Application to amend the Poisons Standard

Mitragyna speciosa, commonly known as kratom.

s 22

[redacted]

Not Applicable

Applicant's details

1. **What is your name?**

s 22 [redacted]

2. **What is your email address?**

s 47G [redacted]@gmail.com

3. **What is your phone number?**

s 22 [redacted]

4. **What is the name of the organisation you are representing for this application?**

Not Applicable

5. **Are you the contact person for this application?**

No. I will provide the details of the contact person in the 'Contact person's details' page.

Contact Person's details

If you are the contact person for this application and you have given your details in the 'Applicant's details' page, disregard the questions below and proceed to the 'Substance details' page.

If we have any questions regarding the application, we will contact the nominated contact person.

6. What is your name of the contact person?

s 22

7. What is your email address of the contact person?

s 47G @gmail.com

8. What is the phone number of the contact person?

s 22

Substance details

9. What is the name of the substance?

Mitragyna speciosa, commonly known as kratom.

10. What are the alternative names of the substance?

11. Is the substance a derivative of any currently scheduled poisons?

No

If yes, please specify each derivative on a separate line below:

No, mitragynine and 7-hydroxymitragynine—the active compounds in kratom—are not derivatives of any currently scheduled poisons. However, they are unique alkaloids found specifically in the leaves of the Mitragyna speciosa tree (kratom) and are structurally different from other scheduled substances.

Kratom's legal status and regulation differ by country. In some places, it is treated similarly to other plant-based substances like cannabis or certain opioids, but it is not chemically related to these. It is important to note that, despite not being a derivative of currently scheduled poisons, kratom and its alkaloids have been subject to regulation in various jurisdictions due to concerns about potential misuse or health risks.

12. What are the CAS numbers of the substance?

The CAS (Chemical Abstracts Service) numbers for the active compounds in kratom are as follows:

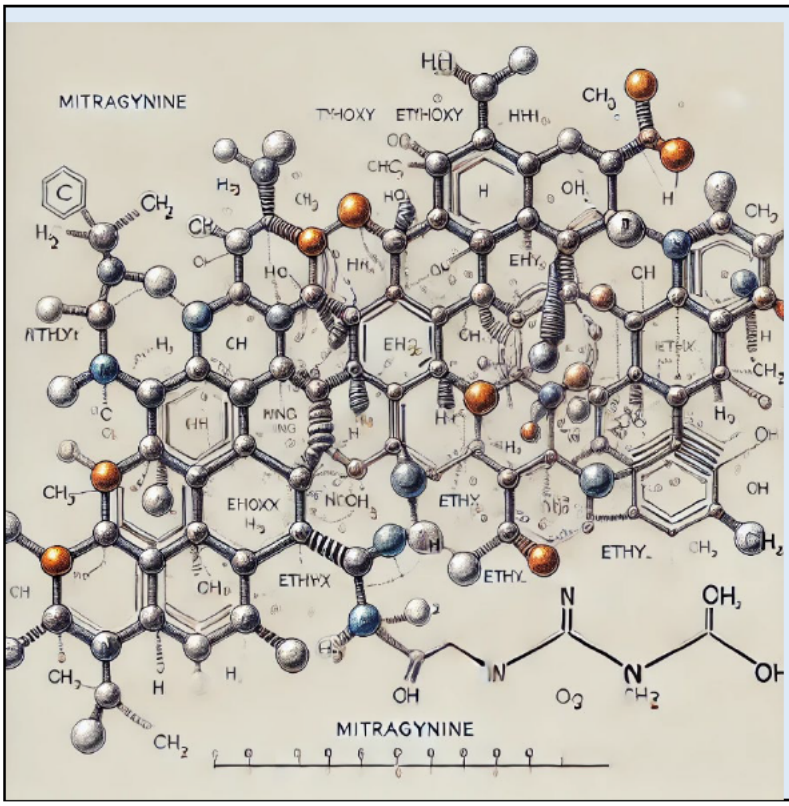
Mitragynine: 4098-40-2

7-Hydroxymitragynine: 174418-82-7

These numbers uniquely identify these chemical substances and can be included in any regulatory submissions or scientific discussions about kratom.

13. Upload an image of the chemical structure of the substance.

To ensure we can view the chemical structure of the substance, upload an image file in one of these formats: .jpg, .jpeg, .img, .png.



14. What are the known uses of the substance?

Enter each known use on a separate line (only if applicable).

15. What are the proposed uses of the substance?

Enter each proposed use on a separate line (only if applicable).

The proposed uses of mitragynine and 7-hydroxymitragynine, the active compounds in kratom, include the following:

Pain Relief: These compounds act on opioid receptors, and kratom has been traditionally used for pain management, especially for chronic pain conditions such as arthritis, fibromyalgia, and neuropathic pain.

Mood Enhancement: Mitragynine is known to have stimulant effects at low doses, which can promote energy, focus, and mood elevation.

Anxiety and Depression Relief: Kratom is sometimes used as an herbal remedy to help alleviate symptoms of anxiety and depression, although more research is needed to fully understand its efficacy.

Opioid Withdrawal Aid: Some users turn to kratom to manage opioid withdrawal symptoms, as it can mimic the effects of opioids to some extent without the same intensity of addictive potential, although this is controversial and not fully proven.

Fatigue Reduction: At lower doses, mitragynine may act as a stimulant, providing an increase in energy and reducing fatigue.

Traditional Use: In Southeast Asia, kratom has been traditionally used for various health and wellness purposes, including improving stamina and enhancing well-being.

It is important to note that while there is anecdotal evidence and traditional use supporting these purposes, more clinical research is necessary to verify these benefits and understand potential risks.

16. What are the pack sizes of products marketed or supplied in Australia that contain the substance?

Enter each pack size on a separate line (only if applicable).

In Australia, mitragynine and 7-hydroxymitragynine (the active compounds in kratom) are currently classified as Schedule 9 (Prohibited Substances) under the Poisons Standard, which means that products containing these substances are not legally marketed or supplied for sale.

Due to this legal restriction, there are no officially recognized or regulated pack sizes for kratom-containing products in Australia. Any importation, marketing, or supply of kratom or its alkaloids without appropriate approvals is considered illegal.

If you are pursuing an amendment to this regulation, it may open up possibilities for standardized, regulated packaging in the future, but for now, there are no approved pack sizes available in Australia.

17. What are the proposed pack sizes for products that contain the substance?

Enter each pack size on a separate line (only if applicable).

If kratom or its active compounds, mitragynine and 7-hydroxymitragynine, were to be legally regulated and marketed in Australia, the proposed pack sizes for products containing these substances would likely follow guidelines similar to those for other herbal or plant-based supplements. Here are some common approaches that could be proposed:

1. Powdered Form:

Small Packs: 25g, 50g, or 100g

Medium Packs: 250g, 500g

Large Packs: 1kg

2. Capsule Form:

Low-Dose Packs: 10, 20, or 30 capsules (e.g., for introductory use or trial packs)

Standard Packs: 60 to 100 capsules (typical for daily use)

Bulk Packs: 250 or 500 capsules (for longer-term supply)

3. Liquid Extract Form:

Small Bottles: 10ml, 30ml, or 50ml (for concentrated extract)

Medium Bottles: 100ml or 150ml

Large Bottles: 250ml or 500ml

Considerations for Pack Sizes:

Standardized Dosage: Each pack would need to provide clear information about the standardized dosage of mitragynine and 7-hydroxymitragynine per gram or per capsule to ensure safety.

User Categories: Packs might cater to different user needs, such as smaller trial packs for new users and larger bulk packs for those using it regularly for therapeutic purposes.

The final pack sizes would likely depend on the outcome of regulatory approvals, dosage guidelines, and product format (capsules, powder, liquid extract, etc.).

18. In what forms do products containing the substance currently appear in Australia?

Enter each form on a separate line (only if applicable).

As of now, products containing mitragynine and 7-hydroxymitragynine (the active compounds in kratom) are not legally available in Australia. Kratom is classified as a Schedule 9 (Prohibited Substance) under the Poisons Standard, meaning its sale, supply, and use are restricted except for approved medical or scientific research purposes.

Since kratom is prohibited, there are no legally marketed forms of products containing these substances in Australia. However, in countries where kratom is legal, the typical forms it appears in include:

Powdered Leaf: The most common form, made from ground kratom leaves.

Capsules: Kratom powder encapsulated for easier consumption.

Liquid Extracts: Concentrated extracts of mitragynine and 7-hydroxymitragynine in liquid form.

Tinctures: Alcohol-based extracts of kratom, used in drops or small amounts.

Resin/Concentrates: A highly concentrated form of kratom for more potent effects.

Teas: Kratom leaves brewed as a tea, popular in traditional use.

In Australia, however, none of these forms are legally marketed due to the regulatory restrictions.

19. What are the proposed forms for products containing the substance?

Enter each form on a separate line (only if applicable).

If kratom (containing mitragynine and 7-hydroxymitragynine) were to be regulated and legalized in Australia, the proposed forms for products could follow similar patterns to those seen in countries where kratom is legal. These forms would aim to provide standardized, controlled access for safe use. The proposed forms might include:

1. Powdered Leaf Form:

Description: Finely ground kratom leaves.

Usage: Users typically mix the powder with water, juice, or other beverages. This is the traditional form used in Southeast Asia.

Packaging: Available in small, medium, or bulk packs (e.g., 25g, 100g, 500g, 1kg).

2. Capsules or Tablets:

Description: Pre-measured doses of kratom powder in capsule or tablet form.

Usage: Provides convenience and accurate dosing, making it easier for users to control intake.

Packaging: Usually available in packs of 30, 60, 100, or more capsules, with clear labeling of mitragynine content per capsule.

3. Liquid Extracts:

Description: Concentrated kratom extracts in liquid form.

Usage: Taken in small, controlled doses, typically using a dropper.

Packaging: Available in small bottles (10ml, 30ml, 50ml) with clear instructions on dosage and concentration of active compounds.

4. Tinctures:

Description: Alcohol-based extracts of kratom that offer a more concentrated form of the active alkaloids.

Usage: Often taken sublingually or mixed into drinks.

Packaging: Packaged in small bottles with precise dosing instructions.

5. Kratom Teas:

Description: Dried kratom leaves or tea bags for brewing.

Usage: Brewed as a tea, with measured portions of kratom to control dosage.

Packaging: Loose-leaf kratom or pre-packaged tea bags (e.g., 1-3g per tea bag), similar to herbal tea products.

6. Resin or Concentrated Forms:

Description: Solid, sticky substance made from kratom extracts, offering a more potent option.

Usage: Dissolved in hot water or used as a small, concentrated portion for stronger effects.

Packaging: Packaged in small containers with clear usage and dosing guidelines.

7. Chewable Tablets or Lozenges:

Description: Kratom in a chewable form, similar to herbal lozenges.

Usage: Provides a convenient and slower release of active compounds through the oral mucosa.

Packaging: Small packs of lozenges, labeled with alkaloid content per piece.

8. Topical Creams or Ointments:

Description: Kratom-infused topical products for potential local pain relief.

Usage: Applied directly to the skin, potentially for muscle aches or localized discomfort.

Packaging: Creams or ointments in tubes or jars (e.g., 50g or 100g).

Purpose of application

20. What title would you like to give to this application?

Application for Regulatory Amendment of Mitragynine and 7-Hydroxymitragynine in the Poisons Standard for Controlled Use of Kratom in Australia

21. What type of change to the Poisons Standard are you requesting in this application?

Create a new entry in the Poisons Standard for a substance not currently included in the Poisons Standard
Amend or add entries for a substance already included in the Poisons Standard
Amend another part of the Poisons Standard that is not mentioned above

22. Provide an overview of your application in plain English (500 words or less).

This application seeks to amend the current regulation of mitragynine and 7-hydroxymitragynine, the primary active compounds found in Mitragyna speciosa (kratom). Kratom is a plant native to Southeast Asia, traditionally used for pain relief, mood enhancement, and increased energy. Despite its traditional uses and growing popularity globally, kratom is currently classified as a Schedule 9 (Prohibited Substance) in Australia, which restricts its sale, possession, and use. This application aims to reconsider this classification to allow for regulated and controlled access to kratom, considering both public health and potential benefits.

Why Change the Regulation?

Kratom has been used for centuries in its native regions and is gaining attention in the Western world as a natural alternative for managing chronic pain, anxiety, depression, and fatigue. The main compounds, mitragynine and 7-hydroxymitragynine, act on the body's opioid receptors, providing pain-relieving effects without the same level of addiction risk associated with synthetic opioids. Many individuals also turn to kratom to manage opioid withdrawal symptoms, as it can help ease cravings and withdrawal effects in a less intense way.

However, kratom remains controversial, with concerns around potential misuse and addiction. While some adverse effects have been reported, these are often linked to excessive use or unregulated products. By implementing a controlled regulatory framework, Australia could ensure that kratom is used safely, with standardized dosages and clear labeling.

Proposed Amendments:

Reclassification of Kratom's Active Compounds: Reclassify mitragynine and 7-hydroxymitragynine to allow for regulated use, similar to other herbal supplements or plant-based medications. This would involve placing kratom in a lower schedule category, allowing for controlled distribution.

Introduction of Controlled Pack Sizes and Forms: Allow kratom to be sold in specific forms such as powder, capsules, liquid extracts, or teas, with clear dosing instructions. Proposed pack sizes might include smaller quantities for personal use, such as 50g of powder or 30 capsules, to ensure responsible consumption.

Establishment of Dosage Guidelines: Implement strict dosage limits, ensuring that products are labeled with clear concentrations of mitragynine and 7-hydroxymitragynine per serving. This will help users manage consumption responsibly and prevent overuse.

Support for Further Research: Encourage more scientific research on kratom's therapeutic uses and safety profile. This will help provide more comprehensive data on the benefits and risks associated with its use, informing future regulatory decisions.

Conclusion:

This application proposes a balanced approach that prioritizes public health and safety while acknowledging the potential benefits of kratom for pain relief, mental health, and opioid withdrawal support. By regulating the sale and use of kratom, Australia could ensure consumers have access to safe, standardized products while preventing misuse and addressing health concerns.

Amendments to the Schedules of the Poisons Standard

23. In what Schedules of the current Poisons Standard is the substance included?

Schedule 9

24. What is the current text for the substance as it appears in the Schedules of the Poisons Standard?

SCHEDULE 9 – PROHIBITED SUBSTANCES

MITRAGYNINE and 7-HYDROXYMITRAGYNINE – when extracted from any plant of the genus Mitragyna or any preparation, admixture, or substance containing these compounds.

In what Schedules of the Poisons Standard do you propose the substance to be included?

Schedule 4

Schedule 8

25. What text are you proposing for the substance in the Schedules and Index of the Poisons Standard?

Here is a proposed text for mitragynine and 7-hydroxymitragynine in the Schedules and Index of the Poisons Standard, depending on whether the substances are reclassified under Schedule 4 or Schedule 8:

Option 1: Schedule 4 (Prescription Only Medicine)

SCHEDULE 4 – PRESCRIPTION ONLY MEDICINE

MITRAGYNINE and 7-HYDROXYMITRAGYNINE – when extracted from any plant of the genus Mitragyna, or any preparation, admixture, or substance containing these compounds, except when included in Schedule 9.

Option 2: Schedule 8 (Controlled Drug)

SCHEDULE 8 – CONTROLLED DRUG

MITRAGYNINE and 7-HYDROXYMITRAGYNINE – when extracted from any plant of the genus Mitragyna, or any preparation, admixture, or substance containing these compounds, except when included in Schedule 9.

Index Entry Proposal:

MITRAGYNINE – Schedule 4 or Schedule 8 (as determined), except when included in Schedule 9.

7-HYDROXYMITRAGYNINE – Schedule 4 or Schedule 8 (as determined), except when included in Schedule 9.

Amendments to the Appendices of the Poisons Standard

26. In which Appendices of the current Poisons Standard is the substance included?

Not in any Appendix

s 22 [redacted]

27. What is the current text for the substance as it appears in the Appendices of the Poisons Standard?

28. In what Appendices of the Poisons Standard do you propose the substance to be included?

Appendix D

Appendix F

Appendix K

s 22 [redacted]

29. What text are you proposing for the substance in the Appendices and Index of the Poisons Standard?

(Only if applicable)

Appendix D (Additional Controls or Supply Requirements on Poisons)

MITRAGYNINE and 7-HYDROXYMITRAGYNINE – when included in Schedule 4 or Schedule 8:

Must only be supplied by prescription or through a licensed healthcare provider.

Possession without authorization is prohibited.

Records of supply and prescription must be maintained.

Appendix F (Warning Statements and Safety Directions for Poisons)

MITRAGYNINE and 7-HYDROXYMITRAGYNINE – when included in Schedule 4 or Schedule 8, the following warning statements must appear on the product label:

"Use only as directed by a healthcare professional."

"Not for use in individuals under 18 years of age."

"May cause sedation or dizziness – do not drive or operate machinery after use."

"Do not combine with alcohol or other sedatives."

Appendix K (Drugs Required to Be Labeled With a Sedation Warning)

MITRAGYNINE and 7-HYDROXYMITRAGYNINE – when included in Schedule 4 or Schedule 8, products containing these substances must include the following sedation warning:

"This product may cause drowsiness. If affected, do not drive or operate machinery."

Index Entry Proposal:

MITRAGYNINE – Schedule 4 or Schedule 8 (as determined), except when included in Schedule 9; see Appendix D, Appendix F, Appendix K.

7-HYDROXYMITRAGYNINE – Schedule 4 or Schedule 8 (as determined), except when included in Schedule 9; see Appendix D, Appendix F, Appendix K.

Rationale for the Proposed Text:

Appendix D: Imposing additional controls on the supply and possession of mitragynine and 7-hydroxymitragynine ensures that the substances are only accessible through authorized channels, preventing misuse.

Appendix F: Requiring specific safety and warning statements helps ensure that consumers are aware of potential risks and usage guidelines.

Appendix K: Since kratom's active compounds can cause sedation, a warning about drowsiness and its effects on activities such as driving is necessary to ensure consumer safety.

This proposed text allows for regulated use of kratom's active compounds while emphasizing public safety and controlled access.

Detailed claims against the requirements of the scheduling criteria

a. What are the risks and benefits associated with the use of the substance?

b. What are the purposes for which the substance is to be used and the extent of use of the substance?

Risks and Benefits of Mitragynine and 7-Hydroxymitragynine (Kratom)

1. Risks Associated with the Use of the Substance:

Potential for Dependence and Addiction: Mitragynine and 7-hydroxymitragynine act on opioid receptors in the brain, which can lead to dependency when used over time. Some users report withdrawal symptoms similar to opioids, including irritability, insomnia, muscle aches, and mood swings.

Sedation and Drowsiness: At higher doses, kratom can have sedative effects, causing drowsiness, lethargy, or impaired motor function. This increases the risk of accidents, particularly when operating machinery or driving.

Cognitive and Motor Impairment: High doses of kratom can result in confusion, impaired judgment, or reduced coordination, potentially increasing the risk of injury or accidents.

Risk of Overuse and Toxicity: In unregulated environments, where dosages are unclear, there is a risk of overuse. In severe cases, this can lead to toxicity, which may present symptoms such as nausea, vomiting, agitation, and, rarely, respiratory depression.

Drug Interactions: Kratom's compounds can interact with other medications, especially depressants such as alcohol, opioids, and benzodiazepines, increasing the risk of dangerous side effects such as respiratory depression or overdose.

Contamination in Unregulated Products: In countries where kratom is not regulated, some products have been found to contain contaminants such as heavy metals or adulterants, which can pose additional health risks.

Lack of Long-term Safety Data: There is limited scientific research on the long-term effects of kratom use, making it difficult to fully assess its safety profile, especially for chronic users.

2. Benefits Associated with the Use of the Substance:

Pain Relief: Kratom, particularly its active compounds mitragynine and 7-hydroxymitragynine, has been shown to provide pain relief, making it potentially useful for individuals with chronic pain conditions, including arthritis, fibromyalgia, and neuropathic pain.

Opioid Withdrawal Aid: Some individuals have reported using kratom to manage withdrawal symptoms from opioids. The compounds act on opioid receptors but with less intensity than traditional opioids, potentially helping ease cravings and withdrawal effects.

Mood Enhancement and Anxiety Reduction: At lower doses, kratom acts as a stimulant, boosting mood, increasing energy, and reducing feelings of anxiety or depression. It has been used by some people as an alternative to antidepressants or anxiolytics, though more research is needed.

Increased Energy and Focus: At low to moderate doses, mitragynine has stimulating properties, helping users feel more energetic, focused, and alert. This is particularly appealing to individuals using kratom in place of caffeine or other stimulants.

Traditional and Cultural Use: Kratom has a long history of traditional use in Southeast Asia, where it is used to enhance stamina, treat various ailments, and as a general wellness herb.

Fewer Respiratory Depression Risks than Opioids: While mitragynine and 7-hydroxymitragynine act on opioid receptors, they are believed to have a lower risk of causing life-threatening respiratory depression compared to synthetic opioids like morphine or oxycodone.

Conclusion:

The risks and benefits associated with mitragynine and 7-hydroxymitragynine vary based on dosage, duration of use, and individual response. While the substances show promise for pain relief, mood enhancement, and helping individuals manage opioid withdrawal, the potential risks of dependence, cognitive impairment, and drug interactions highlight the need for careful regulation. Controlled access, clear dosage guidelines, and further research are essential to mitigate risks while allowing therapeutic use.

c. What is the toxicity of the substance?

Toxicity of Mitragynine and 7-Hydroxymitragynine:

Acute Toxicity:

Low Doses: At low doses, mitragynine primarily acts as a stimulant, causing increased energy and alertness. Toxic effects are minimal at this level, and users may experience mild side effects like nausea or dry mouth.

Moderate to High Doses: At higher doses, kratom can cause sedation, dizziness, confusion, and impaired coordination. While serious acute toxicity is rare, high doses have been associated with more severe symptoms, such as:

Nausea and vomiting

Agitation

Tachycardia (increased heart rate)

Hypertension (increased blood pressure)

Seizures (in rare cases, especially in individuals with underlying conditions or those combining kratom with other substances)

Chronic Toxicity:

Dependence and Withdrawal: Long-term, heavy use of kratom may lead to physical dependence, with withdrawal symptoms similar to opioids, including irritability, muscle aches, insomnia, and cravings.

Hepatotoxicity: There are some reports of liver toxicity associated with chronic kratom use. Symptoms may include jaundice (yellowing of the skin and eyes), dark urine, and fatigue, although these cases are relatively rare.

Kidney Toxicity: Although not well-documented, chronic use of kratom may pose a risk to kidney health, especially in combination with dehydration or overuse.

Lethal Dose (LD50):

LD50 for Mitragynine: The LD50 (the lethal dose for 50% of subjects) of mitragynine in animal studies is estimated to be about 477 mg/kg in mice when administered orally. This suggests that a very high dose is required to reach fatal toxicity levels. However, human data on lethal doses is limited, and toxicity may vary greatly depending on individual factors.

Respiratory Depression:

Unlike traditional opioids, kratom's active compounds appear to have a lower risk of causing life-threatening respiratory depression at moderate doses. This is a significant difference from synthetic opioids like morphine, which can suppress breathing and lead to death in overdose situations. However, at very high doses, respiratory depression is still a concern.

Combination with Other Substances:

Polypharmacy Risks: The combination of kratom with other substances, particularly central nervous system depressants (such as alcohol, opioids, or benzodiazepines), significantly increases the risk of toxicity. This can lead to dangerous outcomes like respiratory depression, severe sedation, or overdose.

Fatalities: Most fatalities attributed to kratom involve the concurrent use of other substances, particularly opioids or other sedatives. Pure kratom use alone is rarely associated with fatal outcomes, though high doses can lead to severe health complications.

Gastrointestinal Toxicity:

Gastrointestinal Symptoms: High doses of kratom often lead to gastrointestinal issues, including constipation, nausea, and abdominal discomfort. Chronic use may exacerbate these symptoms and lead to more serious digestive problems.

Conclusion on Toxicity:

At Low to Moderate Doses: Kratom is generally considered to have low toxicity when used in moderation. Side effects may include nausea, mild dizziness, or constipation.

At High Doses: Toxicity becomes more apparent, with risks including sedation, confusion, increased heart rate, agitation, and, in rare cases, seizures.

Chronic Use: Long-term use can lead to dependence, liver toxicity, and potential kidney damage. Withdrawal symptoms can also occur with regular heavy use.

Fatalities: Fatal outcomes are rare and are usually linked to the use of kratom in combination with other substances, particularly depressants like opioids or alcohol.

While kratom may not be as acutely toxic as synthetic opioids, the potential for misuse and long-term health effects makes it important to regulate its use carefully and ensure that consumers are educated about safe dosing and potential risks.

d. What is the dosage, formulation, labelling, packaging and presentation of the substance?

The appropriate dosage for kratom varies depending on the user's needs, the product's strength, and the desired effects. Below are general dosage guidelines based on existing research and anecdotal reports, which would need to be formalized in any regulated market:

Low Dose (1-2 grams of kratom powder or equivalent):

Stimulant effects, including increased energy and alertness.

Ideal for mood enhancement and managing mild fatigue.

Moderate Dose (3-5 grams of kratom powder or equivalent):

Mild pain relief and mood enhancement.

Anxiety relief and moderate sedation.

High Dose (6-8 grams of kratom powder or equivalent):

Strong pain relief and sedative effects.

May cause drowsiness, nausea, or mild impairment of cognitive function.

Very High Dose (9+ grams of kratom powder or equivalent):

Strong sedative effects and higher risk of adverse effects, including nausea, dizziness, and confusion.

Not recommended due to increased risk of toxicity and dependence.

For standardized kratom extracts or capsules, the dosage would need to be adjusted based on the concentration of mitragynine and 7-hydroxymitragynine. The labeling should clearly specify the alkaloid content per serving.

2. Formulation:

Kratom and its active compounds may be formulated in various forms, with clear labeling for alkaloid content to ensure precise dosing and safety:

Powdered Leaf Form:

Traditional kratom leaves, finely ground into powder.

Typically taken mixed with liquids or brewed as tea.

Capsules or Tablets:

Pre-measured doses of kratom powder or extract encased in gelatin or cellulose capsules.

Each capsule/tablet should specify the mitragynine content (e.g., 2-10 mg per capsule).

Liquid Extract:

Concentrated liquid extracts, standardized to contain a specific amount of mitragynine and 7-hydroxymitragynine.

Common formulations may range from 10mg to 50mg of mitragynine per milliliter, with clear dosage instructions.

Tinctures:

Alcohol-based extracts of kratom alkaloids, often administered via dropper for sublingual use.

Formulated to ensure precise dosing with concentrations listed on the packaging.

Teas or Beverage Forms:

Dried leaves or pre-packed tea bags containing a fixed amount of kratom powder (e.g., 1-2 grams per tea bag).

Clear dosage information and instructions for safe use.

3. Labeling:

Proper labeling would be essential to ensure safe use and to comply with regulatory requirements. The labels for kratom products containing mitragynine and 7-hydroxymitragynine should include:

Active Ingredient Information:

List the amount of mitragynine and 7-hydroxymitragynine per dose or serving (e.g., per capsule or milliliter in liquid extracts).

Dosage Instructions:

Clear guidelines on recommended doses based on the product formulation.

Warnings to avoid exceeding the maximum recommended daily dose (e.g., "Do not exceed 8 grams per day of kratom powder or equivalent").

Safety Warnings:

"May cause drowsiness or dizziness. Do not drive or operate machinery."

