



Proposed Classification of Kratom as a Schedule I Controlled Substance for Stakeholder Comment

The State of Ohio Board of Pharmacy pursuant to section 3719.44 of the Ohio Revised Code, proposes the placement of the following into Schedule I:

Mitragynine and 7-hydroxymitragynine, which are the main active constituents of the plant kratom.

At this time, public comment is being sought on this rule change prior to being filed with Common Sense Initiative.

Comments on the proposed rule will be accepted until close of business of **October 18, 2018**. Please send all comments to the following email address: contact@pharmacy.ohio.gov.





RESOLUTION: CLASSIFICATION OF KRATOM AS A SCHEDULE I CONTROLLED SUBSTANCE

Section 1: Summary

The State of Ohio Board of Pharmacy (BOP), pursuant to section 3719.44 of the Ohio Revised Code, proposes the placement of the following into Schedule I:

Mitragynine and 7-hydroxymitragynine, which are the main active constituents of the plant kratom.

Section 2: Background

Pursuant to section 3719.44 the Board may add or transfer a compound, mixture, preparation, or substance to schedule I when it appears that there is a high potential for abuse, that it has no accepted medical use in treatment in this state, or that it lacks accepted safety for use in treatment under medical supervision.

In making a determination to add an unscheduled compound, the Board is required to consider the following 8 criteria:

- (1) The actual or relative potential for abuse;
- (2) The scientific evidence of the pharmacological effect of the substance;
- (3) The state of current scientific knowledge regarding the substance;
- (4) The history and current pattern of abuse;
- (5) The scope, duration, and significance of abuse;
- (6) The risk to the public health;
- (7) The potential of the substance to produce psychic or physiological dependence liability; and
- (8) Whether the substance is an immediate precursor.

Section 3: Evaluating Kratom Under the Eight Criteria

(1) The actual or relative potential for abuse.

Scientists at the US Food and Drug Administration (FDA) first analyzed the chemical structures of the 25 most prevalent compounds in kratom. From this analysis, the agency concluded that all of the compounds share the most structural similarities with controlled



opioid analgesics, such as morphine derivatives. Further analysis by the FDA determined that 22 (including mitragynine) of the 25 compounds in kratom bind to mu-opioid receptors. The FDA further notes:

The data from the PHASE model shows us that kratom compounds are predicted to affect the body just like opioids. Based on the scientific information in the literature and further supported by our computational modeling and the reports of its adverse effects in humans, we feel confident in calling compounds found in kratom, opioids.ⁱ

(2) The scientific evidence of the pharmacological effect of the substance.

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) notes that mitragynine and 7-hydroxymitragynine are selective and full agonists of the mu-opioid receptor. The receptor agonist effect of kratom alkaloids is antagonized by the opioid receptor antagonist naloxone. In addition, 5-HT_{2a} and postsynaptic α₂-adrenergic receptors, as well as neuronal Ca²⁺ channels are also involved in the unique pharmacological and behavioral activity of mitragynine.

The EMCDDA reports the effects of kratom in humans are dose-dependent: small doses produce 'cocaine-like' stimulation while larger dosages cause 'morphine-like' sedative-narcotic effects.

After taking a few grams of dried leaves, the invigorating effects and euphoria are felt within 10 minutes and last for one to one and a half hours. Kratom users report increased work capacity, alertness, sociability and sometimes heightened sexual desire. The pupils are usually normal or very slightly contracted; blushing may be noted. In one of the few human clinical experiments, a 50 mg oral dose of mitragynine produced motor excitement, followed by giddiness, loss of motor coordination, and tremors of the extremities and face.

Kratom taken in large, sedating doses corresponding to 10–25 g of dried leaves may initially produce sweating, dizziness, nausea and dysphoria but these effects are shortly superseded with calmness, euphoria and a dreamlike state that last for up to six hours.

In animal studies, the antinociceptive and cough-suppressant effects of mitragynine were comparable to those of codeine. In mice, 7-hydroxymitragynine was several times more potent analgesic than morphine even upon oral administration.ⁱⁱ

Kratom is slightly toxic to animals. Mice chronically treated with 7-hydroxymitragynine developed tolerance, cross-tolerance to morphine and withdrawal signs that could be precipitated by naloxone administration.ⁱⁱⁱ

(3) The state of current scientific knowledge regarding the substance.

