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To cite this article: Kimberly Snow Caroti, Alen Joseph, Amy Sapowadia & C. Michael White (2024) Elemental impurities (heavy metals) in kratom products: an assessment of published individual product analyses, *Clinical Toxicology*, 62:10, 651-660, DOI: [10.1080/15563650.2024.2395552](https://doi.org/10.1080/15563650.2024.2395552)

To link to this article: <https://doi.org/10.1080/15563650.2024.2395552>



Published online: 05 Sep 2024.



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CLINICAL RESEARCH



Elemental impurities (heavy metals) in kratom products: an assessment of published individual product analyses

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ABSTRACT

Introduction: Kratom is commonly used by consumers, and the elemental impurity exposure that consumers would have at different kratom ingestion doses has been determined.

Methods: This assessment used original data from independent third-party laboratory testing of kratom products to identify the percentage of products that exceeded permissible daily exposure limits for lead (5 µg/day), nickel (200 µg/day), arsenic (15 µg/day), and cadmium (5 µg/day), the interim reference level for lead in adults (12.5 µg/day), and the tolerable upper intake level for manganese (11 mg/day) and nickel (1 mg/day). We assessed all products regardless of type and then evaluated non-extract products, extract products, and a soda preparation separately for elemental impurities.

Results: Three assessments of elemental impurities in kratom products have been published, totaling 68 products. Assessing all products and assuming a 3 g daily dose of kratom, 7.4% would exceed the permissible daily exposure limits for lead, 0% for nickel, 3.1% for arsenic, and 0% for cadmium. At a kratom dose of 25 g daily, 70.6% would exceed the permissible daily exposure limits for lead, 20.6% for nickel, 9.4% for arsenic, and 0% for cadmium. The interim reference level for lead would be exceeded by 1.5% of products at a kratom daily dose of 3 g and 33.8% of products at 25 g. The tolerable upper intake level for manganese would be exceeded by 12.5% of products at a kratom daily dose of 3 g and 41.7% of products at 25 g. Non-extract products generally contain greater concentrations of elemental impurities than extract products or the soda preparation.

Discussion: Apart from their concentrations in a gram of product, assessing the amount of exposure to elemental impurities at different kratom ingestion doses is also important. Elemental impurities exceeding regulatory permissible concentrations for many products, especially with greater daily kratom ingestion doses, may impact human health.

Conclusions: Some kratom products contain excessive concentrations of elemental impurities of toxicological concern, such as lead and arsenic. Non-extract products (powders, capsules, tablets) generally contain greater concentrations of elemental impurities than extract products or the soda preparation. Daily use of these products can result in exposures exceeding regulatory thresholds and adverse health effects.

ARTICLE HISTORY

Received 3 May 2024
Revised 7 August 2024
Accepted 16 August 2024

KEYWORDS

Arsenic; elemental impurities; heavy metals; kratom; lead; manganese; nickel

Introduction

The herbal substance kratom is derived from the leaves of a Southeast Asian tree, *Mitragyna speciosa* [1]. The leaves are harvested, washed, and then either kept whole, compressed or boiled to release the juice or dried into a powder [2]. The whole leaves can be chewed fresh or brewed into a decoction or tisane with or without sweeteners. The dried leaf can be sold in a powder form for consumption as a suspension or tea, placed into capsules, or compressed into tablets. The liquid or dried forms of kratom can also undergo extraction, with the extracts used in liquids or tablets, as well as sublingual and gummy products [2]. Kratom is listed by the United States (US) Drug Enforcement Administration as a “drug or substance of concern,” and its use is limited or banned in some states and cities in the US [3]. In December of 2021, the World Health Organization recommended keeping kratom under surveillance [4].

In the US, one estimate was that approximately two million people used kratom in 2020, but the actual utilization is not well substantiated, with estimates of 0.7% to 6% of the US population having used a kratom-containing product in the past [2,5]. The demographics of users are also changing from predominantly middle-aged males to increased utilization in younger people and women [2]. Kratom causes opioid-like effects, stimulant-like effects, and potassium channel blockade [1]. The reasons for kratom use also vary from recreational use, pain relief, replacement for prescription or illicit opioids, opioid use disorder, other substance use disorders, or anxiety [1,2,6].

Many natural products, especially ones that come from developing countries, can be contaminated with elemental impurities [7]. Most recently, cinnamon products were found to contain elevated concentrations of lead [8]. There is evidence that clinician, consumer, and regulator awareness of

lead contamination in calcium supplement products has led to a marked reduction in lead found in products produced since 2007 [9]. As such, we assessed published and regulatory body grey literature to identify kratom products that had been independently tested for the presence of elemental impurities and then determined the amounts the products would deliver to patients and the percentage of products exceeding the regulatory thresholds at different kratom doses.