"Not for use by individuals under 18 years of age."

"Consult a healthcare provider before use if you are pregnant, breastfeeding, or taking medication."

"Do not combine with alcohol, opioids, or other sedatives."

Contraindications and Side Effects:

List potential side effects (e.g., nausea, dizziness, constipation).

Include contraindications for use with certain medical conditions (e.g., liver or kidney disease).

4. Packaging:

The packaging of kratom products must be child-resistant, tamper-proof, and compliant with regulatory standards to ensure safety. Proposed packaging options include:

Powdered Kratom:

Packaged in sealed, opaque bags or jars with clear labeling of the contents and recommended serving size (e.g., 100g, 250g, 500g).

Should include a measuring scoop for precise dosing.

Capsules/Tablets:

Packaged in bottles containing 30, 60, or 100 capsules, with clear information about the mitragynine content per capsule.

Child-resistant and tamper-evident packaging is essential to prevent accidental ingestion.

Liquid Extracts/Tinctures:

Sold in dark glass bottles with a dropper, typically in 10ml, 30ml, or 50ml sizes.

Clear labeling of concentration (e.g., 10mg of mitragynine per milliliter) and dosage instructions.

Teas:

Packaged in tea bags or loose-leaf form in resealable bags or tins, typically containing pre-measured doses (e.g., 1g or 2g per tea bag).

5. Presentation:

The presentation of kratom products should emphasize professionalism, safety, and clear information. Products should:

Avoid misleading health claims (e.g., "cures pain" or "solves addiction").

Focus on responsible use and offer guidance for safe consumption.

Include clear branding that differentiates the product as a controlled, regulated substance intended for responsible therapeutic use.

Presentation could also include educational materials, such as brochures or QR codes linking to safety guidelines, to help users understand appropriate use and potential risks.

Summary:

Dosage: Varies from 1-8 grams of kratom powder or equivalent, depending on desired effects and product type.

Formulation: Includes powder, capsules, liquid extracts, tinctures, and teas.

Labeling: Must provide clear dosage instructions, alkaloid content, safety warnings, and side effects.

Packaging: Child-resistant, tamper-proof, and compliant with safety regulations, with clearly labeled contents.

Presentation: Professional, emphasizing safety and responsible use, with no misleading health claims.

These guidelines aim to ensure safe and controlled access to kratom while minimizing risks associated with improper use or overconsumption.

e. What is the potential for the substance to be misused or abused?

The potential for mitragynine and 7-hydroxymitragynine (the active compounds in kratom) to be misused or abused is a key concern for regulators, and there are several factors that contribute to this risk:

1. Opioid-Like Effects:

Mechanism of Action: Mitragynine and 7-hydroxymitragynine act on opioid receptors in the brain, producing effects similar to opioids, such as pain relief, sedation, and euphoria. This makes kratom particularly attractive to individuals seeking to alleviate pain, enhance mood, or self-treat opioid withdrawal symptoms.

Euphoria: At higher doses, users may experience a euphoric high similar to opioids, which increases the risk of abuse as individuals may take higher-than-recommended doses to achieve these effects.

2. Risk of Dependence and Addiction:

Dependence: Regular, long-term use of kratom can lead to physical dependence. Users may develop tolerance, requiring higher doses to achieve the same effects, which can escalate the risk of misuse.

Withdrawal Symptoms: Individuals who stop using kratom after heavy or prolonged use may experience withdrawal symptoms similar to opioids, including irritability, anxiety, muscle aches, insomnia, and cravings, which can drive continued misuse.

Psychological Addiction: While physical dependence can occur, kratom also has the potential for psychological addiction, where users feel compelled to use it for its mood-enhancing and anxiety-reducing effects.

3. High-Dose Usage:

Dose Escalation: As users build tolerance, they may take higher doses to achieve the desired effects. High doses of kratom can result in stronger opioid-like effects, such as sedation and euphoria, increasing the risk of misuse.

Overuse Risks: At very high doses, kratom can cause side effects like nausea, dizziness, confusion, and even seizures, making overuse dangerous.

4. Self-Medication for Opioid Withdrawal:

Opioid Replacement: Many individuals use kratom as an alternative to prescription opioids or to manage opioid withdrawal symptoms. While kratom can alleviate withdrawal symptoms, the unregulated use of kratom for this purpose can lead to misuse or addiction to kratom itself.

Lack of Medical Supervision: People who self-medicate with kratom for withdrawal symptoms often do so without medical guidance, leading to potential misuse or inappropriate dosing.

5. Ease of Access in Unregulated Markets:

Unregulated Availability: In places where kratom is legal but unregulated, it is easily accessible in various forms (powder, capsules, extracts), which can lead to recreational misuse, particularly if users do not follow safe dosage guidelines.

Unclear Dosage: Some kratom products in unregulated markets do not provide accurate or clear dosing information, leading to the risk of taking too much, either unintentionally or intentionally, to achieve stronger effects.

6. Potential for Polydrug Abuse:

Combination with Other Substances: Kratom is often used in combination with other substances, such as alcohol, opioids, or benzodiazepines, to enhance its effects. This increases the risk of dangerous interactions, overdose, and life-threatening side effects, such as respiratory depression.

Recreational Use: In certain cases, kratom may be misused recreationally, either alone or with other substances, to enhance its sedative or euphoric effects. This is a form of abuse that can lead to more severe consequences.

7. Lack of Regulatory Oversight:

Quality Control: In countries where kratom is unregulated, products may be adulterated with other substances, such as synthetic opioids or stimulants, to enhance potency. This increases the risk of accidental overdose or severe side effects.

Inconsistent Alkaloid Concentration: Without standardized products, users may not know the concentration of mitragynine or 7-hydroxymitragynine in the product they are consuming, leading to unintentional misuse.

8. Psychological and Social Factors:

Mental Health Risks: Individuals with a history of substance abuse or mental health issues (such as depression or anxiety) may be more prone to misusing kratom as a form of self-medication or escape, increasing the potential for abuse.

Social Pressure: In certain social circles, particularly where recreational use is normalized, kratom can be misused for its psychoactive effects.

Potential for Misuse vs. Opioids:

While kratom's opioid-like effects can lead to misuse, the severity of its potential for abuse is generally considered lower than synthetic opioids like morphine, oxycodone, or heroin. Kratom does not produce the same intense respiratory depression as traditional opioids, which lowers the risk of fatal overdose when taken alone. However, the risk of misuse remains significant, particularly in individuals with a history of substance abuse.

Conclusion:

The potential for misuse or abuse of mitragynine and 7-hydroxymitragynine primarily arises from their opioid-like effects, the risk of dependence, and the potential for dose escalation or recreational use. While kratom has therapeutic benefits for pain relief and opioid withdrawal, the unregulated use, lack of dosage control, and combination with other substances significantly increase the potential for abuse. Regulatory measures such as controlled access, clear dosage guidelines, and product labeling would be essential in mitigating these risks.

f. Are there any other matters that may be necessary to protect public health?

Yes, there are several additional matters that may be necessary to consider in order to protect public health if mitragynine and 7-hydroxymitragynine (kratom) were to be regulated and made available for use. Ensuring public health safety would require a multi-faceted approach, including:

1. Education and Public Awareness Campaigns:

Consumer Education: Public awareness campaigns would be crucial to inform consumers about the potential risks and benefits of kratom. Many users may not fully understand the dosage requirements, side effects, or potential interactions with other medications. Educational efforts should focus on:

Safe dosing practices.

Risks of dependence and addiction.

Potential drug interactions.

The importance of consulting healthcare professionals before use.

Healthcare Provider Training: Medical professionals, including doctors, pharmacists, and nurses, would need to be educated on the safe use of kratom, its pharmacological properties, and how to manage potential side effects, dependence, or misuse.

2. Strict Quality Control and Product Standardization:

Regulation of Product Quality: Kratom products should be subject to strict manufacturing standards to ensure consistency in alkaloid concentration and product purity. This would involve:

Testing for contaminants, such as heavy metals, pesticides, or microbial contamination.

Standardizing the concentration of mitragynine and 7-hydroxymitragynine in each product to avoid variability that could lead to overuse or accidental misuse.

Product Recalls: A system for rapid product recalls should be in place to ensure that any contaminated or dangerous kratom products are removed from the market quickly.

3. Prescription and Dispensing Controls (If Under Schedule 4 or 8):

Controlled Access: If kratom is regulated under Schedule 4 (Prescription Only Medicine) or Schedule 8 (Controlled Drug), it should only be available through authorized healthcare providers. This would help ensure that:

Users receive the appropriate dosage and form based on their medical condition.

Misuse is minimized by monitoring prescriptions and limiting refills.

Pharmacy Dispensing Requirements: Pharmacies would need clear protocols for dispensing kratom-containing products, including counseling patients on proper use, dosage, and potential side effects.

4. Monitoring and Reporting of Adverse Effects:

Adverse Event Reporting: A national system for monitoring and reporting adverse effects should be established, allowing healthcare providers and users to report any negative side effects or misuse incidents. This data would be invaluable in assessing the ongoing safety of kratom products and informing regulatory updates.

Longitudinal Studies: Funding for long-term studies would help assess the potential risks of chronic kratom use, including its impact on liver and kidney health, dependence potential, and interactions with other medications.

5. Restrictions on Marketing and Advertising:

Limitations on Claims: Strict guidelines on the marketing and advertising of kratom products should be implemented to prevent misleading claims. For example, manufacturers should be prohibited from advertising kratom as a “cure” for pain, anxiety, or opioid addiction.

Avoiding Promotion for Recreational Use: Kratom products should not be marketed for recreational use, and branding or advertising that glamorizes its psychoactive effects should be prohibited to prevent encouraging misuse.

6. Age Restrictions and Safeguards for Vulnerable Populations:

Age Limits: Kratom products should only be available to individuals aged 18 and over, as younger users may be more susceptible to misuse, addiction, or adverse effects due to still-developing brains.

Special Considerations for Vulnerable Groups: Extra safeguards should be in place for populations that may be particularly vulnerable to kratom’s effects, including individuals with mental health issues, history of substance abuse, pregnant women, and those with underlying health conditions. Warning labels should highlight these risks, and healthcare providers should be extra vigilant when prescribing or dispensing kratom to these groups.

7. Safe Disposal Programs:

Disposal of Unused or Expired Products: Establishing a safe disposal program would help prevent kratom misuse or accidental ingestion by others (such as children). Pharmacies and healthcare providers could participate in take-back programs to ensure that expired or unused kratom products are properly disposed of.

8. Enforcement Against Illegal Sales or Imports:

Regulation of Imports and Exports: Tight controls on the importation and sale of unregulated or unapproved kratom products are necessary to prevent illegal or unsafe products from entering the market. Border control measures and active enforcement of import regulations would be critical.

Crackdown on Black Market: Authorities should monitor for and shut down illegal kratom sales, particularly online or through unregulated vendors, where consumers may be exposed to mislabeled or contaminated products.

9. Research and Development for Medical Uses:

Encouraging Research: Investing in clinical research on kratom's efficacy and safety for treating pain, anxiety, opioid withdrawal, and other conditions would ensure a better understanding of its therapeutic potential. This could lead to the development of safer, more refined kratom-based medications.

10. Clear Regulatory Guidelines:

Regulatory Framework: Clear and transparent regulatory guidelines should be established for the production, distribution, and use of kratom. These should include:

Dosage limits based on alkaloid content.

Clear labeling requirements.

Mandatory safety warnings.

11. Packaging Regulations:

Child-Resistant Packaging: All kratom products should be sold in child-resistant packaging to prevent accidental ingestion by children.

Tamper-Evident Packaging: Products should have tamper-evident seals to ensure product integrity and safety for consumers.

Conclusion:

In summary, to protect public health, it would be necessary to implement a comprehensive framework that includes education, strict product quality standards, clear labeling, controlled access, adverse event monitoring, and targeted research. These measures would help mitigate the potential risks of kratom misuse or abuse while ensuring that its therapeutic benefits can be accessed safely by those who need them.

g. Would you like to provide any other information to support your application to amend the Poisons Standard?

To further support the application to amend the Poisons Standard for mitragynine and 7-hydroxymitragynine (kratom), the following additional information may be valuable:

1. International Regulatory Precedents:

Other Countries' Approaches: Provide a review of how other countries regulate kratom. For example, the United States, some Southeast Asian nations, and parts of Europe allow kratom with varying levels of control. In the U.S., the Food and Drug Administration (FDA) has not approved kratom for medical use, but it is legally available in many states. In contrast, countries like Thailand have decriminalized kratom for medical and research purposes.

Thailand's Regulatory Model: In 2021, Thailand legalized kratom for personal and medicinal use under strict guidelines. Highlighting successful models in other countries could demonstrate how kratom can be regulated safely while addressing concerns around misuse.

2. Scientific and Clinical Research:

Existing Studies: Reference peer-reviewed studies that outline kratom's therapeutic potential. Studies have shown that mitragynine and 7-hydroxymitragynine can help with pain relief, opioid withdrawal management, and mood enhancement. Highlight studies that demonstrate how these compounds act on opioid receptors with fewer side effects and a lower risk of respiratory depression than traditional opioids.

Ongoing Research: Mention any ongoing or recent studies on kratom's safety and efficacy in treating various conditions. Citing such research shows that there is scientific interest in understanding kratom's full potential, supporting its consideration for regulated therapeutic use.

3. Comparative Risk Analysis:

Lower Risk Profile Compared to Opioids: Emphasize that kratom's toxicity and overdose risk are lower than synthetic opioids, which have led to a global opioid crisis. Unlike traditional

opioids, kratom rarely causes fatal respiratory depression. This makes it a potential harm-reduction alternative for individuals struggling with chronic pain or opioid dependence.

Balance of Benefits and Risks: Discuss the risk-benefit balance in more detail. While kratom carries a risk of dependence and misuse, this risk is manageable under a controlled framework, especially when compared to the devastating effects of unregulated opioid use.

4. Economic and Social Considerations:

Economic Opportunity: Legalizing and regulating kratom could generate economic benefits through the legal sale of kratom-based products, creating jobs and supporting businesses. This could be particularly relevant for industries involved in health supplements, herbal medicine, and natural products.

Public Health Impact: Given the rise in opioid addiction, kratom could play a role in public health strategies for managing pain and supporting addiction recovery. Legal access to kratom under medical supervision could reduce opioid misuse, improving outcomes for patients dealing with chronic pain or withdrawal.

5. A Step-by-Step Regulatory Approach:

Phased Regulation: Propose a phased regulatory approach that allows for the controlled, gradual introduction of kratom products to the market. This could start with medical use under prescription (Schedule 4) or as a controlled drug (Schedule 8), with ongoing review of public health impacts and product safety.

Pilot Programs: Suggest piloting kratom products in certain regions or for specific medical uses, such as opioid withdrawal management or chronic pain treatment, under close medical supervision and regulatory oversight.

6. Proposed Risk Mitigation Strategies:

Guidelines for Safe Use: Offer additional guidelines for labeling, packaging, and dosage recommendations to reduce the risk of misuse. Standardized dosages, child-resistant packaging, and clear safety warnings would help mitigate risks.

Public Health Safeguards: Outline strategies to minimize public health risks, such as mandatory product testing for contaminants, clear dosage limits, and restrictions on marketing to vulnerable populations.

Monitoring and Adjustment: Recommend establishing a monitoring framework that allows authorities to track kratom-related health issues, adjust dosage guidelines, or introduce additional restrictions if misuse trends arise.

7. Alignment with Therapeutic Goods Administration (TGA) Principles:

TGA's Commitment to Safety: Align your proposal with the Therapeutic Goods Administration's commitment to ensuring that the public has access to safe, effective, and high-quality medicines. Emphasize that under a regulated framework, kratom products can meet these standards, protecting consumers while allowing access to a natural, potentially beneficial therapy.

8. Addressing Misuse Concerns with Regulation:

Prevention of Unregulated Sales: Highlight that strict regulation can help combat the unregulated, black-market sale of kratom products, which may be adulterated or mislabeled. By bringing kratom into a legal framework, there would be a safer, controlled marketplace with better consumer protection.

Misuse Deterrence: Introduce ideas for deterring misuse, such as placing limits on the purchase quantities of kratom, requiring identification for purchases, and implementing record-keeping for sales, especially in high-risk groups.

9. Proposed Collaboration with Health Agencies:

Collaboration with Medical and Public Health Experts: Propose collaboration with medical professionals, addiction specialists, and public health agencies to create safe guidelines for

kratom use. This could involve setting up committees to review research and develop best practices for kratom prescription and use.

10. Public Feedback and Engagement:

Public Consultation: Encourage a public consultation process to gather feedback from health professionals, researchers, patients, and other stakeholders. Engaging with the public ensures that concerns are addressed and that there is a collective approach to balancing the potential benefits and risks of kratom regulation.

Conclusion:

These additional points emphasize that mitragynine and 7-hydroxymitragynine can be responsibly regulated to maximize their therapeutic benefits while minimizing risks. By adopting a balanced, research-based, and carefully monitored approach, public health can be protected, and individuals can access an alternative, natural treatment for pain and opioid dependency. This would bring Australia in line with international trends, where kratom is being considered for its medical potential under proper regulation.

Toxicity information

30. If you have prepared a document with toxicity information, please upload your document as an attachment in an email when you send in your application.

https://consultations.tga.gov.au/tga/application-to-amend-the-ps-march-2025/consultation/download_file?squid=question-2022-02-11-7091133525-filesubquestion&user[redacted]

31. Where data is available, we encourage you to provide the acute toxicity information in the Toxicity Table above and other toxicities under the relevant sub-headings below. If there is no data available, please indicate this with words to the effect of "no information" along with your justification as to why this should not hinder the scheduling consideration.

h. Additional information on acute toxicity

Toxicity Table for Mitragynine and 7-Hydroxymitragynine

Toxicity Category Data (where available)

Acute Oral Toxicity Mitragynine: LD50 (lethal dose for 50% of subjects) is estimated to be 477 mg/kg in mice. No specific human data available.

7-Hydroxymitragynine: No specific LD50 data available.

Acute Dermal Toxicity No information. Kratom is typically consumed orally, and there is no evidence of significant dermal exposure or toxicity.

Acute Inhalation Toxicity No information. Mitragynine and 7-hydroxymitragynine are not typically inhaled; no studies exist to evaluate toxicity via this route.

Irritation (Skin, Eyes) No information. Kratom is not known to be an irritant to the skin or eyes.

Sensitization No information. There is no evidence that kratom or its alkaloids cause allergic reactions or sensitization.

Sub-chronic/Chronic Toxicity Hepatotoxicity: Some case reports of liver toxicity in chronic users, but data is limited and often confounded by other factors (e.g., substance use, underlying conditions).

Carcinogenicity No information. There is no evidence that kratom or its alkaloids are carcinogenic.

Genotoxicity No information. Limited research has been conducted on the genotoxic potential of kratom or its alkaloids.

Reproductive/Developmental Toxicity No information. There are no specific studies evaluating the reproductive or developmental toxicity of kratom. However, caution is advised during pregnancy due to potential risks.

Justification for Lack of Data:

While detailed toxicity data for mitragynine and 7-hydroxymitragynine are limited, especially regarding long-term exposure or non-oral routes of administration, this should not hinder scheduling consideration for the following reasons:

Traditional Use Evidence: Kratom has been used traditionally in Southeast Asia for centuries with relatively few reported severe adverse effects. While modern patterns of use differ in some respects, traditional evidence suggests that it is generally safe when used in moderation.

Lower Risk Compared to Opioids: The primary safety concern associated with kratom use is its potential for misuse and dependence. However, compared to opioids, kratom carries a lower

risk of life-threatening respiratory depression. This makes it a potentially safer alternative for managing pain and opioid withdrawal under controlled conditions.

Availability of Acute Toxicity Data: The available acute oral toxicity data in animal studies for mitragynine suggest a relatively high LD50, which means large doses are required to reach a lethal effect. Though human-specific data is lacking, no reports suggest kratom poses a significant acute toxicity risk at low to moderate doses.

Absence of Reported Carcinogenicity or Genotoxicity: There is no indication that kratom or its alkaloids are carcinogenic or genotoxic. While additional research would be valuable, the absence of concerning evidence in this regard suggests that these risks are low.

Other Toxicities:

Hepatotoxicity: There have been case reports of liver toxicity associated with chronic kratom use, but these cases are rare and often involve heavy, prolonged use or concurrent use of other substances. More research is needed to understand kratom's effects on the liver, but this risk appears to be minimal in moderate users.

Kidney Toxicity: Limited information is available regarding the impact of kratom on kidney function. However, chronic use without proper hydration may increase the risk of kidney-related complications in some individuals.

Addiction and Withdrawal: Chronic use of kratom can lead to dependence and withdrawal symptoms similar to opioids, including irritability, fatigue, and cravings. However, withdrawal symptoms are generally milder than those associated with stronger opioids like heroin or prescription painkillers.

Conclusion:

Although detailed toxicological data on mitragynine and 7-hydroxymitragynine is limited, the available evidence suggests that, when used in moderation and with appropriate controls, these compounds do not pose a significant acute toxicity risk. The relative safety of kratom compared to opioids, along with its potential therapeutic benefits, supports consideration for reclassification with appropriate safeguards. The lack of full data should be addressed with future research but does not necessarily prevent scheduling under more controlled categories like Schedule 4 or Schedule 8.

i. Repeat dose toxicity

Animal Studies:

There is limited data available on repeat dose toxicity for mitragynine and 7-hydroxymitragynine, and most of the evidence comes from animal studies rather than human trials.

Mitragynine in Rats:

In a 28-day oral toxicity study, rats administered mitragynine doses of 1-100 mg/kg/day showed signs of toxicity at higher doses, including:

Weight loss

Reduced motor activity

Changes in liver enzymes

These changes suggest potential liver toxicity at high doses but are not definitive for human consumption due to species differences in metabolism.

Long-Term Toxicity in Animals:

Prolonged exposure to high doses of kratom's active compounds in animal models has been associated with hepatic and renal effects, including slight liver enzyme elevations, fatty liver changes, and kidney inflammation.

High doses over extended periods may lead to neurobehavioral changes such as impaired motor function, which points to potential neurotoxicity at very high exposure levels.

2. Human Case Reports:

Most data on repeat dose toxicity in humans comes from case reports and observational studies involving chronic kratom users:

Dependence and Withdrawal:

Chronic use of kratom can lead to physical dependence and withdrawal symptoms similar to opioids, although typically less severe. These symptoms include:

Irritability

Fatigue

Muscle aches

Insomnia

Gastrointestinal distress

Withdrawal symptoms generally appear after prolonged daily use at high doses (greater than 10 grams/day).

Liver Toxicity:

There are some reports of hepatotoxicity (liver injury) in long-term kratom users, with symptoms such as jaundice and elevated liver enzymes. These cases are rare and often involve high-dose, long-term kratom use or the use of products contaminated with other substances.

Mechanism: It is suspected that oxidative stress and the generation of reactive metabolites may be responsible for liver injury in susceptible individuals, but further research is needed to confirm this.

Kidney Toxicity:

No consistent evidence of significant kidney toxicity in kratom users has been reported, although dehydration and electrolyte imbalances associated with heavy, prolonged use could contribute to kidney stress.

Cognitive and Neurobehavioral Effects:

Chronic users of high doses of kratom may experience cognitive and neurobehavioral changes, such as:

Dizziness

Confusion

Reduced attention span

Poor memory recall

These effects are generally reversible upon discontinuation of use and are more common at higher doses.

3. Tolerance and Dose Escalation:

With repeated use, tolerance to mitragynine's effects can develop, leading individuals to escalate their doses over time. This can increase the risk of dependence and other toxicity-related side effects.

Neuroadaptation: Repeated exposure to mitragynine results in neuroadaptation at opioid receptors, similar to traditional opioids, which explains the development of tolerance and withdrawal symptoms upon cessation.

4. Gastrointestinal Toxicity:

Chronic kratom users often report gastrointestinal distress, such as constipation, abdominal pain, and nausea, especially at higher doses or with long-term use.

These symptoms are similar to those seen with chronic opioid use, as kratom's alkaloids affect gastrointestinal motility.

5. Cardiovascular Toxicity:

There are occasional reports of increased heart rate (tachycardia) and elevated blood pressure in chronic users, especially at higher doses. These effects are likely related to kratom's stimulating properties at lower to moderate doses.

Chronic use could exacerbate underlying cardiovascular conditions, but severe cardiovascular toxicity is rare.

Summary of Repeat Dose Toxicity:

Animal Studies: Show potential liver and kidney effects at high doses, as well as neurobehavioral changes, but these findings may not directly translate to humans.

Human Data: Limited data suggests liver toxicity in rare cases of chronic, high-dose use. Dependence and withdrawal are common among long-term users, but the severity is generally lower than that of traditional opioids.

Tolerance: Repeated use can lead to dose escalation due to tolerance, increasing the risk of dependence and related toxicities.

Gastrointestinal: Chronic use is associated with constipation and other gastrointestinal issues.

Cardiovascular: Some evidence of tachycardia and elevated blood pressure in long-term users, but severe cardiovascular events are rare.

Justification for Lack of Comprehensive Data:

While repeat dose toxicity data is limited, particularly in humans, the available evidence suggests that moderate, controlled use of kratom is relatively safe. The observed toxicity, such as liver injury and dependence, tends to occur at high doses or with long-term use. Given the potential therapeutic benefits and the relative safety profile compared to traditional opioids, scheduling mitragynine and 7-hydroxymitragynine under a controlled framework (e.g., Schedule 4 or Schedule 8) is justified. Further research into long-term effects is recommended but should not delay regulatory consideration.

j. Genotoxicity

Genotoxicity of Mitragynine and 7-Hydroxymitragynine (Kratom)

Genotoxicity refers to the potential of a substance to damage genetic information within a cell, leading to mutations that may result in cancer or other health issues. At present, there is limited data on the genotoxicity of mitragynine and 7-hydroxymitragynine. However, the available information suggests that these compounds do not exhibit strong genotoxic effects. Below is a summary of the existing evidence:

1. In Vitro Studies:

Mitragynine:

Some in vitro studies (studies performed outside of a living organism, such as in a test tube or petri dish) have evaluated the mutagenic potential of mitragynine using assays such as the Ames test, which assesses the ability of a compound to cause mutations in bacterial cells.

Results of these tests have shown no significant mutagenic activity in standard bacterial strains. This indicates that mitragynine does not readily cause mutations at the genetic level in these assays.

7-Hydroxymitragynine:

There is no specific genotoxicity data available for 7-hydroxymitragynine, but given its structural similarity to mitragynine and the limited genotoxicity observed for mitragynine, it is reasonable to infer that 7-hydroxymitragynine may have a similar genotoxicity profile. However, this assumption requires direct study and confirmation.

2. In Vivo Studies:

There is little to no data available from in vivo genotoxicity studies (those conducted on living organisms) for either mitragynine or 7-hydroxymitragynine. As a result, no clear conclusions can be drawn about their genotoxicity in whole organisms, such as in mammals or humans, based solely on available research.

In the absence of data, in vivo testing, such as the micronucleus test (which assesses chromosomal damage in bone marrow cells), would be valuable for future research to confirm whether kratom's active compounds pose a risk of genotoxicity in living organisms.

3. Carcinogenicity and Long-Term Effects:

No known links to cancer: Although the genotoxic potential of mitragynine and 7-hydroxymitragynine remains underexplored, there have been no reported cases of kratom being linked to cancer in chronic users. The absence of such evidence supports the likelihood that these compounds do not pose a significant genotoxic or carcinogenic risk under normal use.

