concerning kratom's side effects, "addictiveness" and negative health impacts. For instance, although kratom is known to cause weight loss, it has also been proposed as a potential treatment for obesity.[93] Additionally, studies that reported symptoms upon kratom use cessation may have been at dose levels less likely to occur in the U.S. (i.e., daily habitual chewing of leaves while performing farm work).

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[92] Amattayakul, T., "The kratom leaves," Journal of Department of Medical Sciences, Thailand, 1960. Vol. 2(2) pgs. 104-108 in Suwanlert, S., "A Study of Kratom Eaters in Thailand," 1975, Bulletin on Narcotics, Vol 27(3), pgs. 21-27.

[93] Yuliana, N., "Obesity Management: Comprehensive review on herbal medicine for energy intake suppression," 2010, Obesity Reviews, International Association for the Study of Obesity.

Pre-Clinical Pharmacology (Animal Studies)

65. Extracts (primarily mitragynine) from kratom leaves have been scientifically studied in animal models with respect to physiological, neurological and behavioral effects.

66. Kratom extract provided a dose dependent protection to rats that were fed with castor oil to induce diarrhea by a direct effect on the gastrointestinal tract. Kratom extract slowed intestinal transit and also lowered the volume of intestinal fluid similar to the antidiarrheal drug, Loperamide.[94]

67. Kratom extracts have also been found to have an analgesic effect[95] increasing the latency period of nociceptive/pain response in mice in thermal pain tolerance tests.[96,97] However, the kratom extract was found to be an order of magnitude less potent than morphine in eliciting nociceptive responses.[98] The results of the Stolt study (2014) revealed that the kratom extract "demonstrated weak behavioral effects mediated via μ and κ opioid receptors."[99] Another study found that kratom alkaloid extract and kratom methanol extract were found to increase the latency period of nociceptive/pain response in mice in response to a hot plate. The kratom extracts were also less potent than morphine in eliciting a nociceptive response.

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[94] Chittrakarn, S., et al., "Inhibitory effects of kratom leaf extract (*mitragyna speciosa* Korth on the rat gastrointestinal tract," 2008, Journal of Ethnopharmacology, Vol. 116, pgs. 173–178.

[95] Stolt, A., et al., "Behavioral and neurochemical characterization of kratom (*Mitragyna speciosa*) extract," 2014, Psychopharmacology, Vol. 231, pgs.13–25.

[96] Id..

[97] Reanmongkol, W., "Effects of the extracts from *Mitragyna speciosa* Korth leaves on analgesic and behavioral activities in experimental animals," 2007, Songklanakarin Journal of Science and Technology, Vol. 29 (Suppl. 1), pg. 39 - 48.

[98] Id.

[99] Stolt, A., et al., "Behavioral and neurochemical characterization of kratom (*Mitragyna speciosa*) extract," 2014, Psychopharmacology, Vol. 231, pgs.13–25.

68. Kratom extracts were also evaluated for locomotor activity in mice measuring their performance in an activity cage. Kratom extracts did not significantly change spontaneous motor activity and was about five times less potent when compared to methamphetamine's response. Kratom extracts also had no significant effect on pentobarbital-induced sleep. [100]

69. Kratom extracts have also been demonstrated in rats to have some anesthetic properties by increasing muscle relaxation; however, it was not as potent as Xylocaine® (anesthetic drug, lidocaine) which could achieve 100% block in nerve action potential within 25 minutes compared to 87.5% nerve block after 60 minutes using kratom extract. [101]

70. *Mitragynine* has also been demonstrated in rats to have anesthetic properties causing muscle relaxation and decreasing muscle twitch. High concentrations of *mitragynine* were shown to block nerve conduction acting at the neuromuscular junction while not being a competitive agonist of acetylcholine. *Mitragynine* was not as effective as xylocaine in block action potential in the nerve. [102]

71. Furthermore, in addition to the physiological changes, kratom extracts have also been demonstrated to exhibit antioxidant and antibacterial properties.[103]

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[100] Reanmongkol, W., et al, "Effects of the extracts from *Mitragyna speciosa* Korth leaves on analgesic and behavioral activities in experimental animals," 2007, Songklanakarin, Journal of Science and Technology, Vol. 29 (Suppl. 1), pp. 39 - 48.

[101] Chittrakarn, S., "The neuromuscular blockade produced by pure alkaloid, mitragynine and methanol extract of kratom leaves *(Mitragyna speciosa* Korth)," 2010, Journal of Ethnopharmacology, Vol. 129, pp. 344 – 349.

[102] Id.

[103] Parthasarathy, S., et al., "Evaluation of Antioxidant and Antibacterial Activities of Aqueous, Methanolic and Alkaloid Extracts from *Mitragyna speciosa* (Rubiaceae Family) Leaves," 2009, Molecules, Vol. 14, pgs. 3964-3974.

Mitragynine Pre-Clinical Pharmacology

72. Mitragynine, being the most abundant alkaloid found in kratom leaves, is often credited as being responsible for the pharmacological effects of kratom. However, the true pharmacological impact results from the combined effects of the 20+ known alkaloids operating at several different sets of receptors. The vast majority of in vitro and animal model studies have been conducted only on mitragynine. The primary pharmacological findings of various animal studies on mitragynine have demonstrated anesthetic (sedating) properties with simultaneous analgesia,[104] antinociceptive effects (analgesia by blocking painful or injurious stimulus by sensory neurons),[105] antidepressant,[106] and antitussive[107] physiological effects. Additionally, mitragynine has also been demonstrated to help reduce the severity of opioid withdrawal symptoms.[108]

73. Antinociceptive activity: *Mitragynine* was demonstrated to induce a dose-dependent antinociceptive response in mice[109] and was more effective than morphine.[110] In the Shamima study, *mitragynine* was found to exert antinociceptive activity through descending noradrenergic and serotonergic systems as both were involved in the antinociceptive activity of *mitragynine.* The descending noradrenergic system contributes predominantly to the action of *mitragynine* on thermal noxious stimulation. Although the antinociceptive action of *mitragynine* is sensitive to an opioid receptor antagonist, the mechanism(s) underlying the action are not restricted to the action of the opioid receptors as seen with morphine.

74. It has been demonstrated that *mitragynine* effects that operate through the supra spinal opioid system operate through both μ and δ opioid receptors in order to block the

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[104] Shamima, A., et al., "Antinociceptive Action of Isolated *Mitragynine* from *Mitragyna speciosa* through Activation of Opioid Receptor System," 2012, International Journal of Molecular Sciences, Vol. 13, pg. 11427 -11442.

[105] Id.

[106] Idayu, N., et al., "Antidepressant-like effect of *mitragynine* isolated from *Mitragyna speciosa* Korth in mice model of depression," 2011, Phytomedicine, Vol. 18(5), pg. 402-407.

[107] Macko, E.,et al., "Some observations on the pharmacology of *mitragynine*," 1972, Arch Int Pharmacodyn Ther. Vol. 198, pgs. 145–61 in Matsumoto, K., "Chapter 13: Analgesic Effects of *Mitragynine* and Analogs," 2015, in Raffa, "Kratom and other *Mitragynines* - The Chemistry and Pharmacology of Opioids from a Non-Opium Source," 2015, CRC Press, Taylor and Francis Co.

[108] Khor B. et al., "*Mitragynine* Attenuates Withdrawal Syndrome in Morphine-Withdrawn Zebra fish," 2011, PLoS ONE 6(12): e28340. doi:10.1371/journal.pone.0028340.

[109] Matsumoto, K, et al., "Central antinociceptive effects of *mitragynine* in mice: contribution of descending noradrenergic and serotonergic systems," 1996, European Journal of Pharmacology, Vol. 317, pg. 75-81.

[110] Shamima, A., et al., "Antinociceptive Action of Isolated *Mitragynine* from *Mitragyna speciosa* through Activation of Opioid Receptor System," 2012, International Journal of Molecular Sciences, Vol. 13, pg. 11427 -11442.

detection of painful stimulus.[111,112] A study with kratom extract found that it acted on the μ, δ and k opioid receptors as well as the dopamine D1 receptor.[113]

75. Antidepressant-like effects: These have been identified by Idayu, et al., (2011). This study demonstrated that *mitragynine* has an antidepressant-like effect by using a forced-to-swim and tail-suspension test in mice. These two models are predictive of antidepressant activity. In the forced-to-swim test, the duration of immobility was measured. The high dose treatment of *mitragynine* resulted in effects that were not significantly different from the antidepressant drug Fluoxetine (Prozac®). *Mitragynine* reduced serum cortisol (stress hormone) levels to those comparable to the antidepressant drug amitriptyline (Elavil®). *Mitragynine* reduced the release of corticosterone indicating that it possibly influences the neuroendocrine hypothalamic-pituitary-adrenal (HPA) system.[114]

76. Many studies refer to kratom as allegedly having stimulant effects.[115,116] However, several animal studies have failed to reveal any locomotion stimulating impact from kratom extract[117,118] or *mitragynine* treatments especially when compared against such drugs as amphetamine.[119] The claimed "stimulating" effects of *mitragynine* may have been confused with actual antidepressant-like activity.

77. Opioid addiction: A study using zebra fish chronically exposed to morphine and then treated with *mitragynine* explored the ability for *mitragynine* to alleviate withdrawal symptoms from opioid addiction. The study demonstrated that *mitragynine* lessened stress-related swimming behaviors including decreased exploratory behavior and lowered the whole body cortisol levels. *Mitragynine* was associated with reduced

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[111] Id.

[112] Matsumoto, K., et al., Central antinociceptive effects of *mitragynine* in mice: contribution of descending noradrenergic and serotonergic systems," 1996, European Journal of Pharmacology, Vol. 17, pg. 75-81.

[113] Stolt, A., et al., "Behavioral and neurochemical characterization of kratom (*Mitragyna speciosa*) extract," 2014, Psychopharmacology, Vol. 231, pgs.13–25.

