

Written Summary of Oral Testimony for the State of Wisconsin Controlled Substances Board
August 14, 2015

Jack E. Henningfield, Ph.D.

Vice President for Research, Health Policy and Abuse Liability, Pinney Associates

Adjunct Professor of Behavioral Biology, The Johns Hopkins University School of Medicine

Focus of Testimony: Factors Related to the Relative Abuse Potential of *Mitragyna Speciosa* (Kratom) and Mitragynine in the form of VivaZen

Thank you for the opportunity to comment. I am Jack E. Henningfield, Vice President for Research, Health Policy and Abuse Liability at Pinney Associates, and Adjunct Professor of Behavioral Biology at The Johns Hopkins University School of Medicine. I have been involved in the assessment of the abuse and dependence potential of substances since my undergraduate employment and then fellowship in the Psychopharmacology Training Program at the University of Minnesota, in the early 1970s, then at The Johns Hopkins University School of Medicine, and National Institute on Drug Abuse since 1978, and as a consultant to pharmaceutical developers since the 1990s. Much of this work involves assessing the abuse potential and public health risks and benefits of drugs to help sponsors and the Food and Drug Administration (FDA) develop the most appropriate recommendations and policies concerning the most appropriate regulatory approaches for legally marketed products.

I have been invited by United Naturals to comment on the pharmacology of their marketed dietary supplement, VivaZen, and its most appropriate regulation. The opinions I present today are my own and have emerged in collaboration with my colleagues at Pinney Associates, most notably, Edward Cone, Ph.D. and Reginald Fant, Ph.D. Our initial assessment of the abuse potential of VivaZen is summarized in this written testimony. My oral testimony will summarize this assessment, focusing on our conclusions and recommendations. I will be pleased to take questions to further discuss our opinions on additional background provided in the written testimony.

My group at Pinney Associates reviewed many of the recent studies and other publications related to the abuse potential and toxicity of *Mitragyna speciosa* (also known as kratom), and its most abundant alkaloid, mitragynine (MG), and the relevance of those data to the doses found in the dietary supplement VivaZen. This included a preliminary assessment of another major alkaloid of kratom, 7 α -hydroxy-7H-mitragynine (7-OH MG); however, since 7-OH MG is not present in VivaZen, our focus was on MG. 7-OH MG is a minor constituent of kratom leaves (2.0% based on the crude base, (Ponglux et al. 1994), and its antinociceptive activity of 7-OH-MG has been estimated to be approximately 40-fold more potent than MG.

We concur with major conclusions of several other recent reviews including those summarized in the book "Kratom and Other Mitragynines," published in 2014, edited by Robert B. Raffa, Ph.D., Professor of Pharmacology in the Department of Pharmaceutical Sciences at Temple University School of Pharmacy. In brief, *Mitragyna speciosa* is a tropical deciduous tree within

the coffee family (Rubiaceae) that is indigenous to Southeast Asia, particularly Thailand, Malaysia, Indonesia, Philippines, and Vietnam. Consumption of kratom is common in these Southeast Asia countries due to its abundance and effects regarded to be generally beneficial. In this region, kratom leaves are commonly chewed, used to make tea, or concentrated into an extract for addition to other beverages. It is occasionally smoked, however, the relatively low potency of leaf material may be a factor that discourages this route (and nasal insufflation) as common routes of administration.

Effects are dose-related, generally mildly stimulant-like at lower active doses and more sedative/opioid-like at higher dosages (Raffa, 2015; see also the European Monitoring Center on Drugs and Addiction (<http://www.emcdda.europa.eu/publications/drug-profiles/kratom>)). In Southeast Asia kratom and its extracts have been used for decades to provide relief of pain, counteract work-related fatigue, for fever reduction, diarrhea, coughing, hypertension, depression, and as a treatment for opiate withdrawal. The pharmacological basis for these effects appears in part due to partial mu opioid agonist activity of MG and 7-OH MG. Although dependence is reported, overdose, death and serious adverse events appear rare in Southeast Asia, despite widespread use, and ready access to the natural plant material and various manufactured preparations.

VivaZen.