The metabolism of mitragynine in humans occurs via hydrolysis of the side-chain ester, *O*-demethylation of the methoxy groups, oxidative and/or reductive transformations, and the formation of glucuronide and sulfate conjugates. In a man who fatally overdosed propylhexedrine and kratom, the postmortem mitragynine concentrations ranged from 0.01 mg/kg to 1.20 mg/l.^{iv}

The FDA through their Public Health Assessment via Structural Evaluation (PHASE) methodology found that there is no evidence to indicate that kratom is safe or effective for any medical use. The compounds in kratom were found to bind to mu-opioid receptors similar to other opioids. The FDA also found serious side effects associated with kratom, including seizures and respiratory depression.^v

(4) The history and current pattern of abuse.

Kratom, which contains the main active alkaloids mitragynine and 7-hydroxymitragynine, has a long history of use in Southeast Asia as an opium substitute. Kratom is also known in Southeast Asia as thang, thom, krathom, kakuam, ketum, and biak. In recent years, the presence of the psychoactive plant kratom has increased significantly on the recreational market in the United States. It has been marketed in the US as a plant-based product with broad healing properties mostly sold in smoke shops, gas stations, and over the internet.

On May 22, 2018, the FDA issued three warning letters to three marketers and distributors of kratom products for illegally selling unapproved kratom-containing drug products. These products were marketed with unproven claims about treating pain, lowering blood pressure, treating cancer, and reducing neuron damage caused by strokes.

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In a 2016 publication, the Centers for Disease Control (CDC) characterized kratom exposures reported to poison centers and uploaded to the National Poison Data System (NPDS) from January 2010 through December 2015. During the stated timeframe, U.S. poison centers received 660 calls related to kratom exposure. Of the calls reported, 487 (73.8%) reported intentional exposure to kratom, and 595 (90.2%) reported ingestion of the drug. In addition to reports of isolated exposures to kratom (428 (64.8%)), reports of

kratom being used with other substances (ethanol, benzodiazepines, narcotics, acetaminophen, and other botanicals) were also recorded. Additionally, forensic laboratory analyses of drug evidence have identified kratom/mitragynine, along with synthetic cannabinoids and synthetic opioids during the analyses of products seized on the illicit market. The consumption of kratom individually, or in conjunction with alcohol or other drugs, is of serious concern as it can lead to severe adverse effects and death.^{vii}

According to research conducted by the FDA, no marketer has sought to develop a drug that includes kratom in the US. Kratom is a controlled substance in 16 countries, including Thailand and Malaysia where it is found naturally. It is also banned in several states including Alabama, Arkansas, Indiana, Vermont, Rhode Island, Wisconsin and the District of Columbia have banned kratom, along with at least three cities — Denver, San Diego and Sarasota, Florida.^{viii} Currently, the Drug Enforcement Administration (DEA) has listed kratom as a Drug and Chemical of Concern.^{ix}

(5) The scope, duration, and significance of abuse.

According to the DEA, reports from law enforcement indicate that kratom is being imported for widespread distribution to the public within the United States. Between February 2014 and July 2016, over 55,000 kilograms (kg) of kratom material were encountered by law enforcement at various ports of entry within the United States. Additionally, over 57,000 kg of kratom material offered for import at numerous ports of entry, between 2014 and 2016, are awaiting an FDA admissibility decision. The amount of kratom currently seized or awaiting an admissibility decision by law enforcement, between 2014 and 2016, is enough to produce over 12 million doses of kratom.^x

Drug reports pertaining to the trafficking, distribution, and abuse of kratom/mitragynine were analyzed by Federal, State, and local forensic laboratories. According to data from the System to Retrieve Information from Drug Evidence (STRIDE) and STARLiMS (a web-based, commercial laboratory information management system), from January 2006 through March 2016, there were 293 records for kratom and/or mitragynine. From January 2010 through May 2016, the National Forensic Laboratory Information System (NFLIS) registered 720 reports containing mitragynine. NFLIS and STRIDE/STARLiMS records/reports were reported across 43 States, thus showing the widespread abuse and trafficking of kratom/mitragynine. The presence of these substances during drug evidence analyses demonstrates the presence of these substances on the recreational drug market.^{xi}