[114] Idayu, N., et al., "Antidepressant-like effect of *mitragynine* isolated from *Mitragyna speciosa* Korth in mice model of depression," 2011, Phytomedicine, Vol. 18(5), pg. 402-407.

[115] Prozialeck W., et al., "Pharmacology of Kratom: An Emerging Botanical Agent with Stimulant, Analgesic and Opioid-Like Effects," 2012, The Journal of the American Osteopathic Association, Vol. 112(12), pg. 792-799.

[116] Babu, K., McCurdy, C., and Boyer, E., "Opioid receptors and legal highs: *Salvia divinorum* and kratom," 2008, Clinical Toxicology, Vol. 46(2), pg. 146 – 152.

[117] Reanmongkol, W., et al, "Effects of the extracts from *Mitragyna speciosa* Korth Leaves on analgesic and behavioral activities in experimental animals," 2007, Songklanakarin Journal of Science and Technology, Vol. 29(1), pgs. 39-48.

[118] Stolt, A., et al., "Behavioral and neurochemical characterization of kratom (*Mitragyna speciosa*) extract," 2014, Psychopharmacology, Vol. 231, pgs.13–25.

[119] Moklas, M., et al., "A preliminary toxicity study of *mitragynine,* an alkaloid from *Mitragyna speciosa* korth, and its effects on locomotor activity in rats," 2008, Advances in Medical and Dental Sciences, Vol. 2(3) pg. 56 - 60.

genetic expression of corticotropin release factor receptors and prodynorphin (hormone that influences susceptibility to drug dependence) in the zebra fish brain.[120]

78. Antitussive actions: The only study that has been performed on the antitussive actions of *mitragynine* was performed by Macko, et al., (1972) in which he reported that *mitragynine* had an antitussive action in mice similar to that of codeine.[121]

79. Kratom is a combination of different alkaloids and plant phytochemicals that can balance out and lower physiological response. Another studied and important alkaloid in kratom – *7-hydroxymitragynine* (an oxidized form of *mitragynine*) - has been demonstrated to induce a potent and dose-dependent, pain-blocking response in laboratory studies.[122,123] 7-*Hydroxymitragynine* activated the μ-opioid receptors, as occurs with morphine, and has a higher potency than morphine.[124]

80. Kratom produces different pharmacological effects linked to the dosage of the plant material consumed. Experiments with kratom alkaloid extract and kratom methanol extract in mice models present a better understanding of the effects of kratom leaf consumption compared to testing with the single, isolated *mitragynine* alkaloid.

D. Mortality and Toxicological Effects

81. It is significant, from an evidence-based toxicological perspective, that high kratom doses have not been reported to cause mortality in the prevailing toxicological literature. An acute toxicity study following the standard, generally-accepted OECD 425 methodology (Sprague Dawley rat study) documented that kratom leaf aqueous extract produced *"*only slight toxic effects*"* at the highest dose level of 2,000 mg/kg body weight.[125] The toxicity within the high dose group of rats was limited to a decrease in mean corpuscular hemoglobin concentration (MCHC), albumin, calcium and

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[120] Knor, B., et al., "*Mitragynine* attenuates withdrawal syndrome in morphine-withdrawn zebra fish," 2011, PLos ONE, Vol. 6(12) e28340.

[121] Macko, E., et al., "Some observations on the pharmacology of *mitragynine*," 1972, Arch Int Pharmacodyn Ther. Vol. 198, pgs. 145–61 in Matsumoto, K., "Chapter 13: Analgesic Effects of *Mitragynine* and Analogs," 2015, in Raffa, "Kratom and other *Mitragynines* - The Chemistry and Pharmacology of Opioids from a Non-Opium Source," 2015, CRC Press, Taylor and Francis Co.

[122] Takayama, H., "Chemistry and Pharmacology of Analgesic Indole Alkaloids from the Rubiaceous Plant, *Mitragyna speciosa,"* 2004, Chem. Pharm. Bull. Vol. 52(8), pg. 916—928.

[123] Matsumotoa, K., et al., "Antinociceptive effect of 7-*hydroxymitragynine* in mice: Discovery of an orally active opioid analgesic from the Thai medicinal herb *Mitragyna speciosa*," 2004, Life Sciences, Vol. 74, pg. 2143–2155.

[124] Takayama, H., et al. "Studies on the Synthesis and Opioid Agonistic Activities of *Mitragynine*-Related Indole Alkaloids: Discovery of Opioid Agonists Structurally Different from Other Opioid Ligands," 2002, Journal of Med. Chem. Vol. 45, pg. 1949-1956.

[125] Kamal, et al., "Acute toxicity of standardized *Mitragyna speciosa* Korth aqueous extract in Sprague Dawley rats," 2012, Journal of Plant Studies, Vol.1 2), pg. 120-129.

cholesterol serum levels. The only chronic adverse health effects noted by the study's authors were that the kratom aqueous extract "has potential to lead to anemia as a hepatoprotective, anti-calcium and anti-cholesterol agent in the future."

82. In contrast, the pure *mitragynine* study of Yusoff, *et al*., did find evidence of cognitive impairment and addiction potential; however, these results were for a super-concentrated *mitragynine* extract.[126] This is a radically-different substance than the simple aqueous leaf extract found in kratom herbal supplements. As previously noted, such concentrates used for experimental purposes greatly inflate or exaggerate any toxicity or undesirable effects. It is, therefore, important to put the results of such studies into the proper toxicological context.

83. International, peer-reviewed studies as well as the NLM (National Library of Medicine) TOXNET toxicology data network do not document any deaths attributable solely to kratom. Significantly, the TOXNET database states "Acute overdose is not frequently reported" and "There is **no** well-defined toxic dose."[127]

84. Although concentrated *mitragynine* can cause lethality, the available case histories do not document *mitragynine* as the sole causative factor in those instances. Various case reports have been published of postmortem positive findings of *mitragynine* in the presence of heroin, alprazolam, ethanol, fentanyl, propylhexedrine and other pharmaceuticals or drugs of abuse that are known to cause fatalities.

85. There have been case reports of deaths in Europe and Sweden in which kratom was a co-ingredient in a substance called "Krypton." As stated above, this particular substance includes a powerful synthetic narcotic (*O-desmethyltramadol*) known to have been a causative factor in deaths.

[126] Yusoff, et al., "Abuse potential and adverse cognitive effects of mitragynine (kratom)," 2016, Addict Biol., Vol. 21 (1), pg. 98-110.

[127] National Library of Medicine (NLM), "*Mitragynin*e CASRN: 4098-40-2," 2012, TOXNET (Toxicology Data Network).

86. However, none of these reports cite kratom leaf alone as a causative factor in deaths. This is a significant toxicological finding as a determination of toxicological causation must satisfy multiple investigative criteria which are not presently in evidence. Causation is the process by which the expert toxicologist establishes or refutes whether a potential adverse health effect is truly caused by an exposure, dose or duration. In 1950, Sir Bradford Hill and his colleague, Sir Richard Doll, were the first to apply a scientific methodology to demonstrate the causal connection between cigarette smoking and lung cancer.[128] Since that time, toxicologists have applied the "Bradford Hill" criteria in causation determination. This criteria states that "the mere presence of a substance at autopsy does not equal causation."

87. For example, caffeine is extremely prevalent in postmortem toxicology results, but the mere presence of caffeine does not imply causation. Even when oxycodone or other potent narcotics are present in postmortem toxicology blood, the actual blood level and dose must be critically considered prior to opining "causation."

88. Of those reports offering causative assessments, most cite other drugs with well-documented and generally-recognized toxicological properties. Thus, it is not possible to conclude that kratom is a causative mortality factor solely from the aforementioned studies.

Summary of a Death Allegedly Caused by Kratom

89. In my role as a toxicologist, I have conducted toxicological assessments in cases in which kratom was alleged to be a causative mortality factor. The following summary of a relevant case offers insights into an alleged kratom-induced death. It illustrates how a lack of accurate, peer-reviewed knowledge pertaining to kratom among medical professionals can lead to erroneous conclusions.

90. Forty-four year old John Doe[129] (redacted autopsy report provided in **Attachment C**) was found dead in August, 2015. He had a prior history of alcohol and drug addiction but had been sober for 5 to 7 years. A body builder, John had injected steroids for more than 20 years. His wife Jane[130] said John consumed supplements twice daily: phenibut, kratom and a mixture of vitamins, amino acids and caffeine (John's so-called "pre-workout" mixture). Body builders use Phenibut (a gamma aminobutyric acid derivative) as a growth hormone. John consumed about 5 grams of kratom powder per dose, but the phenibut and "pre-workout" mixture were taken "a scoop at a time." The recommended phenibut dose is only 0.25 gm to 1 gm.

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[128] Doll, R. and Hill, AB, "Smoking and carcinoma of the lung: Preliminary report." 1950, British Medical Journal, pg. 739-748.

[129] John and Jane are not their real names (identity is known by the MEO).

[130] Id.

91. Jane reported that John had been taking far too much of the phenibut. To help with phenibut withdrawal, he began taking a "research chemical" called etizolam a week before his death. A powerful benzodiazepine analog, etizolam is a sedative/hypnotic with extremely high potency at low doses. Jane said the etizolam made her husband "inebriated." After John's death, Jane found a needle and syringe when cleaning their residence. She notified police who informed her that the needle had been disregarded (and thus, not included in the police report) because she had told them that John used steroids. However, Jane thought that her husband injected the etizolam.

92. An autopsy was conducted and the attending medical examiner's final report noted (a) dilated cardiomegaly, a disease of the heart muscle, (b) a history of drug addiction, and (c) the presence of *mitragynine* and caffeine in the toxicological tests. In the absence of any clear causation or mitigating factors, the cause of death was ruled as *mitragynine* toxicity. However, there was evidence that made this unlikely.