Methods

Search strategy and inclusion criteria

We searched PubMed from the earliest date through 1 April 2024, using the search terms: [(lead or Pb or cadmium or Cd or arsenic or manganese or nickel or heavy metals or heavy metal) and (kratom or mitragynine or Maeng Da)] and searched the US Food and Drug Administration website for evaluations of heavy metals in kratom products [10]. To be included in our review, the citations had to meet our inclusion criteria. Products and preparations: products that have been tested individually for the presence of a target elemental impurity (lead, arsenic, nickel, cadmium, and manganese). Laboratory assessments: independent laboratory assessments of products for elemental impurities. Risk assessment: amounts of elemental impurities reported for kratom products individually to allow them to be assessed for exceeding the regulatory thresholds (US Food and Drug Administration elemental impurities standards in applicable oral drugs and other products, US Food and Drug Administration interim reference levels, and tolerable upper intake levels). We did not search for or assess the certificates of analysis for kratom products posted on their own company websites. Language: English language manuscripts or reports.

Extraction and transformation of data

For each study assessing the amount of an elemental impurity, we extracted the name of the product and/or the manufacturer or distributor, the dosage form (loose powders, capsules or tablets, extracts, or soda), and the amount of lead, arsenic, nickel, cadmium, and manganese in the product, which was usually presented in nanogram (ng) or microgram (μg) of element per gram (g) of powder or as parts per million (ppm).

Since the data were non-normally distributed, they were presented as medians and interquartile ranges (IQR). The median concentrations of elemental impurities per g in the types of kratom products (non-extract, extract, soda and total) were used for calculation of exposure doses and the percentage of products exceeding the regulatory thresholds in relation to the ingestion doses described below.

We determined that a typical dose of 3 g of “premium quality” kratom powder (either free powder or in capsules/tablets) is needed to achieve “minor” effects, 6 g for “moderate” effects, 8 g or 9 g for “strong” effects, and doses of 15 g to 25 g for “very strong” effects [11–15]. The usual

consumption of dry kratom products was established to be between 6 g and 9 g per day for powder products [11–15]. For liquid formations, 10 cups of kratom tisane, equivalent to 8 g of dry powder, was the usual daily consumption [16].

Permissible daily exposure, interim reference level, and tolerable upper intake level

According to the US Food and Drug Administration, as defined by the International Council for Harmonization for Pharmaceuticals for Human Use and aligned with the US Pharmacopeia guidance, the permissible daily exposure to lead ($5\text{ }\mu\text{g/day}$), inorganic arsenic ($15\text{ }\mu\text{g/day}$), nickel ($200\text{ }\mu\text{g/day}$), and cadmium ($5\text{ }\mu\text{g/day}$) is specified [17–20]. The permissible daily exposure is the maximum acceptable intake of elemental impurities of toxicological concern in pharmaceutical products or dietary supplements. For arsenic, the permissible daily exposure is based on inorganic arsenic, which is the more dangerous form of this elemental impurity. For maximum daily intake of not more than 10 g of finished products, the individual component limit for arsenic ($1.5\text{ }\mu\text{g/g}$), cadmium ($0.5\text{ }\mu\text{g/g}$), and lead ($0.5\text{ }\mu\text{g/g}$) is applicable. Speciation of arsenic is not necessary when the total arsenic is less than $1.5\text{ }\mu\text{g/g}$. We focused on the permissible daily exposure only because those were the data available to us. The studies we included did not specify the form of arsenic that they assessed. For lead, there is an interim reference level of $12.5\text{ }\mu\text{g/day}$ ($8.8\text{ }\mu\text{g/day}$ for females of childbearing age), which is the maximum dose of lead that could be ingested from all food sources, drugs and supplements combined [21]. We used the interim reference level of $12.5\text{ }\mu\text{g/day}$ in males and females of non-childbearing age. Both manganese (11 mg/day) and nickel (1 mg/day) have a tolerable upper intake level for consumption from all sources as determined by the Food and Nutrition Board of the National Academy of Sciences, Engineering, and Medicine [22,23].

Determining the percentage of products exceeding a regulatory threshold

The number and percentage of products exceeding any of these thresholds were determined at each of our a priori daily dosing concentrations. We assessed the overall dataset with all kratom products included and then looked at subgroups where the elemental impurity amounts in extracts were reported separately from the non-extract products. The kratom constituents in the soda (a canned beverage) preparation are likely an extract as well, but based on the potential differences, we reported the results separately.