United Naturals currently markets a dietary supplement called VivaZen which contains *Mitragyna speciosa* leaf extract, also known as kratom. The VivaZen formula is based on a specific traditional use of *Mitragyna speciosa*. Traditionally Southeast Asia laborers have used small quantities of kratom throughout the workday for the energizing and pain-relieving (minor aches and pains) effects. Kratom has been safely consumed as dietary supplement and folk remedy in Southeast Asia for centuries (Tanguay, 2011). It generally is consumed orally, either by chewing fresh leaves or as a brewed tea, specifically for the benefits derived from the bioactive alkaloids. VivaZen contains a standardized extract of kratom that is qualitatively and quantitatively similar in terms of the biologically-active alkaloid constituents of a single serve of the traditional kratom tea (but less than the average traditional daily consumption levels reported in the literature).

Kratom contains two primary alkaloids that have been shown to have opioid activity. The first, more potent, alkaloid is 7-hydroxymitragynine¹. However this substance is not present in VivaZen at detectable levels, and therefore does not present a safety concern. The second alkaloid is mitragynine (MG), which is 40 times less potent than 7-hydroxymitragynine at the mu opioid receptor. MG can make up as much as 2/3 of the alkaloid content of kratom leaf (Hassan et al., 2013), and appears in VivaZen at a dose of about 45 mg/serving (currently one bottle). VivaZen is formulated as a two-ounce liquid dietary supplement. The format as a 2-oz.

¹ 7 α -hydroxy-7H-mitragynine (7-OH MG) is a minor constituent (2.0% based on the crude base (Ponglux et al. 1994)) of the leaves. However, the antinociceptive activity of 7-OH-MG is approximately 40-fold more potent than mitragynine and approximately 10-fold more potent than morphine (Matsumoto et al. 2004).

liquid limits the number of servings that can be consumed. Specifically, whereas it might be possible to take 100 servings in capsule format, consuming 200 oz. of a bitter liquid would be very challenging.

Safety, abuse and dependence.

Many kratom-based preparations are available in the United States and used with little evidence of dependence or serious adverse events and no documented kratom-caused overdose deaths. Moreover, a preliminary assessment of major national substance abuse related surveillance systems reveal little evidence of abuse in youth (e.g., University of Michigan, National Institute on Drug Abuser Monitoring the Future Survey), adults (e.g., the Substance Abuse and Mental Health Services Administration's National Survey on Drug Use and Health), in persons with substance use disorders and dependence who are seeking treatment (e.g., Treatment Episodes Data Set).

This is a remarkable record of safety and low abuse risk for any substance used by millions of Americans, as described by other witnesses in this hearing, and it is especially remarkable for a substance with some opiate-like pharmacological activity. However, the low apparent real world abuse and dependence potential and its excellent safety record are consistent with findings from scientific studies of its abuse potential and descriptions of its use and effects on internet websites and discussion groups by users.

Basic research relevant to abuse and dependence assessment.

Research relevant to assessment of the abuse and dependence potential has been increasing in recent years. This primarily involves animal models but some human research has also been conducted. These studies provide a basis for estimating the relative potency of kratom containing products such as VivaZen. In this regard it is important to keep in mind that the primary active alkaloid in VivaZen is approximately 45 mg of MG. MG has been estimated to be approximately 3% bioavailable when taken by the oral route.

Safety and toxicology of kratom and mitragynine.

An analysis of serious adverse events and deaths by United Naturals demonstrates a very strong safety profile. SAEs were identified from the literature, by a review of the American Association of Poison Control Centers (AAPCC) Annual Reports (from 1999 through 2013), and by a FDA FOIA request initiated by a third party.

Globally fewer than 100 SAEs, primarily from Southeast Asia, have been reported including kratom consumption. For perspective, it should be considered that kratom use is quite high in Southeast Asia, with likely over 1 million regular adult users in Thailand alone. A careful review of the case reports indicates that in most cases other causes, especially co-administered chemical substances or drugs, were likely responsible.

In a study of 149 long-term regular users of kratom (who chewed the leaves) in Thailand, the percentage of users reporting the negative effects of using kratom was relatively low (4–14% of all users) (Assanangkornchai et al., 2007). The negative effects included a perception of less

productivity, a decreased sexual drive, fatigue, poor health, wasteful spending habits, dizziness, poor concentration and distractedness, difficulty sleeping, wasting working time, irritability, poor thinking ability, impaired memory, laziness, and social withdrawal. The perceived benefits of kratom use included helping users work longer and harder, feeling happy/sprightly, maintaining a good mood, sleeping soundly, and being healthy.