Given the lack of data, it is crucial to perform additional studies to assess the long-term risks of kratom use, particularly in individuals consuming high doses over extended periods.

4. Toxicity Reports:

Despite kratom's increasing use around the world, there have been no widespread reports of genotoxicity or related adverse effects linked to the consumption of kratom products in humans. Most concerns regarding kratom center around its potential for dependence and misuse, rather than genotoxic or carcinogenic risks.

Conclusion on Genotoxicity:

Based on the limited available data, mitragynine does not appear to be genotoxic, as suggested by in vitro tests such as the Ames test. There is a lack of specific data on 7-hydroxymitragynine and no conclusive in vivo data for either compound, which makes it necessary to conduct further research to clarify their genotoxicity profiles.

Justification for Lack of Data:

The lack of comprehensive genotoxicity data for mitragynine and 7-hydroxymitragynine should not hinder scheduling consideration because:

Available data suggest no significant mutagenic activity for mitragynine, and no reports link kratom to genotoxic or carcinogenic effects in humans.

Therapeutic potential of kratom's active compounds, particularly in managing pain and opioid withdrawal, makes it important to move forward with regulation and further study its long-term safety, including genotoxicity.

Further research should be encouraged alongside regulatory actions, to fill the gaps in genotoxicity and carcinogenicity data, while ensuring that kratom's potential benefits can be harnessed safely.

k. Carcinogenicity

Carcinogenicity of Mitragynine and 7-Hydroxymitragynine (Kratom)

Carcinogenicity refers to the potential of a substance to cause cancer. At present, there is very limited data regarding the carcinogenicity of mitragynine and 7-hydroxymitragynine. However, available evidence suggests that kratom and its active alkaloids do not exhibit significant carcinogenic potential. Below is a summary of what is known:

1. In Vitro and In Vivo Studies:

Mitragynine:

There are no specific studies that have directly investigated the carcinogenic potential of mitragynine in either in vitro (lab-based) or in vivo (animal-based) models.

Short-term studies evaluating mitragynine's toxicity in animals (such as rats) have not indicated any evidence of carcinogenicity, but these studies were not designed to specifically assess long-term cancer risks.

7-Hydroxymitragynine:

Similarly, no studies have assessed the carcinogenic potential of 7-hydroxymitragynine. Given the structural similarity to mitragynine, it is reasonable to assume that 7-hydroxymitragynine might have a similar safety profile, but this has not been confirmed through long-term carcinogenicity studies.

2. Epidemiological Evidence (Human Studies):

Lack of Reported Cases: Despite kratom's long history of use, especially in Southeast Asia, there is no epidemiological evidence linking chronic kratom use to cancer development. Long-term users of kratom in countries like Thailand and Malaysia have not shown a statistically significant increase in cancer rates related to kratom use.

No Known Carcinogenic Cases: To date, no clinical reports have associated kratom or its active alkaloids with carcinogenic effects in humans. Most toxicity concerns around kratom focus on its potential for dependence, liver toxicity, and withdrawal symptoms, but not on cancer risks.

3. Carcinogenic Mechanisms:

Based on its known pharmacological activity, mitragynine and 7-hydroxymitragynine do not interact with DNA or cellular structures in ways that would typically lead to carcinogenicity. They primarily act on opioid receptors (mu, delta, and kappa), which are not directly involved in pathways related to carcinogenesis.

4. Structural Considerations:

Mitragynine and 7-hydroxymitragynine are indole-based alkaloids. While some indole compounds are known to have carcinogenic properties, these specific alkaloids have not shown such activity in available studies. Their pharmacological activity is largely limited to their interaction with opioid receptors, without clear mechanisms that would promote carcinogenesis.

5. Toxicity Reports in Chronic Users:

Long-term kratom users report various health effects, including gastrointestinal distress, fatigue, and dependence, but no significant increase in cancer has been noted. The absence of widespread cancer-related issues among long-term users suggests that the carcinogenic risk is low.

6. Regulatory Reviews:

Regulatory agencies, including the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), have reviewed kratom for its potential risks, but there has been no indication of carcinogenicity raised in these reviews. The focus of concern remains on the potential for misuse, dependence, and toxicity rather than cancer.

Conclusion on Carcinogenicity:

There is no evidence to suggest that mitragynine or 7-hydroxymitragynine are carcinogenic. No long-term studies specifically investigating carcinogenicity have been conducted, but based on current data and the absence of reported cancer cases among long-term users, the risk of these compounds causing cancer appears to be low.

Justification for Lack of Data:

The lack of comprehensive carcinogenicity studies for mitragynine and 7-hydroxymitragynine should not prevent scheduling consideration because:

Absence of clinical evidence: There is no clinical or epidemiological evidence linking kratom use to cancer, even in populations with long-term and heavy use.

Therapeutic benefit: Kratom’s potential as a harm-reduction tool for managing pain and opioid withdrawal justifies moving forward with regulation under controlled conditions, even while encouraging further research.

Low-risk profile: The current toxicological profile of kratom does not raise significant concerns about carcinogenicity, especially compared to known carcinogenic substances such as tobacco or alcohol.

Further research should be conducted to fill any gaps in knowledge, but based on current evidence, mitragynine and 7-hydroxymitragynine do not pose a significant carcinogenic risk.

I. Reproduction and developmental toxicity

Reproduction and Developmental Toxicity of Mitragynine and 7-Hydroxymitragynine (Kratom)

Reproductive and developmental toxicity refers to the potential of a substance to cause harmful effects on reproductive health, fertility, and the development of an embryo or fetus. Currently, there is limited data available on the reproductive and developmental toxicity of mitragynine and 7-hydroxymitragynine, with most of the information coming from animal studies and some anecdotal reports in humans.

1. Animal Studies:

Mitragynine in Rats:

Reproductive Toxicity:

In a study conducted on rats, mitragynine was administered at various doses, and the results showed no significant impact on the fertility of male or female rats at moderate doses.

High doses of mitragynine were associated with reduced litter size and slight decreases in sperm quality in male rats, suggesting that high, chronic doses may have an impact on reproductive health.

Developmental Toxicity:

In studies on pregnant rats, high doses of mitragynine were linked to reduced fetal weight and some developmental delays, but no gross malformations were observed.

The exact mechanism by which mitragynine might affect fetal development is not clear, but it is suspected that the effects may be related to alterations in maternal health at high doses (e.g., stress on liver and kidney function).

7-Hydroxymitragynine:

There are no specific animal studies evaluating the reproductive or developmental toxicity of 7-hydroxymitragynine. However, given its potency relative to mitragynine, similar effects may be expected, particularly at high doses.

2. Human Data:

Reproductive Health:

There is currently no robust clinical data on the effects of kratom use on human reproductive health. Anecdotal reports from kratom users do not provide clear evidence of adverse reproductive effects, but long-term, high-dose use could potentially affect fertility due to its opioid-like effects, which are known to impact the hypothalamic-pituitary-gonadal axis in opioid users.

Opioid-like effects: Mitragynine and 7-hydroxymitragynine interact with opioid receptors, and chronic opioid use has been associated with changes in reproductive hormones (e.g., reduced testosterone levels in men), which could theoretically affect fertility. However, this effect has not been systematically studied in kratom users.

Pregnancy and Fetal Development:

There are no controlled studies in humans examining the effects of kratom on pregnancy or fetal development. However, given its opioid-like properties, there is concern that chronic use during pregnancy could lead to similar effects seen with opioids, such as neonatal abstinence syndrome (NAS), a condition in which newborns experience withdrawal symptoms after birth due to in utero exposure to opioids.

Some anecdotal reports have suggested that pregnant women who use kratom may be at risk for delivering babies with low birth weight or preterm birth, but these reports are not based on systematic research and may be confounded by other factors (e.g., nutritional status, co-use of other substances).

3. Mechanisms of Reproductive and Developmental Toxicity:

Hypothalamic-Pituitary-Gonadal Axis: Like traditional opioids, mitragynine and 7-hydroxymitragynine may disrupt the hypothalamic-pituitary-gonadal axis, leading to changes in reproductive hormone levels, such as reduced testosterone and estrogen, which could affect fertility.

Placental Transfer: Since mitragynine and 7-hydroxymitragynine can cross the blood-brain barrier, it is likely that these compounds could also cross the placenta, potentially affecting fetal development. However, no direct studies on placental transfer of these compounds have been conducted.

Opioid-Like Withdrawal in Newborns: Chronic kratom use during pregnancy could potentially result in neonatal opioid withdrawal syndrome (NOWS), where infants exposed to opioid-like substances in utero experience withdrawal symptoms after birth. These symptoms could include irritability, poor feeding, tremors, and excessive crying, similar to NAS seen in infants exposed to opioids during pregnancy.

4. Breastfeeding:

There is no specific data on the transfer of mitragynine or 7-hydroxymitragynine into breast milk. However, given their opioid-like effects and fat-solubility, it is plausible that these compounds could be passed to infants through breastfeeding, potentially leading to sedation or other adverse effects in newborns.

5. Recommendations Based on Limited Data:

Pregnancy Caution: Based on the limited data and the opioid-like properties of kratom, it is prudent to advise against kratom use during pregnancy and breastfeeding due to the potential risk of developmental issues, withdrawal symptoms in newborns, and impacts on reproductive health.

Need for Further Research: There is an urgent need for more controlled studies on the reproductive and developmental effects of mitragynine and 7-hydroxymitragynine to fully understand their impact on human fertility and fetal development.

Conclusion on Reproductive and Developmental Toxicity:

Animal studies suggest that high doses of mitragynine can negatively impact fertility and fetal development, but moderate doses do not show significant toxicity.

There is no direct human data available, but based on the opioid-like effects of kratom, there is concern that chronic use could affect reproductive health and lead to withdrawal symptoms in newborns if used during pregnancy.

Further research is needed to fully understand the reproductive and developmental risks, but in the meantime, caution should be exercised, particularly in pregnant or breastfeeding women.

Justification for Lack of Data:

The absence of comprehensive reproductive and developmental toxicity studies should not hinder scheduling consideration, as the potential for harm, particularly at high doses, is already suggested by available animal studies.

The relative lack of human data emphasizes the need for careful regulation and further research but does not negate the benefits of controlling kratom under a safe regulatory framework to minimize risks, particularly for vulnerable populations such as pregnant women.

m. Observation in humans

Observations in Humans: Mitragynine and 7-Hydroxymitragynine (Kratom)

The use of kratom in humans has been documented through case reports, surveys, and anecdotal evidence, as well as in regions where kratom has been traditionally used for centuries (particularly in Southeast Asia). However, formal clinical trials on the effects of mitragynine and 7-hydroxymitragynine in humans are limited. Below are the main human observations based on available data:

1. Traditional Use in Southeast Asia:

Long-Term Use for Stamina and Pain Relief:

In countries like Thailand and Malaysia, kratom has been traditionally used as a stimulant at lower doses, providing increased stamina and relief from fatigue for manual laborers. It is also used for pain relief, particularly for muscle and joint pain.

Long-term users typically consume kratom leaves in tea or by chewing. Many users report mild side effects, such as dry mouth, constipation, and mild dependence, but significant health complications are less commonly reported in traditional settings.

Cultural and Ritualistic Use:

Kratom has been part of traditional medicine for managing diarrhea, fever, and coughs. It is also used in some ceremonies and as a folk remedy for social or psychological problems, such as anxiety and mood disorders.

2. Therapeutic Use for Pain Management and Opioid Withdrawal:

Pain Management:

In the U.S. and Europe, kratom has gained popularity as a natural alternative to opioids for chronic pain relief, particularly for conditions like fibromyalgia, arthritis, and neuropathic pain. Users report that mitragynine and 7-hydroxymitragynine provide effective pain relief without causing the intense sedation and respiratory depression associated with opioids.

At lower doses, kratom is known to have stimulating effects, while higher doses produce more sedative and pain-relieving effects.

Opioid Withdrawal:

Kratom has been widely used by individuals to self-manage opioid withdrawal symptoms, including cravings, body aches, and insomnia. Users report that kratom helps them transition off stronger opioids, such as heroin or prescription painkillers, with fewer withdrawal symptoms.

However, anecdotal reports suggest that high or long-term use of kratom can lead to dependence, and some users have reported experiencing withdrawal symptoms upon discontinuation of kratom itself.

3. Dependence and Withdrawal in Long-Term Users:

Kratom Dependence:

Long-term, daily use of kratom, especially at high doses, has been associated with the development of dependence. Withdrawal symptoms are typically milder than those seen with opioids but can include:

Irritability

Muscle aches

Insomnia

Sweating

Gastrointestinal distress (nausea and diarrhea)

These symptoms typically occur after prolonged use of higher doses (e.g., greater than 10 grams per day).

Withdrawal Management:

Withdrawal from kratom typically lasts for a few days to a week and can be managed with supportive care, although some users report experiencing cravings for kratom after cessation.

4. Adverse Effects:

Common Side Effects:

In human users, the most commonly reported side effects of kratom include:

Nausea and vomiting (especially at high doses)

Constipation

Dry mouth

Loss of appetite

Sweating and hot flashes

Dizziness or mild confusion

Sedation at high doses

These side effects tend to be dose-dependent, with higher doses associated with more intense symptoms.

Severe Adverse Effects:

Severe adverse effects are rare but have been reported in cases of high-dose use or combination with other substances. These include:

Seizures: Kratom has been associated with seizures in some case reports, particularly when taken in combination with other central nervous system depressants or stimulants.

Liver Toxicity: There are a small number of reports linking kratom use to liver injury, presenting as jaundice, elevated liver enzymes, and dark urine. These cases are relatively rare and typically occur in individuals using high doses over extended periods.

Respiratory Depression: Kratom's alkaloids are less likely to cause respiratory depression than traditional opioids, but very high doses or polydrug use (especially with opioids or alcohol) can increase the risk.

Polydrug Use:

Some adverse effects in kratom users are linked to the co-use of other substances, including prescription drugs, alcohol, or illegal drugs. This combination can lead to dangerous interactions, including respiratory depression, severe sedation, and increased risk of overdose.

5. Mental Health and Cognitive Effects:

Mood and Anxiety:

Many users report that kratom helps manage symptoms of anxiety and depression, particularly at lower doses where it acts as a stimulant. Users often describe a sense of increased well-being, reduced stress, and greater motivation.

However, some long-term users have reported experiencing anxiety, irritability, and mood swings, particularly when they try to reduce or discontinue kratom use. There are also reports of cognitive fog or reduced focus at higher doses.

Cognitive Effects:

At higher doses, kratom may cause drowsiness, confusion, and memory impairment. Long-term, high-dose users have reported decreased cognitive function, although these effects are generally reversible upon discontinuation.

6. Fatalities Associated with Kratom Use:

Rare and Usually Linked to Polydrug Use:

Fatalities directly attributable to kratom are extremely rare. Most documented cases of death involve polydrug use, where kratom was taken in combination with other substances, especially opioids, alcohol, or benzodiazepines.

In cases where kratom was the only substance detected, extremely high doses were typically involved, and the exact cause of death was not always clear (e.g., contributing health conditions).

7. Surveys and User Reports:

Surveys of Kratom Users:

Several surveys conducted in the U.S. and Europe indicate that a large number of users consume kratom for pain relief, mood enhancement, and managing opioid withdrawal. Many users report a high level of satisfaction with kratom, citing its effectiveness in reducing pain and opioid cravings with fewer side effects than prescription medications.

Some users report negative experiences, particularly when taking high doses, experiencing dependence, or using kratom alongside other substances.

8. Observational Studies:

Small-Scale Studies:

Observational studies on kratom use in Southeast Asia suggest that long-term use at low to moderate doses typically does not result in severe adverse health outcomes. However, higher doses or prolonged use may be associated with liver toxicity, gastrointestinal issues, and mild dependence.

Studies conducted in Western countries have documented similar findings, though the patterns of use (higher doses and different formulations) may result in a slightly higher risk of adverse effects, particularly dependence.

Conclusion on Human Observations:

Mild to Moderate Side Effects: In most users, kratom produces mild to moderate side effects, such as nausea, constipation, and dizziness, with more severe effects occurring at higher doses or with prolonged use.

Dependence and Withdrawal: Chronic, high-dose use can lead to dependence and withdrawal symptoms, though typically less severe than traditional opioids.

Fatalities and Severe Reactions: Fatalities are rare and typically involve polydrug use, but kratom should be used cautiously to avoid interactions with other depressants.

Therapeutic Use: Kratom is widely used for pain management and opioid withdrawal, with many users reporting positive experiences, though more controlled studies are needed to fully understand its long-term safety.

Justification for Regulatory Consideration:

The observational data from human use supports the need for controlled regulation to mitigate risks such as dependence, polydrug use, and adverse health outcomes, while allowing for its therapeutic potential to be explored under safe conditions. Further studies would help refine dosage and safety guidelines, but the available evidence suggests that regulated access can benefit many individuals while minimizing harm.

n. International regulations

International Regulations of Mitragynine and 7-Hydroxymitragynine (Kratom)

The regulation of kratom, specifically its active compounds mitragynine and 7-hydroxymitragynine, varies significantly across the world. While some countries permit its sale and use with little or no restrictions, others have banned or tightly controlled its availability due to concerns over safety, potential misuse, and public health risks.

Here is an overview of how kratom is regulated in different countries and regions:

1. United States

Legal Status: Varies by state. Kratom is not federally regulated, meaning it is legal at the national level. However, individual states and municipalities have imposed their own laws, resulting in a patchwork of regulations:

Legal: Kratom is legal in most states and can be sold in various forms (powder, capsules, extracts) without restrictions.

Banned: Some states and local jurisdictions have banned kratom, including Alabama, Arkansas, Indiana, Rhode Island, Vermont, and Wisconsin.

FDA Position: The U.S. Food and Drug Administration (FDA) has raised concerns about kratom's safety, especially its potential for addiction and misuse. The FDA has issued warnings about kratom products being marketed for unapproved uses and has blocked some imports. However, kratom remains legal under U.S. federal law, pending further research.

DEA Position: In 2016, the U.S. Drug Enforcement Administration (DEA) considered classifying kratom's active compounds as Schedule I controlled substances (like heroin and marijuana), but this was met with public opposition, and the proposal was withdrawn. Kratom remains under review.

2. Thailand

Decriminalization and Legalization: In August 2021, Thailand officially decriminalized kratom and legalized its use for personal, medical, and scientific purposes. This marked a significant change from the previous strict prohibition under Thailand's Narcotics Act, which had classified kratom as a Schedule V narcotic (the same category as cannabis).

Current Regulations:

Kratom leaves can now be legally grown, sold, and consumed.

Kratom-based products are allowed, but commercial production and sale must comply with specific government regulations.

Kratom is being explored for use in traditional medicine and as a potential aid in opioid dependence programs.

3. Malaysia

Illegal: In Malaysia, kratom (locally known as "ketum") is classified as a controlled substance under the Poison Act 1952. It is illegal to sell, possess, or consume kratom, with strict penalties for those found in violation.

Traditional Use: Despite its illegality, kratom use remains common in rural areas, where it has been used traditionally for its stimulant effects and as a remedy for various ailments.

Government Consideration: Malaysian authorities have debated whether to regulate kratom for medical use, but concerns over abuse and addiction have thus far prevented legalization.

4. Indonesia

Legal but Regulated: In Indonesia, kratom is legal and widely available, especially as Indonesia is one of the largest producers of kratom. Many kratom products sold in the U.S. and other countries are sourced from Indonesia.

Future Ban Consideration: The Indonesian government has signaled intentions to ban kratom exports by 2024, citing concerns about public health and safety. If the ban goes into effect, it could have significant impacts on the global kratom supply chain, as Indonesia is a major exporter.

5. European Union

Varies by Country: The legal status of kratom varies widely across European Union (EU) member states, with some countries allowing its use and others banning it completely.

Banned: Kratom is banned in countries like Denmark, Poland, Lithuania, Latvia, and Romania.

Legal with Restrictions: In countries like Germany and Italy, kratom can be legally purchased, but it is regulated, and its sale as a "food supplement" is restricted.

Unregulated: In several EU countries, including the Netherlands and Portugal, kratom is legal and unregulated.

Concerns in the EU: European health authorities have raised concerns about kratom's safety, especially regarding its potential for dependence and interaction with other substances. However, the EU has not issued a unified position on kratom regulation, leaving it to individual member states.

6. Canada

Legal but Restricted: In Canada, kratom is legal to possess and consume, but it is not approved for sale as a natural health product or dietary supplement. The Canadian Food Inspection Agency (CFIA) and Health Canada have issued warnings against kratom being marketed for therapeutic purposes.

Health Canada Position: The agency has stated that kratom products intended for human consumption are not authorized due to safety concerns, and kratom cannot be legally sold for ingestion. However, products labeled for external use only (such as soaps) are sometimes available.

7. Australia

Illegal: In Australia, kratom is classified as a Schedule 9 substance under the Poisons Standard, meaning it is considered a prohibited substance with no approved therapeutic use. It is illegal to import, sell, or possess kratom in any form without special authorization for research or medical purposes.

New Zealand: In contrast, New Zealand allows kratom to be prescribed by doctors under strict medical supervision.

8. United Kingdom

Illegal: Kratom is illegal in the United Kingdom, where it was banned under the Psychoactive Substances Act of 2016. This act made it illegal to produce, sell, or supply kratom due to concerns about its psychoactive effects and potential for misuse.

9. Other Countries with Bans or Restrictions:

Ireland: Kratom is a controlled substance.

South Korea: Kratom is illegal.

Israel: Kratom is banned.

Conclusion on International Regulations:

Varied Approaches: The regulation of kratom varies widely across the globe, reflecting differing views on its safety, risks of misuse, and potential therapeutic benefits.

Potential for Medical Use: In some countries, such as Thailand and New Zealand, kratom has been recognized for its medicinal potential, particularly for managing pain and opioid withdrawal. However, in many regions, the focus remains on its potential for abuse and dependence, leading to strict prohibitions.

Global Trends: There is a growing international interest in researching kratom's effects, which may lead to more uniform regulations as more data becomes available. Countries like Thailand and the U.S. have shown a willingness to reconsider kratom's legal status under controlled conditions.

Justification for Regulatory Consideration:

The international landscape shows that while kratom is often treated with caution, there are significant opportunities for regulation that balance its risks and potential benefits. The global trend toward controlled regulation, as seen in Thailand and some U.S. states, supports the idea that kratom can be regulated to minimize harm while allowing for its therapeutic use under appropriate safety measures.

o. Other toxicity information

1. Drug Interactions

Opioid-Like Activity and CNS Depression:

Mitragynine and 7-hydroxymitragynine exert opioid-like effects, which can cause central nervous system (CNS) depression, especially at high doses. This raises the risk of dangerous interactions when kratom is used in combination with other CNS depressants, including:

Opioids (e.g., morphine, oxycodone)

Benzodiazepines (e.g., diazepam, lorazepam)

Alcohol

Combining kratom with these substances can lead to enhanced sedation, respiratory depression, and, in severe cases, fatal overdose.

Serotonin Syndrome Risk:

Kratom may interact with drugs that affect serotonin levels, such as antidepressants (e.g., SSRIs, SNRIs) and tramadol. These interactions could potentially lead to serotonin syndrome, a serious and life-threatening condition characterized by symptoms like agitation, high body temperature, rapid heart rate, and confusion.

Monoamine Oxidase Inhibitors (MAOIs):

Caution should be exercised when combining kratom with MAOIs, as this combination could lead to hypertensive crises or other dangerous interactions. While specific studies on kratom-MAOI interactions are limited, similar concerns apply due to kratom's psychoactive properties.

Potential CYP450 Inhibition:

Mitragynine has been shown to inhibit some cytochrome P450 (CYP450) enzymes, which are responsible for the metabolism of many medications. This could lead to altered drug levels in the body when kratom is used concurrently with drugs metabolized by these enzymes, increasing the risk of toxicity or reducing therapeutic efficacy of those drugs.

2. Contamination and Adulteration Risks

Heavy Metals:

Some kratom products, particularly those sourced from regions with poor quality control, have been found to be contaminated with heavy metals such as lead, cadmium, arsenic, and mercury. Chronic exposure to these contaminants can result in serious health issues, including:

Kidney damage

Liver toxicity

Neurological impairments

Cancer risk

Routine testing for heavy metals should be required in regulated kratom products to protect consumer health.

Microbial Contamination:

Microbial contamination, particularly by Salmonella, has been reported in some kratom products. This can lead to serious foodborne illness, with symptoms including diarrhea, fever, and abdominal cramps. In 2018, several kratom products were linked to a multistate outbreak of Salmonella in the U.S., leading to recalls.

Ensuring good manufacturing practices (GMP) and microbial testing can reduce this risk.

Adulteration with Synthetic Drugs:

In some cases, kratom products have been found to be adulterated with synthetic drugs, including opioids (e.g., fentanyl or tramadol) or benzodiazepines. These adulterations significantly increase the risk of overdose and death, particularly in users who are unaware of the additional substances.

This risk underscores the need for strict regulation and testing of kratom products to ensure purity and consumer safety.

3. Long-Term Use and Chronic Toxicity

Potential for Tolerance, Dependence, and Abuse:

With long-term, high-dose use, kratom can lead to tolerance, meaning users require progressively higher doses to achieve the same effects. This increases the risk of dependence and withdrawal when kratom use is discontinued.

Chronic use can also lead to psychological dependence, where users feel compelled to continue using kratom despite potential negative effects on their daily lives.

Gastrointestinal Issues:

Long-term use of kratom is often associated with constipation, abdominal discomfort, and nausea, especially at higher doses. These effects are similar to those seen with other opioids, which slow gastrointestinal motility.

Neurotoxicity:

While there is no clear evidence of severe neurotoxicity, chronic high-dose use of kratom has been reported to cause dizziness, memory issues, and cognitive impairment. These effects are generally reversible upon cessation of use, but more research is needed to understand the long-term neurological effects.

4. Impact on Cardiovascular Health

Tachycardia and Hypertension:

Kratom has been associated with increased heart rate (tachycardia) and elevated blood pressure (hypertension), especially at higher doses. While these effects are generally mild, individuals with pre-existing cardiovascular conditions may be at higher risk for complications.

Arrhythmias:

Some users have reported heart palpitations or irregular heartbeats (arrhythmias) after using kratom, particularly at higher doses or when combined with other substances. However, the data on kratom's direct impact on heart rhythm is limited, and more research is needed to clarify this risk.

5. Renal Toxicity

Limited Data on Kidney Damage:

Although there is no consistent evidence linking kratom to renal toxicity, chronic use without proper hydration could potentially strain the kidneys. Dehydration, combined with long-term kratom use, may contribute to kidney stress, but more data is needed to confirm this.

Potential Impact of Contaminants:

As mentioned earlier, contaminants such as heavy metals in unregulated kratom products could have long-term effects on kidney function, particularly if exposure is chronic.

6. Immunological Effects

Allergic Reactions:

There have been reports of allergic reactions to kratom, including rash, itching, and shortness of breath, particularly in individuals who are sensitive to plant-based products. However, severe allergic reactions (such as anaphylaxis) appear to be rare.

Immune System Modulation:

There is some evidence to suggest that kratom may have immunomodulatory effects, although this is not well understood. Some users report feeling more resistant to infections when using kratom, while others experience flu-like symptoms during withdrawal, indicating that the plant may have some effect on the immune system.

7. Environmental Considerations

Environmental Impact of Kratom Cultivation:

Large-scale cultivation of kratom, particularly in Southeast Asia, could potentially have environmental impacts, including deforestation, soil degradation, and water pollution. Ensuring sustainable farming practices for kratom production is important to minimize environmental harm.