93. The medical examiner's report was erroneous for several significant reasons:

- Lack of critical facts: The medical examiner was not aware that John had abused etizolam beginning the week prior to his death because the syringe did not appear in the police report. Although toxicology revealed the presence of "other organic bases," no specific identification was made. This was due to the simple fact that no one was looking for it.
- High relative potency: Etizolam has very high potency at low doses. One mg of etizolam has roughly the same potency as a 10 mg dose of Valium (diazepam).[131]
- The 1-ounce bottle in John's possession would have contained approximately 28,500 mg of etizolam - equivalent to 285,000 mg of Valium.
- Behavioral factors: John's "inebriated" behavior, which corresponded to the time he began using etizolam, provides reasonable probable cause that this toxicant was the most significant contributing factor in his death.

94. Therefore, the erroneous determination at autopsy resulted from a lack of relevant information. Under such circumstances, a presumption of causation is perhaps not surprising. However, toxicological causation criteria is *extremely strict.* It mandates that the mere presence of a substance does not equal causation.

[131] WHO, "WHO Expert Committee on Drug Dependence," 1991, WHO Technical Report Series, Twenty-seventh report, pg. 5 – 6.

95. A basic principle of toxicology is "S*ola dosis facit venenum"* meaning *"The dose makes the poison."* Any substance (including such common substances as table salt) can be potentially lethal when ingested at a high enough dose. Even water will kill if enough is ingested causing a condition called *hyponatremia* (insufficient sodium with convulsions and death). Another fundamental scientific principle is "*Correlation does not equal causation.*" This means that two events occurring simultaneously (such as consuming kratom in combination with other substances followed by subsequent death) does not infer that the first caused the second in the presence of other potent toxic compounds. It is notable that caffeine was also reported in kratom case studies but its presence also does not support causation.

96. Thus, it was demonstrated that kratom was not likely a causative factor in the above case history. Its detection in the blood was a normal and expected outcome of autopsy testing as were the presence of caffeine and other substances unrelated to the fatality.

Case Reports of Adverse Health Effects or Death

97. It is important to recognize that the individual clinical/forensic case reports emerging from the West (United States and Europe) that attempt to link kratom use to adverse reactions or fatalities all pertain to kratom used in combination with other substances. Biased opponents of kratom misuse these reports to strengthen their case to instill legal sanction against this substance.

98. Relaxing/Appetite Loss/Possible Intrahepatic Cholestatis: Kapp, et al., (2011) reported the case of a subject who started ingesting one teaspoon (2.3–3.5 grams; corresponding to approximately five to eight dried leaves) of powdered kratom twice daily and had reached four to six teaspoons daily over the course of two weeks. He was taking no other supplements or alcohol. He found that the powdered kratom was mildly relaxing but induced tiredness and a loss of appetite. He did not observe any stimulating effects. After cessation of the kratom, the subject developed subjective fever and chills on day two which lasted for about one week. On day five after cessation, he noticed slight abdominal discomfort which developed into intense abdominal pain on day eight with noticeable jaundice and pruritus which was documented by an elevated direct bilirubin of 28.6 mg/dl (reference value <0.3 mg/dl) with abdominal imaging showing signs of steatosis of the liver and a diagnosis of intrahepatic cholestasis. Liver enzymes were only slightly elevated. The authors concluded that this would be the first case of *probable* kratom-induced hepatotoxicity. However, it is not clear that kratom was responsible. It is also unlikely that steatosis could develop in only two weeks. (Steatosis, or a "fatty liver," occurs as an accumulation of triglycerides and other fats within the hepatocytes and is common among alcoholics or patients with certain genetic enzyme deficiencies.)

99. Hypothyroidism: Sheleg and Collins (2011) presented a case of hypothyroidism in an oxycodone/kratom-using male and discuss the theory that the major alkaloid identified

in kratom might interfere with thyroid function.[132] The man had gained 60 pounds, become lethargic and developed myxedematous facies (puffy face with thickened, edematous skin) - extreme manifestations of hypothyroidism. The man was being prescribed the opiate Percocet (oxycodone) and then added kratom. Buprenorphine was prescribed resulting in opiate-type withdrawal symptoms that resolved within three days. The minor withdrawal symptoms may have been primarily from the oxycodone use. With respect to the thyroid dysfunction, Hassan, et al., (2013)[133] reported that a causal relationship between kratom use and thyroid dysfunction has not been identified yet. With respect to the possible impact of kratom on the thyroid-stimulating hormone (TSH) function, morphine has been found to suppress TSH in animal models. In the current case history, however, the patient was using the opiate oxycodone that may have been implicated in the thyroid dysfunction.

100. Seizures: Two cases of kratom use potentially associated with seizures were reported. In the case history presented by Boyer, et al.,[134] the subject was self-injecting crushed hydromorphone (a highly potent opiate) along with the tablet excipients which included microcrystalline cellulose and binders. However, after three years of uneventful kratom use, he tried to improve his alertness by taking Provigil® (modafinil) which binds to the dopamine transporter and inhibits dopamine reuptake. The new use of modafinil resulted in the subject presenting at the hospital with tonic-clonic seizures. Causation could not be established.

101. In another study, Nelson, et al., (2010) failed to provide firmer evidence of seizure following the ingestion of kratom.[135] A 64 year old man had been using kratom for several months; however, he experienced multiple witnessed seizures requiring intubation 30 minutes after ingesting a tea made with kratom and Datura stramonium. Datura, commonly known as jimsonweed (a plant in the nightshade family) is known to be a poisonous plant and has been associated with seizures and death at high dosage due to its anticholinergic properties.[136,137] Based on the known poisonous properties of jimsonweed, it is not scientifically credible to classify kratom as the punitive agent.

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[132] Sheleg and Collins, 2011, in Singh, D., "Traditional and non-traditional uses of *Mitragynine* (kratom): A survey of the literature," 2016, Brain Research Bulletin.

[133] Hassan, Z., et al., "From kratom to *mitragynine* and its derivatives: Physiological and behavioral effects related to use, abuse and addiction," 2013, Neuroscience and Biobehavioral Reviews, Vol. 37, pg. 138-151.

[134] Boyer, E., et al., "Self-treatment of opioid withdrawal using kratom (*Mitragynia speciosa* korth)," 2008, Addiction, Vol. 103(6), pgs. 1048-1050.

[135] Nelson, J., "Seizure and coma following kratom (*mitragynine speciosa* korth) exposure," 2010, Journal of Medical Toxicology, Vol. 6, pg. 424-426.

[136] Rech, M., "New drugs of abuse," 2015, Pharmacotherapy, Vol. 35(2), pg. 189-197.

[137] https://medlineplus.gov/ency/article/002881.htm

102. Reports of serious toxicological effects have been rare and usually involve relatively high doses (more than 15,000 mg of kratom) or co-ingestants.[138]

103. Other adverse effects: Forrester (2013) discusses 14 cases including eight cases of exposures involving kratom alone and six cases involving additional substances (e.g., wild dagga, wormwood, alprazolam and synthetic cannabinoid, synthetic tryptamine, alcohol and methamphetamine and risperidone). Four patients had a medical outcome with minor effects, five patients experienced moderate effects, one patient had major effects, two were followed with no more than minor adverse effects and two were unable to be followed but judged to have potentially toxic exposures. There were no deaths.[139] The reported clinical symptoms were tachycardia (n = 5), hypertension (n = 4), agitation (n = 4), nausea (n = 3), vomiting (n = 3), confusion (n = 3), tremor (n = 3), diaphoresis (n = 3), drowsiness (n = 2), hallucinations (n = 2), mydriasis (n = 2), dyspnea (n = 2), bradycardia (n = 1), abdominal pain (n = 1), slurred speech (n = 1), hyperventilation (n = 1) and elevated creatinine phosphokinase (n = 1).

104. Various side effects reported in Norakarnphadung, 1968, were hyperpigmentation on the face, micturition (urination), constipation, mouth dryness, dark and small feces.[140] Sudden cessation of daily kratom use resulted in symptoms including increased hostility, inability to work, aching muscles and bones, jerky movement of limbs, teary eyes and runny nose.[141]

105. Mixed positive and negative effects: Based on 161 reports that included 109 males, 13 females and 39 who did not identify their gender, Swogger, et al., (2015) reported the following positive and negative effects. On the positive side, many users reported at least some of the following effects: euphoria, a sense of wellbeing, relaxation, enhanced sociability, more energy, analgesia, sensory enhancement and a warm and tingly feeling. On the negative side, reports of nausea, stomach ache, alternation between chills and sweats, dizziness, vomiting, itching, numbness in the mouth and throat, sedation, visual alterations and unsteadiness were reported.[142]

106. Kratom fatalities always involve co-ingestants[143] such as those reported in the literature and, thus, these reports cannot independently demonstrate causation of fatalities by kratom. For example, as previously noted, several case reports have been published

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[138] Rech, M., "New drugs of abuse," 2015, Pharmacotherapy, Vol. 35(2), pg. 189-197.

[139] Forrester, M.B., "Kratom exposures reported to Texas Poison Centers," 2013, Journal of Addictive Disease, Vol. 32(4), pg. 396-400.

[140] Norakarnphadung, 1968 in Suwanlert, S., "A Study of Kratom Eaters in Thailand," 1975, Bulletin on Narcotics, Vol 27(3); pg. 21-27.

[141] Suwanlert, S., A Study of Kratom Eaters in Thailand," 1975, Bulletin on Narcotics, Vol 27(3); pg. 21-27.

[142] Swogger et al., 2015 in Singh, D., "Traditional and non-traditional uses of *Mitragynine* (kratom): A survey of the literature," 2016, Brain Research Bulletin.

[143] Id.

reporting death resulting from *"*krypton*,"* a powder mixture containing *mitragynine* and *O-desmethyltramadol*.

107. If kratom (by itself) caused fatalities, such reports would be expected from the over 1 million individuals who have used kratom in Thailand (many chewing massive doses of leaves). To date, there have been no such reports.