There were 14 deaths reported globally. Of these 9 (in Sweden) appear to have been related to use of an herbal blend called Krypton that was adulterated with O-desmethyltramadol, an active metabolite of the analgesic drug tramadol (Backstrom et al., 2010). The other five, three in the US, one in Norway, and one in Thailand, included co-administration of other drug substances. To date, there have been no reports of fatal overdose from kratom *per se*. (Raffa, 2014, and references cited therein). Although, there has been little systematic study of the pharmacodynamic effects of kratom, there is little evidence of respiratory depression and this would be consistent with the absence of documented overdose deaths attributable to kratom.

The safety of low doses of MG has also been evaluated in animal toxicology studies. Hassan and colleagues (2013) reviewed the data on the toxicology of MG as follows: In animal models, the toxicity of MG was claimed to be relatively low. Macko and colleagues (1972) found no evidence of toxicity, measured as tremors or convulsions, at doses as high as 920 mg/kg in dogs. However, a more recent study in rats reported lethal effects of 200 mg/kg total alkaloid extract of *M. speciosa* (Azizi et al., 2010). Janchawee and colleagues (2007) reported lethal effects after an oral dose of 200 mg MG in rats.

Sabetghadam and colleagues (2013) administered three doses of MG (1, 10, 100mg/kg, p.o.) to rats for 28 days respectively. The groups of rats treated with the lower and intermediate doses showed no toxic effects during the study. Only relative liver weight increased after treatment with the high dose of MG (100mg/kg) in both the male and female treatment groups of rats. Biochemical and hematological parameters were also altered especially in high dose treatment group which corresponds to the histopathological changes. It should be noted that 100 mg/kg would equate to 7,000 mg in a 70 kg human, which would be a level extremely high to reach with VivaZen at 45 mg per serving.

Internet monitoring.

The dramatic growth of the Internet in the past 20 years has substantially changed the dissemination of ideas, contributed to trends in product use and misuse, and added new means of monitoring such change. There are many websites that focus specifically on drug misuse and abuse, some intended to discourage such use as well as those that appear dedicated to providing information in support of, if not to encourage, misuse and abuse of drugs. An important limitation of the data is that they do not necessarily relate to incidence, prevalence, or to increases or decreases in population trends. For example, a single provocative posting might precipitate a series of postings (known as a “tread”) thereby creating a “bump” in the number of postings on a given topic which may not necessarily be related to population trends.

With the foregoing caveats in mind, and understanding that my team has not conducted an extensive evaluation of internet postings, the following provides representative examples of how serious substance abusing persons view kratom relative to their preferred substances.

Taken together, most of the postings involve what appear to be extremely high dosages of kratom substances and extracts, and self-made extracts from, for example several grams of kratom powder, several ounces of kratom leaves, and indeterminate forms. Some people have experienced intoxication, euphoria, and other effects at these very high dosages, though typically, their comparisons to other drugs provide a basis for understanding why kratom and kratom products apparently are rarely the substance of choice among people who seek abused drugs and are in search of better ways to get better highs and euphoria. There are self-reports of dependence and withdrawal, but these tended to involve extremely high intakes of kratom and apparently along with other substances.

Table 1 provides what my team's experience offers as a reasonable representation of kratom experiences.

Table 1. Verbatim accounts from Internet reports from a website that typically attracts people with histories of diverse substance use and abuse to describe their experiences
<http://www.bluelight.org/vb/threads/398307-Kratom-experiences!>

27-09-2008 03:28: *Here's my personal opinion, others have had better experiences: Kratom offers a pleasing buzz, but it only lasts about an hour. Then it's gone and I can't redose for another 12 or so hours. It just won't work again if I try to dose sooner. When I use it every day, the buzz gets less and less until it's practically worthless. Kratom just didn't do me very well. I hope you have a better experience with it.*

27-09-2008 04:28: *Kratom is somewhat self limiting when it comes to abuse, or daily recreational use, yes. Each day you use it, it becomes a bit less warm and less euphoric. But its pain relieving properties continue after those effects fade. Even after continued daily use there will always be noticeable anxiety relieving, and pain relieving properties. You can avoid losing some of the glow and euphoria by switching to different strains every so often.*