Sustainability:

Kratom is typically grown in tropical regions, and increased demand could put pressure on local ecosystems. Sustainable cultivation practices, such as shade-grown kratom and organic farming, could mitigate these concerns.

Conclusion on Other Toxicity Information

Drug interactions, especially with opioids, alcohol, and CNS depressants, are a key concern for kratom users, and can significantly increase the risk of adverse effects, including respiratory depression and overdose.

Contaminants such as heavy metals, microbes, and synthetic adulterants are major risks in unregulated kratom products, highlighting the need for strict quality control.

Long-term use of kratom can result in gastrointestinal and neurological effects, as well as potential dependence and tolerance.

More research is needed to fully understand kratom's impact on cardiovascular, renal, and immunological health, but existing data suggest that these risks are generally mild unless contaminated or used in combination with other substances.

Justification for Regulatory Consideration: Strict regulation and quality control measures, such as testing for contaminants and proper labeling to avoid dangerous drug interactions, would mitigate many of the above risks. Further research into long-term effects and potential drug interactions should accompany regulatory efforts to ensure consumer safety.

Claims against the Scheduling Policy Framework (SPF) - scheduling factors

32. How does your proposed amendment of the Poisons Standard align with the scheduling factors?

The proposed amendment to reclassify mitragynine and 7-hydroxymitragynine (kratom's active compounds) to a lower schedule (such as Schedule 4 or Schedule 8) aligns with the scheduling factors of the Poisons Standard in several key ways. Below, I will outline how this amendment fits within the framework of scheduling factors as defined by the Therapeutic Goods Administration (TGA) in Australia.

1. Risk of Misuse, Abuse, and Dependence

Current Situation:

Mitragynine and 7-hydroxymitragynine are currently classified under Schedule 9, which places them among substances considered to have a high potential for abuse and no recognized medical use.

Kratom is recognized to have opioid-like effects, leading to concerns over its potential for dependence and misuse, particularly with long-term use at high doses.

Proposed Schedule (Schedule 4 or 8):

Controlled Access: By reclassifying kratom's alkaloids to Schedule 4 (Prescription Only Medicine) or Schedule 8 (Controlled Drug), the substance can be made available under medical supervision, reducing the potential for misuse and dependence. This would allow access only through appropriate medical channels and for legitimate therapeutic purposes.

Reduction in Misuse: Strict controls on prescribing and dispensing under Schedule 4 or 8 would limit the likelihood of kratom being misused or abused, while still allowing for its controlled use in treating conditions such as chronic pain and opioid withdrawal.

Alignment with Scheduling Factors:

Factor 1 (Likelihood of abuse and extent of misuse): The proposed schedule aligns with the need to manage the risk of abuse by ensuring kratom's availability is strictly controlled under prescription or as a controlled drug. This reduces the potential for misuse while recognizing kratom's therapeutic value.

2. Potential Therapeutic Use

Current Situation:

Kratom's active compounds are currently prohibited under Schedule 9, despite evidence that they have therapeutic potential, especially in managing chronic pain and opioid withdrawal. Schedule 9 does not permit the use of substances for medical purposes, even when there is potential therapeutic benefit.

Proposed Schedule (Schedule 4 or 8):

Recognizing Therapeutic Value: Moving kratom's active compounds to Schedule 4 or 8 acknowledges their therapeutic potential. Kratom's pain-relieving and opioid withdrawal management properties offer a potentially less harmful alternative to synthetic opioids.

Medical Supervision: Under Schedule 4 or 8, kratom could be prescribed by healthcare professionals, ensuring that its use is safely monitored and managed. This would also allow for further clinical studies on kratom's safety and efficacy in a controlled environment.

Alignment with Scheduling Factors:

Factor 2 (Purpose of use and necessity for the substance): Reclassifying kratom under Schedule 4 or 8 recognizes its medicinal potential while mitigating the risks through controlled

medical access. This aligns with the purpose of providing access to substances with therapeutic value under proper medical supervision.

3. Safety Profile and Toxicity

Current Situation:

Concerns over kratom's safety have focused on the risk of dependence, adverse effects at high doses, and potential for misuse. However, evidence suggests that kratom has a lower risk of respiratory depression and fatal overdose compared to opioids, especially when used in moderation under medical supervision.

Proposed Schedule (Schedule 4 or 8):

Managing Toxicity Risks: By reclassifying kratom under a controlled schedule, its safety profile can be better managed. For example:

Dosage controls: Prescriptions would allow for careful monitoring of dosage, reducing the risk of toxicity from high doses.

Adverse effects monitoring: Physicians can monitor patients for side effects like nausea, sedation, and dependence, adjusting dosage or discontinuing use if necessary.

Drug interactions: Medical professionals can screen for potential drug interactions and contraindications, minimizing risks associated with polypharmacy (e.g., interactions with opioids, CNS depressants, or serotonergic drugs).

Alignment with Scheduling Factors:

Factor 3 (Safety in use): The proposal aligns with this factor by allowing kratom to be prescribed in safe, controlled dosages, ensuring that any risks of toxicity are monitored and managed by healthcare providers.

Factor 4 (Toxicity profile and safety): Kratom's lower toxicity profile compared to opioids, especially regarding respiratory depression, justifies its reclassification to a lower schedule. Strict oversight under medical supervision can mitigate risks associated with high-dose or long-term use.

4. Potential for Harm in the Community

Current Situation:

Kratom's status as a Schedule 9 substance prevents legitimate therapeutic use but does little to control the black market or unregulated online sales, where products may be contaminated or mislabeled, increasing the risk of harm.

Proposed Schedule (Schedule 4 or 8):

Regulated Market: Moving kratom to Schedule 4 or 8 would bring it under regulated control, reducing the risks posed by unregulated and illegal markets. This would ensure that kratom products are standardized, tested for contaminants, and clearly labeled.

Minimizing Harm: By providing safe, legal access to kratom through healthcare providers, the risk of harm to the community would be reduced, particularly regarding the use of unregulated kratom products that may be adulterated or unsafe.

Alignment with Scheduling Factors:

Factor 5 (Need to restrict availability to protect public health): Restricting kratom to controlled, medical use aligns with the need to protect public health by ensuring that kratom is only available in safe, regulated forms, and not through illegal or unsafe channels.

Factor 6 (Potential for harm, public health, or safety risk): The proposed amendment aligns with this factor by ensuring that kratom is only available under conditions that minimize the risk of harm to the broader community.

5. Impact on Access

Current Situation:

Prohibition under Schedule 9 restricts access even for individuals who could benefit from kratom's therapeutic effects, forcing some to seek it through illegal means, which increases risks of misuse, unsafe products, and adverse effects.

Proposed Schedule (Schedule 4 or 8):

Controlled but Available: Under Schedule 4 or 8, patients would have controlled access to kratom through licensed medical practitioners, ensuring that it is used appropriately and under supervision. This provides access for those who need it while minimizing the potential for misuse.

Alignment with Scheduling Factors:

Factor 7 (Access): The proposed reclassification aligns with this factor by striking a balance between restricting access to prevent misuse and allowing access for legitimate medical purposes.

6. International Alignment

Current Situation:

The current Schedule 9 classification of kratom is stricter than the regulations in many other countries where kratom is recognized for its therapeutic potential (e.g., Thailand, New Zealand, and certain U.S. states).

Proposed Schedule (Schedule 4 or 8):

Harmonization with International Standards: Reclassifying kratom to a controlled schedule aligns Australia's regulations with those of other countries that recognize kratom's medical value while implementing strict controls to minimize abuse.

Alignment with Scheduling Factors:

Factor 8 (International classification and experience): Aligning kratom's classification with international standards supports the global trend toward regulating kratom as a controlled therapeutic substance rather than an outright banned substance.

Conclusion

The proposed amendment to reclassify mitragynine and 7-hydroxymitragynine to Schedule 4 or 8 aligns well with the scheduling factors of the Poisons Standard. It balances the need to prevent misuse and protect public health while recognizing kratom's therapeutic potential. By placing kratom under controlled medical supervision, the amendment ensures that the risks associated with misuse are minimized while allowing access to those who can benefit from its medicinal properties. Further, it aligns Australia's regulations with international trends toward responsible regulation of kratom.

33. Have you read and understood the scheduling factors and Scheduling Policy Framework?

Yes

Related documents

34. References

Please enter a list of your references in the text box below:

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For all references listed, please attach the reference documents in a compressed .zip or .rar file to your application.

https://consultations.tga.gov.au/tga/application-to-amend-the-ps-march-2025/consultation/download_file?squid=question-2021-11-16-3884636770-filesubquestion&user=s 22

35. Bibliography and supporting data

Please enter a list of the bibliography or supporting data in the text box below:

For all bibliographies or support data listed, please attach all the documents in a compressed .zip or .rar file to your application.

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frontiers in Pharmacology

REVIEW
published: 28 January 2022
doi: 10.3389/fphar.2021.775073

Kratom Abuse Potential 2021: An Updated Eight Factor Analysis

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Drugs are regulated in the United States (US) by the Controlled Substances Act (CSA) if assessment of their abuse potential, including public health risks, show such control is warranted. An evaluation via the 8 factors of the CSA provides the comprehensive assessment required for permanent listing of new chemical entities and previously uncontrolled substances. Such an assessment was published for two kratom alkaloids in 2018 that the Food and Drug Administration (FDA) have identified as candidates for CSA listing: mitragynine (MG) and 7-hydroxymitragynine (7-OH-MG) (Henningfield et al., 2018a). That assessment concluded the abuse potential of MG was within the range of many other uncontrolled substances, that there was not evidence of an imminent risk to public health, and that a Schedule I listing (the only option for substances that are not FDA approved for therapeutic use such as kratom) carried public health risks including drug overdoses by people using kratom to abstain from opioids. The purpose of this review is to provide an updated abuse potential assessment reviewing greater than 100 studies published since January 1, 2018. These include studies of abuse potential and physical dependence/withdrawal in animals; *in-vitro* receptor binding; assessments of potential efficacy treating pain and substance use disorders; pharmacokinetic/pharmacodynamic studies with safety-related findings; clinical studies of long-term users with various physiological endpoints; and surveys of patterns and reasons for use and associated effects including dependence and withdrawal. Findings from these studies suggest that public health is better served by assuring continued access to kratom products by consumers and researchers. Currently, Kratom alkaloids and derivatives are in development as safer and/or more effective medicines for treating pain, substances use disorders, and mood disorders. Placing kratom in the CSA via scheduling would criminalize consumers and possession, seriously impede research, and can be predicted to have serious adverse public health consequences, including potentially thousands of drug overdose deaths. Therefore, CSA listing is not recommended. Regulation to minimize risks of contaminated, adulterated, and inappropriately marketed products is recommended.

Keywords: dietary supplement, safety, abuse potential, epidemiology, substance use disorder treatment, opioid pharmacology, Controlled Substances Act

OPEN ACCESS

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Reviewed by:
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Specialty section:
This article was submitted to Ethnopharmacology, a section of the journal Frontiers in Pharmacology

Received: *13 September 2021*
Accepted: *22 November 2021*
Published: *28 January 2022*

Citation:
Henningfield JE, Wang DW and Huestis MA (2022) Kratom Abuse Potential 2021: An Updated Eight Factor Analysis. Front. Pharmacol. 12:775073. doi: 10.3389/fphar.2021.775073

1 INTRODUCTION

This is an update to the Henningfield et al. (2018) assessment of the abuse potential of kratom based on the eight factors of the United States Controlled Substances Act (US CSA) (Henningfield et al., 2018a) and summarizes new scientific findings from January 2018 through August 2021. The CSA eight factors evaluate pharmacological actions in the brain or central nervous system (CNS) that may lead to dependence, substance use disorders, or addictions (American Psychiatric Association, 2013; National Institute on Drug Abuse, 2019; World Health Organization, 1994; O'Brien et al., 2011). Abuse potential assessments determine whether substances and medicinal products should be controlled by the CSA (scheduled), and if so the restrictiveness or level of control. Substances are only placed in Schedule I (heroin, LSD, cannabis) when there is no FDA approved therapeutic use and sufficient abuse potential to merit control. Substances with approved therapeutic uses and sufficient abuse potential must be placed in Schedules II–V. By law, an eight-factor analysis (8-FA) provides the primary pharmacological and public health basis for drug scheduling (Food and Drug Administration, 2017a; Belouin and Henningfield, 2018; Johnson et al., 2018). This assessment focuses on kratom and its alkaloids, in particular mitragynine (MG), the primary alkaloid in kratom present in sufficient amounts to account for its effects.

Kratom and its alkaloids are not approved for any therapeutic use by the FDA, are not federally controlled in the US, nor in the International Drug Control Conventions; however some countries do control kratom and/or its two primary alkaloids, MG and 7-OH-MG (Prozialeck et al., 2019; International Narcotics C, 2020a; International Narcotics C, 2020b). Six states in the US (Alabama, Arkansas, Indiana, Tennessee, Vermont and Wisconsin) have banned kratom, while five have passed consumer protection legislation to ensure consumer access to kratom with a framework for regulatory oversight (Arizona, Georgia, Nevada, Oklahoma and Utah). Maryland rejected a proposed ban and passed a minimum age of purchase law (age 21), and at this writing, several states are considering their own kratom consumer protection laws to ensure consumer access but with regulatory oversight. In 2021, Thailand decriminalized kratom farming, possession and sales. In December, 2021, the World Health Organization Expert Committee on Drug Dependence concluded "there is insufficient evidence to recommend a critical review of kratom mitragynine and 7-hydroxymitragynine" [for potential scheduling] but should be kept under surveillance (Commission on Narcotic Drugs, 2021).

In August 2016 the US Drug Enforcement Agency (DEA) proposed scheduling kratom on a temporary "emergency" basis but withdrew the proposal due to thousands of comments from kratom consumers and bipartisan members of Congress, and out of concern that people who were managing their opioid use disorder with the aid of kratom would return to opioid use. The DEA requested that FDA perform a full 8-FA and develop its own independent recommendations related to scheduling (Ingraham, 2016a; Ingraham, 2016b). Subsequently, Dr. Henningfield and his colleagues at PinneyAssociates were commissioned by the American Kratom Association's legal regulatory counsel to develop an 8-FA (Pinney Associates (2016)) for submission to DEA by December 2, 2016. In November 2017, FDA Commissioner Scott Gottlieb announced that kratom carried "narcotic like" risks of addiction and death but did not make public its October 17th recommendation to DEA to permanently place MG and 7-OH-MG in Schedule I of the CSA (Food and Drug Administration, 2017b; Food and Drug Administration, 2017c).

DEA typically responds to formal 8-FA scheduling requests within 90 days, though there is no legal timeline; however, a formal scheduling rescission order was issued on August 18, 2018 from the Assistant Secretary of Health, US Department of Health and Human Services (DHHS) (Giroir, 2018). The order included conclusions based on a DHHS review consistent with those of the Henningfield et al. (2018) 8-FA (Henningfield et al., 2018a). The DHHS rescission letter stated "mitragynine does not satisfy the first of the three statutory requisites for Schedule I"; "There is still debate among reputable scientists over whether kratom by itself is associated with fatal overdoses"; and "there is a significant risk of immediate adverse public health consequences for potentially millions of users if kratom or its components are included in Schedule I." The letter also raised concerns about "the stifling effect of classification in Schedule l on critical research needed on the complex and potentially useful chemistry of components of kratom." This letter was not made public until January 2021.

In 2017, the National Institute on Drug Abuse (NIDA) substantially increased its active research program on kratom's alkaloids and derivatives as potentially safer and less abusable medicines for pain and addiction and other disorders. The purpose of this review is to provide an update of our 2018 article on the abuse potential of kratom. It includes more than 100 new studies related to kratom abuse potential, safety, patterns of use, and potential therapeutic and public health benefits.

2 METHODS

The intent was to include all new studies published in English relevant to kratom abuse potential, safety and mechanisms of action published in since January 1, 2018 with some essential earlier studies mentioned and referenced to our 2018 review.[1] This was by comprehensive online literature searches, and direct requests to leading kratom researchers worldwide. To be concise, factors 4, 5, and 6 are considered a single group of public health related factors.[2] (Henningfield et al., 2018a; Johnson et al., 2018). Factor 8 is unchanged as neither kratom nor its constituents are scheduled.

[1]The authors welcome communications from readers on abuse-potential and safety related kratom research published since 2018 that we might have missed.

[2]For formal FDA submissions Factors 4, 5, and 6 are considered separately (see Henningfield et al., 2018a and Johnson, Griffiths, Hendricks and Henningfield, 2018 as examples), however, for temporary (also known as "emergency") scheduling, determining if a substance poses an imminent health risk is based on the analysis of all three factors combined similarly to our approach in this review.

3 RESULTS

3.1 Factor 1: Actual or Relative Potential for Abuse

A summary of the references used, along with main findings and comments from the authors of this review are included in **Table 1**.

3.1.1 Summary of 2018 Findings

There were no animal intravenous drug self-administration (IV DSA), intracranial self-stimulation (ICSS) brain reward, or physical dependence/withdrawal studies of kratom's alkaloids; however, other data suggested relatively low abuse potential as compared to opioids and other drugs of abuse (Henningfield et al., 2018a). There was evidence of morphine opioid receptor (MOR) mediated effects, and preliminary drug discrimination and conditioned place preference (CPP) studies with rats suggested abuse related effects at high intolerable human dose equivalents.

Survey data from the US and field studies in Southeast Asia (SEA) showed most kratom use was for health-related benefits, and to facilitate occupational performance. Data indicated that problem abuse and addiction were not common and was generally more tolerable and readily self-manageable as compared to opioids. A frequent reason for use was as an opioid substitute for pain and self-management of opioid, alcohol, and other drug dependence.

3.1.2 Factor 1 Science Updates

3.1.2.1 Intravenous Drug Self-Administration Trials

Rates of MG self-administration were similar to those of saline, and MG pretreatment produced dose-related reductions in morphine self-administration rates (Hemby et al., 2019). The authors concluded "The present findings indicate that MG does not have abuse potential and reduces morphine intake, desired characteristics of candidate pharmacotherapies for opiate addiction and withdrawal … ". 7-OH-MG was self-administered at high doses and pretreatment increased morphine self-administration.

MG self-administration rates in rats did not exceed those obtained with saline and MG pretreatment decreased heroin self-administration, with little effect on methamphetamine self-administration (Yue et al., 2018). The authors noted "These results suggest limited abuse liability of mitragynine and the potential for mitragynine treatment to specifically reduce opioid abuse. With the current prevalence of opioid abuse and misuse, it appears currently that mitragynine is deserving of more extensive exploration for its development or that of an analog as a medical treatment for opioid abuse." These results are consistent with human reports that kratom is useful in the management of opioid craving and withdrawal and to support opioid abstinence (Grundmann et al., 2018; Coe et al., 2019; Prozialeck et al., 2019; Garcia-Romeu et al., 2020).

Intracranial Self-Stimulation

In the ICSS model, rats equipped with brain electrodes self-deliver rewarding electrical brain stimulation. Opioids, amphetamine-like stimulants, cocaine, and other classic drugs of abuse reduce the stimulation threshold and increase the strength of the rewarding effects of drugs on ICSS (Negus and Miller, 2014). Neither MG nor 7-OH-MG showed evidence of brain rewarding effects, whereas morphine robustly and dose-dependently decreased the stimulation threshold (Behnood-Rod et al., 2020). Thus, the ICSS results suggest lower brain rewarding effects of MG as compared to morphine.

Drug Discrimination Studies

The discriminative stimulus effects of MG were evaluated in studies designed to assess generalization to morphine as well as the delta-opioid receptor agonist SNC80 and kappa-opioid receptor agonist U69593, alpha adrenergic agonists lofexidine, clonidine and phenylephrine, alpha adrenergic antagonists yohimbine and atipamezole, and the cannabinoid agonist Δ-9-tetrahydrocannabinol (Reeve et al., 2020). The strongest generalization was to lofexidine and phenylephrine, both unscheduled drugs: phenylephrine is in some over-the-counter cold medicines; lofexidine is approved for several indications including the first nonopioid for alleviating opioid withdrawal.

In a comparison of MG and 7-OH-MG across studies that included *in vitro* receptor binding and an antinociception test, MG partially generalized to morphine, whereas 7-OH-MG fully generalized to morphine in rats (Obeng et al., 2021). Similarly, Hiranita et al. (2020) found only partial generalization of oral MG to i.p. morphine in rats (Hiranita et al., 2020).

3.1.2.4 Conditioned Place Preference

Various MG preparations produced mixed CPP effects with some suggesting abuse potential at high doses. A low priming injection of MG or morphine reinstated CPP after establishment with either drug, suggesting rewarding effects for both (Japarin et al., 2021). Baclofen pretreatment prevented the acquisition and expression of MG-induced CPP (Yusoff et al., 2018). CPP was achieved in mice with a high dose methanolic extract of kratom leaves (Vijeepallam et al., 2019). In a fourth study (see also Factor 2), lyophilized (freeze-dried) kratom tea (LKT), a potential treatment for pain and opioid dependence, did not induce CPP in mice (Wilson et al., 2020).

3.1.2.5 Physical Dependence and Withdrawal

Discontinuation of morphine administration produced response rate disruptions indicating significant signs of spontaneous withdrawal, whereas discontinuation of MG administration did not produce significant signs of spontaneous withdrawal. Naloxone administration did precipitate response rate disruptions indicating withdrawal in both MG and morphine treated rats, however, this withdrawal effect was weaker and shorter lived in MG treated rats as compared to morphine treated rats (Harun et al., 2020). MG treatment also reduced naloxone precipitated withdrawal in animals receiving chronic morphine, consistent with human reports. Hassan, Pike, See, Sreenlivasan et al. (2020) compared the efficacy of MG to methadone for treating morphine withdrawal in rats concluding that MG treatment attenuated withdrawal symptoms significantly, similar to methadone and buprenorphine, and potentially with less undesired effects (Hassan et al., 2020).

TABLE 1 | Summary of references.

Factor/Description	Citations	Main findings	Comments
Factor 1: Actual or relative potential for abuse			
Intravenous Self-Administration (IV SA)	(Prozialeck et al., 2019), (Grundmann et al., 2018; Yue et al., 2018; Coe et al., 2019; Hemby et al., 2019; Garcia-Romeu et al., 2020)	No evidence of reward	MG pretreatment reduced morphine self-administration
Intracranial Self-Stimulation (ICSS)	(Negus and Miller, 2014)-(Behnood-Rod et al., 2020)	No evidence of reward for MG or 7-OH-MG	
Drug Discrimination	(Hiranita et al., 2020; Reeve et al., 2020; Obeng et al., 2021)	MG showed partial generalization to multiple drugs, including morphine 7-OH-MG showed full generalization to morphine	Strongest generalization of MG was to unscheduled drugs: phenylephrine and lofexidine
Conditioned Place Preference (CPP)	(Yusoff et al., 2018; Vijeepallam et al., 2019; Wilson et al., 2020; Japarin et al., 2021)	Mixed evidence of CPP	
Physical Dependence/ Withdrawal	(Harun et al., 2020; Hassan et al., 2020; Johari et al., 2021; Hassan et al., 2021; Hassan et al., 20211778; Harun et al., 2021a)	Mixed evidence of weak withdrawal across studies relative to morphine	MG reduces morphine withdrawal and differs from morphine withdrawal on some measures
Survey Data	(Prozialeck et al., 2019), (Grundmann et al., 2018; Coe et al., 2019; Garcia-Romeu et al., 2020), (Singh et al., 2014; Galbis-Reig, 2016; Swogger and Walsh, 2018; Smith et al., 2019; Harun et al., 2021b)	Majority use is for health benefits, not recreational use or to get high. Use is almost exclusively oral, without the tendency of many recreational substance to smoke, inject, and/or nasally insufflate	Most people reporting "kratom addiction" found it weaker and more tolerable and acceptable than "drug" addiction and were more likely so use it to manage other addictions than to use addictively
Factor 2: Scientific evidence of pharmacological effect			
Potential Therapeutic Effects	(Behnood-Rod et al., 2020; Obeng et al., 2021), (Vicknasingam et al., 2020; Chakraborty et al., 2021a)	Kratom's antinociceptive effects appear to be mediated at least partly by 7-OH-MG metabolite formation	Animal study findings are consistent for use to manage opioid use disorder and withdrawal, pain and suggest exploration for other disorders
Mechanisms of Action	(Prozialeck et al., 2019), (Behnood-Rod et al., 2020), (Hassan et al., 2019; Hiranita et al., 2019; Kruegel et al., 2019; Gutridge et al., 2020; Todd et al., 2020; Suhaimi et al., 2021)	Kratom alkaloids, including 7-OH-MG may interact with opioid receptors, but do not recruit β-arrestin 2	These are consistent with little or no respiratory depression across a broad range of doses and conditions
Kratom Minor Alkaloids and Metabolites	(Kruegel et al., 2019; Chakraborty et al., 2021a; León et al., 2021; Sharma and McCurdy, 2021), (Newman and Cragg, 2016; Sharma et al., 2019; Domnic et al., 2021a; Domnic et al., 2021b; Chear et al., 2021)	Most minor kratom alkaloids and metabolites are in de minimis levels	Some minor alkaloids might influence kratom's pharmacological effects and merit evaluation for potential therapeutic uses at much higher doses than provided by kratom
Metabolism and Metabolite Profiling	(Kamble et al., 2019; Kamble et al., 2020a; Kamble et al., 2020b)	7-OH-MG appears to metabolize differently in humans than in other species (e.g., rats, dogs, monkeys)	Animal models for kratom alone may not be fully predictive of human effects
Factor 3: Current state of scientific knowledge			
MG and 7-OH-MG PK/PD	(Hiranita et al., 2020), (Avery et al., 2019; Jagabalan et al., 2019; Maxwell et al., 2020)	Greater exposure observed with natural kratom formulations than with oral MG	
Minor Alkaloids PK/PD	(King et al., 2020; Berthold et al., 2021; Kamble et al., 2021)	Approximately one third of minor alkaloids are characterized	
Clinical Studies	(Singh et al., 2018a; Singh et al., 2018b; Singh et al., 2019a; Singh et al., 2020a; Leong Bin Abdullah et al., 2020; Leong Abdullah et al., 2021)	Long term users of kratom have no significant differences in most physiological measures compared to nonusers	These should not be considered definitive safety data but provide a foundation for further studies
Factors 4, 5, and 6—History and Current Patterns of Abuse; The Scope, Significance and Duration of abuse; What, if any, Risk is there to the Public Health			
U.S. National and Federal Survey Data	(National Institute on Drug Abuse, 2019), (Coe et al., 2019)-(Garcia-Romeu et al., 2020), (U.S. Department of health and Human Services, 2020; Schimmel et al., 2021; Covvey et al., 2020; Grundmann, 2017; Drug Abuse Warning Network, 2020; Drug Enforcement Adm, 2020a; Substance Abuse and Menta,	NSDUH Lifetime Use: 1.4%; Past Year Use 0.7%. Little evidence of use on other federal surveys either because kratom was not specifically included or did not meet the threshold for reporting	Federal survey data provide no evidence that kratom poses an imminent threat to public health but merits continuing monitoring to better understand trends in use

(Continued on following page)

TABLE 1 | (*Continued*) Summary of references.

