

2023 FDA SCIENCE FORUM

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 properties.



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. FCC received 26 different unapproved kratom 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 and used Q3D Elemental Impurities Guidance to determine reporting limits. 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.

1. <https://www.fda.gov/news-events/public-health-focus/laboratory-analysis-kratom-products-heavy-metals> (<https://www.fda.gov/news-events/public-health-focus/laboratory-analysis-kratom-products-heavy-metals>)

Elemental Analysis of Kratom Products using ICP-MS

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Abstract

Mitragyna species (kratom) grows naturally in South-East Asian countries and contains two psychoactive compounds, mitragynine and 7-hydroxymitragynine. Kratom, an unapproved drug by FDA, is highly marketed in United States as a drug or dietary supplement and has undesirable properties. The US FDA's Pediatric Chemistry Center (PCC) receives elevated levels of requests for research analysis, often without sufficient analytical. A relatively recent product was the 2019 kratom product survey for a general analysis including samples of bulk, powdered kratom related products. The PCC received 26 different unapproved kratom containing products with uncharacteristic claims about treating various medical conditions. The lack of validated methods for screening of kratom elements in kratom-related products resulted in significant challenges due to the complex and diverse sample matrices. With the information about the levels of concern for metals in kratom products, PCC Elemental Impurities Research Unit (EIUR) is now 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 species (kratom) grows naturally in Thailand, Malaysia, Indonesia, and Papua New Guinea
- Contains two psychoactive compounds, mitragynine and 7-hydroxymitragynine, that act on the same opioid brain receptors as morphine
- Legally marketed in United States as drugs or dietary supplement
- Has opioid properties that expose users to the risks of addiction, abuse and dependence
- No FDA-approved uses

Health Impacts of Kratom

- Toxicity of kratom in multiple organ systems has been shown
- Respiratory depression, vomiting, neurotoxicity, weight loss and constipation
- Narcosis and skeletal-like effects
- Withdrawal symptoms may include hostility, aggression, excessive tearing, aching of muscles and bones, and jerky limb movement

Kratom and the FDA

- U.S. Marshall, at the FDA's request, seized:
 - > 25,000 pounds of raw kratom material worth more than \$5 million from Van Nuys, California (Sep 2016).
 - ~ 50,000 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 > \$100,000 from Grover Beach, California. (Aug 2016).
- Several deaths are believed to be linked to the use of kratom^{1,2}

Materials and Methods

Kratom and the FCC

- Early 2019, FCC received 26 different kratom products
 - Paid for, Paid Ready, Whole-leafy, Green, Black, etc.
- Claims of treating various conditions like chronic pain, migraines, opiate addiction, ADHD/ADD, anxiety, depression, ADHD, insomnia and much more
- Analysis on Kratom
 - GC-MS (Mitragynine)
 - LC-MS (7-Hydroxy Mitragynine) (Xylene)
 - GC-QMG (Piperidine)
 - ICP-MS (Metals)
 - Metro (Anticoagulant)

Portable Devices for the analysis of Mitragynine

- QART-TO-Go
- CONSCAN 600
- Pregnity FlexQ
- M5900

ICP-MS Method and Analysis

0.5g of sample + 8 mL HNO₃ (red. H₂O₂ + 10% HCl)
 Step 1: 1600W 20 min to 120°C for 5 min
 Step 2: 1800W 20 min to 200°C for 20 min

↓ ~300 fold dilution

Q3D Guidelines for Elemental Impurities
 Class 1 (Co, Fe, As, and Ni), Class 2A (Co, V and Ni), Class 2B (Ti and Sn), Class 3 (Cr)

Methadone
 FDA IAM 4.7 (Version 1.1, modified)

Results and Discussion

Elemental Concentration Results (n = 26)

Element	ICP PPM, µg/g wet	Inclusions PPM, µg/g wet	Inclusion Detection Limits (µg/L)	Method Detection Limits (µg/L)	Concentration Range (µg/L)
Co	3	3	0.001	0.001	ND
Fe	1	1	0.001	0.001	0.001 - 233
As	3	3	0.019	0.016	0.001 - 0.002
Ni	1	1	0.001	0.001	ND
V	16	1	0.001	0.001	0.001 - 0.010
Nb	16	1	0.001	0.001	0.001 - 0.010
Ti	26	6	0.001	0.004	ND
Sn	26	130	0.001	0.003	ND
Cr	3	3	0.001	0.001	0.001 - 66.2

- Elements were grouped based on the ICH Class
- ASDL and MDL are based on ~5.0g 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	3	432
As	0.187	4.695	15	31.3
Co	0.03	2.44	50	14.9
V	2.36	18.88	100	18.9
Ni	29	232	200	116
Cr	69.2	482.6	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 any element in any sample
- This is an example calculation not a regulatory limit

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	3	1206
As	0.187	14.088	15	93.9
Co	0.03	11.82	50	45.6
V	2.36	18.44	100	36.6
Ni	29	696	200	348
Cr	69.2	1644.8	11000	15.1

- 24 grams/day is for heavy users
- Known Dangers of Chronic Metal Exposures
 - Lead exposure in adults is associated with neurologic symptoms, anemia, hypertension and nephropathy.
 - 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 possible 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 uses³
- FDA Announced Seizure of Unapproved Dietary Supplements Containing Kratom⁴
- U.S. Marshall, 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 24,000 kilograms of bulk kratom.⁵
- The seized products are worth approximately \$1.3 million.⁶

References

1. <https://www.fda.gov/news-events/press-announcements/uh-south-alabama-seizes-kratom>
2. <https://www.fda.gov/news-events/press-announcements/uh-south-alabama-seizes-kratom>
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4. <https://www.fda.gov/news-events/press-announcements/fda-announces-seizure-of-unapproved-dietary-supplements-containing-kratom>
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6. <https://www.fda.gov/news-events/press-announcements/fda-seizes-more-than-207-000-units-of-dietary-supplements-and-bulk-dietary-ingredients-that-are-or-contain-kratom>

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