27-09-2008 08:15: *After LOVING oxy to death and losing my source, I sought out some Kratom to act as a substitute. If you're expecting something amazing, you will definitely be disappointed. It DOES feel like an opiate, kind of, but it's very very limited. I tried several strains in several different dosages, and yeah, it doesn't have that much to offer. Doing too much is awful - I felt nauseous for DAYS. Doing too little is just boring. There IS somewhat of a sweet spot but it just doesn't scratch where I itch, compared to oxy (and I never did that much oxy that frequently, and I hadn't in weeks before kratom, and so it's not just an addiction thing).*

28-09-2008 05:49: *Personally I like the taste of pod tea, the stronger the better. It's preferable to the odd taste of kratom (even though I will drink kratom tea straight as well). But Kratom has a numbing sensation on my mouth when I drink it, like pins and needles on the tongue. I've never really felt too much from kratom. I've had the so-called 10x extracts and the leaves, with the extracts I'd just down them with alot of water, and with the leaves just make some tea. I'd say that the effects were a bit stronger from the leaves, however. I had to use about 1/4 an ounce, which (if I remember correctly) was a few cups of tea...a french press would probably be even more effective, though. Subjectively the effects felt similar to a moderate dose of tramadol...especially the serotonergic wakefulness type of feeling. It was great for staving off withdrawals, but I couldn't see it being my drug of choice. After a certain point taking more kratom doesn't seem to increase or prolong the euphoria much. I'm willing to bet*

though that people who have never been addicted to opiates would enjoy this drug much more than those who are or have been.

28-09-2008 06:00: *"Yes the taste of Kratom tea is disgusting. Thats why tea is no-longer the preferred method of ingestion by Kratom users. We use TNW= puddle on tongue, plop kratom in, swallow, follow with water. You wont feel too much from kratom. Its very subtle for most. The extracts are usually unbalanced and stimulative, rather than relaxing and euphoric. You took far too many leaves. I did the same thing when I first tried Kratom. You only need 2-3 tea spoons. Taking too much will make you sick, or could even ruin the effects all together. I guess you can't really take it and then just forget you took it. You need to recognize the effects and focus on them to feel nice. And yes, Re-dosing Kratom is useless, you will feel nothing more. It may make the aroma last longer, but it wont increase the potency of the smell."*

Following is a summary our main conclusions.

- 1) Kratom, its extracts, and at least two alkaloids (MG and 7-OH MG) produce mixed pharmacological effects that are generally mild and stimulant-like at typical dosages. Consumption does not typically interfere with work or social activities and commitments, and in fact are widely reported in the U.S., as in Southeast Asia, to contribute to work productivity, quality of life, and social relationships.
- 2) The primary effects of kratom are likely predominantly produced by MG and 7-OH MG which have been characterized as partial mu opioid receptor activity including anti-nociception (pain relief), mild pleasurable effects, constipation at high doses but an apparent lower risk of constipation at typical levels of consumption as compared to opioids. Respiratory depressant effects appear substantially lower than those produced by opioids and this would be consistent with the absence of verified kratom caused overdose death.
- 3) MG (and hence kratom) can produce discriminative stimulant effects and reinforcement in rodents, however, these effects occur at doses that appear far higher than those commonly ingested by people in the United States.
- 4) The doses of MG required to produce discriminative stimulant effects and reinforcement in rodents are much higher than the doses that could be readily obtained from VivaZen. Specifically, a person would have to consume over 200 2-oz bottles of VivaZen to obtain the equivalent levels of MG that produced reinforcing effects in rodents. This is in contrast to many other consumer products, including dextromethorphan and nutmeg, in which it is relatively easy to consume enough doses to achieve a reinforcing and/or intoxicating effects effect.
- 5) Animal studies have demonstrated signs of physical dependence and withdrawal at what appear to be extraordinarily high dosages of MG, as compared to typical human use in the United States, and it is not clear that such doses could be practically achieved by consumption of a product such as Viva Zen. Specifically, laboratory rats were given 30 mg/kg/day i.p., equating to an oral dose of about 990 mg/kg. Thus, to obtain equivalent doses of MG that produce physical dependence in the animal models, a 70kg human might need to consume 1,540 bottles per day, presumably for several weeks, at a cost of more than \$10,000 per day. In fact, it is not known what the threshold is for production of physical dependence and withdrawal. However, while this might be theoretically

possible, the desirability of the effects would seem to make such a heroic effort extremely unlikely because the pleasure derived from consumption does not appear similar in magnitude to that produced by far less costly and readily available doses of typical substances of abuse including marijuana, alcohol, stimulants, sedatives, and opioids.