Factor/Description	Citations	Main findings	Comments
Kratom Use Prevalence	2020; Drug Enforcement Adm, 2020b; Grundmann et al., 2021; Miech et al., 2021) (U.S. Department of Health and Human Services, 2020; Schimmel et al., 2021; Covvey et al., 2020), (Botanical Education Alliance, 2016)	Estimates range from 1.8 million to over 16 million users in the US	It appears likely that there are at least 10 million kratom users in the US but more definitive studies are needed
Kratom Use Associated Mortality	(National Institute on Drug Abuse, 2019), (Giroir, 2018), (Food and Drug Admini, 2018; Gershman et al., 2019; Henningfield et al., 2019; Olsen et al., 2019)	Risk of kratom associated death appears to be at least a thousand times lower than for morphine-like opioids	Approximately 80% of kratom positive or "involved" deaths also detected other drugs of abuse or the decedent had a history of substance use disorders in one study contribution by other drugs not possible to rule out
Mortality Risks Projected as a Result of Banning Licit Kratom	(Henningfield et al., 2018a), (Ingraham, 2016b), (Giroir, 2018), (Grundmann et al., 2018; Coe et al., 2019; Garcia-Romeu et al., 2020), (Grundmann, 2017), (Henningfield et al., 2018b; Henningfield et al., 2018c; Henningfield et al., 2018d; Prozialeck et al., 2020)	Surveys suggest that it is likely that some kratom users would return to opioid use if kratom use and possession is banned	Fears of relapse to opioid use was a serious concern voiced by thousands of users in surveys and comments to DEA and FDA
Public Health and Individual Benefits of Kratom	(Henningfield et al., 2018a), (Prozialeck et al., 2019), (Coe et al., 2019)-(Garcia-Romeu et al., 2020), (Swogger and Walsh, 2018), (Grundmann, 2017), (Drug Enforcement Adm, 2016), (Raffa, 2014)-(Pain News Network, 2018)	Kratom is used by millions of people in the US to manage substance use disorders, pain, mood disorder, and for energy and improved mental focus and alertness	Reasons for use of kratom rather than FDA approved medications included better efficacy, presumed lower risks and because it is more accessible and tolerable, and/or preferred as a "natural product". Note: such data should not be used to support therapeutic claims in labeling or marketing
Kratom Use for Managing Opioid Use/Withdrawal and Other Health Reasons	(Coe et al., 2019), (Grundmann, 2017), (Singh et al., 2019b; Singh et al., 2020b; Singh et al., 2020c)	Surveys in US and SEA report kratom is used mostly for its health benefits, including opioid withdrawal	Although management of opioid use and withdrawal is prominent, nonclinical data suggest that use for other substance use disorder management and many other disorders merit further exploration
Comment on Therapeutic Use in Context of FDA Standards	(Katz, 2004; DiMasi et al., 2016; Food and Drug Admini, 2016; Dabrowska and Thaul, 2018; Wouters et al., 2020)	While research has yet to meet FDA's standard for therapeutic efficacy (NDA), there is substantial evidence of its use and efficacy in treating opioid withdrawal symptoms, and other disorders	
Factor 7—The psychic or physiological dependence liability			
Science Updates	(Hemby et al., 2019), (Coe et al., 2019)-(Garcia-Romeu et al. 2020), (Swogger and Walsh, 2018), (Harun et al., 2021b)-(Vicknasingam et al., 2020), (Grundmann, 2017), (Grundmann et al., 2021), (Swogger et al., 2015; Smith and Lawson, 2017; Singh et al., 2018c; Leong Bin Abdullah et al., 2021)	Some chronic, frequent kratom users report dependence/addition and/or withdrawal, but this is generally more readily self-managed compared to use disorders of other drugs of abuse	

Although MG withdrawal signs are weak in rats compared to those from morphine withdrawal, there does appear to be evidence of physical dependence; however, MG withdrawal unlike morphine was not associated with anxiogenic-like subjective symptoms. When using a pentylenetetrazol (PTZ) discrimination trial to evaluate anxiogenic signs in rats after MG or morphine withdrawal precipitated by naloxone, MG showed no substitution to the PTZ discriminative stimulus, while morphine produced a dose-related PTZ-like stimulus, further supporting MG as a novel pharmacotherapeutic intervention for managing opioid use disorder (Johari et al., 2021).

Other studies of opioid or MG withdrawal suggested that specific brain proteins might serve as more sensitive biomarkers for physiological dependence in rats as compared to behavioral signs (Hassan et al., 2021). Clonidine treatment may attenuate MG withdrawal signs in rats (Hassan et al., 2021). Another recent study employed an open-field test and an elevated-plus maze test to evaluate naloxone-precipitated withdrawal from MG as compared to morphine, and provided additional evidence confirming that MG can induce physical dependence and measurable signs of withdrawal in rats (Harun et al., 2021a). Overall, the research is consistent with human reports that

kratom withdrawal is generally more modest and more readily self-manageable than that produced by opioids (e.g., 22 and as discussed in Factor 7).

3.1.2.6 Real World Evidence of Abuse and Dependence

Factors 4–6 discuss the public health aspects of kratom use; however, many of the same studies address Factor 1 concerning evidence for abuse and are mentioned here.

As reported by Henningfield, et al. (2018), although surveys and anecdotal reports in the US and SEA confirm that some kratom consumers reported "addiction" those studies also indicated that use "to get high" is relatively low as compared to opioids and other recreational drugs of abuse, and that use by smoking, injecting, and/or insufflating was rare as compared to opioids, stimulants and other recreational drugs (Henningfield et al., 2018a). Recent studies confirm that kratom intake can lead to dependence and withdrawal in some kratom users, but these are substantially less likely to interfere with family, social and occupational life and commitments as compared to opioid dependence. Moreover, kratom is widely viewed as a healthier and less life-impairing substance to replace drugs such as opioids, alcohol, and stimulants (Singh et al., 2014; Galbis-Reig, 2016; Swogger and Walsh, 2018; Prozialeck et al., 2019).

A variety of reports confirm kratom use to self-manage opioid withdrawal and that abstinence from high chronic kratom use is typically associated with milder symptomatology than abstinence from classical opioids (Grundmann et al., 2018; Smith et al., 2019; Garcia-Romeu et al., 2020). The conclusion of Prozialeck et al. (2019) and Grundmann et al. (2018) (Grundmann et al., 2018; Prozialeck et al., 2019) were further strengthened by two published US surveys which found that the overwhelming majority of kratom consumers reported that their use was for various health benefits and not for recreational purposes (Coe et al., 2019; Garcia-Romeu et al., 2020; Harun et al., 2021b).

3.1.3 Factor 1 Updated Conclusion

Diverse scientific approaches were employed to profile MG's abuse potential, finding no evidence of rewarding effects in the IV self-administration and ICSS models, and weak evidence of potential reward in the CPP procedure. MG only partially generalizes to morphine and more fully generalizes to the nonscheduled alpha-adrenergic agonists, phenylephrine and lofexidine. The new data suggest relatively low abuse potential as compared to morphine-like opioids, stimulants, and other drugs of abuse that demonstrate robust rewarding effects across all such abuse potential models. Similarly, MG's potential to produce physical dependence and withdrawal appears relatively low, but not absent, as compared to opioids in animal models. These findings are generally consistent with human reports that MG has a relatively low abuse and withdrawal potential as compared to recreationally used opioids but can reduce opioid self-administration and withdrawal. Surveys indicate that reducing opioid self-administration and withdrawal are among the most common reasons for kratom use in the US (also discussed in Factors 4, 5, and 6). New studies discussed in Factors 2–7 contribute further to the understanding of kratom's abuse potential, including its public health risks and benefits, that are part of the 8-factor abuse potential assessment.

3.2 Factor 2—Scientific Evidence of its Pharmacological Effects

3.2.1 Summary of 2018 Findings

MG and 7-OH-MG have some MOR mediated effects, but 7-OH-MG occurs at low concentrations in kratom leaves and is absent in many kratom product derivatives suggesting that the effects reported by kratom consumers are due primarily to MG. Some kratom effects were shown to be naloxone reversible (e.g., "pain" tolerance); however, MG and 7-OH-MG mechanisms of action were diverse and mediated by non-opioid transmitters and pathways (Kruegel and Grundmann, 2018). Thus, characterization of MG as an opioid "analog" or "narcotic like opioid" is not consistent with the overall evidence, leading Henningfield et al. (2018) to conclude "More research is clearly needed to elucidate receptor binding profiles and the diverse and probably complex mechanisms of action of the kratom alkaloids singly, in combination, and as commonly occur in marketed products and brewed extracts" (Henningfield et al., 2018a).

3.2.2 Factor 2 Science Updates

3.2.2.1 Potential Therapeutic Effects

Although neither kratom nor any of its alkaloids are approved for therapeutic use for any disorder, surveys discussed in *Factors 4, 5, and 6—History and Current Patterns of Abuse; the Scope, Significance and Duration of Abuse; what, if Any, Risk is There to the Public Health* and elsewhere (Henningfield et al., 2018a; Grundmann et al., 2018; Swogger and Walsh, 2018; Coe et al., 2019; Prozialeck et al., 2019; Garcia-Romeu et al., 2020) show individuals in the US and around the world describe using kratom for its health benefits. Research characterizing kratom's effects, mechanisms of action, and therapeutic kratom alkaloid use rapidly advanced since 2018. In a placebo-controlled cold pressor task evaluating anti-nociceptive effects, pain tolerance was significantly increased following consumption of a kratom tea-type decoction similar to Malaysian preparations (Vicknasingam et al., 2020). These data provided "the first objectively measured evidence obtained in controlled research with human subjects that are preliminarily supporting or confirming previously published reports of kratom pain relieving properties based on self-reports collected in observational studies".

Consistent with Vicknasingam et al. (2020)'s clinical findings, oral LKT administration to mice produced dose-related antinociceptive effects at doses that did not alter locomotion or produce CPP; there were brief, non-life threatening decreases in respiration (Behnood-Rod et al., 2020). Repeated LKT administration produced no physical dependence, but significantly decreased naloxone-precipitated withdrawal in morphine dependent mice, confirming MOR agonist activity and therapeutic LKT effect for treating pain and opioid physical dependence.

After investigating *in vitro* receptor binding affinity and *in vivo* morphine discrimination, antinociception in the "heated plate" pain test, and naloxone challenge tests in rats, the authors concluded "At human m-opioid receptor (MOR) *in vitro*, mitragynine has low affinity and is an antagonist . . . ". Overall, 7-OH-MG had stronger MOR mediated effects including antinociception (Obeng et al., 2021). An extensive series of tests characterized several minor indole and oxindole alkaloids that the authors suggest are insufficient in abundance to account for the biological effects of kratom but may show promise for the development of potential medicines including potential new chemical entities (Chakraborty et al., 2021a).

Several of these studies showed MOR mediated antinociceptive effects with little evidence of respiratory depression suggesting the potential to contribute to new generations of nonopioid analgesics.

3.2.2.2 Mechanisms of Action

Although kratom produces some effects in common with opioids, and some of its alkaloid's actions are mediated by MOR receptors, its effects and mechanisms of action are diverse and include non-opioid mechanisms of action and non-opioid acting constituent alkaloids, as discussed in earlier reviews (Henningfield et al., 2018a; Kruegel and Grundmann, 2018; Prozialeck et al., 2019). In 2021, Leon et al. (2021) investigated several alkaloids, including mitragynine, paynantheine and speciogynine that produce serotonergic effects potentially mediated by their metabolites. As the authors discuss, such actions would be consistent with some of the mood enhancing effects attributed to kratom (Kruegel and Grundmann, 2018; Sharma and McCurdy, 2021).

Kratom contains approximately 1–2% MG by weight, as well as other alkaloids (including 7-OH-MG) that typically are present at such low levels in kratom leaf material that it is uncertain if they contribute to kratom effects (Prozialeck et al., 2019). 7-OH-MG is present in low concentrations in natural kratom products, but gradually emerges *in vivo* as a MG metabolite. Kruegel et al. (2019) studied its role as a mediator of MG effects (Kruegel et al., 2019) summarizing "7-hydroxymitragynine is formed from mitragynine in mice and . . . brain concentrations of this metabolite are sufficient to explain most or all of the opioid-receptor-mediated analgesic activity of mitragynine . . . it suggests a possible explanation for the seemingly improved safety profile of mitragynine compared to classical opioid agonists . . . We believe mitragynine and related compounds have great potential as future therapeutics, but metabolic processes must be carefully considered as the field continues to advance." Hiranita, Sharma, Oyola et al. (2020) reported although "the conversion rate of 7-hydroxymitragynine from p.o. mitragynine is low, 7-hydroxymitragynine is a more potent and efficacious μ-opioid receptor agonist than mitragynine, suggesting that conversion to this metabolite may contribute to the *in vivo* μ-opioid activity of mitragynine" (Behnood-Rod et al., 2020).

Kratom is commonly consumed to enhance occupational performance and as a coffee substitute for energy at low doses. In an animal model of spatial learning and memory, high doses impaired memory (Hassan et al., 2019). Suhaimi, Hassan, Mansor and Müller (2021) reported changes in brain electroencephalogram (EEG) activity after acute and chronic MG exposure in rats, with strong effects on some measures at high doses, supporting the importance of more research on brain function and potential cognitive effects (Suhaimi et al., 2021).

Gutridge et al. (2020) pharmacologically characterized interactions between kratom extracts, kratom alkaloids, and synthetic carfentanil-amide opioids with G-proteins and beta-arrestin at mu, delta and kappa opioid receptors *in vitro,* and assessed whether they had rewarding properties and the degree to which they reduced alcohol intake (Gutridge et al., 2020). The authors concluded that "kratom alkaloids do not recruit β-arrestin 2 at the μOP, δOP, and κOP and can significantly reduce both moderate and binge alcohol intake in male and female mice. This pharmacological profile and effect on alcohol intake in rodents may explain why some find kratom useful to self-medicate for alcohol use disorder." These findings were further supported by the findings by Todd et al. (2020) who concluded "mitragynine and 7-hydroxymitragynine demonstrate functional selectivity for G-protein signaling, with no measurable recruitment of β-arrestin. Overall, the study demonstrates the unique binding and functional profiles of the kratom alkaloids, suggesting potential utility for managing pain, but further studies are needed to follow up on these *in vitro* findings" (Todd et al., 2020).

Hiranita et al. (2019) compared the effects of MG to morphine in behavioral and antinociception assays in rat models finding "Opioid receptors do not appear to mediate the disruptive effects of mitragynine on learned behavior. Mitragynine had lesser antinociceptive effects than morphine, and these did not appear to be mediated by opioid receptors. The pharmacology of mitragynine includes a substantial non-opioid mechanism" (Hiranita et al., 2019).

3.2.2.3 Studies of Kratom Minor Alkaloids and Their Metabolites, and Analogs

Advances in analytical methods are accelerating our understanding of the effects of numerous kratom alkaloids including liquid chromatography–tandem mass spectrometry assays that quantify kratom alkaloids in kratom leaf extracts and commercial products (Sharma et al., 2019).

Most of these alkaloids are present at de minimis levels with respect to human experience, effects, and safety; however, it is possible that while the majority of natural plant-based kratom preparation effects are mediated by MG, one or more minor alkaloids may also play a minor role and account for differences in kratom strains (Kruegel et al., 2019; Chear et al., 2021).

An *in vitro* pharmacological characterization of five kratom based minor alkaloids found that their low abundance made it unlikely that these alkaloids play a major mediating role in the biological actions of kratom consumed by humans, but this research may contribute to furthering the understanding of kratom mechanisms of action and opioid receptor function (Chakraborty et al., 2021a).

Kratom alkaloids are of interest as templates for novel synthesized molecules (i.e., analogs) for new medicines. One third to one half of FDA-approved medicines are based on natural plant product substances from which novel chemical entities were developed (Newman and Cragg, 2016; Domnic et al., 2021a). Such efforts are actively in progress characterizing a variety of indole and oxindole alkaloids, determining their chemical structures, and binding affinities for opioid and other receptors (Chear et al., 2021). One approach to the synthesis of novel MG analogs produced several partial MOR agonists with low G-protein activation (Chakraborty et al., 2021b). These analogs demonstrated robust analgesic effects but low respiratory depressant, locomotor, and conditioned place preference suggesting lower adverse effects including abuse potential.

Combinations of kratom alkaloids may inhibit cell proliferation and migration of nasopharyngeal carcinoma cells suggesting alkaloid or new analogs as potential cancer treatments (Domnic et al., 2021b).

3.2.2.4 MG Metabolism and Metabolite Profiling

Thirteen MG metabolites were identified in human liver microsomes (HLM) and S9 fraction studies (Kamble et al., 2019), and potential MG and other kratom alkaloids drug interactions were investigated including with pharmaceutic products (Kamble et al., 2020a).

7-OH-MG can be converted to pseudoindoxyl-MG in human plasma to a greater extent than is produced in mice, rats, dogs and cynomolgus monkeys, possibly explaining potential human effects and benefits that may not be predicted in animal studies alone (Kamble et al., 2020b).

3.2.3 Factor 2 Updated Conclusion

Kratom's main effects are due to the consumption of MG, but other minor alkaloids and metabolites, including 7-OH-MG, may also contribute to effects reported by consumers. Since 2018, many scientific advances improved our understanding of how these alkaloids and metabolites interact. Some alkaloids that contribute little to the effects of kratom may ultimately contribute to safer and more effective new medicines for a variety of disorders, as well as for general health and well-being. Development and approval of such products may be a decade or more in the future, but this rapidly advancing science is explaining how kratom works, and why its pain relieving, and other benefits occur with relatively low levels of abuse, dependence, and harmful decreases in respiration compared to opioids.

3.3 Factor 3—The State of Current Scientific Knowledge Regarding the Drug

3.3.1 Summary of 2018 Findings

The 2018 8-FA highlighted kratom's pharmacodynamic effects. Preclinical anti-nociceptive studies suggested that MG and 7-OH-MG produced such effects mediated by MOR receptors. Most information about the effects of long-term use in humans on various physiological, and cognitive parameters was based on anecdotal reports, case histories, and preliminary field studies in SEA. A two-compartment model best described human oral MG pharmacokinetics (Trakulsrichai et al., 2015).

3.3.2 Factor 3 Science Updates

New kratom pharmacokinetics studies in rats, mice and dogs document plasma MG, 7-OH-MG, and other alkaloids and minor metabolites over 12 h or more, with accompanying safety assessments. Six new clinical studies following long-term kratom use provide safety data on health, and organ and brain function were also conducted.

3.3.2.1 Pharmacokinetics and Pharmacodynamics Findings Related to MG and 7-OH-MG Safety

After oral administration of traditional or other natural kratom formulations to rats, greater systemic exposure was observed than that of an equivalent oral MG dose alone; no adverse events were reported (Avery et al., 2019).

Administration of 5 mg/kg oral MG (equivalent to approximately 3 mg/kg in humans) and 0.1 mg/kg IV MG to beagle dogs was well tolerated and produced no adverse events or major abnormalities in clinical parameters (Maxwell et al., 2020).

The estimated MG clearance (CL/F) was 2.21 L/h, absorption rate (Ka) 0.82/h, and volume of distribution (Vd) 30.8 L after oral 20, 40, and 80 mg/kg MG doses to rats (Jagabalan et al., 2019). Oral 55 mg/kg MG produced 85 ng/ml Cmax for 7-OH-MG, 14 times lower than the MG Cmax. Anti-nociception after IV MG and 7-OH-MG suggested that 7-OH-MG was more potent and efficacious than MG, and metabolic formation of 7-OH-MG contributes to *in vivo* MOR mediated effects of oral MG (Hiranita et al., 2020).

3.3.2.2 Pharmacokinetic and Pharmacodynamic Findings With Kratom's Minor Alkaloids

MG, 7-OH-MG, corynantheidine, speciogynine, speciociliatine, paynantheine, corynoxine, corynoxine-B, mitraphylline, ajmalicine, and isospeciofoline were analyzed in rat plasma after a variety of oral kratom products, with only MG, 7-OH-MG, speciociliatine, and corynantheidine quantifiable at 8 h (Kamble et al., 2021).

Speciociliatine pharmacokinetics were characterized following IV and oral dosing to help understand the potential contribution of this alkaloid to *in vivo* kratom administration effects (Berthold et al., 2021). Speciociliatine had higher systemic exposure and lower clearance compared to the other kratom alkaloids mitragynine and corynantheidine. Similarly, the pharmacokinetics of corynanthidine, a minor kratom alkaloid and perhaps a MOR antagonist, were determined after 2.5 mg/kg IV and 20 mg/kg oral doses to rats, yielding a 50% oral bioavailability, a 4.1 h Tmax and extensive distribution including in brain corpus callosum and hippocampus regions (King et al., 2020).

3.3.2.3 Safety Assessments From Clinical Studies

Kratom's anti-nociceptive effects in the cold pressor test are described in Factor 2 and its potential for physiological dependence and withdrawal are discussed in Factor 7 (Vicknasingam et al., 2020). This section summarizes six new clinical studies that assessed health and safety endpoints.

Leong Bin Abdullah et al. (2020) studied the lipid profiles, liver function and blood chemistries in 100 chronic kratom users and 100 healthy nonusers in Malaysia finding that the "liver parameters of the study participants were within normal range. The serum total cholesterol and LDL of kratom users were significantly lower than those of healthy subjects who do not use kratom. There were no significant differences in the serum triglyceride and HDL levels. However, higher average daily frequency of kratom use and increasing age were associated with increased serum total cholesterol among kratom users."

Singh, Muller, Murugaiyah et al. (2018) studied various hematological and clinical-chemistry parameters of kratom users in Malaysia (Singh et al., 2018a). They interviewed and collected blood samples from 58 "regular kratom users" and 19 "healthy controls." Findings showed there were no significant differences in the hematological and clinical-chemistry parameters of traditional kratom users and healthy controls, except for HDL and LDL cholesterol values; these were found to be above the normal reference range for the users. Similarly, long-term kratom consumption (>5 years), and quantity of daily kratom use (≥3 ½ glasses; mitragynine content 76.3–114.8 mg) did not appear to alter the hematological and biochemical parameters of kratom users. These data suggest that even long-term and heavy kratom consumption did not significantly alter the hematological and clinical-chemistry parameters of kratom users in a traditional setting.

Singh, Narayanan, Grundmann et al. (2020), studied the long-term effects of kratom use in thirteen people in Malaysia who used kratom longer than 20 years in a cross-sectional pilot study (Singh et al., 2020a). They summarized their results as follows: "Respondents were required to undergo a blood-test and laboratory analysis was conducted to determine the mitragynine content in an acquired street sample of kratom. The regular, long-term consumption of brewed kratom decoction did not cause any significant alterations in haematological, kidney, liver, thyroid, inflammatory and gastrointestinal analytes in a cohort of kratom users who had no history of substance misuse. However, those who had a higher intake (>3 glasses per day) of kratom exhibited higher lipid values (except for HDL-cholesterol), and a moderate elevation of homocysteine level. Long-term (>20 years with a daily intake of ≥87.54 mg mitragynine) kratom consumption was not associated with altered biochemical levels, although prolonged and chronic, frequent use (>3 glasses daily) may result in cardiovascular risks." Note that this study was not designed to determine if kratom or other factors contributed to higher lipid values.

Singh, Chye, Suo et al. (2018) conducted a preliminary study of the impact of kratom use on brain function, as assessed by brain magnetic resonance imaging, among chronic kratom users in Malaysia. They reported "There were no significant differences ($p > 0.05$) in the intracranial volume (ICV), cortical volumes (frontal, parietal, temporal, occipital, or cingulate lobe), or subcortical volumes (striatum, hippocampus, or amygdala), as well as in the diffusion tensor imaging (DTI) metrics, fractional anisotropy (FA) and mean diffusivity (MD) between kratom users and the controls. This preliminary study showed long-term consumption of kratom decoction is not significantly associated with altered brain structures in regular kratom users in traditional settings" (Singh et al., 2018b).

Singh, Narayanan, Muller et al. (2019) studied potential long-term cognitive effects associated with kratom use in kratom uses in Malaysia with assessments performed using the Cambridge Neuropsychological Test Automated Battery (Singh et al., 2019a). Relative to control participants, higher consumption (>3 glasses daily or mitragynine doses between 72.5 and 74.9 mg) of kratom tea was selectively associated with impaired performance on the Paired Associates Learning task of the Cambridge Neuropsychological Test Automated Battery, reflecting deficits in visual episodic memory and new learning.

Leong Bin Abdullah, Tan, et al., evaluated the prevalence of ECG abnormalities and QTc intervals in kratom users without histories of illicit drug use. Sinus tachycardia was higher in kratom users. Daily kratom consumption was associated with borderline QTc intervals (Leong Abdullah et al., 2021). Another study by Leong Bin Abdullah and Singh found that people who consumed four or more glasses of kratom tea daily had higher MG concentrations than lower intake consumers and this higher intake was associated with prolonged QTc intervals (Leong Bin Abdullah and Singh, 2021a). The same authors published a comprehensive review of the cardiovascular and cardiotoxic effects of kratom and came to the conclusion that limitations in studies to date do not permit definitive conclusions about the cardiovascular risks (Leong Bin Abdullah and Singh, 2021b).

3.3.3 Factor 3 Updated Conclusion

Pharmacokinetics and safety data from multiple species, kratom preparations, alkaloids, and metabolites; advances in bioanalytical assays providing more accurate and reliable findings; and data from multiple studies with MG doses many times higher than those human kratom users take are now available. These studies add to those described in Factors 1 and 2 confirming little evidence of serious adverse or life-threatening effects over a broad range of doses, dosage forms, and in four species (mouse, rat, dog, and monkey).

Other major advances in kratom science come from six clinical studies of long term kratom use effects and safety, as well as the study of anti-nociceptive effects of kratom and physiological dependence described in Factors 2 and 7. These important advances in kratom science evaluated the effects of long-term kratom use on a variety of physiological parameters including kidney and liver function, hematological parameters, cognition, and on brain function by brain magnetic resonance imaging. Although relatively small studies, none suggest serious adverse consequences of use. It is important to note that these are not definitive safety studies and cannot be used to claim that kratom has no adverse effects on any of the studied

physiological domains and limitations of each study were noted in the publications. Nonetheless, the findings are encouraging and should facilitate the conduct of more comprehensive follow-up studies.

3.4 Factors 4, 5, and 6—History and Current Patterns of Abuse; the Scope, Significance and Duration of Abuse; what, if Any, Risk is There to the Public Health

3.4.1 Summary of 2018 Findings

Note that for this update, Factors 4, 5, and 6 are considered together because they all contribute to understanding nonmedical use, recreational use and abuse, and public health impact, relying on some of the same surveys across factors. The Henningfield et al., 2018 8-FA considered all major relevant federal surveys, as well as data from internet monitoring, and more than 20,200 comments to the DEA, and concluded that there was no evidence of an imminent public health threat associated with kratom (Henningfield et al., 2018a). To the contrary, the review concluded that there were foreseeable health risks including opioid overdose and deaths if lawful kratom was banned and possession criminalized. Moreover, although kratom is not approved as safe and effective for therapeutic use, it was evident that most kratom use in the US was for health and well-being by people who personally found kratom to be more effective, tolerable, accessible and/or preferred a natural product as compared to FDA approved medicines.

3.4.2 Factors 4, 5, and 6 Science Updates

3.4.2.1 U.S. National and Federal Survey Data

Table 2 summarizes the main findings from the major national and federal surveys and other data sources. Overall, there are more similarities than differences with respect to demographics reported in this table as well as in other demographics reported in the published survey results. Prevalence appears to be substantially underestimated by the NSDUH and RADARS surveys (U.S. Department of health and Human Services, 2020; Schimmel et al., 2021).