Growing concern over the use of kratom is reflected in the increased requests for analyses of mitragynine and 7-hydroxymitragynine in human toxicology panels (blood/urine samples) to private analytical laboratories. These analyses have been requested by

addiction treatment facilities/pain management doctors, drug courts, medical examiner/coroner offices, drug testing facilities, state laboratory systems, state police department, and private entities. The number of positive results from these analyses increased as follows: 31 positive results from August 2012 to July 2013 for mitragynine and/or 7-hydroxymitragynine; 274 positive results for mitragynine between July 2013 and May 2014; 555 positive results for mitragynine between December 2014 and March 2016. According to DEA, the increasing trend in the number of positive results from these analyses demonstrates the growing abuse and popularity of these substances and the concern related to the abuse of this plant material and its psychoactive constituents.^{xii}

The most recent Drug Trend Report from the Ohio Substance Abuse Monitoring Network (June 2017 - January 2018) finds that Kratom is available in the Akron-Canton and Cleveland regions. Notably, participants in the Akron-Canton region reported being able to purchase the drug from heroin dealers and through Internet purchase, while community professionals indicated that the drug can be purchased at head shops. Participants in the Cleveland region reported being able to purchase the drug in powdered form and in capsules. Participants reported that the drug looks similar to brown powdered heroin, produces similar effects as heroin, and is primarily used by individuals subject to drug screening and by people addicted to heroin who use the drug to alleviate opiate withdrawal symptoms. Participants reported that the most common route of administration for kratom is intravenous injection (aka "shooting"). Participants in the Akron-Canton region estimated that out of 10 kratom users, seven would shoot the drug and three would orally consume the drug (including drinking it as a tea).^{xiii}

(6) The risk to the public health.

Information from the scientific literature also demonstrates the health risks associated with kratom use. Reports of hepatotoxicity, psychosis, seizure, weight loss, insomnia, tachycardia, vomiting, poor concentration, hallucinations, and death associated with kratom use have been documented.^{xiv}

Numerous deaths associated with kratom, which contains the main active constituents mitragynine and 7-hydroxymitragynine, have been reported indicating that this substance is a risk to the public health. Deaths related to kratom exposure have been reported in the scientific literature beginning in 2009-2010, with a cluster of nine deaths in Sweden from use of the kratom product "Krypton". Since then, five more deaths related to kratom exposure were reported in the scientific literature, and sixteen other deaths related to kratom exposure, have been confirmed by autopsy/medical examiner reports (mitragynine and/or 7-hydroxymitragynine were identified in biological samples). Of these deaths, 15 occurred between 2014 and 2016.^{xv}

In November 2017, the FDA published a public health advisory urging consumers not to use kratom or any compounds in the plant.^{xvi} In February 2018, the FDA was aware of 44 deaths associated with kratom-containing products and reports of kratom being laced with other opioids like hydrocodone. In some cases, kratom was being used in combination with other drugs, including illicit drugs, prescription opioids, benzodiazepines and over the counter medications. According to FDA, mixing kratom with other opioids is a serious concern because the activity of kratom at opioid receptors has similar risks to combining FDA-approved opioids. Additionally, the agency found that there may be serious side effects associated with kratom including seizures, liver damage, withdrawal symptoms and respiratory depression.^{xvii}

Recent data from the Ohio Department of Health found deaths specifically linked to kratom. In 2016 and 2017 Kratom was indicated as the primary cause of death for six Ohioans.^{xviii}

There are also concerns regarding the conditions under which the drug is produced. For example, there was recently a multi-state recall of kratom products that tested positive for salmonella contamination. On April 6, 2018, in response to a mandatory recall order from the FDA after several of its kratom products were found to contain *Salmonella*, Triangle Pharmedicals, LLC of Las Vegas, NV, initiated a recall of such products. As of April 17, 2018, the firm is recalling all kratom powder products it manufactured, processed, packed and/or held from April 4, 2017 to present. This recall includes at least 26 different products. As of May 24, 2018, a total of 199 people infected with the outbreak strains of *Salmonella* were reported from 41 states. According to FDA, thirty-eight percent of ill people were hospitalized, and no deaths were reported.^{xix}

(7) The potential of the substance to produce psychic or physiological dependence liability.