- 6) MG and kratom have very low toxicity, and thus a favorable safety profile. There have been few reports of serious adverse events or death associated with kratom. Documented deaths have all been either related to use of an herbal blend called Krypton that was adulterated with the narcotic O-desmethyltramadol, or included co-administration of other drug substances. To date, there have been no reports of fatal overdose from kratom *per se*.
- 7) Taking together basic research finding, available epidemiology, clinical observations, and anecdotal self-reports, it is clear that kratom and various preparations can cause physiological dependence and withdrawal and some degree of psychological dependence, however, in many respects, the factors that appear important in sustaining kratom use appear more similar to those that sustain dietary caffeine use, namely to better manage fatigue and daily life demands and provide mild effects considered enhancing to quality of life. Like caffeine, daily use can lead to dependence and withdrawal (as is more prevalent in Thailand and other Southeast Asia countries with heavier and more frequent consumption). In addition, the partial mu agonist activity of two alkaloids, MG and 7-OH MG, likely confer some degree of relief of at least minor pain, diarrhea, and coughing, and it is plausible that high dosages could provide some relief of symptoms of opioid withdrawal, however there has been little systematic study of such potential benefits that would meet the standards expected for approval of a pharmaceutical product.
- 8) VivaZen is a complex mixture of substances that provide product differentiation and may contribute to its reported benefits (e.g., helping users work longer and harder, feeling happy/sprightly, maintaining a good mood, sleeping soundly, and being healthy), and a small amount of kratom extract which is devoid of 7-OH MG due to a proprietary processing procedure. It is plausible that VivaZen provides mild effects, including benefits, attributable to kratom and MG, however, its low total content of kratom extract and of MG in particular, would limit the strength of its benefits. Of course these same limitations would also limit its ability to cause dependence, withdrawal, and direct effects often considered as factors in substance abuse and dependence, namely, reinforcement, euphoria, and intoxication. These attributes of the product, along with its specific labeling concerning use, and maximally recommended use would be expected to contribute to consumption with low risk of dependence, abuse, and other undesirable and unintended effects.

Comparisons with other consumer products and dietary substances that meet criteria for at least mild potential for dependence and abuse.

Although cross-drug class comparisons must be made with caution, such comparisons can be useful in drug scheduling decisions because they provide a real world perspective of relative actual risks, as well as insights that help understand why a relatively small number of the many

potentially abuseable and dependence producing substances actually lead to widespread abuse, dependence, and associated public health problems. In assessing the abuse potential of a particular product, it is important to consider the dose and route of administration. VivaZen is designed to be consumed via the oral route, and it is likely that it would be difficult to extract MG from the formulation without extensive experience in chemistry and access to laboratory equipment. In contrast, the rodent research cited in the section above administered the drug via the i.p. route. Oral absorption of MG is slow, prolonged and was incomplete, with a calculated absolute oral bioavailability value of 3.03% (Parthasarathy et al., 2010).

Herbs that are commonly used and sometimes abused for energy bursts include guarana and kola nut, both of which contain caffeine.

Poppy seeds are harvested from the opium poppy and contain a mixture of opium alkaloids (e.g., morphine, codeine, thebaine). Poppy seeds are used as foodstuffs in many parts of the world. Depending upon the seed source, harvesting practices, and washing procedures, the content of opium alkaloids in poppy seed is widely variable. A serving of poppy seeds (e.g., poppy seed bagel) may contain a few micrograms to a few milligrams. Some foodstuffs contain larger amounts of poppy seeds (strudel prepared with poppy seeds). In the US, there have been reports of individuals who consumed these products, testing positive for morphine in workplace drug testing program. Due to the variable alkaloid content in poppy seeds, it is not possible to estimate what a standard serving of poppy seeds contains in terms of morphine content.

Hemp seeds and oil are harvested from the cannabis plant and may contain tetrahydrocannabinol (THC), the psychoactive ingredient in cannabis material. Normally, the THC in these products are quite low, but some individuals have tested positive for THC metabolites following ingestion of these products, most notably, with hemp oil products. DEA regulation was recently instituted that specified the maximum content of THC in hemp oil allowed in the US.

