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December 1, 2016

Drug Enforcement Administration
Attn: DEA Federal Register Representative/ODW
8701 Morrissette Drive
Springfield, Virginia 22152

Re: **Solicitation of Comments**
Withdrawal of Notice of Intent to Temporarily Place
Mitragynine and 7-Hydroxymitragynine into Schedule I
Docket No. DEA-442W
[81 *Federal Register* 70652; October 13, 2016]

Dear Madam or Sir:

The American Botanical Council (ABC) is submitting the following comments in response to the Drug Enforcement Administration (DEA) Solicitation of Comments regarding the scheduling of mitragynine and 7-hydroxymitragynine into Schedule I of the Controlled Substances Act (CSA). Based on the science and data available and reviewed to date, ABC respectfully requests that the DEA not proceed with scheduling these substances into Schedule I of the CSA.[1]

ABC is an independent nonprofit research and education organization that promotes the responsible use of herbal medicine based on scientific and clinical research and a rational interpretation of traditional use. Its members include medicinal plant and natural product researchers; educators; health care professionals; members of the herb, tea, dietary supplement, food, and cosmetic industries; the media; consumers, and other parties interested in medicinal plant and related research.

For the past several years ABC has been reviewing and monitoring the scientific literature related to kratom (*Mitragyna speciosa*), the plant that contains the constituent substances the DEA has been seeking to schedule. ABC recently published a peer-reviewed comprehensive review of the plant,[2] which explores the complex science of kratom, and examines the data that the DEA cited to support the temporary scheduling of mitragynine and 7-hydroxymitragynine.[3] ABC's publication provides additional context for understanding the factors that the DEA considers in its statutory analysis prior to scheduling a substance.[4]

[1] 21 U.S.C. §801-971 (Comprehensive Drug Abuse Prevention and Control Act of 1970).
[2] Yearsley C. Kratom: Medicine or Menace? *HerbalGram*. 2016;112:46-59.
[3] Schedules of Controlled Substances: Temporary Placement of Mitragynine and 7-Hydroxymitragynine Into Schedule I. *The Federal Register*. 81 FR 59929. Docket No. DEA-442. August 31, 2016.
[4] 21 U.S.C. §811(b), (h).

1. Medical uses

ABC's review of the scientific literature on kratom indicates there has been an increase in reputable institutions and scientists researching this plant to gain a better understanding of the plant's chemistry and its potential medical uses and risks. Based on limited evidence, some researchers suggest that kratom appears to be an affordable and relatively safe treatment to manage pain and opioid withdrawal symptoms.[5] The ABC review also provides evidence for a therapeutic profile that differs substantially from that of known full mu-opioid receptor [MOR] agonists such as morphine. We cite the following examples:

a. A study on the pharmacology of kratom published in December 2012 in *The Journal of the American Osteopathic Association* concluded the plant has potential for medical uses (e.g., management of pain) and that questions remain (e.g., about potential toxic effects).[6]

b. A Columbia University study on the *M. speciosa* alkaloids in May 2016 that found mitragynine and 7-hydroxymitragynine to be partial agonists at mu-opioid receptors [MORs] distinguishes them from strong prescription opioids like morphine and oxycodone. As partial MOR agonists, mitragynine and 7-hydroxymitragynine have a ceiling effect that minimizes their risks of physical dependence and acute side effects such as respiratory depression.[7,8]

c. In collaboration with researchers at Memorial Sloan-Kettering Cancer Center, the Columbia University team showed that the *M. speciosa* alkaloids produce analgesia approaching that of morphine with less respiratory depression. Mitragynine and 7-hydroxymitragynine, unlike other more common opioids, transduced signals via the G-protein pathway instead of the beta-arrestin-2 pathway. The Memorial Sloan-Kettering group showed further in July 2016 that this mechanism almost completely eliminated the addictive potential of the *M. speciosa* alkaloids when compared with morphine.[9]

d. Mitragynine and 7-hydroxymitragynine had a second noteworthy effect as both were antagonists at kappa-opioid receptors [KORs]. This means the alkaloids have analgesic effects while further minimizing the unpleasant (dysphoric) effects that some people associate with typical opioid pain killers. Moreover, the combination of MOR partial agonism and KOR antagonism is suggestive that the *M. speciosa* alkaloids may have significant potential beyond pain relief, such as promoting stress resilience, which may help treat certain types of anxiety, depression, and addiction disorders.

These studies articulate the firm distinctions between *M. speciosa* alkaloids and full mu-opioid receptor agonists.

The established body of evidence included in ABC's review article on kratom and other studies demonstrate the medical and therapeutic potential of the plant and its constituents; however, additional

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[5] *Vicknasingam* B, Narayanan S, Beng GT, Mansor SM. The *informal use* of *ketum* (*Mitragyna speciosa*) for *opioid withdrawal* in the *northern states* of *peninsular Malaysia* and *implications* for *drug substitution therapy*. The International Journal on *Drug* Policy. 2010;21:283-288.