The FDA through their Public Health Assessment via Structural Evaluation (PHASE) methodology found that there is no evidence to indicate that kratom is safe or effective for any medical use. The compounds in kratom were found to bind to mu-opioid receptors similar to other opioids.

A 2014 study of regular Kratom users found that more than half of the regular users (>6 month of use) developed severe dependence problems, while 45 percent showed a moderate kratom dependence. Such dependence problems included physical and psychological withdrawal symptoms.^{xx} Additionally, a 2018 case report from Canada found evidence of maternal and neonatal kratom dependence and withdrawal.^{xxi}

The European Monitoring Centre for Drugs and Drug Addiction as noted that regular kratom use can produce dependence. Such dependence produces withdrawal symptoms including include craving, weakness and lethargy, anxiety, restlessness, rhinorrhea, myalgia, nausea, sweating, muscle pain, jerky movements of the limbs, tremor as well as sleep disturbances and hallucinations.^{xxii}

(8) Whether the substance is an immediate precursor.

Kratom is not known to be an immediate precursor.

Section 5: Finding of the Board

Section 3719.44 of the Ohio Revised Code authorizes that the State of Ohio Board of Pharmacy may add or transfer a compound, mixture, preparation, or substance to schedule I when it appears that there is a high potential for abuse, that it has no accepted medical use in treatment in this state, or that it lacks accepted safety for use in treatment under medical supervision.

After a thorough review of all available data, the State of Ohio Board of Pharmacy finds that kratom:

- 1.** Has a high potential for abuse;
- 2.** Has no accepted medical use in treatment in this state;
- 3.** Lacks accepted safety for use in treatment under medical supervision; and
- 4.** Poses a risk to the public health of the citizens in this state.

Based on these findings, the Board hereby concludes that kratom be controlled in Schedule I and authorizes the filing of amended rule 4729-11-02 of the Administrative Code.

4729-11-02 Schedule I controlled substances.

(A) The state board of pharmacy hereby schedules the following synthetic cannabinoid compounds as schedule I controlled substance hallucinogens:

- (1) PB-22 (chemical name: quinolin-8-yl 1-pentyl-1H-indole-3-carboxylate);
- (2) 5-Fluoro-PB-22 (chemical name: quinolin-8-yl 1-(5-fluoropentyl)-1H-indole-3-carboxylate).

(B) Except as otherwise provided in section [3719.41](#) of the Revised Code, any compound that meets at least three of the following pharmacophore requirements to bind at the CB1 and CB2 receptors, as identified by a report from an established forensic laboratory, is a schedule I controlled substance hallucinogen:

- (1) A chemical scaffold consisting of substituted or non-substituted ring structures that facilitate binding of required elements (such as: indole compounds, indazoles, benzimidazoles or other ring types);
- (2) Alkyl or aryl side chain off the chemical scaffold providing hydrophobic interaction with the CB1 and CB2 receptors;
- (3) Carbonyl or ester or equivalent for hydrogen bonding;
- (4) Cyclohexane, naphthalene ring, substituted butanamide or equivalent for steric requirements for CB1 and CB2 receptor binding.

(C) Except as otherwise provided in section [3719.41](#) of the Revised Code, any compound that contains the structural requirements of the cathinone pharmacophore, as identified by a report from an established forensic laboratory, is a schedule I controlled substance.

(D) Except as otherwise provided in section [3719.41](#) of the Revised Code, any compound that meets the following fentanyl pharmacophore requirements to bind at the mu receptor, as identified by a report from an established forensic laboratory, is a schedule I controlled substance opiate:

- (1) A chemical scaffold consisting of:
 - (a) A five, six or seven member ring structure containing a nitrogen, whether or not further substituted; and

- (b) An attached nitrogen to the ring, whether or not that nitrogen is enclosed in a ring structure, including an attached aromatic ring or other lipophilic group to that nitrogen;
- (2) A polar functional group attached to the chemical scaffold, including but not limited to, a hydroxyl, ketone, amide or ester;
- (3) An alkyl or aryl substitution off the ring nitrogen of the chemical scaffold; and
- (4) The compound has not been approved for medical use by the United States food and drug administration.
- (E) 6-monoacetylmorphine (6-MAM) is a schedule I controlled substance opium derivative.
- (F) 3,4-dichloro-N-[2-(dimethylamino)cyclohexyl]-N-methyl-benzamide (U-47700) is a schedule I controlled substance opium derivative.
- (G) Etizolam (4-(2-chlorophenyl)-2-ethyl-9-methyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine) is a schedule I controlled substance depressant.