It should also be noted that there are a variety of other herbal and consumer products that likely have some reinforcing effects, but are not subject to regulation related to abuse or toxicity. For example, nutmeg contains myristicin, a natural compound that can produce hallucinogenic effects if taken in doses of around five teaspoons. When taking large amounts of nutmeg, it may take hours for auditory hallucinations to occur. This could result in increased overdose risk if the user thinks they haven't taken enough.

There are a variety of herbs and products with sedative effects, some of which are included in very small amounts in VivaZen and these include the following:

- Chamomile
- Passionflower
- Ashwagandha
- Schisandra
- California Poppy
- Hops

- Kava Kava
- Lavender
- Lemon Balm
- St. John’s Wort
- Red Clover
- Catnip
- Valerian
- Motherwort
- Skullcap
- Poppy seeds
- Hemp seeds/oil

Relevance of Doses to Humans and VivaZen, and Equivalencies with Other Unscheduled Drugs.

The table below compares the number of units and cost that would be required to achieve the equivalent dose levels demonstrated to produce discrimination and reinforcement from several over-the-counter products. As shown, the MG dose found in VivaZen compares favorably to caffeine, dextromethorphan, diphenhydramine, and even “non-alcoholic” beer.

Note that all of these substances would meet criteria for Controlled Substance Act scheduling if submitted as new drugs by current standards.

Drug	Discriminable Dose	Reinforcing Dose	Dose in Common Products	Required Number of Units and Cost
Mitragynine	10 mg/kg, i.p. (Harun et al., 2015)	5 mg/kg, i.p. (Sufka et al., 2014)	VivaZen – 45 mg/serving (one bottle)	257 bottles would be required to achieve a dose equivalent to that which was found to be reinforcing in animals dose of MG (recommended retail at \$6.99 a bottle would cost almost \$1,800) and would require drinking over 500 oz of liquid
Caffeine	(N=7)- Three subjects discriminated 56 mg, three discriminated 18 mg and one	At the two lowest doses (100 and 200 mg) 5 of the 12 subjects demonstrated	Excedrin Extra Strength Caplets – 65 mg/caplet 10 Hour Energy	Many products contain a reinforcing dose of caffeine in a single unit of the product (5 hr energy

Drug	Discriminable Dose	Reinforcing Dose	Dose in Common Products	Required Number of Units and Cost
	discriminated 10 mg (Griffiths et al., 1990)	significant caffeine positive reinforcement at one or both doses (Griffiths & Woodson, 1988)	Shot- 422 mg 5 Hour Energy- 200 mg Brewed coffee 163 mg/8 oz Monster energy drink- 160 mg/16 oz Starbucks Tall Coffee – 260 mg Classic Coca Cola- 34 mg/12 oz Diet Coke – 45 mg/12 oz (http://www.caffeineinformer.com/the-caffeine-database; https://news.starbucks.com/uploads/documents/nutrition.pdf)	\$3-4)
Dextromethophan	No human studies 30 mg/kg, i.p. in rats (Gavend et al., 1995)	Doses of 400 and 800 mg/70 kg) increased drug liking scores. 92% of subjects reported 400 mg/70 kg as feeling like they had received a “classic hallucinogen” (Reissig et al.,	Robitussin Maximum Strength 10 mg//5 ml – 480 mg/8 oz bottle Mucinex DM Max Strength – 60 mg/tablet. 840 mg/14 count package	A dose that feels like a hallucinogen and is “liked” can be obtained by drinking a single bottle of cough syrup or taking 8 crushed capsules (Robitussin 8 oz for \$7.50. Generics at lower cost)