[6] Prozialeck WC, Jivan JK, Andurkar. Pharmacology of Kratom: An Emerging Botanical Agent With Stimulant, Analgesic and Opioid-Like Effects. *J Am Osteopath Assoc*. 2012;112(12):792-799.

[7] Kruegel AC, Gassaway MM, Kapoor A, et al. Synthetic and receptor signaling explorations of the *Mitragyna* alkaloids: Mitragynine as an atypical molecular framework for opioid receptor modulators. *J Am Chem Soc*. 2016;138(21):6754-6764.

[8] Chavkin C. The therapeutic potential of κ-opioids for treatment of pain and addiction. *Neuropsychopharmacology*. 2011;36:369-370.

[9] Varadi A, Marrone GF, Palmer TC, et al. Mitragynine/corynantheidine pseudoindoxyls as opioid analgesics with mu agonism and delta antagonism, which do not recruit beta-arrestin-2. *J Med Chem*. 2016;59(18):8381-8397.

questions, particularly those related to the potential benefits of kratom to alleviate the symptoms of opioid withdrawal, need to be resolved via further research.

2. Constraints on research efforts

As a science-based organization that promotes botanical research and the safe and responsible use of botanicals and their preparations, ABC emphasizes the additional challenges that come into play in researching a substance that is placed in Schedule I under the CSA. The increased challenges for researchers in obtaining a registration and operating within the DEA's production quotas, in addition to establishing security measures and the extensive record and reporting requirements required to research a scheduled substance, may significantly curtail the current and/or future research efforts on kratom.

ABC strongly supports the ongoing research of this plant to discover its full medicinal value and — just as importantly — the need for a better understanding of the risks involved in using the plant, which includes safety considerations such as possible adverse events, herb-drug interactions, and contraindications.

3. Concerns regarding the data cited by DEA

ABC agrees that the safety profile of kratom is not comprehensively established. However, the data cited by the DEA in its three-factor analysis[10] to support the temporary scheduling of mitragynine and 7-hydroxymitragynine need appropriate context for an accurate interpretation. We include the following examples to support this:

a. The DEA references 660 kratom-related reports to poison control centers over a six-year period; however, as is often the case with such reports, a better understanding of the importance of this statistic requires additional context.

i. Estimates suggest the number of kratom consumers in the United States is between several hundred thousand and 3-5 million, which means the 660 calls that were received over a six-year period are statistically insignificant even with the lower number of estimated kratom consumers.

ii. In 2013, poison control centers throughout the United States received a total of more than 3.1 million calls,[11] and in 2014 the centers received a total of 2.9 million calls.[12]

iii. Of the 660 calls, no effects were reported, or poison center staff was unable to follow up in 173 (26.2%) cases. Additionally, in 162 (24.5%) cases, the medical assessment reported minor signs or symptoms, while in 275 (41.7%), a moderate exposure was reported. Life-threatening signs or symptoms were observed for 49 (7.4%) exposures. Finally, there was one reported fatal outcome in a person additionally consuming the medications paroxetine and lamotrigine.[13]

iv. Additionally, of these 660 calls, 64.8% of the calls were reportedly based on isolated kratom use, with the balance of calls most likely involving concomitant use of other substances, including depressants such as ethanol and benzodiazepines.[14] Polysubstance

[10] U.S. Department of Justice, Background Information and Evaluation of 'Three Factor Analysis' (Factors 4, 5 and 6) for Temporary Scheduling; Schedules of Controlled Substances: Temporary Placement of Mitragynine and 7-Hydroxymitragynine Into Schedule I. *The Federal Register.* 81 FR 59929. Docket No. DEA-442. August 31, 2016.
[11] Mowry JB, Spyker DA, Cantilena Jr. LR, McMillan N, Ford M. 2013 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 31st Annual Report
[12] Mowry JB, Spyker DA, Brooks DE, McMillan N, Schauben JL. 2014 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 32nd Annual Report, Clinical Toxicology, 53:10, 962-1147, DOI: 10.3109/15563650.2015.1102927
[13] Anwar M, Law R, Schier J. Notes from the Field. Kratom (*Mitragyna speciosa*) exposures reported to poison centers — United States, 2010–2015. *MMWR Morb Mortal Wkly Rep.* 2016;65:748–749.
[14] U.S. Department of Justice, Background Information and Evaluation of 'Three Factor Analysis' (Factors 4, 5 and 6) for Temporary Scheduling; Schedules of Controlled Substances: Temporary Placement of Mitragynine and 7-

use creates a challenge in identifying an offending substance, and without a full investigation into each report, implicating kratom as the offending substance is not sound practice.

v. The DEA also correctly points out that products labeled as containing kratom are often adulterated with other substances.[15] Therefore, without comprehensive testing to determine the amount of kratom and the amounts of other substances in the product, one cannot conclude that kratom was the offending substance that caused the adverse effect.