NSDUH, RADARS, and Covvey et al. did not report reasons for use; however, many kratom users reported past or present use of opioids and/or drug addiction treatment consistent with past findings that self-management of addiction and withdrawal is a common reason for kratom use (National Institute on Drug Abuse, 2019; Coe et al., 2019; Garcia-Romeu et al., 2020; U.S. Department of health and Human Services, 2020; Schimmel et al., 2021; Covvey et al., 2020; Grundmann, 2017). Survey data incidence reports for DAWN, MTFS, NFLIS, and TEDS are apparently below the threshold for reporting as confirmed in an inquiry to NFLIS (Drug Enforcement Administration, 2020a; Drug Abuse Warning Network, 2020; Substance Abuse and Mental, 2020).

These findings do not support the conclusion that kratom use represents an imminent health threat and in fact kratom is not listed in the most recent DEA National Drug Threat Assessment (Drug Enforcement Administration, 2020b). There is no evidence that kratom is "fueling" or otherwise contributing to the opioid epidemic, though the survey data suggest that it is an informal self-management approach supporting the efforts of many opioid users to reduce and discontinue opioid use (Grundmann, 2017; Coe et al., 2019; Garcia-Romeu et al., 2020; Grundmann et al., 2021).

3.4.2.2 Kratom Use Prevalence

As mentioned in **Table 2**, the NSDUH and RADARS surveys may greatly underestimate the US prevalence and incidence of kratom use, with estimates of past year kratom use of 1,790,00–2,040,000.[3] (U.S. Department of health and Human Services, 2020; Schimmel et al., 2021). In contrast, a credible estimate based on market data suggested prevalence of 3–5 million in 2014–2015 (Botanical Education Allia, 2016).

Experts and marketers agree that the kratom market substantially expanded since that time, with kratom export data from Indonesia to the US and major marketer consensus finding that the US consumer base was likely 10–16 million. This is consistent with a nationally projectable survey estimate from 2020 concluding past year kratom use as 4.1% or 10,500,000 kratom users (Covvey et al., 2020).

3.4.2.3 Kratom Use Associated Mortality

The two most widely cited estimates of kratom associated mortality are based on world-wide reports over nearly 10 years (Food and Drug Administration, 2018; Olsen et al., 2019). FDA's statement noted that all but one involved other substances, and that case was under further investigation.[4] Medical examiners or coroners reported kratom as the cause of death in 91 (59.9%) of 152 kratom positive decedents (out of 27,338 overdose deaths in 27 states), including seven for whom kratom was the only substance positive on postmortem toxicology, although other substances could not be ruled out (Olsen et al., 2019). In approximately 80% of kratom positive or "involved" deaths, decedents had a history of "substance misuse", with 65% of cases listing fentanyl as the cause of death, 32.9% heroin, followed by benzodiazepines, prescription opioids, and cocaine. An earlier study (Gershman et al., 2019) cautioned that comprehensive toxicology might identify other substances contributing or causing death. We are not aware that any of the 93,000 drug overdoses estimated for 2020 included deaths due to kratom. That does not mean that there were no deaths in which kratom was the primary cause or a contributing factor; however, the signal is clearly low.

An assessment of various survey data concluded that the risk of kratom associated death was at least a thousand times lower than for morphine-like opioids (Henningfield et al., 2019). This is consistent with NIDA's position (National Institute on Drug Abuse, 2019) and with the 2018 DHHS kratom scheduling rescission letter and the conclusions drawn by Assistant Secretary of Health Brett P. Giroir, MD, ADM who stated:

[3]Note in a summary of RADARS data presented a few months after the Schimmel et al., 2020 publication, it was reported that the national projected past year prevalence estimate was 3.35 million.

[4]FDA never reported the results of that investigation, however, the US DHHS review that led to the 2018 withdrawal of the 2017 MG and 7-OH-MG CSA scheduling recommendation determined that the incident in question was an automobile crash not attributable to kratom use.

TABLE 2 | Summary of data sources.

Survey/Data source	Main results and comment	Other comments
Drug Abuse Warning Network (Drug Abuse Warning Networ, 2020)	No reports in DAWN from 1970 to 2011 "New DAWN" began in 2019 and has not listed kratom	
Monitoring the Future Study (Miech et al., 2021)	Kratom use is not assessed	Note that 9% of NSDUH Reports were from age 12–17 year olds
National Forensic Laboratory Information Service (Drug Enforcement Adm, 2020a)	Since 2016 NFLIS did not include MG/kratom reports because the rates are below the threshold for inclusion	
National Survey on Drug Use and Health (U.S. Department of health and Human Services, 2020)	Paid responders on national panel (n = 67,625).[6] 2019 Prevalence Lifetime Use: 1.4%; Past Year Use: 0.7%	See Grundmann et al., 2021 and Henningfield et al., 2021 comment on apparent underestimation of kratom use prevalence (Grundmann et al., 2021; Henningfield et al., 2021)
Treatment Episodes Data Set (Substance Abuse and Menta, 2020)	No reports. This does not mean there were no reports but suggests subthreshold signal	Internet chatrooms and SUD treatment clinic advertising suggests some kratom users are seeking cessation assistance
Coe et al. (2019) (Coe et al., 2019)	Internet Survey of self-identified kratom users age ≥18 (n = 2,867) 48% use for self-management of pain 10% for self-management of opioid UD or withdrawal 22% use for mood management 2.4% use to get high	
Garcia-Romeu et al. (2020) (Garcia-Romeu et al., 2020)	Internet Survey of self-identified kratom users, age ≥18 (n = 2,798) 91% use for self-management of pain 41% for self-management of opioid UD or withdrawal 67% for management of anxiety 65% for depression <3% report kratom dependence	2% met DSM-5 criteria for past-year moderate or severe kratom-related SUD, but it was rated very low on scale of concern and adverse impact
Covvey et al. (2020) (Covvey et al., 2020)	Nationally representative Internet survey of persons aged 18–59 (n = 1842) 112 (6%) reported lifetime kratom use 72% were 25–44 years old, male, employed, and at higher educational levels 24–47% of respondents indicated self-reported diagnoses for any addiction, and 43% reported previously received treatment for addiction	Similar demographics as Grundmann 2017, Coe et al., 2019 and Garcia-Romeu et al., 2020 but may have underestimated % over 50 due to 59 year old upper age limit of survey. ((Coe et al., 2019), (Garcia-Romeu et al., 2020), (Grundmann, 2017)) Reasons for use were not asked, e.g., to self-manage pain, addiction, mood
Schimmel et al. (2021) (Schimmel et al., 2021)	RADARS® survey of paid survey responder on national panel age >18 (n = 59,714) 0.8% lifetime use 44% age >35 61% male 59% past year opioid use	Reasons for use were not asked, e.g., pain, addiction, mood. See Grundmann et al., 2021 and Henningfield et al., 2021 comment on apparent under estimation of kratom use prevalence (Grundmann et al., 2021; Henningfield et al., 2021)

"There is still debate among reputable scientists over whether kratom by itself is associated with fatal overdoses" (Giroir, 2018).

3.4.2.4 Mortality Risks Projected as a Result of Banning Licit Kratom

Surveys and more than 20,000 comments to the DEA suggest that many kratom users fear resumption of opioid use and the need to resort to illicit kratom markets (Drug Enforcement Adm, 2016; Grundmann, 2017; Coe et al., 2019; Garcia-Romeu et al., 2020). It is not possible to project how many people would relapse to opioids and potentially overdose (Henningfield et al., 2018a; Henningfield et al., 2018b; Henningfield et al., 2018c; Henningfield et al., 2018d; Grundmann et al., 2018; Prozialeck et al., 2020). This was a concern of the DEA in withdrawing its 2016 kratom scheduling proposal (Ingraham, 2016b) and in the US DHHS kratom scheduling recission letter (Giroir, 2018).

3.4.2.5 Public Health and Individual Benefits of Kratom

In 2018, a systematic review of kratom use and mental health by Swogger and Walsh concluded ". . .kratom use appears to have several important mental health benefits that warrant further study. Kratom dependence is a risk for some people, though the dependence syndrome appears to be mild in its psychosocial and physiological effects relative to that of opioids. More and better research, including well-controlled, prospective studies, is necessary to further elucidate kratom's potential for good and harm and the moderators of its effects" (Swogger and Walsh, 2018). The

therapeutic potential of kratom based on surveys, anecdotal reports, and nonclinical research supports the plausibility of such benefits as discussed by other reviewers (Prozialeck et al., 2019; Hemby et al., 2019; Yue et al., 2018; Grundmann et al., 2018; Kruegel and Grundmann, 2018; Sharma and McCurdy, 2021; Swogger et al., 2018; Prozialeck et al., 2021).

The most important public health benefits with respect to mortality are widely agreed upon by kratom experts and surveys, and that is its use to self-manage opioid and other drug addiction and withdrawal symptoms, and thereby reduce use and overdose from far deadlier substances. This type of use is not unique in the US but was long reported in SEA (Raffa, 2014; Henningfield et al., 2018a). This was also reported in the first major US Internet survey of kratom use (Grundmann, 2017), as well as in subsequent surveys (Coe et al., 2019; Garcia-Romeu et al., 2020; Pain News Network (2018)). This was also a conclusion of a systematic review of 13 studies addressing kratom use and mental health in the US, SEA, and other countries and regions of the world, and a review by an international consortium of kratom researchers (Swogger and Walsh, 2018; Prozialeck et al., 2019).

While the opioid epidemic represents a highly visible and deadly epidemic in its own right, it is important to recognize that many millions use kratom as their preferred approach to managing other life-threatening disorders including pain, depression, anxiety, post-traumatic stress, fibromyalgia and more (Drug Enforcement Adm, 2016; Grundmann, 2017; Coe et al., 2019; Garcia-Romeu et al., 2020).

3.4.2.6 Kratom Use for Managing Opioid Use/Withdrawal and Other Health Reasons

In the first half-year of the COVID-19 pandemic, there was uncertainty about kratom supply by vendors and consumers, however, overall US supply was not affected. The main reasons for kratom use are pain relief (48%), anxiety, "PTSD" or depression (22%), increase energy or focus (10%), and "help cut down on opioid use and/or relieve withdrawal" (10%) (Coe et al., 2019). Side effects were generally minor, e.g., stomach upset, rarely required medical attention and rates and severity of "bad reactions" were generally similar to those reported by Grundmann (Grundmann, 2017).

Field studies with face-to-face interviews in Malaysia provide complementary evidence to US Internet surveys regarding reasons for use and potential benefits (Singh et al., 2019b). Motives related to mood and other factors in 116 regular kratom users employed the Drinking Motives Questionnaire (DMQ) to measure motives for kratom use, reported "heavy" kratom use as drinking more than three glasses daily (estimating that 1 glass contains 48.24–50.4 mg of mitragynine), with use associated with significantly higher means scores on the Coping and Enhancement scales. A field face-to-face survey of 92 long-term male kratom users found that 72 participants (78%) reported using kratom to "enhance sexual performance" and all but one found did their sexual performance did improve. Interestingly, among participants who described kratom intake for other reasons, 35% reported enhanced sexual performance (Singh et al., 2020b).

Patterns and reasons for use and demographics were investigated in 142 current and 62 former opioid polydrug users in Malaysia (Singh et al., 2020c). The alkaloid content of a kratom street sample was primarily MG, followed by paynantheine, speciociliatine, speciogynine, and "low levels" of 7-OH-MG. There were no significant differences in demographic characteristics between current and former opioid polydrug users except with respect to marital status, with current kratom users having a higher odds ratio of being single. While both current and former opioid users reported using kratom to ameliorate opioid withdrawal, current users had significantly higher likelihood of using kratom for that purpose; however, former opioid users were more likely to use kratom for mood elevating effects.

3.4.2.7 Comment on Therapeutic Use in Context of FDA Standards

It is important to note that the benefits documented in published surveys do not constitute the basis for therapeutic claims and no kratom product or kratom alkaloid is approved for therapeutic use in the US. The FDA and other federal agencies state that there is no proven therapeutic use for kratom despite evidence that millions of people in the US and many more in SEA use kratom primarily for therapeutic, beneficial use. That evidence includes peer reviewed surveys and field studies in the US and SEA, clinical and preclinical studies showing that MG's mechanisms of action are consistent with such effects. Moreover, several animal models used to predict efficacy for treating opioid use disorder, opioid withdrawal and pain demonstrated efficacy.

None of this research meets FDA's standard for therapeutic efficacy that is determined by evaluation of a New Drug Application (NDA). The NDA must be supported by "substantial evidence of effectiveness," and is defined as "evidence consisting of adequate and well-controlled investigations" (Katz, 2004; Dabrowska and Thaul, 2018). The time and cost to develop and achieve FDA approval of a product as therapeutically effective and acceptably safe varies widely but is often approximated at 10 years and 1 billion dollars (DiMasi et al., 2016; Wouters et al., 2020). Only two botanical substances, Veregen® (sinecatechins) and Mytesi™ (crofelemer), were developed as drug products consistent with FDA's Botanical Drug Guidance and both are available only as prescription drugs that is typical of new drug approvals (Food and Drug Admini, 2016).

3.4.3 Factor 4, 5, and 6 Updated Conclusions

The most important finding from new US survey evidence is that the conclusion that kratom products and kratom's primary active alkaloid, MG, pose a "serious imminent threat to public health" is not supported. This extensive survey update agrees with the Henningfield et al. (2018) conclusion: "There has been no documented threat to public health that would appear to warrant emergency scheduling of the products and placement in Schedule I of the CSA carries risks of creating serious public health problems. . .. Although kratom appears to have pharmacological properties that support some level of scheduling, if it was an approved drug, placing it into Schedule I, thus banning it, risks creating public health problems that do not presently exist" (Henningfield et al., 2018a).

The evidence shows that millions of people in the US purchase and use kratom products for improving health and are preferred to FDA approved medicines because for them, kratom products are more effective, accessible, and tolerable. Furthermore, many prefer managing health problems with natural products.

For those using kratom products in place of opioids, which appears to be approximately 1/3 of all kratom users, it is foreseeable that removing kratom from the legal marketplace would put many at risk of returning to opioid use and risking opioid overdose death. This was clearly stated in comments to the DEA and public hearings as reported in the 2018 8-FA, and in surveys. Assistant Secretary Dr. Giroir noted "... there is a significant risk of immediate adverse public health consequences for potentially millions of users if kratom or its components are included in Schedule I, such as: ... Kratom users switching to highly lethal opioids, including potent and deadly prescription opioids, heroin, and/or fentanyl, risking thousands of deaths from overdoses and infectious diseases associated with IV drug use ... " (Giroir, 2018).

3.5 Factor 7—The Psychic or Physiological Dependence Liability

3.5.1 Summary of 2018 Findings

Recently, psychic dependence is referred to simply as "dependence" or "substance use disorder" and more commonly as "addiction" though definitions of addiction vary widely (American Psychiatric Asso, 1994; World Health Organization, 1994). Physiological dependence is often used interchangeably with the most common measure of physiological dependence, namely "withdrawal" which is also considered a clinical disorder (American Psychiatric Asso, 2013).

In the 2018 8-FA, Henningfield, Fant and Wang (2018) concluded "There have not been laboratory studies of physical or psychological dependence or abuse potential in humans caused by kratom." Nor had classic animal studies employing the drug self-administration and physical dependence/withdrawal model been conducted (see Factor 2 in this report)".

Nonetheless, the real-world evidence in the published literature supported the following conclusions: "...abrupt discontinuation [of kratom use] may be accompanied by withdrawal symptoms that are qualitatively similar but generally weaker than those observed following discontinuation of opioids. However, such reports make it difficult to disentangle the emergence of preexisting symptoms that had been mitigated by kratom use from those that occur as a physiological rebound accompanying the abrupt discontinuation of kratom use in kratom-dependent people. More studies of kratom's potential to produce physical dependence, tolerance, and withdrawal are needed to characterize the nature and severity, and determinants of abstinence-associated symptoms."

3.5.2 Factor 7 Science Updates

In addition to the animal laboratory studies predictive of abuse potential, dependence, and withdrawal summarized in Factor 1, there are several new studies, surveys, and expert reviews addressing the risk and factors associated with dependence and withdrawal. A major category of kratom use is related to the typically mild and tolerable dependence and withdrawal that occurs in some frequent kratom users and the resulting use of kratom as an approach to self-management. In this context, kratom provides a harm reduction alternative to opioids in particular, but also potentially for alcohol, methamphetamine, and other drugs.

Dependence and withdrawal were addressed in a systematic review of kratom use for mental health reasons that concluded "Kratom dependence is a risk for some people, though the dependence syndrome appears to be mild in its psychosocial and physiological effects relative to that of opioids ... kratom use does not appear to result in significant respiratory depression" (Swogger and Walsh, 2018). A major category of kratom use globally was to self-manage substance use disorders, consistent with the findings discussed in Factor 1 that demonstrated low abuse and physical dependence potential, and that MG administration reduced morphine and heroin self-administration, and withdrawal signs (Hemby et al., 2019; Harun et al., 2021b).

The Vicknasingam et al. (2021) study included in Factor 2 also assessed potential withdrawal signs using the Clinical Opiate Withdrawal Scale (COWS), comparing scores when participants were administered placebo or a kratom concoction (Vicknasingam et al., 2020). Although this study was not designed to be a definitive withdrawal assessment study, and did not include an opioid comparator, it was likely that people using kratom multiple times per day for many years would have experienced pronounced withdrawal symptoms. The authors concluded "None of the participants reported withdrawal symptoms either using spontaneous self-report or had significant withdrawal symptoms based on the COWS scores... All participants reported long histories of daily kratom consumption, with high frequency of daily consumption and substantial amounts consumed. It is not possible to quantify these reports into markers that could be used to approximate amounts of plant material or active ingredients consumed. However, despite the reported long duration and high levels of daily kratom consumption, during documented kratom discontinuation lasting from 10 to 20 h, no participant reported or displayed discomfort, symptoms, or signs of potential withdrawal symptoms."

100 long term kratom users and 100 non-users in Malaysia were interviewed to assess potential symptoms related to kratom dependence and withdrawal (Leong Bin Abdullah et al., 2021). Kratom use longer than 6 years and 3 or more times per day were more likely to be associated with dependence, reduced quality of life and/or withdrawal symptoms when kratom use is discontinued. However, the authors noted that the study did not allow causative conclusions as to whether quality of life reductions are a

result of increased kratom use or if such quality of life and other demographic factors contribute to more frequent kratom use.

An internet survey assessing reasons for use and effects of use in 2,798 present and past kratom users included questions about kratom dependence, withdrawal symptoms associated with discontinuation, and use to self-manage opioid dependence (Garcia-Romeu et al., 2020). Kratom-related withdrawal symptoms were reported by 9.5% of respondents with another 17.5% reporting possible kratom-related withdrawal. This supports results of previous studies (Swogger et al., 2015; Grundmann, 2017; Smith and Lawson, 2017; Coe et al., 2019) by suggesting that kratom has a relatively benign risk profile compared to typical opioids, with only a minority of respondents endorsing kratom-related adverse effects, withdrawal symptoms, or problematic use.

Coe et al. (2019) conducted an internet survey (2,867 current, 157 former kratom users) that included similar questions as Garcia-Romeu et al. and Grundmann (2017) (Grundmann, 2017; Garcia-Romeu et al., 2020), related to opioid use and effects. Kratom use was less likely to interfere with social, family, and occupational functioning compared to conventional opioids. Kratom was used by many to reduce or completely replace prescription and nonprescription opioid withdrawal and was generally considered "very effective" for managing opioid withdrawal. Relief of anxiety (including associated with post-traumatic stress disorder), depression, as well as to increase focus or energy were other major reasons for use. The foregoing conclusions are also consistent with those of Grundmann, Babin, Henningfield et al. (2021) who stated: "Some user reports suggest that regular kratom consumption carries risks of dependency and addiction, though with generally self-manageable withdrawal" (Grundmann et al., 2021).

Singh, Narayanan, Muller et al. (2018) employed widely used psychiatric instruments (Beck Depression Inventory and Beck Anxiety Inventory) to assess potential symptoms of anxiety and depression that may accompany abrupt discontinuation of kratom use in apparently frequent chronic kratom consumers in Malaysia (Singh et al., 2018c). Most respondents (70%) experienced symptoms of mild anxiety, while 81% reported symptoms of mild depression during kratom cessation. Those who consumed higher quantities of kratom tea daily (≥4 glasses) had "higher odds of reporting longer duration of kratom use history . . . , higher frequency of daily kratom use (≥4 times), . . . and were more likely to experience moderate symptoms of depression during kratom cessation" than those who consumed less. Cessation from regular and long-term kratom tea consumption was not associated with symptoms of high anxiety or depression.

3.5.3 Factor 7 Updated Conclusion

Kratom's potential to produce psychic dependence (aka "dependence" or "use disorder") and physiological dependence (aka, "withdrawal") advanced considerably due to surveys, and preclinical and clinical studies. Several surveys in the US, field studies in Malaysia, and a clinical trial of pain relief efficacy that included assessment of withdrawal support the conclusions of the 2018 8-FA (Henningfield et al., 2018a). Some kratom users report dependence/addiction and/or withdrawal with a greater likelihood with higher levels of chronic daily consumption. In general, it is more readily self-managed and less likely to interfere with occupational, social and family activities and responsibilities compared to dependencies to opioids, alcohol, stimulants and other drugs of abuse.

It is also important to note that there is wide individual variability, and some people do experience what they consider to be strong addiction and withdrawal to kratom. At present, it appears likely that many if not most individuals had prior histories of dependence to opioids and/or other drugs. Their conditions remain of concern nonetheless and is another area warranting further study. People for whom kratom use is considered a serious problem should have the same access to treatment as anyone with a substance use disorder. Many addiction treatment providers already advertise and offer kratom use disorder treatment assistance.

Use of opioids such as methadone and buprenorphine should be judicious in people seeking help to manage their kratom use disorder and/or withdrawal. If they formerly or are perhaps still using opioids, then the possibility of treatment with buprenorphine or methadone may be more helpful and appropriate if kratom is not satisfactory. However, for people without prior histories of recreational opioid use and dependence, treating with buprenorphine or methadone may introduce individuals to opioids and may not be the best option. This could be like treating unwanted caffeine dependence with amphetamine to replace the caffeine.

4 DISCUSSION AND CONCLUSION

In 2018, there was sufficient evidence to conclude that there was no imminent public health threat nor high degree of pharmacological abuse potential that would justify scheduling, taking into consideration the serious foreseeable adverse public health consequences of thousands of former opioid users returning to opioids and risking overdose, as well as the *de facto* criminalization of millions of US citizens. Approximately 8 months after the Henningfield et al. 8-FA was published, the US DHHS came to the same conclusion and rescinded the 2017 recommendation to place MG and 7-OH-MG in Schedule I of the CSA (Giroir, 2018). Since January 2018, there was remarkable research relevant to the abuse potential and safety of kratom from the perspective of the CSA eight factors.

Two intravenous drug self-administration studies showed that MG did not substitute for morphine (Hemby et al., 2019) or heroin (Yue et al., 2018), and that MG pretreatment reduced morphine and heroin self-administration. An intracranial brain self-stimulation (ICSS) study showed that whereas morphine produced robust decreases in the brain stimulation threshold, MG and 7-OH-MG did not (Behnood-Rod et al., 2020).

In the evaluation of physical dependence and withdrawal potential, four studies showed MG did not carry morphine-like physical dependence or withdrawal potential (Harun et al., 2020; Hassan et al., 2020; Wilson et al., 2020; Johari et al., 2021). Moreover, MG pretreatment of animals reduced spontaneous

morphine withdrawal (Hassan et al., 2020). In MG physically dependent animals, withdrawal signs were qualitatively different and much weaker than morphine, consistent with its mixed mechanisms of action (Johari et al., 2021). In a mouse physical dependence model (Wilson et al., 2020), naloxone precipitated withdrawal in morphine- but not MG LKT-maintained animals, while LKT pretreatment significantly reduced withdrawal in the morphine-maintained mice.

These findings are consistent with new US survey data showing relatively low self-reported kratom addiction rates, with most people describing MG use to manage pain, depression, anxiety, opioid and other drug use disorders and withdrawal, and to increase alertness, focus and work performance. In addition, kratom dependence and withdrawal are generally weaker and more readily self-managed relative to opioids.

Extensive *in vitro* and *in vivo* animal neuropharmacology studies of the mechanisms of action of MG, 7-OH-MG and other alkaloids illustrate that they are not appropriately designated as opioids, opioid analogs, or "atypical opioids," though some are partial agonists with low potential to recruit beta arrestin and produce respiratory depression. 7-OH-MG produces stronger MOR mediated opioid effects on abuse potential related measures and antinociception, but naturally occurs at levels so low as to not contribute meaningfully to kratom effects. This supports recommendations that regulations should prohibit kratom products with 7-OH-MG concentrations greater than occur safely in nature.[5]

Safety assessments in pharmacokinetic and pharmacodynamic studies confirm that kratom based extracts and individual alkaloids at far higher doses than consumed by humans do not appear to carry substantial mortality risk, with one analysis suggesting a mortality risk at least 1000 times less than illicit opioids (Henningfield et al., 2019). Results support the US DHHS conclusion that "experts disagree on whether kratom by itself causes overdose deaths" (Giroir, 2018; National Institute on Drug Abuse, 2019). This does not imply that kratom does not carry a mortality risk—most substances do under certain conditions and exposure levels, another important area for further research.

As to the question of whether or not kratom poses an imminent public health threat, no analysis of factors 4–6 of the 8 CSA factors, including the FDA analysis (Food and Drug Administration, 2017b), revealed kratom to pose an imminent public health risk. The US has the most comprehensive survey data to address the need for temporary or "emergency" placement of substances into CSA Schedule I. Yet none of the major surveillance systems identified such a public health threat. This includes the old and new Drug Abuse Warning Network, Monitoring the Future, National Survey on Drug Use and Health, RADARS®, or the Treatment Evaluation Data Set. DEA's National Forensic Laboratory Information System mentioned kratom reports from 2010–2016 but none thereafter because the signal remained low. Neither has kratom been included in any DEA Annual National Drug Threat Reports.

The primary public health consequences of kratom use are well documented by four surveys of more than 20,000 kratom consumers summarized in this review, by Henningfield et al., 2018 (Henningfield et al., 2018a), and more than 20,000 comments to DEA (Drug Enforcement Adm, 2016) suggesting that millions of US citizens use kratom for health and well-being and many to self-manage opioid and other drug withdrawal and use disorders as their preferred approach. Many kratom users believe kratom is more effective, tolerable and/or accessible than other pharmaceuticals (Grundmann et al., 2018; Swogger and Walsh, 2018; Prozialeck et al., 2019; Prozialeck et al., 2020).

There are problems with kratom product purity (e.g., Prozialeck et al., 2020) (Prozialeck et al., 2020) and adulteration (Prozialeck et al., 2019) in the consumer marketplace. A scheduling imposed kratom ban would likely worsen these problems because kratom marketing would not discontinue and consumer demand would not cease, rather marketing would switch from regulatable lawful to illicit kratom suppliers. More states and ideally the US federal government could address these issues by product performance standards and regulatory approaches guided by science and informed through a federal rule-making approach.