Drug	Discriminable Dose	Reinforcing Dose	Dose in Common Products	Required Number of Units and Cost
		2012)		
Diphenhydramine	In rats, partial generalization to cocaine (78%) at 17.8 mg/kg (Gauvin, 1995)	400 mg increased end of day scores on liking and take drug again (Preston et al., 1992)	Sleep aid liquidcaps – 50 mg/cap, package of 32 (1600 mg total) Equate nighttime sleep aid – 25 mg-100 capsules per box (2500 mg)	An abusable dose of 400 mg can be obtained by taking 8 50 mg tablets or 14 25 mg tablets (100 50 mg capsules for \$6)
Non-Alcoholic Beer	55% of subjects could be trained to discriminate 0.2 g/kg alcohol from placebo (Jackson et al., 2001)	Self-administration of ethanol at doses of 5-7 grams (Bigelow et al., 1977)	In the United States, one "standard" drink contains roughly 14 grams of pure alcohol, which is found in: <ul style="list-style-type: none"> • 12 ounces of regular beer, which is usually about 5% alcohol • 5 ounces of wine, which is typically about 12% alcohol • 1.5 ounces of distilled spirits, which is about 40% alcohol O'Douls ("non-alcoholic" beer-	The alcohol provided by a standard drink would be the equivalent of around 12 bottles of O'Douls (\$13)

Drug	Discriminable Dose	Reinforcing Dose	Dose in Common Products	Required Number of Units and Cost
			0.4%- 1.12g	
Nicotine	<1 mg by smoked, oral “chew”, or intravenous in humans	<1 mg by smoked, oral “chew”, or intravenous in humans (Henningfield et al., 2005; US DHHS, 2010)	All common tobacco products contain and deliver substantially higher doses but are typically used only as much as necessary to produce the desired effects. Former Surgeon General Koop, the first S.G. to conclude that nicotine met all criteria as an addictive drug, testified on behalf of allowing then prescription nicotine gum and patches to be approved for over the counter sales to make it more readily available for consumers to use as the desired to quit smoking.	Such doses can be achieved and easily exceeded by ordinary tobacco products, nicotine gum, and nasal spray, or electronic nicotine delivery systems (ENDS) or “E-Cigs. FDA concluded that nicotine met criteria for Schedule 3 of the Controlled Substances Act but that the overall risks and abuse potential were low compared to readily available tobacco products

Conclusion

Recommendation: While much of the data presented here focuses on VivaZen in particular, the safety profile of this botanical and its traditional use should be reviewed

by this panel and the scheduling of kratom revised to allow Wisconsin consumers access to products such as VivaZen.

Comment: There are many substances that are not scheduled, but which certainly meet criteria for controlled substances scheduling and these include dietary ingredients, over the counter drugs, and prescription drugs. Such scheduling decisions (and inactions) involve a balancing act of determining at what point controlled substance scheduling actions should be taken to protect the public health. There is an admittedly gray area represented, in my opinion, by kratom, caffeine, nicotine, over the counter cough, cold, and allergy medications, many herbals and spices, and quite frankly many prescription medications used to treat depression and other disorders, but which are not scheduled. In some cases, e.g., the synthetic cannabinoids, I support precautionary administrative scheduling decisions as for thebaine-derived new opioid molecules. In other cases, such as those summarized above, I believe that there should be clear evidence of actual or imminent public health harm, especially when there is also evidence of apparent consumer benefit before precautionary scheduling actions are taken. At this point, I do not believe precautionary scheduling is warranted for kratom products in general.

For VivaZen and like products, scheduling makes no more sense than would be the scheduling of hemp.

Major Sources

Assanangkornchai S, Muekthong A, Sam-Angsri N, Pattanasattayawong U. The Use of *Mitragynine speciosa* ("Kratom"), an addictive plant, in Thailand. *Subst Use Misuse*. 2007;42(14):2145-57.

Bigelow GE, Griffiths RR, Liebson IA. Pharmacological influences upon human ethanol self-administration. *Adv Exp Med Biol*. 1977;85B:523-38.

European Monitoring Center on Drugs and Addiction, *Kratom Profile* (<http://www.emcdda.europa.eu/publications/drug-profiles/kratom>)

Gauvin DV, Carl KL, Briscoe RJ, Vallett M, Holloway FA. Cross-generalization between a cocaine cue and two antihistamines. *Eur J Pharmacol*. 1995 Dec 27;294(1):281-8.

Gavend M, Mallaret M, Dematteis M, Baragatti G. Discriminative stimulus properties of dextromethorphan in rats. *Biomed Pharmacother*. 1995;49(10):456-64

Griffiths RR, Evans SM, Heishman SJ, Preston KL, Sannerud CA, Wolf B, Woodson PP. Low-dose caffeine discrimination in humans. *J Pharmacol Exp Ther*. 1990 Mar;252(3):970-8.

