

Elemental Analysis of Kratom Products using ICP-MS

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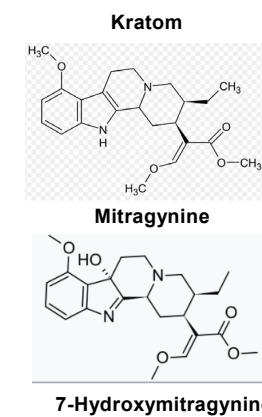


Abstract

Mitragyna speciosa (kratom) grows naturally in South-East Asian countries and contains two psychoactive compounds, mitragynine and 7-hydroxymitragynine. Kratom, an unapproved drug by FDA, is illegally marketed in United States as a drug or dietary supplement and has opioid-like properties. The US FDA's Forensic Chemistry Center (FCC) receives different kinds of samples for forensic analysis, often without defined methods. A relatively recent project was the 2018 kratom product survey for a gamut of analyses including analysis of toxic elements in kratom related products. The FCC received 26 different unapproved kratom containing products with unsubstantiated claims about treating serious medical conditions. The lack of validated methods for screening of toxic elements in kratom-related products resulted in significant challenges due to the complex and diverse sample matrices. With little information about the levels of concern for metals in kratom products, FDA Elemental Analysis Manual Method (EAM 4.7) was modified to fit the purpose of analysis. The results from the analysis indicated high levels (0.2 ppm - 60 ppm) of heavy metals, including V, Cr, Co, Ni, As, and Pb in nearly all the samples tested. Hazardous levels of Pb and Ni were identified in several samples at concentrations that exceed safe exposure for oral daily intake based on a toxicological evaluation conducted by CDER, which accounted for kratom usage patterns and the safe daily exposure limits found in the Q3D guidelines.

Introduction

Background



- Mitragyna speciosa (kratom) grows naturally in Thailand, Malaysia, Indonesia, and Papua New Guinea¹
- Contains two psychoactive compounds, mitragynine and 7-hydroxymitragynine, that act on the same opioid brain receptors as morphine¹
- Illegally marketed in United States as drugs or dietary supplements²
- Has opioid properties that expose users to the risks of addiction, abuse and dependence²
- No FDA-approved uses²

Health impacts of Kratom

- Toxicity of kratom in multiple organ systems has been shown³
- Respiratory depression, vomiting, nervousness, weight loss and constipation
- Narcotic and stimulant-like effects³
- Withdrawal symptoms may include hostility, aggression, excessive tearing, aching of muscles and bones, and jerky limb movements³

Kratom and the FDA

- U.S. Marshals, at the FDA's request, seized¹
 - > 25,000 pounds of raw kratom material worth more than \$5 million from Van Nuys, California (Sep 2014).
 - ~ 90,000 bottles of dietary supplements labeled as containing kratom and worth > \$400,000 from South Beloit, Illinois. (Jan 2016).
 - > 100 cases of products labeled as containing kratom and worth > \$150,000 from Grover Beach, California. (Aug 2016).
- Several deaths are believed to be linked to the use of kratom^{4,5}

Materials and Methods

Kratom and the FCC

- Early 2018, FCC received 26 different kratom products
 - Red tea, Red Ruby, White Ivory, Green Blend, etc.
- Claims of treating serious conditions like chronic pain, migraines, opiate addiction, ADHD/ADD, anxiety, depression, arthritis, insomnia and much more
- Analysis on Kratom
 - GC-MS (Mitragynine)
 - LC-MS ((7-hydroxy Mitragynine)Opioids)
 - GC-QQQ (Pesticide)
 - ICP-MS (Metals)
 - Micro (*salmonella*)

Portable Devices for the analysis of Mitragynine

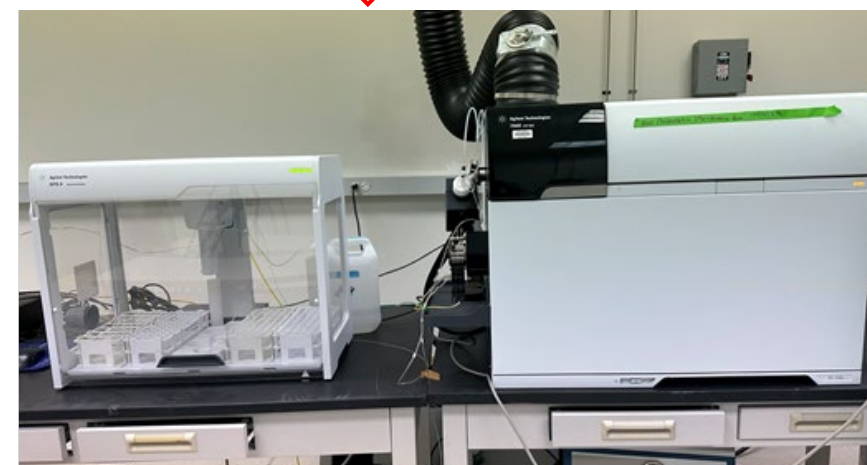
- DART-TD-Qda
- IONSCAN 600
- Progeny ResQ
- MX908