108. Non-Causative Fatalities: Kronstrand et al. (2011)[144] reported on nine subjects who died from accidental drug intoxication. Although *mitragynine* was present in blood samples, 150 different pharmaceutical drugs/drugs of abuse were also present, as well as speciogynine, speciociliatine, mitraciliatine, LSD-d3, O-desmethyltramadol and tramadol. Post-mortem analysis revealed O-desmethyltramadol concentrations ranging from 0.4 to 4.3 µg/g (1.3 ug/L-20 ug/L, lethal range) and *mitragynine* concentrations ranging from 0.02 to 0.18 µg/g. Other drugs in the blood samples included alprazolam, ethanol, alimemazine, DMA, venlafaxine, O-DMV, fluoxetine, norfluoxetine, phenazon, aolanzapine, diazepam, nordiazepam, pregabalin amphetamine, DMA, THC, mirtazapine, buprenorphine, zopiclone, citalopram and others. Owing to the plethora of confounding substances, the contribution of *mitragynine* and its effect on the µ-agonist receptor in the deaths is unknown.

109. Unknown Causation: Holler, et al., (2011)[145] reported on a 20 year old male found dead at home. Kratom, propylhexedrine (an OTC nasal decongestant and a structural analog of methamphetamine) and 39 other prescription and nonprescription medications and nutritional supplements were found at the scene. The subject's computer revealed research on kratom and other herbal supplements and how to concentrate propylhexedrine from inhalers. A standard drug screen showed no ethanol in the blood and vitreous fluid, but was positive for morphine and acetaminophen in the urine. Propylhexedrine levels in the blood (1.74 mg/L) and tissue were similar to other reported deaths caused by propylhexedrine. Urine levels of propylhexedrine and *mitragynine* were 51.96 mg/L and 1.20 mg/L, respectively. The *mitragynine* blood level was 0.39 mg/L. Cause of death was ruled propylhexedrine toxicity, although the contribution of kratom was unknown.

110. Inconclusive Causation: Neerman et. al., (2013)[146] reported on the fatality of a 17 year old man with a well-documented history of heroin abuse. The subject was found with a bottle of promethazine and a bottle of kratom (not characterized) which the subject had reportedly taken the night before. Whole blood taken from the femoral vein and vitreous fluid was analyzed for alcohols, alkaline drugs, acid neutral drugs, opiates, cocaine,

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[144] Kronstrand R., et al., "Unintentional fatal intoxications with *mitragynine* and *O-desmethyltramadol* from the herbal blend Krypton," 2011, Journal of Anal. Toxicology, Vol. 35(4), pg. 242-247.

[145] Holler JM, et al., "A drug toxicity death involving propylhexedrine and *mitragynine*," 2011, Journal of Anal. Toxicology, Vol. 35(1), pg. 54-59.

[146] Neerman MF, et al., "A drug fatality involving kratom," 2013, Journal of Forensic Sci., Vol. 58(1) S278-9.

benzodiazepines, cannabinoids, oxycodone/oxymorphone, fentanyl and mitragynine. The autopsy was remarkable only for pulmonary congestion and edema and a distended bladder, both of which are consistent with (though not diagnostic of) opiate use. A laboratory work-up revealed therapeutic levels of over-the-counter cold medications and benzodiazepines. Findings included temazepam (0.21 mg/L), dextromethorphan (0.28 mg/L), diphenhydramine (0.33 mg/L), 7-amino-clonazepam (0.21 mg/L) and *mitragynine* (0.60 mg/L). Given the facts in the case, the medical examiner certified the cause of death as "possible kratom toxicity" although no accepted standard exists to assess kratom toxicity and render an objective determination.

E. Dependency and Addiction Factors

111. Kratom extracts vary widely in composition and potency. Although human studies suggest a potential for addiction, there is no toxicologically-sound method to quantify an addiction threshold. This lack of standardization prevents accurate determination of dose-response for safety endpoints.

112. As previously noted, kratom leaves contain more than 20 different, known alkaloids. The vast majority of kratom use in the U.S. is via ground leaves sold as dietary supplements rather than as concentrated mitragynine extracts. However, it is important to note that the alkaloid content of kratom leaves varies widely from location to location and at different times. This finding led Shellard, et al.,[147] to conclude that there are geographical variants within the species. Within each location, there is a quantitative variation in alkaloid content from month to month as well. The alkaloid content of dried leaves was reported to vary as much as 0.5% to 1.5%.

113. Dependency and Withdrawal: McWhirter and Morris (2010) [148] published a case report of inpatient detoxification in which a 44 year old man with a history of alcohol abuse and anxiety disorder was treated for kratom detoxification. The man had a 3 year history of kratom use. He initially self-administered a daily 4 gram dose, increasing to twice daily after three months. By nine months, he had further increased his dose to 8 grams and then to 12.5 grams twice daily due to tolerance, eventually consuming 40 grams of kratom divided into four doses. On admission for detoxification, no laboratory analysis for kratom was performed. This case supports the hypothesis that high doses of *mitragynine* and *7-hydroxymitragynine* cause a dependence syndrome via agonist activity at opioid receptors. However, since dihydrocodeine and lofexidine were

[147] Shellard, E. J., "The alkaloids of *mitragyna* with special reference to those of *mitragyna* speciosa korth," 1974, Bulletin on Narcotics, Vol. 2, pg. 41-55.

[148] McWhirter L, Morris S., “A case report of inpatient detoxification after kratom (*Mitragyna speciosa*) dependence,” 2010, European Addict Res. Vol. 16(4), pg. 229-231.

commenced simultaneously, the independent effects of each drug on withdrawal symptoms could not be assessed.

114. A dependence study[149] (Singh, et. al., 2014) noted varying degrees of dependency and addiction potential, but the ingestion levels cited were extremely high. The study results stated:

> "More than half of the regular users (>6 month of use) developed severe kratom dependence problems while 45% showed moderate kratom dependence. Physical withdrawal symptoms commonly experienced include muscle spasms and pain, sleeping difficulty, watery eyes/nose, hot flashes, fever, decreased appetite and diarrhea. Psychological withdrawal symptoms commonly reported were restlessness, tension, anger, sadness and nervousness. The average amount of the psychoactive compound, *mitragynine*, in a single dose of a kratom drink was 79 mg, suggesting an average daily intake of 276.5 mg."

115. Given the fact that twenty kratom leaves contain approximately 17 mg of *mitragynine*[150] and or a total of 1,748 eighty (80) mg kratom capsules per day. Such a dose is not reasonable without an abundant supply of leaves to chew on throughout the day as in Southeast Asia or by preparing high potency pharmacological extract drinks as reported above. It is also important to note that the Singh study recruited a total of 293 male kratom users from communities in Malaysia on the south Thailand border. These are states where kratom is most prevalent with trees present to harvest.

116. Thus, the Singh study can be regarded as an extreme scenario requiring an abundant source of trees available to users with varying degrees of addiction and dependency within a large population ingesting extraordinarily high levels of kratom over a prolonged period. It is also probable that the percentage levels of *mitragynine* were correspondingly high as these are regions where kratom has been cultivated and used for centuries.

117. Although the terms "dependency" and "addiction" are occasionally (and incorrectly) used interchangeably, they are, in reality, quite different. Physical dependence can occur without addiction such as with chronic pain patients who are given opioid medication but who do not exhibit loss of control, unmanageable urges, compulsions or other addictive behaviors. Such behavioral characteristics are largely governed by dosage. This is one of the most important attributes in any objective toxicological assessment. A study by Assanangkornchai, et. al.,[151] (supported by the Thailand Narcotics Control Board) noted that:

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[149] Singh, et al., "Kratom (*Mitragyna speciosa*) dependence, withdrawal symptoms and craving in regular users," 2014, Drug and Alcohol Dependence, Vol. 139, pg. 132-137.

[150] Id.

[151] Assanangkornchai, et. al.,"The Use of *Mitragynine speciosa* (kratom), an Addictive Plant, in Thailand," Substance Use & Misuse, Informa. Healthcare USA, Vol. 42:, pg. 2145-2157

> "Most respondents, both users and non-users, had a tendency to perceive the advantages of kratom rather than its harmful effects. Although most regular users admitted to being dependent on kratom, they did not see this as a problem as they had learned how to use kratom safely. Chronic adverse effects like constipation were tolerable, and there were no serious medical complications."

118. The studies and case reports illustrate how confounding factors affect a toxicity assessment. Thus, as with any potentially addictive substance capable of providing pain relief or other beneficial health benefits, dosage is the primary mitigating factor with respect to addiction potential. The currently available objective toxicological evidence is insufficient to support claims of kratom addiction at moderate doses. Thus, it is reasonable to presume that the risk of kratom addiction is not a fixed, static quality at any dose, but rather a continuously variable function of extreme high-dose and frequency of ingestion. This characteristic is markedly different from substances with addictive properties prevalent even at low to moderate doses such as cocaine, oxycodone, heroin and various opiates.

119. Whereas any substance is capable of abuse by overdosing (as previously noted), the available toxicological evidence suggests that a high risk of abuse corresponds to extremely high dosing for long durations as in Thailand where abundant sources of leaves are available.

Potential for Dependency

120. Interaction toxicity is a factor in dependency. The majority of U.S. consumers of kratom can be accurately characterized as “mainstream” users, but others create novel mixtures in which kratom enhances the effects of other substances and/or creates new effects through interaction with various drugs of abuse. In such cases, dependency has often been linked to co-administration of opiates or other addictive drugs.

121. These aspects of kratom use have compelling application to toxicology, but it must also be noted that the same interaction principle can be applied to many natural herbs or pharmaceuticals. Combining kratom with any number of different harmful substances may invariably lead to alteration of its basic toxicological properties.

122. Thus, while kratom's primary potential for dependency or addiction is based on extreme high dosage, a different potential undoubtedly exists when taken in combination with various drug of abuse or poisonous substances.

123. In summary, the totality of available toxicological evidence (including the cited studies) suggests that, by itself, long-term ingestion of extremely high dose levels of kratom may result in short duration, low to moderate physical dependence. The precise dose-response levels, endpoints and interaction potentials governing these factors remain approximate at the present time based on the extraordinarily high ingestion rates in Thailand.