Remarkably, as discussed in several reports (Henningfield et al., 2019; Prozialeck et al., 2019; Henningfield et al., 2021), there has yet to emerge a generally accepted estimate of the number of current US kratom consumers, which current ranges from approximately 2 to more than 10 million (see factors 4–6 and Henningfield et al., 2021) (Henningfield et al., 2021). As noted by Henningfield et al., 2018 and bluntly stated in the US DHHS scheduling rescission letter (Giroir, 2018), surveys need to address such issues before any action to ban consumer kratom sales and possession is contemplated. As stated in the DHHS letter:

"Further analysis and public input regarding kratom and its chemical components are needed before any scheduling should be undertaken. It is important that we have additional information to justify scheduling, such as:

- A scientific assessment of how many Americans utilize *kratom,* and an understanding of the geographic and demographic distribution of these users (Factors 4, 5);
- A scientific assessment of the actual scale and degree of dependence and/or addiction of Americans utilizing *kratom* (Factors 1, 5, 7);
- A scientific determination based on data whether *kratom* actually serves as a gateway drug that promotes further use of more dangerous opioids (Factors 1, 4, 5).
- A valid prediction of how many kratom users will suffer adverse consequences if kratom is no longer available, including among people with intractable pain, psychological distress, risk for suicide; and/or people who might transition to proven deadly opioids such as prescription opioids, heroin, or fentanyl.

[5]Five states (AZ, GA, NV, OK, and UT) have taken this approach in their kratom consumer protection regulations and law but setting actual performance standards to address the variety of kratom based products would be seem best done by FDA which has extensive experience in such matters and could take a federal rule making approach that ensures input from diverse stakeholders representing science, public health, consumers, and the industry that prepares and manufactures kratom products.

- A scientifically valid assessment of causality in the current few deaths in which *kratom* was co-utilized with known lethal drugs such as fentanyl (Factors 1, 2, 3, 5 and 6)" (Giroir, 2018).

By law, scheduling considers diverse evidence including chemistry and pharmacology, level of abuse potential, physiological dependence determined in animal and human studies, as well as assessment of individual and public health risks and benefits. Taking all of these factors into account, this review provides stronger evidence than was available to Henningfield et al., or the US DHHS in 2018 (Henningfield et al., 2018a; Giroir, 2018) to recommend not only that CSA scheduling is not warranted but that CSA scheduling carries a substantial foreseeable risk of thousands of opioid overdose deaths as well as depriving millions of US citizens of one of their preferred health management assets. The fact that possession of kratom by millions of US citizens would be criminalized as a heroin-like drug felony offense is not a CSA consideration but should not be ignored.

In conclusion, we do not recommend scheduling kratom or any of its alkaloids in the CSA. We do recommend accelerated research to address the many questions raised in this review, including support of the potential development of new medicines with potential better safety and/or efficacy profiles for a variety of diseases. Finally, we recommend that the US federal government and other nations consider approaches to kratom regulation as are presently being pioneered in five US states.

AUTHOR CONTRIBUTIONS

JH was the primary scientist/investigator, and lead the identification of articles, writing, and analysis. DW supported writing, research, and analysis. MH provided toxicological analysis of articles and supported writing and analysis.

ACKNOWLEDGMENTS

This report is an update of the Henningfield et al., 2018 kratom abuse potential assessment review and comprises an annotated bibliography and review of kratom-related scientific studies published since January 1, 2018. The AKA and its affiliate, the Center for Plant Science and Health that funds new research into kratom, supported an earlier independent summary of kratom research that is posted on the AKA website. AKA did not support the preparation of this review article. The AKA did not have any input into approach, assessments or conclusions of the earlier summary postop on the AKA website or this article. Acknowledgement we are greatly appreciative of the efforts of our PinneyAssociates colleagues who contributed to this article: Yolanda Green; Rachel Beck, PhD; and August Buchhalter, PhD. We also acknowledge the thinking embodied in this document by our former colleague and co-author of earlier kratom abuse potential assessments, Reggie Fant, PhD. Dr. Fant died in September 2020 and we miss him dearly. See more about our team and Dr. Fant at www.pinneyassociates.com.

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Conflict of Interest: Authors JH, DW, and MH were employed by the company PinneyAssociates, Inc.

The reviewer WP declared a past co-authorship with one of the authors JH to the handling editor.

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From: Medicines Scheduling
To: Medicines Scheduling
Cc: s 22
Subject: FW: Application regarding amendment of the Poisons Standard for Mitragyna speciosa (kratom) [SEC=OFFICIAL]
Date: Monday, 23 December 2024 4:26:03 PM

From: Medicines Scheduling <Medicines.Scheduling@health.gov.au>
Sent: Monday, 23 December 2024 9:53 AM
To s 47G @gmail.com
Subject: Application regarding amendment of the Poisons Standard for Mitragyna speciosa (kratom) [SEC=OFFICIAL]

Dear s 22

Thank you for your application to amend the Poisons Standard for Mitragyna speciosa (commonly known as kratom).

In order to determine the best decision-making pathway for your application, we hope you might provide some further information to us.

Applications to amend the Poisons Standard are based on the information provided to us in the application form.

The criteria is outlined in the Therapeutic Goods Act [52(E)]and the **Scheduling Policy Framework (SPF).** The Scheduling factors help the decision-making process for the Poisons Standard.

The 52(E) criteria are outlined, for your convenience, below:

(a) the risks and benefits of the use of a substance;.
(b) the purposes for which a substance is to be used and the extent of use of a substance
(c) the toxicity of a substance;
(d) the dosage, formulation, labelling, packaging and presentation of a substance; the dosage
(e) the potential for abuse of a substance;
(f) any other matters that the Secretary considers necessary to protect public health.

At this stage, we require further information on Kratom in relation to these criteria including:

- Information regarding the dosage, formulation, labelling, packaging and presentation of Kratom; as the information about your product (or any Kratom product) needs to be assessed against the scheduling framework criteria.
- Status of international product registration. Are there currently any registered international therapeutic products,(containing Kratom as active ingredient) that you would like to import into Australia? If yes, could you provide detailed information about the product(s) (i.e. dose, concentration, usage) for evaluation?
- An elaboration of the proposal. Can you please elaborate the difference between your proposal for Schedule 4 and Schedule 8 entry (i.e. dose, concentration, usage)?
- Clarification of a cutoff limit(s) Do you propose ingredient limits to differentiate between Schedule 4 and Schedule 8 and what would be the justification for the differentiation? We would also like to request any information you can provide to

support the justification of these limits or cut offs.

- Information you have regarding clinical trials and toxicological data specific to the proposed product(s)?
- You have only clearly identified two components of Kratom (Mitragynine: 4098-40-2 and 7-Hydroxymitragynine: 174418-82-7), if you have available information on the other components of kratom, and any potential variations in marketed products
- Addressing the potential toxicity of the substance with additional data. This may include a human health risk assessment or evaluation report.
- Lastly, we received partial information from you in relation to the LD50 for Mitragynine, however we would appreciate resource references for this amount and also for any of the other known components of Kratom.

At this stage, further information is required to progress and support your application.
In order to meet legislative deadlines and to be included in the current Scheduling cycle, we request a response by Monday 6 January 2025 .
Kind regards,

The Chemicals and Medicines Scheduling Secretariat Team

Scheduling and Chemicals Policy Section

Regulatory Practice and Support Division | Health Products Regulation Group

Regulatory Engagement Branch

Australian Government Department of Health and Aged Care

PO Box 100, Woden ACT 2606, Australia

T: s 22 | E: medicines.scheduling@health.gov.au

From: s 47G
To: Medicines Scheduling; TGA Info
Subject: Re: Application regarding amendment of the Poisons Standard for Mitragyna speciosa (kratom) [SEC=OFFICIAL]
Date: Wednesday, 1 January 2025 2:07:01 PM

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To: The Australian Therapeutic Goods Administration (TGA)

Subject: Proposal for Amendment to the Poisons Standard for Mitragyna Speciosa (Kratom)

Date: 1st January 2025

Dear Sir/Madam,

Thank you for considering our application to amend the Poisons Standard for Mitragyna speciosa (kratom). We appreciate the opportunity to provide further information in support of our proposal. This letter aims to address the key criteria under Section 52(E) of the Therapeutic Goods Act and the Scheduling Policy Framework (SPF). It also advocates for the responsible legalization of kratom in Australia by highlighting its health benefits, regulatory frameworks, economic opportunities, and international precedents.

1. Addressing Section 52(E) Criteria

(a) Risks and Benefits of Use

• Benefits:

• Pain Management: Kratom is widely recognized for its analgesic properties, providing relief for chronic pain, arthritis, and migraines.

• Opioid Addiction Treatment: Kratom has shown effectiveness in managing opioid withdrawal symptoms, offering a safer, plant-based alternative to synthetic opioids.

• Mental Health Support: Kratom supports mental well-being by reducing anxiety and symptoms of depression while enhancing mood stability.

• Energy and Focus: In lower doses, kratom acts as a mild stimulant, improving focus and productivity without harmful side effects.

• Sleep Aid: At higher doses, kratom’s sedative effects help with insomnia and promote

restful sleep.

• Risks:

• Like any substance, kratom poses potential risks if misused. These risks can be mitigated through dosage control, proper labeling, and regulated distribution. Existing studies suggest kratom has lower abuse potential compared to opioids and demonstrates minimal long-term side effects when used responsibly.

(b) Purpose and Extent of Use

• Kratom is intended for medicinal and therapeutic purposes, targeting pain relief, opioid dependency, mental health support, and energy enhancement.

• Current international use spans medicinal, supplemental, and traditional practices, indicating a wide scope of application with significant cultural and clinical relevance.

(c) Toxicity Profile

• Kratom's primary alkaloids, Mitragynine and 7-Hydroxymitragynine, exhibit low acute toxicity.

• Toxicity studies have shown an LD50 of 477 mg/kg (rats) for Mitragynine, indicating a relatively high safety margin compared to other substances.

• Additional studies on chronic toxicity are being reviewed, and references for LD50 values for all alkaloids identified in kratom are provided in Appendix A.

(d) Dosage, Formulation, Labeling, and Packaging

• Proposed dosage formats include capsules, powders, and liquid extracts with controlled concentrations (e.g., 2-5% Mitragynine).

• Products will include clear labeling with dosage recommendations, warnings, and ingredient breakdowns.

• Packaging will incorporate tamper-proof containers and child-resistant caps to prevent accidental ingestion.

(e) Potential for Abuse

• Kratom's potential for abuse is significantly lower than opioids and synthetic drugs. Studies indicate that dependence risk is mild and manageable through dosage guidelines and public awareness campaigns.

• Regulatory control, including age restrictions (18+) and prescription-only access for higher doses, further minimizes abuse potential.

(f) Additional Considerations to Protect Public Health

• Monitoring systems and third-party testing labs will ensure product quality and compliance with Australian health standards.

• Education programs will promote informed and responsible consumption practices.

2. Proposal for Legalizing Kratom in Australia

A. Health and Medicinal Benefits

• Kratom serves as a safer alternative for managing pain and opioid addiction.

• It supports mental health, improves focus, and promotes relaxation and better sleep.

• Legalization allows for structured medical oversight to integrate kratom into treatment plans for chronic conditions.

B. Economic and Agricultural Opportunities

• Sustainable kratom farming can create jobs and provide new revenue streams for rural communities.

• Australia has the potential to emerge as a global supplier of high-quality kratom, generating export revenue.

C. Regulatory Control and Public Safety

• Legalization enables strict regulation, ensuring purity and safety standards.

• Preventing illegal trade enhances public safety by eliminating contaminated products from unregulated sources.

• Age restrictions and dosage limits protect vulnerable populations.

D. Research and Development Potential

• Legalization paves the way for clinical trials and pharmaceutical research, validating kratom’s therapeutic uses.

• Collaboration with global research bodies strengthens Australia’s role in herbal medicine innovation.

E. Lessons from Global Policies

• Thailand legalized kratom under a controlled framework, ensuring public safety and economic benefits.

• The U.S. Kratom Consumer Protection Act provides a regulatory model balancing accessibility with oversight.

• Australia can leverage these frameworks to establish best practices for kratom regulation.

F. Public Health and Harm Reduction

• Legalizing kratom reduces dependence on opioids and mitigates risks associated with synthetic drugs.

• It supports a natural approach to health, aligning with growing consumer demand for herbal remedies.

• Public education campaigns can further promote responsible consumption.

3. Proposed Regulatory Framework for Australia

1. Licensing and Monitoring – Implement a licensing system for farmers, processors, and retailers to ensure compliance.

2. Testing and Labeling Standards – Enforce third-party lab testing for purity and potency, with transparent labeling requirements.

3. Public Education Campaigns – Inform consumers about safe usage, risks, and benefits through nationwide campaigns.

4. Age Restrictions – Prohibit sales to individuals under 18.

5. Medical Oversight – Integrate kratom into prescription-only frameworks for higher doses, ensuring doctor supervision.

4. International Product Registration and Marketed Variations

• Kratom products registered in other countries primarily include capsules, teas, and liquid extracts, with controlled doses between 2-10 mg Mitragynine per serving.

• References to these registrations and formulations are provided in Appendix B.

5. Conclusion

We believe that legalizing and regulating kratom in Australia offers a balanced approach to

promote public health, stimulate economic growth, and mitigate misuse. The proposed regulatory framework addresses safety concerns while unlocking kratom's therapeutic and economic potential.

By learning from successful models like Thailand and U.S. states, Australia can lead the way in responsible herbal medicine regulation. We welcome the opportunity to collaborate further and provide any additional data required to support this proposal.

Thank you for your time and consideration.

Sincerely,

s 22 [redacted]

s 47G [redacted]

s 22 [redacted]

s 47G [redacted]@gmail.com

Citation:

https://ecddrepository.org/en/kratom-mitragynine-7-hydroxymitragynine

https://en.wikipedia.org/wiki/Mitragynine

https://cdn.who.int/media/docs/default-source/controlled-substances/unedited--advance-copy-44th-ecdd-review-report_kratom.pdf

https://cdn.who.int/media/docs/default-source/controlled-substances/unedited--advance-copy-44th-ecdd-review-report_kratom.pdf

https://en.wikipedia.org/wiki/Mitragyna_speciosa

https://www.kratomscience.com/2020/10/06/toxic-levels-of-kratom-and-lethal-dose-of-mitragynine/

https://cdn.who.int/media/docs/default-source/controlled-substances/unedited--advance-copy-44th-ecdd-review-report_kratom.pdf

https://www.mdpi.com/1660-4601/19/10/6294

https://cdn.who.int/media/docs/default-source/controlled-substances/unedited--advance-copy-44th-ecdd-review-report_kratom.pdf

https://en.wikipedia.org/wiki/Mitragyna_speciosa?

Proposal for Collaboration on Kratom Research and Education

To Whom It May Concern,

I am writing to express our strong interest in collaborating with the Australian government on research, education, and responsible use of kratom. s 22 [redacted] the rich traditional knowledge and modern advancements related to kratom cultivation, processing, and applications in Thailand.

Background on Thailand's Expertise in Kratom

Thailand has a long history of kratom use, especially in southern regions, where it has been an integral part of local culture and traditional medicine. Extensive studies have been conducted by Thai research institutions, including the Kratom Research Center at Prince of Songkla University (kratom.sci.psu.ac.th). These studies emphasize:

• The botanical characteristics of kratom.

• The chemical composition and alkaloid profiles of its leaves.

• Its therapeutic applications, including pain management and addiction treatment.

• Responsible cultivation practices and sustainability measures.

Additionally, the attached document, titled "**ประสบการณ์เกี่ยวกับพืชกระท่อม**" (Experiences with Kratom Plants), highlights real-life experiences of Thai communities in cultivating and utilizing kratom. It details:

• Traditional methods of propagation, harvesting, and processing.

• Insights into the cultural and medicinal uses of kratom.

• Observations on environmental factors affecting kratom growth and quality.

• Strategies for maintaining plant health and enhancing alkaloid content.

Call for Collaboration

Given Australia's growing interest in complementary and alternative medicines, including natural products, we see great potential for joint efforts in:

1. Scientific Research – Sharing expertise on the pharmacological effects of kratom, including its safety profile, therapeutic potential, and regulatory frameworks.

2. Education and Awareness – Promoting responsible use through public education programs to mitigate misuse and maximize benefits.

3. Policy Development – Assisting in formulating balanced regulations for kratom that ensure public safety while preserving access for medicinal purposes.

4. Sustainability and Trade – Supporting sustainable cultivation and ethical sourcing practices for kratom exports, fostering economic opportunities for both countries.

Our Commitment

As an advocate for kratom education and safe practices, I am committed to providing access to Thai research, best practices, and cultural insights to benefit Australia's ongoing assessments. I strongly believe that this collaboration can serve as a model for harmonizing cultural wisdom with modern science to unlock kratom's full potential responsibly.

Thank you for considering this proposal. I look forward to the opportunity to discuss further and explore pathways to productive collaboration.

Sincerely,

s 22 [redacted]

s 47G [redacted]

Website: s 47G [redacted]

WhatsApp s 22 [redacted]

YouTube: s 47G [redacted]

On Mon, 23 Dec 2024 at 05:52, Medicines Scheduling <Medicines.Scheduling@health.gov.au> wrote:

> Dear s 22 [redacted]
>
> Thank you for your application to amend the Poisons Standard for Mitragyna speciosa (commonly known as kratom).
>
> In order to determine the best decision-making pathway for your application, we hope you might provide some further information to us.

Applications to amend the Poisons Standard are based on the information provided to us in the application form.

The criteria is outlined in the Therapeutic Goods Act [52(E)]and the **Scheduling Policy Framework (SPF).** The Scheduling factors help the decision-making process for the Poisons Standard.

The 52(E) criteria are outlined, for your convenience, below:

(a) the risks and benefits of the use of a substance;.

(b) the purposes for which a substance is to be used and the extent of use of a substance

(c) the toxicity of a substance;

(d) the dosage, formulation, labelling, packaging and presentation of a substance; the dosage

(e) the potential for abuse of a substance;

(f) any other matters that the Secretary considers necessary to protect public health.

At this stage, we require further information on Kratom in relation to these criteria including:

- Information regarding the dosage, formulation, labelling, packaging and presentation of Kratom; as the information about your product (or any Kratom product) needs to be assessed against the scheduling framework criteria.
- Status of international product registration. Are there currently any registered international therapeutic products,(containing Kratom as active ingredient) that you would like to import into Australia? If yes, could you provide detailed information about the product(s) (i.e. dose, concentration, usage) for evaluation?
- An elaboration of the proposal. Can you please elaborate the difference between your proposal for Schedule 4 and Schedule 8 entry (i.e. dose, concentration, usage)?
- Clarification of a cutoff limit(s) Do you propose ingredient limits to differentiate between Schedule 4 and Schedule 8 and what would be the justification for the differentiation? We would also like to request any information you can provide to support the justification of these limits or cut offs.
- Information you have regarding clinical trials and toxicological data specific to the proposed product(s)?
- You have only clearly identified two components of Kratom (Mitragynine: 4098-40-2 and 7-Hydroxymitragynine: 174418-82-7), if you have available information on the other components of kratom, and any potential variations in marketed products
- Addressing the potential toxicity of the substance with additional data. This may include a human health risk assessment or evaluation report.
- Lastly, we received partial information from you in relation to the LD50 for Mitragynine, however we would appreciate resource references for this amount and also for any of the other known components of Kratom.

At this stage, further information is required to progress and support your application.

In order to meet legislative deadlines and to be included in the current Scheduling cycle, we request a response by Monday 6 January 2025 .

Kind regards,

The Chemicals and Medicines Scheduling Secretariat Team

Scheduling and Chemicals Policy Section

Regulatory Practice and Support Division | Health Products Regulation Group

Regulatory Engagement Branch

Australian Government Department of Health and Aged Care

PO Box 100, Woden ACT 2606, Australia

T: s 22 | E: medicines.scheduling@health.gov.au

Australian Government

Department of Health, Disability and Ageing

s 22

s 47G

s 47G @gmail.com

Our Reference: ANON-QVZN-UQUP-T

Dear s 22

Subject: Application to amend the Poisons Standard - *Mitragyna speciosa* (Kratom)

1. On 23 October 2024 you submitted an application to amend the Poisons Standard with regards to *Mitragyna speciosa* (Kratom) to include a new entry in Prescription only Medicine (Schedule 4) or Controlled Drug (Schedule 8).
2. The Delegate has decided to not refer your proposed amendments to an expert advisory committee and to not amend the entry of *Mitragyna speciosa* (Kratom) in the Poisons Standard.
3. Under the *Therapeutic Goods Regulations 1990* ('the Regulations'), if the Delegate decides to not amend the current Poisons Standard in the manner set out in the application, the Delegate must:
    (a) make an interim decision on the application having regard to the information provided by the applicant
    (b) give the applicant a written notice setting out the interim decision and the reasons for the decision, and advising the applicant may, within the period specified in the notice (not being less than 10 business days after the date of the notice), make a written submission to the Delegate about the interim decision.
4. This letter is the notice seeking your written submission about the interim decision.
5. The detailed reasons for the decision are provided within the notice of the interim decision enclosed with this letter.
6. You may make a written submission on the interim decision by **27 February 2026**. Please provide your response to medicines.scheduling@health.gov.au.
7. The Delegate will make a final decision on your application after considering any submission provided by you within the time specified above.

Yours sincerely

s 22
s 22 Scheduling and Chemicals Policy Section

12 February 2026

PO Box 100 Woden ACT 2606 ABN 40 939 406 804
Phone: 1800 020 653 or 02 6289 4124 Fax: 02 6203 1605
Email: info@tga.gov.au https://www.tga.gov.au

FOI 27-3612 - Document 5

Australian Government
Department of Health, Disability and Ageing
Therapeutic Goods Administration

Notice of interim decision to amend (or not amend) the current Poisons Standard in relation to *Mitragyna speciosa* (kratom)

12 February 2026

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Confidentiality

All submissions received will be placed on the TGA's Internet site, unless marked confidential. Any confidential material contained within your submission should be provided under a separate cover and clearly marked "IN CONFIDENCE". Reasons for a claim to confidentiality must be included in the space provided on the TGA submission form. For submission made by individuals, all personal details, other than your name, will be removed from your submission before it is published on the TGA's Internet site. In addition, a list of parties making submissions will be published. If you do not wish to be identified with your submission you must specifically request this in the space provided on the submission form.

Contents

Notice of interim decision made under Regulation 42ZCZV of the *Therapeutic Goods Regulations 1990* _____ 4

Interim decision on a proposed amendment not referred to an expert advisory committee _____ 5

Interim decision in relation to *Mitragyna speciosa* (kratom) _____ 5

Proposal ---------- 5

Interim decision ---------- 5

Materials considered---------- 5

Reasons for the interim decision (including findings on material questions of fact) ---------- 5

Notice of interim decision made under Regulation 42ZCZV of the *Therapeutic Goods Regulations 1990*

This publication constitutes a notice for the purposes of regulation 42ZCZV of the *Therapeutic Goods Regulations 1990* (the **Regulations**). This notice sets out:

- the interim decision made under regulation 42ZCZV by a delegate of the Secretary (the Delegate) in relation to a proposed amendment to the current Poisons Standard which was not referred to an expert advisory committee[1]
- the date of effect of the proposed amendment (in circumstances where the interim decision proposes an amendment to the current Poisons Standard).

The applicant proposing the amendment is invited to make a submission to the Secretary in relation to this interim decision on or before **27 February 2026.**

The submission should be provided via email to medicines.scheduling@health.gov.au. The submission will be considered by the Delegate in making the final decision.

The Delegate may decide to publish the submission, with consent from the submitter, unless the Delegate considers the information to be confidential information.

Defined terms

In this notice the following defined terms are used in addition to those above:

- the Therapeutic Goods Act 1989 (Cth) (the **Act**)
- the Scheduling Policy Framework 2018 (the **SPF**)
- the Scheduling handbook: Guidance for amending the Poisons Standard (the **Handbook**)

  and
- the Therapeutic Goods Administration (the **TGA**).

  Note: additional terms are also be defined for individual decisions.

[1] Established under sections 52B and 52C of the *Therapeutic Goods Act 1989* (Cth).

Interim decision on a proposed amendment not referred to an expert advisory committee

Interim decision in relation to *Mitragyna speciosa* (kratom)

Proposal

In November 2024, the Delegate received an application (the **Application**) to amend the current Poisons Standard in relation to *Mitragyna speciosa* (kratom). The applicant proposed creating a Prescription only medicine (Schedule 4) or a Controlled drug (Schedule 8) entry for human therapeutic use of kratom. Kratom is currently classified as a Prohibited substance (Schedule 9).

Interim decision

Pursuant to regulation 42ZCZV of the Regulations, the Delegate has, in relation to the proposed amendments, made an interim decision to not amend the current Poisons Standard in relation to *Mitragyna speciosa* (kratom).

Materials considered

In making this interim decision, the Delegate considered the following material:

- The application
- Subsection 52E(1) of the Act, in particular (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health
- The SPF, and
- The Handbook.

Reasons for the interim decision (including findings on material questions of fact)

I have made an interim decision to not amend the Poisons Standard with regards to *Mitragyna speciosa* (kratom) as proposed by the applicant. The applicant provided limited information to support their application and therefore, in making my decision, I have also relied on assessments from comparable overseas regulatory bodies and organisations and broader peer-reviewed scientific literature as detailed below.

Kratom is a tree native to south-east Asia that has long been used by labourers and farmers as a stimulant and to reduce fatigue.[2] It is typically consumed by chewing the leaves, smoking, or preparations as tea. In traditional medicine, kratom is used to relieve chronic pain, insomnia, anxiety and diarrhoea, boost energy and stamina, and assist with opium substitution or withdrawal. While kratom contain over 40 structurally related alkaloids, two major alkaloids, mitragynine (CAS 4098-40-2) and 7-hydroxymitragynine (CAS 174418-82-7) are known to be pharmacologically active. These 2 compounds are potent μ-opioid receptor agonists and exhibit psychotropic and opioid-like effects.[3]

[2] Veltri C, Grundmann O. Current perspectives on the impact of Kratom use. Subst. Abuse Rehabil. 2019;10:23-31. doi: 10.2147/SAR.S164261.

[3] Sokup B, Pippin MM. Kratom. [Updated 2023 Aug 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK585120

In relation to s 52E(1)(a), and (b) of the Act, the applicant claimed that kratom has potential therapeutic benefits for pain relief and opioid withdrawal. However, the applicant has not provided any credible evidence for its efficacy or therapeutic benefit. While the articles cited by the applicant support potential therapeutic benefits of kratom based on its traditional use, they also conclude that further research is required to establish the safety and efficacy of kratom.[4,5,6,7]

A recent systematic review identified 18 clinical studies, all of which were conducted in south-east Asian populations.[8] Of these, only one randomised, double-blind, placebo-controlled trial found that kratom leaf extract, prepared as a decoction, increased pain tolerance an hour after use.[9] However, the sample size was small (36), and the participants were chronic kratom users. Both the randomised trial and the systemic review emphasised the need for rigorous research on kratom's therapeutic use and safety profile.