Griffiths RR, Woodson PP. Reinforcing effects of caffeine in humans. *J Pharmacol Exp Ther*. 1988 Jul;246(1):21-9.

Harun N, Hassan Z, Navaratnam V, Mansor SM, Shoaib M. Discriminative stimulus properties of mitragynine (kratom) in rats. *Psychopharmacology (Berl)*. 2015 Jul;232(13):2227-38.

Hassan Z, Muzaimi M, Navaratnam V, Yusoff NH, Suhaimi FW, Vadivelu R, Vicknasingam BK, Amato D, von Hörsten S, Ismail NI, Jayabalan N, Hazim AI, Mansor SM, Müller CP. From Kratom to mitragynine and its derivatives: physiological and behavioural effects related to use, abuse, and addiction. *Neurosci Biobehav Rev*. 2013 Feb;37(2):138-51.

Henningfield, J.E., Fant, R.V., Buchhalter, A.R., and Stitzer, M.L. Pharmacotherapy of nicotine dependence. *CA: A Cancer Journal for Clinicians*, 55: 281-299, 2005.

Jackson A, Stephens DN, Duka T. A low dose alcohol drug discrimination in social drinkers: relationship with subjective effects. *Psychopharmacology (Berl)*. 2001 Oct;157(4):411-20.

Matsumoto K, Horie S, Ishikawa H, Takayama H, Aimi N, Ponglux D, Watanabe K. Antinociceptive effect of 7-hydroxymitragynine in mice: Discovery of an orally active opioid analgesic from the Thai medicinal herb *Mitragyna speciosa*. *Life Sci*. 2004 Mar 12;74(17):2143-55.

Parthasarathy S, Ramanathan S, Ismail S, Adenan MI, Mansor SM, Murugaiyah V. Determination of mitragynine in plasma with solid-phase extraction and rapid HPLC-UV analysis, and its application to a pharmacokinetic study in rat. *Anal Bioanal Chem*. 2010 Jul;397(5):2023-30.

Ponglux D, Wongseripipatana S, Takayama H, Kikuchi M, Kurihara M, Kitajima M, Aimi N, Sakai S. A New Indole Alkaloid, 7 alpha-Hydroxy-7H-mitragynine, from *Mitragyna speciosa* in Thailand. *Planta Med*. 1994 Dec;60(6):580-1.

Preston KL, Wolf B, Guarino JJ, Griffiths RR. Subjective and behavioral effects of diphenhydramine, lorazepam and methocarbamol: evaluation of abuse liability. *J Pharmacol Exp Ther*. 1992 Aug;262(2):707-20.

Raffa, R.B., (Ed.) *Kratom and Other Mitragynines: The Chemistry and Pharmacology of Opioids from a Non-Opium Source*. CRC Press 2014.

Reissig CJ, Carter LP, Johnson MW, Mintzer MZ, Klinedinst MA, Griffiths RR. High doses of dextromethorphan, an NMDA antagonist, produce effects similar to classic hallucinogens. *Psychopharmacology (Berl)*. 2012 Sep;223(1):1-15.

Sabetghadam A, Ramanathan S, Sasidharan S, Mansor SM. Subchronic exposure to mitragynine, the principal alkaloid of *Mitragyna speciosa*, in rats. *J Ethnopharmacol*. 2013 Apr 19;146(3):815-23.

Sufka KJ, Loria MJ, Lewellyn K, Zjawiony JK, Ali Z, Abe N, Khan IA. The effect of *Salvia divinorum* and *Mitragyna speciosa* extracts, fraction and major constituents on place aversion and place preference in rats. *J Ethnopharmacol*. 2014;151(1):361-4

Tanguay P. Kratom in Thailand: Decriminalisation and Community Control. Available at <https://www.tni.org/files/download/kratom-briefing-dlr13.pdf>, accessed July 31, 2015.

U.S. Department of Health and Human Services. How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2010.

Yusoff NH, Suhaimi FW, Vadivelu RK, Hassan Z, Rümmler A, Rotter A, Amato D, Dringenberg HC, Mansor SM, Navaratnam V, Müller CP. Abuse potential and adverse cognitive effects of mitragynine (kratom). *Addict Biol.* 2014 Sep 28. doi: 10.1111/adb.12185. [Epub ahead of print] PMID: 25262913