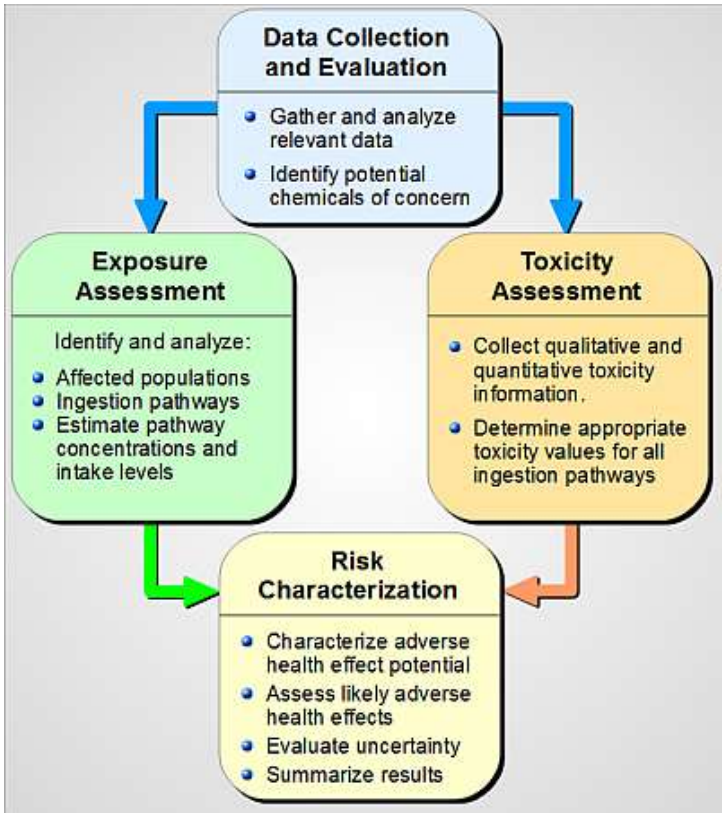
Assessing Risk of Adverse Health Effects

124. Toxicologists can be neither opponents nor advocates when it comes to assessing risk. The role of the toxicologist is to objectively assess the substance(s) to which a person is exposed, collect relevant data describing the known effects from the generally-accepted, peer-reviewed toxicological literature, quantify the available data and formulate exposure and toxicity assessments. To that end, the expert toxicologist's role is primarily to address baseline risk which is the net result of combining the totality of all available information. From this, the toxicologist renders an objective risk assessment with respect to the probability of adverse health effects.

125. It is important to keep in mind that the primary focus of a toxicological risk assessment is human health. In keeping with this mandate, the expert toxicologist must apply a specific set of methods to conduct a reliable risk assessment. Procedural guidance is extremely useful in an evidential investigation. However, objective scientific judgment also plays an important role. Only by strict attention to detail can scientifically credible findings be produced. In all cases, toxicological conclusions must meet the criteria for *reasonable toxicological certainty*.

126. Toxicologists follow a strict methodology to arrive at an objective risk determination. A generally-accepted, toxicological risk assessment model is shown in **Figure 3**.

Figure 3: Toxicological Risk Assessment Methodology



127. Application of the generally-accepted toxicological risk assessment methodology to assess the potential adverse health impacts of kratom must be based on the available biochemical, pre-clinical, clinical and case history study results under varying conditions and circumstances. In that scenario, objective scientific judgment plays an important role in determining what constitutes unbiased assertions and what constitutes information colored by other agendas.

128. There is some ambiguity in the available documentation. For example, to obtain FDA approval for a dietary supplement, the most important information a manufacturer can provide is a long history of safe use. FDA suggests at least 25 years of safe use as a minimum. However, kratom has been used as an herbal medicine for centuries, continues to be widely used in Thailand and has a long history of use in the U.S. as well. Conversely, proponents argue that kratom presents little or no health risks, but there are clearly exceptions. Most studies cite highly concentrated *mitragynine* and/or kratom ingestion in combination with other substances as causative factors. Thus, to render an objective toxicological opinion, the toxicologist must balance the scope of potential adverse health effects against the probability of occurrence.

129. A 2015 study[152] by Cinosi, et. al., concluded that the lack of relevant pharmacological data and peer-reviewed toxicological information concerning kratom was sufficiently limiting as to preclude the possibility of reaching firm conclusions at this time. The study noted that many prevailing sources of information were anecdotal and were useful to the extent that they provided useful preliminary information:

> "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 sedative-narcotic. 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."

130. The Cinosi study highlights the difference between perceived data and objective fact. Kratom can only be put into a proper toxicological context by applying the standard risk assessment methodology (as depicted in **Figure 3**). However, if we look closely at the steps involved, we find that we have data gaps.

131. With respect to anecdotal evidence, a 2015 study[153] conducted by Swogger, et. al., investigated the anecdotal evidence and noted the following:

> "Online drug use forums offer opportunities for the rapid exchange of information and the monitoring of risks associated with use of particular substances. We analyzed and thematically coded kratom experience reports … in order to gather information on human experiences with kratom. In reviewing our findings, it is notable that the theme codes our analysis generated corroborate traditional reports of kratom use from Southeast Asia. Kratom users reported relaxation, a sense of well-being and pain relief along with typical opiate side-effects including stomach upset, vomiting, itching and mild sedation. A subset of users reported both tolerance to and symptoms of withdrawal from kratom although many indicated that, in their experience, these symptoms were milder than those that follow heavy opiate use. A subset of participants also reported using kratom to ease symptoms of opiate withdrawal and many indicated that they had success in discontinuing opiates."

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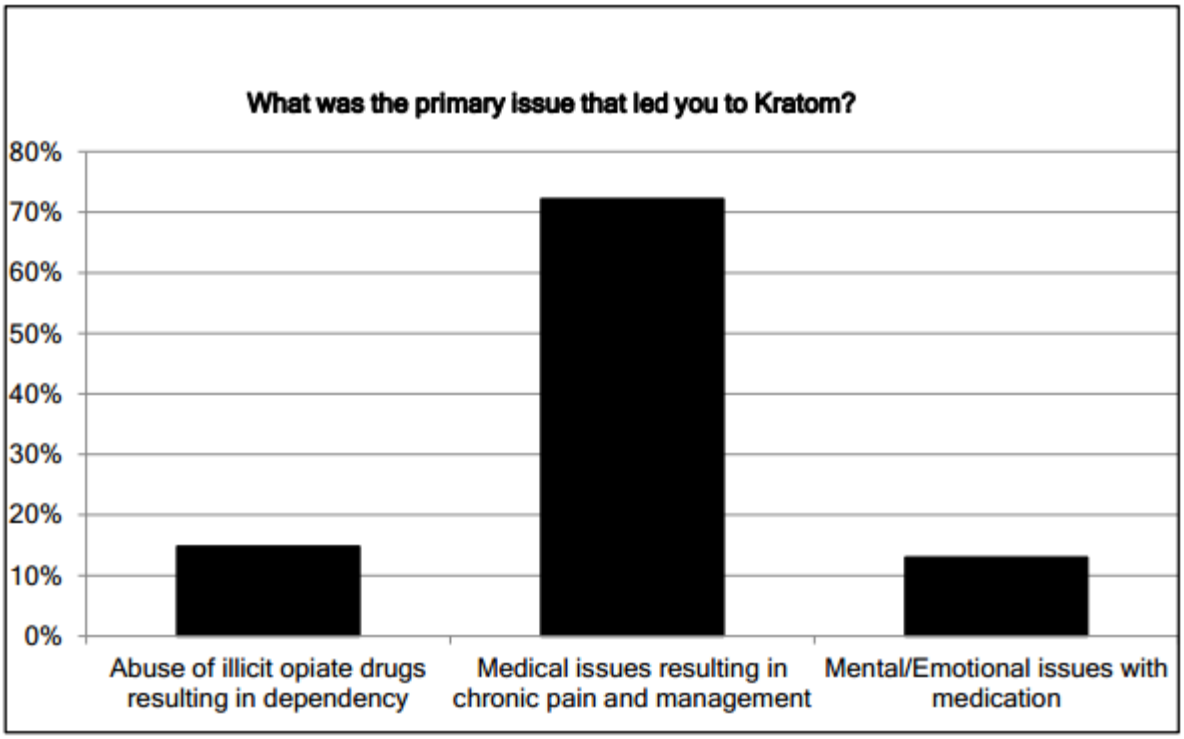
[152] Cinosi, E., et al., "Following 'the roots' of kratom (*Mitragyna speciosa*): The Evolution of an Enhancer from a Traditional Use to Increase Work and Productivity in Southeast Asia to a Recreational Psychoactive Drug in Western Countries," 2015, Biomed Research International, Article ID 968786, 11 pages.

[153] Swogger, et al., "Experiences of kratom users: A qualitative analysis," 2015, Journal of Psychoactive in Singh, D., "Traditional and non-traditional uses of *mitragynine* (kratom): A survey of the literature," 2016, Brain Research Bulletin.

132. A 2007 survey[154] conducted in Thailand noted that some 378,000 people had used kratom in the 12 months prior to the study with 264,000 people using it within 30 days prior to the study and more than 1 million using kratom in their lifetime. However, only a tiny number reported serious side effects from kratom compared to the hundreds of thousands who had used it. While this may be suggestive of benign health effects, it should be noted that possession of kratom is now illegal in Thailand. Admission of use may result in punitive consequences. This is a clear deterrent to objective reporting and, thus, the actual number remains unknown.

133. The motivations for U.S. consumers to engage in kratom use vary widely, but the anecdotal evidence suggests that the majority of users do not appear to be primarily motivated by psychoactive indulgence. A recent survey[155] conducted by the United Kratom Association (an advocacy group) compiled answers to the question *"What was the primary issue that led you to kratom?"* **Figure 4** summarizes the responses of some 466 U.S. survey participants.

Figure 4: Survey Results of Stated Motivations to Use Kratom



[154] Thailand National Household Survey of Substance Use, 2007, in Assanangkornchai, S., et al., "Current situation of substance-related problems in Thailand," 2008, J Psychiatry Assoc., Thailand, Vol. 53 (Supplement 1), pg. 24S-36S.