(H) Mitragynine (to include synthetic equivalents as well as mitragynine naturally contained in the plant of the genus and species name: *Mitragyna speciosa* Korth, also known as kratom) its isomers, esters, ethers, salts and salts of isomers, esters and ethers.

(I) 7-Hydroxymitragynine (to include synthetic equivalents as well as 7-hydroxymitragynine naturally contained in the plant of the genus and species name: *Mitragyna speciosa* Korth, also known as kratom) its isomers, esters, ethers, salts and salts of isomers, esters and ethers.

¹ Office of the Commissioner. (2018, February 6). Press Announcements - Statement from FDA Commissioner Scott Gottlieb, M.D., on the agency's scientific evidence on the presence of opioid compounds in kratom, underscoring its potential for abuse. Retrieved from <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm595622.htm>

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- ⁱⁱ The European Monitoring Centre for Drugs and Drug Addiction. Kratom (*Mitragyna speciosa*) drug profile. <http://www.emcdda.europa.eu/publications/drug-profiles/kratom#pharmacology>
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- ^{iv} The European Monitoring Centre for Drugs and Drug Addiction. Kratom (*Mitragyna speciosa*) drug profile. <http://www.emcdda.europa.eu/publications/drug-profiles/kratom#pharmacology>
- ^v Office of the Commissioner. (2017, November 14). Press Announcements - Statement from FDA Commissioner Scott Gottlieb, M.D. on FDA advisory about deadly risks associated with kratom. Retrieved from <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm584970.htm>
- ^{vi} Press Announcements - FDA warns companies selling illegal, unapproved kratom products marketed for opioid cessation, pain treatment and other medical uses. Retrieved from <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm608447.htm>
- ^{vii} United States Drug Enforcement Administration. Schedules of Controlled Substances: Temporary Placement of Mitragynine and 7-Hydroxymitragynine Into Schedule I. https://www.federalregister.gov/documents/2016/08/31/2016-20803/schedules-of-controlled-substances-temporary-placement-of-mitragynine-and-7-hydroxymitragynine-into?utm_campaign=pi+subscription+mailing+list&utm_medium=email&utm_source=federalregister.gov
- ^{viii} What's Kratom, and Why Are States Banning It? Governing Magazine. <http://www.governing.com/topics/health-human-services/sl-kratom-state-ban.html>
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- ^{xiii} Ohio Department of Mental Health and Addiction Services [OhioMHAS] (2018). Ohio Substance Abuse Monitoring Network: Surveillance of Drug Abuse Trends in the State of Ohio: June 2017 - January 2018. Columbus, OH: State of Ohio.
- ^{xiv} United States Drug Enforcement Administration. Schedules of Controlled Substances: Temporary Placement of Mitragynine and 7-Hydroxymitragynine Into Schedule I. https://www.federalregister.gov/documents/2016/08/31/2016-20803/schedules-of-controlled-substances-temporary-placement-of-mitragynine-and-7-hydroxymitragynine-into?utm_campaign=pi+subscription+mailing+list&utm_medium=email&utm_source=federalregister.gov
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^{xvii} Office of the Commissioner. (2018, February 6). Press Announcements - Statement from FDA Commissioner Scott Gottlieb, M.D., on the agency's scientific evidence on the presence of opioid compounds in kratom, underscoring its potential for abuse. Retrieved from <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm595622.htm>

^{xviii} Ohio Department of Health, Violence and Injury Prevention Program. State Unintentional Drug Overdose Reporting System (SUDORS). Received August 24, 2018.

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^{xxii} The European Monitoring Centre for Drugs and Drug Addiction. Kratom (*Mitragyna speciosa*) drug profile. <http://www.emcdda.europa.eu/publications/drug-profiles/kratom#pharmacology>