By placing the 660 calls that cited kratom exposure over a six-year period of time into context, a more accurate picture of any safety concern is provided. Based on the difficulties in assessing the causality of kratom and the observed medical symptoms, and the estimated number of kratom consumers (between several hundred thousand and 5 million), the risk in consuming kratom seems relatively low.

b. Another example of data referenced without context is the mention of the 2010 report by the International Narcotics Control Board (INCB) in the DEA's three-factor analysis.[16] The DEA includes a paragraph on the INCB report which reads as if kratom were a singled-out and highlighted plant of interest in the INCB report. See immediately below:

> Internationally, the increased presence and abuse of kratom, containing the main active alkaloids mitragynine and 7-hydroxymitragynine, has garnered the attention of the International Narcotics Control Board (INCB) (INCB, 2011). In a 2010 report, the INCB noted the increased interest in the recreational use of kratom, and highlighted the use of the Internet to educate potential users about kratom. The report also notes that any impairing effects from the use of kratom might have serious consequences for the well-being of other persons, similar to driving under the influence of a psychoactive substance. The INCB recommended that governments experiencing problems with persons trafficking or using kratom recreationally, which had not already controlled kratom and kratom preparations, should consider doing so at the national level where necessary.

In actuality, kratom was mentioned once in the INCB report in a list with nine other plants, and any words of caution or recommendations did not reference kratom specifically and were generally intended to encompass all referenced plant materials. The list of these plants is quoted below.[17]

> 284. Many plants that contain psychoactive substances with stimulating or hallucinogenic properties, as well as preparations made from those plants, have traditional uses in some countries or regions; for example, some are used in religious rites. …
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> 285. Examples of such plants or plant material include khat (*Catha edulis*), whose active ingredients cathinone and cathine are listed in Schedules I and III of the 1971 Convention; ayahuasca, a preparation made from plants indigenous to the Amazon basin of South America, mainly a jungle vine (*Banisteriopsis caapi*) and another tryptamine-rich plant, chacruna (*Psychotria viridis*), containing a number of psychoactive alkaloids, including dimethyltryptamine (DMT); the peyote cactus (*Lophophora williamsii*), containing mescaline; magic mushrooms (*Psilocybe* spp.), which contain psilocybin and psilocin; Ephedra, containing ephedrine; "kratom" (*Mitragyna speciosa*), a plant indigenous to South-East Asia that contains mitragynine; iboga (*Tabernanthe iboga*), a plant that contains the hallucinogen ibogaine and is native to the western part of Central Africa; a number of *Datura* spp. containing hyoscyamine and scopolamine; and *Salvia divinorum*, a plant originating in Mexico that contains the hallucinogen salvinorin A.

In summary, the data cited by the DEA in its three-factor analysis to support the temporary scheduling of mitragynine and 7-hydroxymitragynine need appropriate context for an accurate interpretation in

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Hydroxymitragynine Into Schedule 1. *The Federal Register.* 81 FR 59929. Docket No. DEA-442. August 31, 2016. (p. 10).

[15] Id. at 9-10.

[16] US Department of Justice, Background Information and Evaluation of 'Three Factor Analysis' (Factors 4, 5 and 6) for Temporary Scheduling; Schedules of Controlled Substances: Temporary Placement of Mitragynine and 7-Hydroxymitragynine Into Schedule I. *The Federal Register.* 81 FR 59929. Docket No. DEA-442. August 31, 2016. (p.18)

[17] International Narcotics Control Board 2010 Report (2011), p. 46-47.

understanding the safety of kratom.

4. Role of other agencies and existing enforcement authority

ABC believes that it is also of relevance to the discussion of whether to schedule these substances to recognize that there are other agencies on both the state and federal levels engaged in monitoring kratom market activity, as the DEA correctly points out in its notice of intent.

The FDA and the Customs and Border Patrol (CBP) have seized kratom raw material and/or products labeled as containing kratom from the market due to the FDA's position that such products are not in compliance with the regulatory framework for dietary supplements.[18] ABC supports FDA's current enforcement activities to ensure that any kratom products are compliant with the applicable regulatory framework. Additionally, a few states have taken legislative action to control and monitor the sales of products containing kratom within their respective state. Hence, there are other agencies with enforcement authority that are actively engaged in monitoring the market.

Conclusion

ABC supports the role the DEA plays to ensure public safety from the use, misuse, and/or abuse of toxic drugs and substances. However, in light of the above and based on the evidence and data the DEA has set forth, ABC respectfully requests that the DEA not proceed with placing mitragynine and 7-hydroxymitragynine on Schedule I. The plant is worthy of further systematic research to create a more adequate understanding of its medicinal uses and establish a sound safety profile of the whole plant and its individual constituents.

We thank you for your consideration.

Respectfully submitted,

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[18] U.S. Food, Drug, and Cosmetic Act (FDCA), §413(d) (21 USC §350b(d)).