[155] Jerue et al., "Kratom: A Collective Analysis," 2016, United Kratom Association.

134. Although the organization sponsoring the survey is not a peer-reviewed group, the results correspond closely to other similar surveys. If we accept this data, we can infer that the primary motivating factor for kratom use is an analgesic one as opposed to intoxication, thrill-seeking or other motivations commonly associated with hard drug abuse. Again, this is consistent with the motivations expressed by historic kratom users, particularly those in Thailand, Malaysia and other countries who have used kratom for beneficial purposes for centuries. It further suggests that the adverse health effects reported by a small percentage of survey respondents are generally perceived as outweighed by kratom's beneficial health effects.

135. The conclusion presented at the end of the book *"Kratom and Other Mitragynines"*[156] (Raffe, et. al., 2015) cited the potential for both beneficial and adverse health effects and the urgent need for further study:

> "The available information suggests that kratom is being used extensively for its psychoactive effects. Kratom and its alkaloids might be potentially useful for the management of opioid withdrawal symptoms. However, like almost all psychoactive substances, it has the potential to be addictive. Kratom has been reported to produce dependence, especially at the doses and frequency of use in Southeast Asia, where it is readily available and cheap. Further studies to support the efficacy of kratom for managing opioid withdrawal symptoms, safety and its addiction potential are warranted."

136. A 2015 Florida Department of Law Enforcement (FDLE) drug report which examined the extent to which kratom has impacted public safety in the state of Florida[157] concluded that kratom does not currently constitute a significant risk to the safety and welfare of Florida residents. The report cites that the Florida Department of Health has found that there are no pervasive health issues that can be attributed to the ingestion of kratom products in Florida. A 2014 memo[158] from the Broward County Commissioner initiating the report noted:

> "Proponents of the drug point to its use as an analgesic for centuries. It is also purported to effectively manage diarrhea, anxiety and attention deficit. Advocates cite concerns that pharmaceutical companies (which have pursued developing and marketing synthetic versions of the drug over the last fifty years) may be engendering health concerns and encouraging regulatory actions of kratom to limit competition with pharmaceutically-manufactured products."
>
> "Opponents of the drug point to evidence of dependency and questions as to its safety, especially when combined with other drugs/substances. (For example, at least one scientifically-verified instance of a user suffering a seizure after ingesting kratom, an instance where a death was associated with ingestion of Kratom in Denver, or other examples of

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[156] Raffe, R., et. al., "Kratom and Other Mitragynines: The chemistry and pharmacology of opioids from a non-opium source," 2015, CRC Press, Taylor and Francis Group, pg. 9-21.

[157] "House of Representatives Staff Analysis", Bill # HB73, Controlled Substances, 2015.

[158] "Memo to Board of County Commissioners," Bertha Henry, County Administrator, October 24, 2014.

adverse reactions in combination with other substances.) While a suicide reported in Palm Beach County was associated with the use of kratom, other drugs were found in the person's bloodstream; of significance, gabapentin and citalopram (commonly known as Celexa), both of which warn of suicidality and clinical worsening of depression as potential side effects."

F. Summary and Conclusions

137. Although political, cultural and economic agendas undoubtedly exist with respect to kratom, they are unacceptable substitutes for objective toxicological evidence. However, the quantity of generally-accepted, peer-reviewed toxicological literature at this time is somewhat limited. Nonetheless, it is sufficient to determine that kratom is not lethal in animal studies and that human fatalities are extremely rare (if ever) from pure kratom use. The toxicokinetic and pharmacokinetic aspects of kratom use, both singly and in combination with other drugs, has been assessed in animal models and, to a limited extent, in humans. Thus, rendering an objective assessment to *reasonable toxicological certainty* involves interpreting the available studies and comparing them with the anecdotal data to determine which (if any) attributes can be found to be consistent among both sources of information.

138. The objective toxicological evidence in this matter is supported by substantial documentation originating with multiple sources of authority and corroborated by multiple studies. It is both toxicologically relevant and demonstrative in that:

- High kratom doses have not been reported to cause lethality in the toxicological literature; respiratory depression deaths have not been demonstrated with kratom and the pharmacological mechanisms of action of kratom are protective against respiratory depression as compared to that of opiates.
- The TOXNET data network documents no deaths attributable solely to kratom.
- There is no generally-recognized or well-defined toxic dose.
- There is a lack of standardization in product types and alkaloid potency.
- Kratom, in pure leaf herbal form, with no drugs-of-abuse present and at moderate to high doses of less than 10 to 15 grams, is benign based upon the above studies and large population of users.
- The currently available objective toxicological evidence is insufficient to support claims of kratom addiction at moderate to high doses.
- Dependence, as referenced in the Singh study, was supported among subjects who consumed an "average" of 276.5 mg of *mitragynine* per day - the equivalent of 325 kratom leaves per day. Thus, the risk of abuse, dependence or addiction only corresponds to extremely high dosing for long durations as in Thailand where abundant sources of leaves are available – not a reasonable occurrence in the U.S.

139. It appears that only *concentrated mitragynine* extract (a radically different acting substance than that of the combined 20 kratom alkaloids in the herbal supplement product) has significant and quantifiable toxicological potential. Thus, an objective toxicological risk assessment (which identifies and quantifies potential chemicals of concern) must treat *mitragynine* as a separate component from that of the substance of concern (kratom).

140. The above referenced, recent, receptor-based study of Kruegel, et al., (2016) has also clearly distinguished the mixture of kratom alkaloids with different properties as compared to that of opiates.

141. A newly published comprehensive review by Prozialeck (released in the December 2016 edition of The Journal of the American Osteopathic Association)[159] was designed to highlight the current scientific and legal controversies regarding kratom. This review concluded that "*After evaluating the literature, I can reach no other conclusion than, in pure herbal form and when taken at moderate doses of less than 10 to 15 grams, pure leaf kratom appears to be relatively benign in the vast majority of users*."

142. Based on the totality of currently available information, it is my opinion to reasonable toxicological certainty that there is insufficient toxicological evidence at this time to support a Schedule I classification banning the sale, use or possession of kratom.

[159] Prozialeck, WC, "Update on the pharmacology and legal status of kratom," 2016, The Journal of the American Osteopathic Association, Vol. 116, pgs. 802-809.

Further the affiant saith not.

William R. Sawyer, Ph.D., D-ABFM

Chief Toxicologist

SWORN TO and SUBSCRIBED before me by WILLIAM R. SAWYER on November 30, 2016, to certify which witness my hand and official seal.

NOTARY PUBLIC STATE OF FLORIDA
JEANNE VAUGHN
MY COMMISSION # FF947210
EXPIRES: February 23, 2020

Notary Public in and

For the State of Florida

Attachment A: Curriculum Vitae of William R. Sawyer

Curriculum Vitae
William Robert Sawyer
March 2016

Introduction

Dr. William Sawyer is a professional toxicologist with a doctorate in toxicology from Indiana University School of Medicine. He is a diplomate of the American Board of Forensic Medicine with more than 28 years of experience in public health and forensic toxicology including five years of governmental service. His specialized areas of expertise include causation analyses (defendant, plaintiff or criminal), dioxins, solvents, heavy metals, petroleum, crude oil, radionuclides/NORM, alcohol toxicology, drugs-of-abuse, pharmaceuticals, herbal products and other substances.

Contact Information

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Sanibel, Florida 33957

Toxicology Consultants & Assessment Specialists, LLC (*TCAS, LLC*)
29 Fennell Street
Skaneateles, New York 13152

Telephone: 800-308-0080
239-472-2436 (FL)
315-685-2345 (NY)

E-mail**:** drsawyer@experttoxicologist.com

Education

Indiana University School of Medicine 1983 - 1988
Indianapolis, Indiana
Robert B. Forney, Ph.D., Committee Chairman
Ph.D., Toxicology, 1988

State University of New York at Geneseo 1979 -1982
Edward Ritter, Ph.D., Committee Chairman
Master of Science degree, Cellular & Molecular Biology, 1982

State University of New York at Geneseo Bachelor of Science degree, Biology, 1978	1976 -1978
State University of New York Agricultural and Technical College at Morrisville Associate degree, 1976	1974 -1976

Experience

As a scientist and communicator in forensic toxicology, Dr. Sawyer provides services to governmental agencies, corporations, investigators and select defendants or plaintiffs. Dr. Sawyer currently serves as chief toxicologist for Toxicology Consulting and Assessment Specialists, LLC. He has served for 23 years as an assistant professor (adjunct) with the Department of Medicine, Upstate Medical University, Syracuse, New York. Dr. Sawyer also has approximately 14 years of experience as a licensed clinical and environmental laboratory director in several states.

Dr. Sawyer routinely provides impartial toxicological evaluations involving chemical exposures, alcohol ingestion, intentional poisonings, carcinogens, pharmaceuticals, pyrolysis products, heavy metals, organic chemicals and drugs-of-abuse in civil and criminal litigation. Toxic exposure investigations include analytical protocol, referral of autopsy material for analyses, environmental and occupational health risk assessments and site assessment and causation determination. Final work products that include scientific methods and validation, forensic documentation and written reports used on both forensic and routine (non-judicial) assessments are provided to multiple, nationwide clients.

Forensic Environmental and Laboratory Analyses

Through education, training and experience, Dr. Sawyer has gained extensive expertise in forensic petroleum analyses as well as environmental and clinical forensic analyses. With more than 23 years of laboratory experience, Dr. Sawyer has directed laboratory analyses, sampling protocol and chain-of-custody documentation in criminal and civil matters. He has also provided petroleum spill assessments to multiple clients including governmental environmental agencies (NYSDEC), various state attorney general offices (New York), defense and plaintiff law firms and industry. Petroleum spill and exposure

assessment reports have provided objective evidence of characterization, age and source within reasonable scientific certainty.