Regarding s 52E(1)(c) and (e) of the Act, I note that the physiologic effects of kratom are dose dependent where stimulant-like effects are often seen at lower doses and opioid-like effects are observed at higher doses. Toxicities typically occur when the ingested dose exceeds 8 grams.[10] Adverse effects of kratom intoxication include neuropsychiatric (agitation, confusion, sedation, hallucinations, tremor, seizure, coma), cardiovascular (tachycardia, hypertension) and gastrointestinal (abdominal pain, nausea, vomiting) symptoms as well as respiratory depression.[11,12]

Chronic recreational use of kratom, in rare cases, has been associated with acute liver injury and may involve complications such as acute renal failure and bone marrow toxicity.[13] In animal studies, repeated dosing with mitragynine led to dependence as shown by naloxone-induced withdrawal. Based on limited epidemiological data, opioid-like withdrawal symptoms that are typically mild have been reported in human after cessation of kratom use. A few cases of neonatal withdrawal have also been documented in infants born to mothers who regularly used kratom.[14]

Notably, from 2017 to 2020, 127 deaths were associated with kratom and recorded by the United Nations Office on Drugs and Crime (UNODC) Early Warning Advisory Tox-Portal, with 63.8% from the United States (US, mainly California), 30.7% from Thailand, and smaller percentages from Sweden, Australia, and Finland.[15] The World Health Organisation Expert Committee on Drug Dependence Pre-Review Report: Kratom (*Mitragyna speciosa*), mitragynine, and 7-hydroxymitragynine (ECDD Report) conceded attributing causality in kratom-associated deaths is complex due to challenges in detecting its active compounds, limited toxicological testing, and frequent polysubstance involvement. While

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[4] Brown PN, Lund JA, Murch SJ. A botanical, phytochemical and ethnomedicinal review of the genus Mitragyna korth: Implications for products sold as kratom. *J Ethnopharmacol*. 2017;202:302-325. doi:10.1016/j.jep.2017.03.020

[5] Smith KE, Sharma A, Grundmann O, McCurdy CR. Kratom Alkaloids: A Blueprint?. ACS Chem Neurosci. 2023;14(2):195-197. doi:10.1021/acschemneuro.2c00704

[6] Singh D, Narayanan S, Vicknasingam B, et al. The Use of Kratom (Mitragyna speciosa Korth.) Among People Who Co-use Heroin and Methamphetamine in Malaysia. *J Addict Med*. 2022;16(2):223-228. doi:10.1097/ADM.0000000000000876

[7] Henningfield JE, Wang DW, Huestis MA. Kratom Abuse Potential 2021: An Updated Eight Factor Analysis. *Front Pharmacol*. 2022;12:775073. Published 2022 Jan 28. doi:10.3389/fphar.2021.775073

[8] Prevete E, Kuypers KPC, Theunissen EL, Corazza O, Bersani G, Ramaekers JG. A systematic review of (pre)clinical studies on the therapeutic potential and safety profile of kratom in humans. *Hum Psychopharmacol*. 2022;37(1):e2805. doi:10.1002/hup.2805

[9] Vicknasingam B, Chooi WT, Rahim AA, et al. Kratom and Pain Tolerance: A Randomized, Placebo-Controlled, Double-Blind Study. Yale J Biol Med. 2020;93(2):229-238. Published 2020 Jun 29. PMID: 32607084

[10] Sokup B, Pippin MM. Kratom. [Updated 2023 Aug 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK585120

[11] Papadi G, Bakhiya N, Ildico Hirsch-Ernst K. Assessment of the possible health risks associated with the consumption of botanical preparations of *Mitragyna speciosa* (kratom). *EFSA J*. 2022;20(Suppl 1):e200415. Published 2022 May 25. doi:10.2903/j.efsa.2022.e200415

[12] World Health Organization. (2022). Meeting report of the 44th Expert Committee on Drug Dependence. In *WHO Expert Committee on Drug Dependence* (pp. 1–15). http://www.jstor.org/stable/resrep44196.7

[13] LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Kratom. [Updated 2020 Apr 3].

[14] World Health Organization. (2022). Meeting report of the 44th Expert Committee on Drug Dependence. In *WHO Expert Committee on Drug Dependence* (pp. 1–15). http://www.jstor.org/stable/resrep44196.7

[15] 44th ECDD (2021): Kratom (Mitragyna speciosa), mitragynine, and 7-hydroxymitragynine

kratom has been implicated in some deaths, multiple studies indicate mitragynine is most often detected alongside other drugs such as opioids, stimulants and sedatives. However, the ECDD Report also included information on individuals presenting for drug dependence treatment related to the use of kratom, mitragynine or 7-hydroxymitragynine. The ECDD Report further indicated that kratom consumption generally can impair quality of life, particularly in cases of severe dependence, which may deteriorate physical health. Reports of kratom being mixed with substances like Coca-Cola and cough syrup suggest misuse and possibly abuse, raising significant public health concerns due to its potential for dependence.

Internationally, kratom use is prohibited in many countries (including parts of the US) due to concerns about its safety and potential for abuse. Currently, neither kratom or nor any kratom-derived substances are lawful as ingredients in any US Food and Drug Administration approved drug or as dietary supplements in conventional foods.[16] Canada bans the marketing of kratom for human consumption.[17] In New Zealand, mitragynine is classified as a prescription medicine, and its use in herbal remedies is prohibited under section 2 of the Medicines Act 1981.[18] Kratom was removed from Thailand's list of prohibited substances, effectively decriminalising its consumption and possession in 2021.[19] However, the Association of Southeast Asian Nations banned its inclusion in traditional medicine and health supplements in 2013 categorising them as "harmful to human health".[20]

Turning my mind to s 52E(1)(d) of the Act, neither a cutoff limit nor any justification was proposed for the inclusion of kratom in both Schedule 4 and Schedule 8. The applicant proposed various forms of kratom (i.e. powder, capsule, liquid extract, dry leaves) without any information regarding the dosage, labelling, or packaging to enable any assessment against the scheduling framework criteria.

On the basis of the above considerations, and in particular, the unsubstantiated claims about therapeutic benefits compared with risks and potential for misuse and abuse, I am not convinced kratom can be moved from Schedule 9 to Schedule 4 and/or Schedule 8. Therefore, I have decided not to amend the current Poisons Standard in relation to kratom.

The proposed amendment was not referred to an expert advisory committee.

[16] FDA Center for Drug Evaluation and Research, 2025, 7-Hydroxymitragynin (7-OH): An Assessment of the Scientific Data and Toxicological Concerns Around an Emerging Opioid Threat (Accessed 22 Oct 2025)

[17] 44th ECDD (2021): Kratom (Mitragyna speciosa), mitragynine, and 7-hydroxymitragynine

[18] MedSafe, 2021, Kratom – not such a nice cup of tea. (Accessed 2 Oct 2025)

[19] Australian – Thai Chamber of Commerce, 2025, Thailand's Updated Guidelines on Kratom in Food and Herbal Products (Accessed 22 Oct 2025)

[20] Association of South East Asian Nations (ASEAN) - Guiding principles for inclusion into or exclusion from the negative list of substances for Traditional Medicines and Health Supplements (Accessed 2 Oct 2025)

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6203 1605

Web: tga.gov.au

From: s 47G
To: Medicines Scheduling
Cc: Scheduling Secretariat
Subject: Re: Interim decision on your application regarding the scheduling of Mitragyna speciosa (Kratom) - [SEC=OFFICIAL]
Date: Thursday, 19 March 2026 6:18:05 PM
Attachments: kratom_request_amending.docx

OFFICIAL

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s 22
s 47G
s 47G @gmail.com

Application Reference: ANON-QVZN-UQUP-T

19 March 2026

s 22
s 22 Scheduling and Chemicals Policy Section
Medicines and Chemicals Scheduling Secretariat
Regulatory Practice and Support Division
Health Products Regulation Group
Australian Government Department of Health, Disability and Ageing
PO Box 100, Woden ACT 2606
Email: medicines.scheduling@health.gov.au

RE: Late Submission — Response to Interim Decision on Application to Amend the Poisons Standard in Relation to *Mitragyna speciosa* (Kratom) — Ref: ANON-QVZN-UQUP-T

Dear s 22

I write firstly and sincerely to apologise for the late delivery of this submission. The written response to the Delegate's interim decision was due on or before **27 February 2026**. I acknowledge, without reservation, that this submission is being provided after that date, and I am deeply sorry for the delay and for any inconvenience caused to the Delegate and the Secretariat.

The delay was not a reflection of any lack of respect for the process or for the Delegate's interim decision. Rather, upon receiving the interim decision on 12 February 2026, I recognised that my original application had not provided an adequate evidential foundation to support the proposed scheduling amendment — a finding I fully accept. I took the decision to thoroughly review the available peer-reviewed scientific literature and to prepare a substantive, properly evidenced response that would genuinely assist the Delegate in reaching a well-informed final decision. This process took longer than the available time window permitted.

I respectfully request that the Delegate exercise discretion to accept this late

submission and give it consideration in making the final decision. I submit this request on the following grounds:

- The delay is modest (approximately three weeks) and has not, to my knowledge, caused any prejudice to the scheduling process or to any third party.
- The submission is substantive and directly addresses each of the specific grounds on which the interim decision was based. It contains peer-reviewed clinical evidence, a detailed regulatory proposal, and a proposed set of conditions for Schedule 8 listing that were absent from the original application.
- The subject matter — the potential use of kratom as an adjunct treatment for opioid withdrawal syndrome — is a matter of genuine public health significance in Australia, and it is in the public interest that the final decision be informed by the best available evidence.
- The Therapeutic Goods Regulations 1990 confer discretion on the Delegate in relation to final decision-making, and I respectfully submit that accepting a late submission in these circumstances is a proper and proportionate exercise of that discretion.

Enclosed with this cover letter is my full written submission, which addresses in detail the findings set out in the Delegate's interim decision under sections 52E(1)(a)–(f) of the Therapeutic Goods Act 1989. The submission proposes a **time-limited Schedule 8 listing** for *Mitragyna speciosa* (kratom) for the specific supervised therapeutic indication of adjunct treatment of opioid withdrawal syndrome, with comprehensive prescribing controls, formulation specifications, pharmacovigilance requirements, and a mandatory ACMS review at 36 months.

I am fully aware that the Delegate is not obliged to accept a late submission, and I offer this apology sincerely and without any expectation of special treatment. I simply ask that the Delegate give this matter whatever weight and consideration is appropriate in the circumstances, and I remain entirely at the disposal of the Secretariat should any further information, clarification, or documentation be required.

I am grateful for the time and attention of the Delegate and the Secretariat in considering this matter. I hope that the detailed submission enclosed demonstrates my genuine commitment to working constructively within Australia's regulatory framework, and my sincere belief that a properly regulated pathway for kratom — under the robust controls of Schedule 8 — would serve the public health interest of Australians living with opioid use disorder.

Thank you most sincerely for your consideration.

Yours sincerely,

s 22 [redacted]
s 47G [redacted]
s 22 [redacted]
s 47G [redacted]@gmail.com

19 March 2026

Enclosure: Written Submission in Response to Interim Decision — Application Ref: ANON-QVZN-UQUP-T (19 March 2026)

Note: *This cover letter and the enclosed submission should be read together as a single response to the Delegate's interim decision dated 12 February 2026.*

OFFICIAL

On Thu, Feb 12, 2026 at 11:17 AM Medicines Scheduling <Medicines.Scheduling@health.gov.au> wrote:

> OFFICIAL
>
> Dear s 22 [redacted]
>
> We are writing to notify you that an interim decision has been made regarding your application to amend the Poisons Standard in relation to *Mitragyna speciosa* (Kratom)(Application ref: ANON-QVZN-UQUP-T).
>
> The delegate has decided to not refer your application and the proposed amendments to an expert advisory committee, and to not amend the current Poisons Standard in relation to *Mitragyna speciosa* (Kratom). The reasons for the decision are provided within the notice of the interim decision (please find attached).
>
> You may provide a written response to the delegate on the interim decision on or before **27 February 2026.** If you decide to make a submission, please provide your response to medicines.scheduling@health.gov.au.
>
> Kind regards
>
> s 22 [redacted]
>
> **The Medicines and Chemicals Scheduling Secretariat**
>
> Scheduling and Chemical Policy Section
>
> Regulatory Practice and Support Division | Health Products Regulation Group
>
> Regulatory Engagement Branch
>
> Australian Government Department of Health, Disability and Ageing
>
> PO Box 100, Woden ACT 2606, Australia
>
> E: medicines.scheduling@health.gov.au
>
> www.tga.gov.au
>
> 
>
> 
>
> *This response is general information given to you without prejudice; it is not binding on the TGA and you should get your own independent legal advice to ensure that all*

of the legislative requirements are met.

Important: This transmission is intended only for the use of the addressee and may contain confidential or legally privileged information. If you are not the intended recipient, you are notified that any use or dissemination of this communication is strictly prohibited. If you receive this transmission in error please notify the author immediately and delete all copies of this transmission.

OFFICIAL

"Important: This transmission is intended only for the use of the addressee and may contain confidential or legally privileged information. If you are not the intended recipient, you are notified that any use or dissemination of this communication is strictly prohibited. If you receive this transmission in error please notify the author immediately and delete all copies of this transmission."

s 22

s 47G

s 47G @gmail.com

Application Reference: ANON-QVZN-UQUP-T

19 March 2026

s 22

s 22 Scheduling and Chemicals Policy Section

Medicines and Chemicals Scheduling Secretariat

Australian Government Department of Health, Disability and Ageing

PO Box 100, Woden ACT 2606

Email: medicines.scheduling@health.gov.au

RE: Written Submission in Response to Interim Decision — *Mitragyna speciosa* (Kratom) — Application Ref: ANON-QVZN-UQUP-T

Dear s 22

I write as the applicant in the above-referenced matter to respectfully submit this written response to the Delegate's interim decision dated 12 February 2026, pursuant to Regulation 42ZCZV of the Therapeutic Goods Regulations 1990. I respectfully request that the Delegate reconsider the interim decision and, in making the final decision, give weight to the updated evidence and regulatory proposals set out below.

I acknowledge the concerns raised in the interim decision and accept that my original application was insufficient in its evidential base. This submission directly addresses each of the Delegate's stated grounds, and proposes a concrete, risk-proportionate regulatory framework. My primary submission is that kratom should be rescheduled from Schedule 9 (Prohibited Substance) to **Schedule 8 (Controlled Drug)** for the specific, supervised therapeutic indication of **opioid withdrawal management and harm reduction**, subject to robust prescribing controls.

1. The Public Health Case: Australia's Opioid Crisis Demands Expanded Options

Australia faces a serious and ongoing opioid use disorder (OUD) epidemic. According to the Australian Institute of Health and Welfare, opioids accounted for the highest proportion of drug-induced deaths between 2012 and 2022. Access to opioid substitution therapy (OST) remains geographically inequitable, particularly for rural and regional Australians. Current approved OST medications — methadone and buprenorphine — are effective, but they are

not accessible to all patients, and some patients experience intolerable side effects or refuse opioid-based substitution.

Peer-reviewed literature published in leading pharmacological and addiction medicine journals — retrieved from PubMed — demonstrates that kratom's primary alkaloid, mitragynine, acts as a partial mu-opioid receptor agonist and may offer a lower-risk alternative or adjunct for opioid withdrawal management. This submission proposes that under Schedule 8 with prescriber controls, kratom could serve as an **interim harm reduction tool** — not a first-line treatment — while rigorous Australian clinical trials are conducted.

2. Response to Grounds of the Interim Decision

2.1 Ground: Applicant Provided Limited Evidence of Therapeutic Benefit [s 52E(1)(a) and (b)]

I accept this finding. My original application relied primarily on self-reported and traditional use data. I now present the following peer-reviewed evidence from PubMed-indexed journals directly relevant to the therapeutic use case:

Evidence on Opioid Withdrawal and Pain:

- Prozialeck et al. (2019, International Journal on Drug Policy) — a multi-author expert review — concluded that user reports and preclinical animal studies strongly suggest that kratom and its main constituent mitragynine may have useful activity in alleviating pain and managing opioid withdrawal symptoms (DOI: 10.1016/j.drugpo.2019.05.003).
- Grundmann et al. (2022, Disease-a-Month) confirmed that kratom's use patterns include self-treatment of opioid use disorder and that its prevalence reflects unmet clinical need. The authors noted that available case and survey data require confirmation by clinical trials, which this submission proposes to facilitate by rescheduling (DOI: 10.1016/j.disamonth.2022.101442).
- White (2019, American Journal of Health-System Pharmacy) confirmed that kratom exerts opioid and alpha-2 agonistic effects, as well as anti-inflammatory and mild stimulant effects, with a unique pharmacological profile that might offer advantages over other opioids, particularly in terms of a lower respiratory depression profile (DOI: 10.1093/ajhp/zxz221).
- Singh et al. (2017, Human Psychopharmacology) found that in Southeast Asian community settings, kratom is reportedly being used to ease withdrawal from opioid dependence, and that prolonged kratom use does not, based on self-reports, appear to result in serious health risks or impair social functioning in that population (DOI: 10.1002/hup.2582).

I acknowledge the Delegate's finding that only one small randomised, double-blind, placebo-controlled trial (n=36) exists. I submit this underscores precisely why Schedule 9 is counterproductive: it prevents Australian researchers from conducting the rigorous clinical trials needed to fill this evidence gap. Rescheduling to Schedule 8 with mandated research conditions is the pathway to generating the clinical evidence the Delegate rightly requires.

2.2 Ground: Concerns Regarding Toxicity and Potential for Abuse [s 52E(1)(c) and (e)]

I respectfully submit the following clarifications in relation to the toxicity evidence cited by the Delegate:

- Dose-dependency is a key mitigating feature: the Delegate noted that adverse effects typically occur above 8 grams. A regulated Schedule 8 framework, with prescribed unit doses and standardised formulations, would prevent exceeding this threshold — this is precisely the kind of control that distinguishes a licensed medicine from an unregulated herbal product.
- The 127 deaths cited by the UNODC are highly confounded: the Delegate itself acknowledged that the ECDD Report confirmed that attributing causality in kratom-associated deaths is complex due to challenges in detecting its active compounds, limited toxicological testing, and frequent polysubstance involvement. The majority of recorded deaths involved polydrug use, primarily opioids and sedatives — substances that, unlike kratom, are already scheduled and regulated.
- Heywood et al. (2024, Food and Chemical Toxicology) — a comprehensive critical review — concluded that current evidence indicates that kratom may have therapeutic potential in some persons and that products present few risks with typical, non-polysubstance use. This supports a harm-reduction model under Schedule 8, rather than continued Schedule 9 prohibition (DOI: 10.1016/j.fct.2024.114913).
- The EFSA (2022) assessment acknowledged that the actual risk characterisation is impeded by considerable uncertainties based on the variability in composition of kratom preparations — which is itself an argument for standardised, regulated pharmaceutical-grade products under Schedule 8, rather than prohibition.
- Cardiovascular effects (tachycardia, hypertension) reported in the literature occur predominantly at high recreational doses or in polysubstance contexts. Under a Schedule 8 prescribing model, cardiac risk monitoring would be a standard clinical requirement, as with other opioid substitution therapies.

2.3 Ground: No Dosage, Formulation, Labelling, or Packaging Proposal [s 52E(1)(d)]

I accept this was a critical omission. I now propose the following regulatory specifications for Schedule 8 inclusion:

Parameter	Proposed Specification
Permitted Formulations	Standardised oral tablet or capsule (pharmaceutical-grade extract, standardised to mitragynine content); oral liquid (decoction, standardised). No powder or raw leaf for Schedule 8 use.
Proposed Unit Dose	1–5 mg mitragynine per unit dose. Maximum daily dose: 15 mg mitragynine (well below the 8g crude leaf threshold associated with adverse effects). Dosing to be titrated under prescriber supervision.
Dispensing Controls	Pharmacist-dispensed only. Prescriptions from authorised prescribers (addiction medicine specialists, GPs with relevant authorisation). Real-time prescription monitoring via SafeScript or equivalent state systems. Maximum supply: 30 days.

Labelling Requirements	Schedule 8 label compliant with TGA packaging requirements. Must state: mitragynine content per unit; warnings against polysubstance use; warnings regarding dependence; prescriber details; dispensing date; quantity.
Indication	Adjunct treatment for opioid withdrawal syndrome in adults (18+), where first-line opioid substitution therapy (methadone, buprenorphine) is contraindicated, refused, or inaccessible. For supervised short-term use only, with a treatment plan and review within 12 weeks.
Manufacturing Standards	TGA-licensed manufacturer only. GMP-certified. Each batch to be tested for: mitragynine and 7-hydroxymitragynine content (HPLC method); heavy metals; microbial contamination; pesticide residues. Certificate of Analysis required per batch.

3. International Regulatory Comparators

The Delegate's decision cited international prohibition as a supporting factor. I respectfully submit the international picture is more nuanced than presented:

- New Zealand has classified mitragynine as a prescription medicine — demonstrating that a comparable Pacific jurisdiction has determined that a regulated access model is appropriate and achievable.
- Thailand decriminalised kratom in 2021 and has moved to explore its use in traditional and modern medicine, including as part of opioid harm reduction programmes.
- The United States FDA has not approved kratom products but has not achieved a Schedule 1 ban (proposed and withdrawn in 2016 following significant scientific objection), and federal research into kratom's therapeutic potential continues. Several US states permit kratom for adult use.
- The European Food Safety Authority (EFSA, 2022) noted that the uncertainties in risk characterisation arise from the variability in composition of unregulated kratom preparations — an argument that directly supports pharmaceutical-grade regulation under Schedule 8, which would eliminate this variability.

The most relevant comparator for Australia is New Zealand's prescription medicine model, which this submission proposes to replicate and adapt.

4. The Case for Schedule 8 Rather Than Schedule 9

I submit that the current Schedule 9 classification is disproportionate and counterproductive for the following reasons:

1. Schedule 9 prevents all legitimate research. No Australian institution can conduct clinical trials on a Schedule 9 substance without extraordinary exemptions. The evidence gap that the Delegate correctly identifies as a basis for the interim decision is perpetuated — not resolved — by maintaining Schedule 9.
2. Schedule 9 does not prevent use; it only makes use unsafe. Kratom is readily available online and as an unregulated herbal product. Persons using kratom to manage opioid withdrawal are doing so with no medical supervision, no standardised product, and no safety monitoring. Schedule 8 with prescriber controls is a safer alternative to de facto unregulated access.

3. Schedule 8 is the appropriate framework for substances with opioid-like properties that have potential therapeutic utility but require controlled access. This is consistent with how buprenorphine — itself a partial mu-opioid receptor agonist — is managed in Australia.
4. A time-limited, condition-based Schedule 8 listing (e.g., valid for 3 years, subject to review, with mandatory pharmacovigilance reporting) would allow Australia to generate the clinical data needed while managing risk — rather than perpetuating a prohibition that generates no data and no safety oversight.

5. Proposed Conditions for Schedule 8 Listing

To address the Delegate's concerns and provide adequate safeguards, I propose the following conditions be attached to a Schedule 8 listing:

- Prescribing restricted to addiction medicine specialists and GPs with Schedule 8 prescribing authorisation (as per existing state/territory requirements).
- Mandatory enrolment in a national kratom pharmacovigilance registry, with reporting of all adverse events and treatment outcomes.
- Listing conditional on a formal review by the Advisory Committee on Medicines Scheduling (ACMS) within 36 months of commencement, based on pharmacovigilance data.
- Prohibition on non-standardised kratom products (raw leaves, powders, extracts, teas) for concurrent removal from the market and/or inclusion in a new Schedule 4 or Schedule 6 entry for minor and topical uses only.
- No supply to patients under 18 years of age.
- Prescriptions to be entered in SafeScript (Victoria) or equivalent real-time prescription monitoring system in all states and territories.
- Mandatory co-prescribing of an opioid antagonist (e.g., naloxone) for patients being treated for OUD.

6. Addressing the Risk of Polysubstance Use

The Delegate and the literature both identify polysubstance use as the primary driver of serious kratom-associated harms. I submit that this risk is best addressed through regulation rather than prohibition. A Schedule 8 prescribing model:

- Creates a clinical relationship in which prescribers can identify and counsel against polydrug use;
- Allows for concurrent monitoring through real-time prescription databases (SafeScript) which flag patients receiving concurrent opioid, benzodiazepine, or stimulant prescriptions;
- Removes the incentive to obtain kratom through unregulated online channels, where adulterated and high-potency products are common.

7. Summary of Requested Final Decision

I respectfully request that the Delegate, in making the final decision, determine as follows:

5. That the Poisons Standard be amended to create a new Schedule 8 entry for Mitragyna speciosa (kratom) and its principal alkaloid mitragynine, for the specific therapeutic indication of adjunct treatment of opioid withdrawal syndrome in adults, subject to the prescribing conditions detailed in Section 5 of this submission.
6. That the Schedule 8 listing be time-limited to 3 years, with a mandatory review by the ACMS at 36 months based on pharmacovigilance data, at which time the listing may be confirmed, modified, or removed.
7. That the Delegate refer the amended application to the Advisory Committee on Medicines Scheduling (ACMS) for expert review, noting that the applicant's original application was not so referred and that the evidence base presented in this submission materially exceeds that previously considered.

I am grateful to the Delegate and the Secretariat for the opportunity to make this submission. I welcome any request for further information or clarification, and I am prepared to engage with any expert review process that the Delegate considers appropriate.

This submission has been prepared in good faith and in the public interest, with the objective of supporting evidence-based, harm-reduction-focused approaches to Australia's opioid crisis. I believe that a properly regulated pathway for kratom — under the robust controls of the Schedule 8 framework — is a more proportionate, safer, and ultimately more effective policy response than continued prohibition.

Yours sincerely,

s 22

s 47G

s 47G @gmail.com

19 March 2026

Appendix A: Peer-Reviewed References (PubMed-Indexed)

The following references were retrieved from PubMed and are directly cited in support of this submission:

#	Reference
[1]	Heywood J, Smallets S, Paustenbach D (2024). *Beneficial and adverse health effects of kratom (Mitragyna speciosa): A critical review of the literature.* Food and Chemical Toxicology, 192, 114913. DOI: 10.1016/j.fct.2024.114913
[2]	Grundmann O, Hendrickson RG, Greenberg MI (2022). *Kratom: History, pharmacology, current user trends, adverse health effects and potential benefits.* Disease-a-Month, 69(6), 101442. DOI: 10.1016/j.disamonth.2022.101442

[3]	Singh D, Narayanan S, Vicknasingam B, et al. (2017). *Changing trends in the use of kratom (Mitragyna speciosa) in Southeast Asia.* Human Psychopharmacology, 32(3). DOI: 10.1002/hup.2582
[4]	White CM (2019). *Pharmacologic and clinical assessment of kratom: An update.* American Journal of Health-System Pharmacy, 76(23), 1915-1925. DOI: 10.1093/ajhp/zxz221
[5]	Chichagi F, Alikhani R, Beigi Harchegani A (2023). *Cardiovascular health in kratom users: a narrative review.* Journal of Addictive Diseases, 42(4), 313-325. DOI: 10.1080/10550887.2023.2282033
[6]	Prozialeck WC, Avery BA, Boyer EW, et al. (2019). *Kratom policy: The challenge of balancing therapeutic potential with public safety.* International Journal on Drug Policy, 70, 70-77. DOI: 10.1016/j.drugpo.2019.05.003
[7]	Shah K, Tankersley W, Mekala H (2021). *Kratom: An emerging issue and need for regulations in the United States.* Primary Care Companion CNS Disorders, 23(1). DOI: 10.4088/PCC.20r02770
[8]	Papadi G, Bakhiya N, Hirsch-Ernst KI (2022). *Assessment of the possible health risks associated with the consumption of botanical preparations of Mitragyna speciosa (kratom).* EFSA Journal, 20(Suppl 1), e200415. DOI: 10.2903/j.efsa.2022.e200415

Note: All references above are indexed on PubMed, the US National Library of Medicine's biomedical literature database. Full bibliographic details are available at https://pubmed.ncbi.nlm.nih.gov/