ICP-MS Method and Analysis



0.5g of sample + 8 mL HNO₃, 1mL H₂O₂ + 1mL HCl
 Step 1: 1600W 20 min to 120°C for 5 min
 Step 2: 1600W 20 min to 200°C for 25 min

~200 fold dilution



- Q3D Guideline for Elemental Impurities
 - Class 1 (Cd, Pd, As, and Hg), Class 2A (Co, V and Ni), Class 2B (Tl and Se), Class 3 (Cr)
- Methodology
 - FDA EAM 4.7 (Version 1.1, modified)

Results and Discussion

Elemental Concentration Results (n = 26)

| Element | ICH Class | Inhalation PDE, µg/day | Solution Detection Limits (ng/g) | Method Detection Limits (µg/g) | Concentration Range (µg/g) |
|---------|-----------|------------------------|----------------------------------|--------------------------------|----------------------------|
| Cd | 1 | 3 | 0.007 | 0.001 | ND |
| Pb | 1 | 5 | 0.005 | 0.001 | 0.320 – 2.70 |
| As | 1 | 2 | 0.079 | 0.016 | 0.201 – 0.587 |
| Hg | 1 | 1 | 0.006 | 0.001 | ND |
| Co | 2A | 3 | 0.005 | 0.001 | 0.326 – 0.930 |
| V | 2A | 1 | 0.045 | 0.009 | 0.269 – 2.36 |
| Ni | 2A | 5 | 0.017 | 0.003 | 0.576 – 29.0 |
| Tl | 2B | 8 | 0.021 | 0.004 | ND |
| Se | 2B | 130 | 0.116 | 0.023 | ND |
| Cr | 3 | 3 | 0.073 | 0.015 | 0.272 – 60.2 |

- Elements were grouped based on the [ICH Class](#)
- ASDL and MDL are based on ~3.5σ of concentration of 40 method blanks
- Reporting limit is 0.2 µg/g
- Elements above the reporting limits**

Potential Toxic Metal Exposure (8 grams/day daily dose)

| Element | µg metal / g Kratom | Daily Exposure (µg/day) | PDE, oral µg/day | % allowed PDE |
|---------|---------------------|-------------------------|------------------|---------------|
| Pb | 2.7 | 21.6 | 5 | 432 |
| As | 0.587 | 4.696 | 15 | 31.3 |
| Co | 0.93 | 7.44 | 50 | 14.9 |
| V | 2.36 | 18.88 | 100 | 18.9 |
| Ni | 29 | 232 | 200 | 116 |
| Cr | 60.2 | 481.6 | 11000 | 4.4 |

- 8 grams/day is a common dose
- Permissible Daily Exposure (PDE) from [ICH Q3D, Appendix 2](#)
- Value is the maximum value found for each element in any sample
- This is an example calculation not a regulatory action

Potential Toxic Metal Exposure (24 grams/day daily dose)

| Element | µg metal / g Kratom | Daily Exposure (µg/day) | PDE, oral µg/day | % allowed PDE |
|---------|---------------------|-------------------------|------------------|---------------|
| Pb | 2.7 | 64.8 | 5 | 1296 |
| As | 0.587 | 14.088 | 15 | 93.9 |
| Co | 0.93 | 22.32 | 50 | 44.6 |
| V | 2.36 | 56.64 | 100 | 56.6 |
| Ni | 29 | 696 | 200 | 348 |
| Cr | 60.2 | 1444.8 | 11000 | 13.1 |

- 24 grams/day is a for heavy users

Known Dangers of Chronic Metal Exposures

- Lead exposure in adults is associated with neurologic symptoms, anemia, hypertension and nephrotoxicity.
- Nickel is a sensitizer known to produce hypersensitivity reactions and is a recognized carcinogen.
- Arsenic chronic exposure may produce neuropathies. Occupational exposure and exposure to arsenic contaminated water is associated with skin, lung, bladder and possibly liver cancers.

Regulatory Action from the Kratom Survey

- FDA issued warnings to companies selling illegal, unapproved kratom drug products marketed for opioid cessation, pain treatment and other medical uses.⁶
- FDA Announced Seizure of Adulterated Dietary Supplements Containing Kratom.³
- U.S. Marshals, at the agency's request, seized more than 207,000 units of dietary supplements and bulk dietary ingredients that are or contain kratom, including over 34,000 kilograms of bulk kratom.³
- The seized products are worth approximately \$1.3 million.³

References

- <https://www.fda.gov/news-events/public-health-focus/fda-and-kratom>
- <https://www.fda.gov/news-events/press-announcements/fda-issues-warnings-companies-selling-illegal-unapproved-kratom-drug-products-marketed-opioid>
- <https://www.fda.gov/news-events/press-announcements/fda-announces-seizure-adulterated-dietary-supplements-containing-kratom>
- <https://www.fda.gov/media/1109959/download>
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- [FDA issues warnings to companies selling illegal, unapproved kratom drug products marketed for opioid cessation, pain treatment and other medical uses | FDA](https://www.fda.gov/news-events/press-announcements/fda-issues-warnings-to-companies-selling-illegal-unapproved-kratom-drug-products-marketed-for-opioid-cessation-pain-treatment-and-other-medical-uses-fda)

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