Professional Experience

Chief Toxicologist 1990-Present
Toxicology Consultants & Assessment Specialists, LLC
Sanibel, Florida
Registered, DBA, 1990
Incorporated, January, 1994 (New York)
Limited liability corporation, January 2009 (Florida)

Peer Reviewer 1998-Present
Editorial Advisory Board for the "The Forensic Examiner"

Assistant Professor (adjunct) 1988-2012
SUNY Upstate Medical University
Department of Medicine
Syracuse, New York

Laboratory Director 1993-2002
EXPRESSLAB, Inc. (Lozier Laboratories)
Middlesex, New York

- NYSDOH Clinical License #SAWYW1 (1988-2000)
- NYS Environmental License (ELAP) #11369
- National Environmental Laboratory Accreditation Program (NELAP) #11369
- New Jersey DEPE License #73744
- South Carolina License #9101100
- California Environmental License

Associate Editor 1997-2000
Practical Reviews in Forensic Medicine & Sciences
Published by Oakstone Medical Publishing, Inc.
Jointly sponsored by Albert Einstein College of Medicine
and Montefiore Medical Center; CME
(continuing medical education) accredited

Toxicologist 1988-1993
Onondaga County Department of Health
Syracuse, New York

Responsible for municipal and civil risk assessment, evaluation of environmental exposures and design and execution of environmental monitoring studies. Advise and communicate with the Office of the Environment/County Executive and legislative subcommittees with respect to public health and environmental health issues. Established a clinical and environmental toxicology laboratory licensed under the NYS DOH and NYS ELAP agencies (NYSDOH #SAWYW1 and NY ELAP license #10183)

Licensed Laboratory Director 1988-1993
Onondaga County Department of Health
Syracuse, New York
Licensed clinical laboratory, chlorinated hydrocarbons (NYS CLEU)
NYS License #SAWYW1
Assistant Director
NYS ELAP License #10183

Analytical Toxicologist (part-time) 1983-1988
State Department of Toxicology
Indianapolis, Indiana

Laboratory Technician (part-time) 1979-1983
Clinical Research Center
(National Institute of Health)
Strong Memorial Hospital
Rochester, New York

Laboratory Technician (part-time) 1979-1983
Highland Hospital
Special Determinations Laboratory
Rochester, New York

Certifications

Board Certification
Diplomate, American Board of Forensic Medicine (D-ABFM) — 1996-Present

Board Certification
Diplomate, American Board of Forensic Examiners (D-ABFE) — 1994-Present

OSHA 29 CFR1910.120 — Re-certified December 2004
Hazardous Waste Operations & Emergency Response
40 hour certified

Clinical Laboratory Director — Inactive
New York State Department of Health
Certificate of Qualification
License Code #SAWYW1

Environmental Laboratory Director — Inactive
New York State Department of Health
ELAP License #11369
ELAP License #10183

South Carolina Department of Health — Inactive
Environmental Laboratory Director
ELAP License #9101100

New Jersey DEPE Laboratory Director — Inactive
License #73744

Asbestos Inspector — Inactive
EPA Certificate #10-111-50-1303

Societies and Honors

Sigma Xi, The Scientific Research Society — 1986- Present
Associate Member

American College of Forensic Examiners Member	1995-Present
National Myositis Association Medical Advisory Board Member	1995-1997
American Academy of Forensic Sciences Member, promoted to Fellow, 1998	1985-Present
Society of Automotive Engineering Member	1986-Present
International Association of Forensic Toxicologists Member	1985-Present
Sigma Xi Research Competition Fifth place	1987
Sigma Pi Alpha Scholastic Honor Society Academic Award	1984

Professional Presentations

Sawyer, W.R. and Rigle, D.A., Featured continuing medical education credit workshop (2.00 credit hours) entitled, “Fundamentals of Medical Toxicology,” Annual Scientific Meeting of The American College of Forensic Examiners, American Board of Forensic Medicine, Las Vegas, Nevada, October 24 – October 27, 2000.

Sawyer, W.R. and Rigle, D.A., Featured continuing medical education credit workshop (3.75 credit hours) entitled, “Forensic Medicine Toxicology,” and “Reactive Airways Dysfunction Syndrome (RADS),” Annual Scientific Meeting of The American College of Forensic Examiners for the American Board of Forensic Medicine, New York, New York, October 29 - November 1, 1999.

Sawyer, W.R. and Rigle, D.A., “The Medical Aspects of Toxic Exposure Assessments,” Annual Scientific Meeting of The American Board of Forensic Medicine and The American College of Forensic Examiners, Naples, Florida, October 12-14, 1998.

Sawyer, W.R. and Rigle, D.A., “Evaluating Toxic Exposures after Daubert," Featured presentation at the 4th Annual National Expert Witness & Litigation Seminar, Hyannis, Massachusetts, June 23, 1995.

Articles, Abstracts, Treatises and Editorial Publications

Sawyer, W.R. *"Alcohol Content of Beer and Malt Beverages: Forensic Considerations,"* (Special Article Review Presentation, Critical Assessment and Original Abstract), Practical Reviews in Forensic Medicine and Sciences, Vol. 2., No. 6, February 2000, Oakstone Medical Publishing, Inc. from Logan, B.K., et al., Journal of Forensic Sciences, November 1999, Vol. 44, No. 6, pg. 1292-1295.

Sawyer, W.R. *"Fulminant Liver Failure in a Young Child Following Repeated Acetaminophen Overdosing,"* (Special Article Review Presentation, Critical Assessment and Original Abstract), Practical Reviews in Forensic Medicine and Sciences, Vol. 2., No. 6, February 2000, Oakstone Medical Publishing, Inc. from Bauer, M, et al., Journal of Forensic Sciences, November 1999, Vol. 44, No. 6, pg. 1299-1303.

Sawyer, W.R. *"Exposure to Contaminated Milk Presents 'Difficult Case' for Application of Daubert Reliability Standard,"* (Special Article Review Presentation, Critical Assessment and Original Abstract), Practical Reviews in Forensic Medicine and Sciences, Vol. 2., No. 4, December 1999, Oakstone Medical Publishing, Inc. published in Expert Testimony, Evidence, & Trial Consultants, October 1999, Vol. 7, Issue 10, pg. 3.

Sawyer, W.R. *"The Extent of Postmortem Drug Redistribution in a Rat Model,"* (Special Article Review Presentation, Critical Assessment and Original Abstract), Practical Reviews in Forensic Medicine and Sciences, Vol. 2., No. 4, December 1999, Oakstone Medical Publishing, Inc. from Hilberg, M.D., et al., Journal of Forensic Sciences, September 1999, Vol. 44 No. 5, pg. 956-62.

Sawyer, W.R. *"Potassium Nitrite Reaction with 11-Nor-Delta9-Tetrahydrocannabinol-9-Carboxylic Acid in Urine in Relation to the Drug Screening Analysis,"* (Special Article Review Presentation, Critical Assessment and Original Abstract), Practical Reviews in Forensic Medicine and Sciences, Vol. 2., No. 3, November 1999, Oakstone Medical Publishing, Inc. from Lewis, S.A., Journal of Forensic Sciences, September 1999, Vol. 44 No. 5, pg. 951-55.

Sawyer, W.R. *"GC/Mass Spectrometry Data from Fire Debris Samples: Interpretation and Application,"* (Special Article Review Presentation, Critical Assessment and Original Abstract), Practical Reviews in Forensic Medicine and Sciences, Vol. 2., No. 3, November 1999, Oakstone Medical Publishing, Inc. from Wallace, J.R., Journal of Forensic Sciences, September 1999, Vol. 44, No. 5, pg. 996-1012.

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Personal Information

Dr. Sawyer is a member of the Gulf Coast Swim Team as a distance swimmer and completed several "*Swim Around Key West"* 12.5 mile ocean swim races in under six hours. He is also a triathlete with the distinction of being a four-time Ironman. He loves to fish and SCUBA dive in northern New York State and the Gulf of Mexico.

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Citizenship:	United States
Marital Status:	Married, 1989

Attachment B: Kratom Studies and References

Attachment B: Kratom Studies and References

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Attachment C: Redacted Autopsy Report

Coastal Pathology Associates, P.A.

317 Western Boulevard
P.O. Box 1358
Jacksonville, NC 28546
Tel. 910-353-3498 Fax 910-577-2242

AUTOPSY REPORT

Decedent: [redacted]
Age: 44

Autopsy Number: [redacted]
Date Performed: [redacted]
Time: 1030

Gender: M
Race: CA

Medical Examiner Authorization: DENNIS NICKS, MD, ME

County Received From: NEW HANOVER

Body Identified By: ID – BAND ON RIGHT ANKLE

Present At Autopsy: OLIVER ROBERTS, DIENER

Prosector: FRANK J. BROWN, MD

FINAL PATHOLOGIC DIAGNOSIS

1. AUTOPSY FINDINGS INCLUDE DILATED CARDIOMEGALY.
2. DECEDENT HAS REPORTED DRUG ADDICTION.
3. TOXICOLOGY SHOWED MITRAGYNINE AND CAFFEINE PRESENT.

CAUSE OF DEATH

MITRAGYNINE TOXICITY.

EXTERNAL DESCRIPTION

BODY CONDITION: INTACT

LENGTH: (INCHES) 74

WEIGHT: (POUNDS) ESTIMATED 240

BODY HEAT: COLD

RIGOR: 2+

LIVOR: POSTERIOR

The facts stated herein are correct to the best of my knowledge and belief.

[redacted] [redacted]

AUTOPSY REPORT(Continued)

HAIR: RED/BROWN

EYES: BLUE

TEETH: NATURAL

FACIAL HAIR: BEARD AND MOUSTACHE

EXTERNAL GENITALIA: CIRCUMCISED

TATTOOS: NONE

SCARS: NONE

JEWELRY/VALUABLES: NONE

CLOTHING: BLACK T-SHIRT, BLACK BELT, UNDERWEAR AND SHORTS.

MISCELLANEOUS: THIS WAS A 44 YEAR OLD WHO IS REPORTED TO HAVE POSSIBLE OVERDOSE. THERE WAS A HISTORY OF DRUG ADDICTION. PUNCTATE ON LEFT ARM.

EVIDENCE OF INJURY

NONE

EVIDENCE OF MEDICAL ATTENTION

NONE

ADDITIONAL PROCEDURES

PHOTOGRAPHS: NONE.

RADIOGRAPHS: NONE.

MICROBIOLOGY: NONE.

CHEMISTRY: PERIPHERAL AND CENTRAL BLOOD, URINE AND LIVER IS SENT TO THE OCME REQUESTING ETHANOL, LCMS, BASES AND XANAX.

EVIDENCE COLLECTED: NONE.

DISPOSITION OF EFFECTS: CLOTHING DISCARDED.

INTERNAL EXAMINATION

SEROUS CAVITIES: THERE IS NO APPRECIABLE FLUID WITHIN THE ABDOMINAL OR PLEURAL SPACES.

PLEURA: SMOOTH AND UNREMARKABLE.

PERITONEUM: UNREMARKABLE.

PERICARDIUM: UNREMARKABLE.

The facts stated herein are correct to the best of my knowledge and belief.

[redacted] [redacted]

AUTOPSY REPORT(Continued)

HEART: THE HEART WEIGHS 740 GRAMS AND THE CORONARY ARTERIES ARE STENOTIC AS FOLLOWS: RIGHT CORONARY ARTERY, LEFT ANTERIOR DESCENDING AND CIRCUMFLEX IS 0 TO 10% STENOTIC. ON SECTION, THE MYOCARDIUM HAS SOME AREAS OF PALENESS. THE LEFT VENTRICULAR WALL MEASURES 1.8 CM. THE RIGHT VENTRICULAR WALL MEASURES 0.7 CM. THE HEART IS DILATED WITH THE CHAMBERS OF THE RIGHT AND LEFT VENTRICLE WITH GREATER THAN 6.0 CM IN DIAMETER.

LUNGS: THE RIGHT LUNG WEIGHS 1,100 GRAMS AND THE LEFT LUNG WEIGHS 960 GRAMS.

LIVER: THE LIVER WEIGHS 3,720 GRAMS AND THE CAPSULE IS SMOOTH AND INTACT. IT IS UNREMARKABLE ON SECTION. THE GALLBLADDER IS UNREMARKABLE. NO GALLBLADDER STONES ARE PRESENT.

SPLEEN: THE SPLEEN WEIGHS 440 GRAMS AND IS UNREMARKABLE ON SECTION.

PANCREAS: UNREMARKABLE.

ADRENAL GLANDS: UNREMARKABLE.

GI TRACT: THE GASTROINTESTINAL TRACT IS PROPERLY ARRANGED. AN APPENDIX IS PRESENT. THE STOMACH IS WITHOUT PILL FRAGMENTS.

KIDNEYS: THE KIDNEYS WEIGH 400 AND 420 GRAMS. THE CAPSULES STRIP EASILY. THEY ARE UNREMARKABLE ON SECTION.

BLADDER: THE BLADDER IS FULL.

INTERNAL GENITALIA: NOT VISUALIZED.

NECK ORGANS: THERE IS NO EVIDENCE OF TRAUMA ON DISSECTION OF THE NECK. THE LARYNX AND HYOID BONE ARE INTACT. THE POSTERIOR OROPHARYNX IS UNOBSTRUCTED. THE THYROID GLAND IS UNREMARKABLE ON SECTION.

BRAIN AND MENINGES: THE BRAIN WEIGHS 1,620 GRAMS AND THE MENINGES ARE CLEAR. THERE IS NO EVIDENCE OF HEMORRHAGE, NEOPLASIA OR INFECTION ON SECTION.

SKULL: INTACT.

VERTEBRAE: INTACT.

RIBS: INTACT.

PELVIS: INTACT.

FJB:MF 8/3/15

MICROSCOPIC EXAMINATION

CORONARY ARTERIES: MILD STENOSIS OF CORONARY ARTERIES PRESENT.

The facts stated herein are correct to the best of my knowledge and belief.

[redacted] [redacted]

AUTOPSY REPORT(Continued)

HEART: SCATTERED FIBROSIS IS SEEN IN LEFT AND RIGHT VENTRICLE WALLS.

LUNGS: DEGENERATION IS PRESENT. NEGATIVE FOR MALIGNANCY.

LIVER: NEGATIVE FOR MALIGNANCY.

SPLEEN: DEGENERATION IS PRESENT. NEGATIVE FOR MALIGNANCY.

PANCREAS: AUTOLYSIS IS PRESENT.

ADRENAL GLANDS: DEGENERATION IS PRESENT. NEGATIVE FOR MALIGNANCY.

KIDNEYS: DEGENERATION IS PRESENT. NEGATIVE FOR MALIGNANCY.

BRAIN AND MENINGES: NEGATIVE FOR MALIGNANCY.

THYROID GLAND: DEGENERATION IS PRESENT. NEGATIVE FOR MALIGNANCY.

SUMMARY AND INTERPRETATION

THIS WAS A 44 YEAR OLD WHO PASSED AWAY ON 8/1/15 AND WAS FOUND AT HOME. HE WAS REPORTED TO HAVE DRUG ADDICTION. AUTOPSY FINDINGS INCLUDE DILATED CARDIOMEGALY. TOXICOLOGY SHOWED MITRAGYNINE PRESENT IN LIVER (6.2 mg/kg) AND IN THE FEMORAL VESSEL (1.1 mg/L). 7-HYDROXYMITRAGYNINE IS ALSO PRESENT IN THE FEMORAL VESSEL. IN THE AORTA, CAFFEINE IS ALSO DETECTED. CASE DISCUSSED WITH DR. WINECKER.

IN MY OPINION, THE CAUSE OF DEATH IS MITRAGYNINE TOXICITY.

FJB:MF 12/1/15
Signed By: <signature on file> Frank Brown 12/02/151751

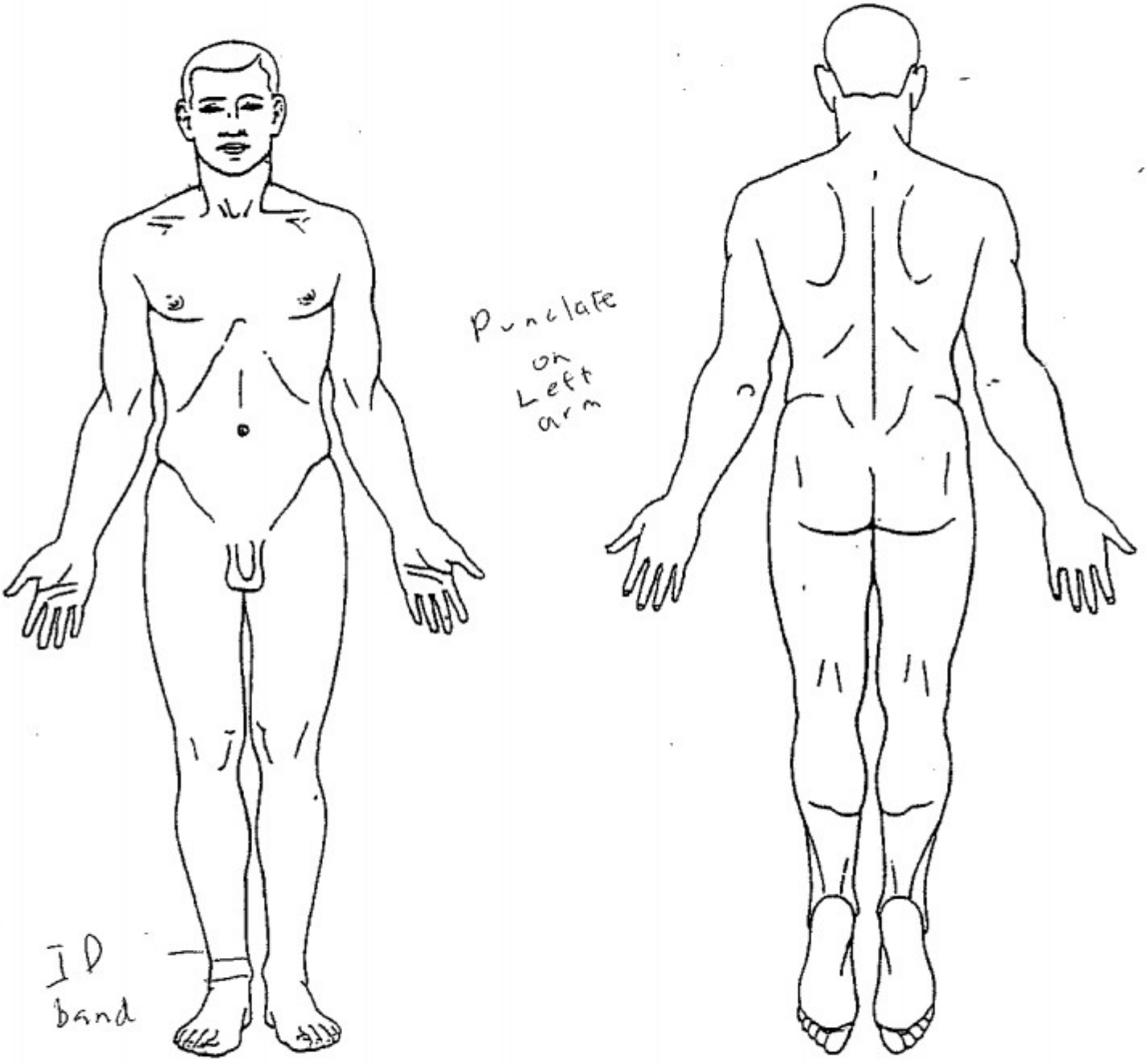
The facts stated herein are correct to the best of my knowledge and belief.

Confidential Business Information

OFFICE OF THE CHIEF MEDICAL EXAMINER

[redacted]

FRONT BACK



[redacted]

AUTOPSY NUMBER: _____ DECEDENT: _____

[redacted]

EXAMINED BY: _____ DATE: _____