Results

Search results

Our search strategy from PubMed yielded 17 citations, and upon backwards tracking, we found another study conducted by the US Food and Drug Administration, which was published on their website [24]. Of these citations (Figure 1),

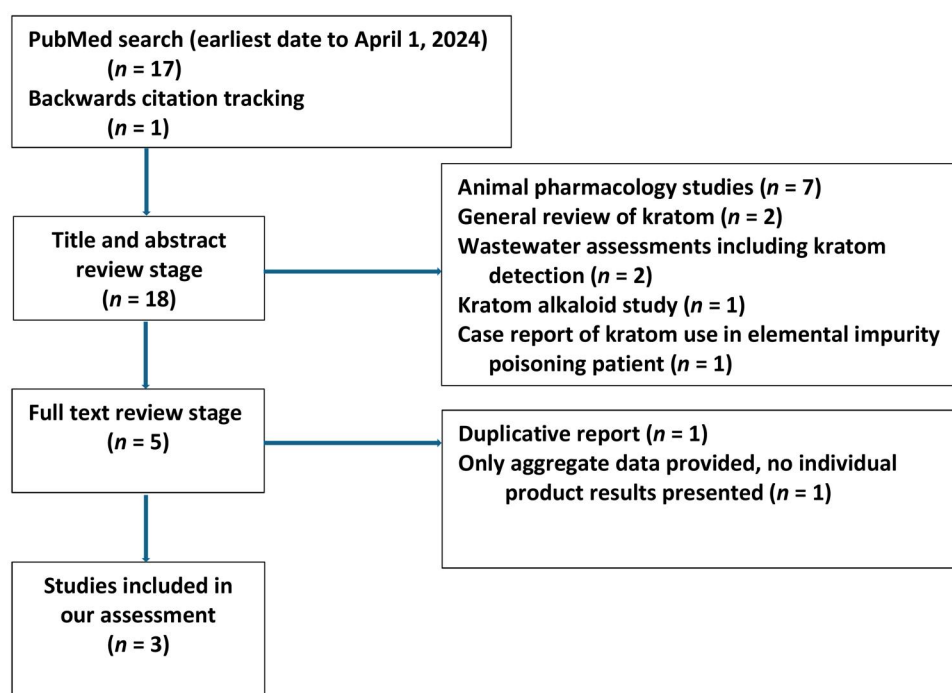


Figure 1. PRISMA evaluation of search strategy results to final accepted assessments.

13 were excluded in the title and abstract stage and two in the full text review stage. One of the citations was subsequently excluded in the full text phase because it was a review that simply re-reported the results of an original study already being used in the analysis [25]. The other citation excluded in the full text stage provided elemental impurity data in aggregate form only, and we could not determine the results on individual products [26]. We thus included three original assessments of the amounts of elemental impurities in kratom products, which totaled 68 products in all [16,24,27]. All three studies had data for lead and nickel (68 products); two assessed arsenic (32 products), one assessed manganese (24 products) and one assessed cadmium (8 products).

Elemental impurities

Table 1 shows the original data, with the medians and interquartile ranges for each study and all three studies combined, with respect to lead, nickel, arsenic, cadmium and manganese concentrations in kratom products. Using the base case scenario, Table 2 displays the median lead concentrations per g and the amounts that would be delivered at kratom ingestion doses of 3, 6, 8, 9, 12, and 25 g daily for all products assessed ($n = 68$), non-extract products (powders, capsules, or tablets, $n = 55$), extract products ($n = 11$) and a soda preparation ($n = 1$). The lead amounts delivered per day would be much greater for the non-extract products than the extract products because of the differences in median lead concentrations ($0.46 \mu\text{g/g}$ versus $0 \mu\text{g/g}$).

Figure 2 displays the percentage of kratom products (non-extract, extract, and total) that exceeded the permissible daily exposure limit for lead ($5 \mu\text{g/day}$) at ingestion

doses of 3–25 g daily. The percentage was much greater in non-extract products (Figure 2(A)) than in extract products (Figure 2(B)), especially at greater ingestion doses. The percentage of total products exceeding the permissible daily exposure limit increased from 7.4% at kratom 3 g daily to 70.6% at 25 g daily (Figure 2(C)).

Figure 3 displays the percentage of kratom products (non-extract, extract, and total) that exceeded the interim reference level ($12.5 \mu\text{g/day}$) for lead at ingestion doses of 3–25 g daily. Again, the percentage was much greater in non-extract products (Figure 3(A)) than in extract products (Figure 3(B)), especially at greater ingestion doses. The percentage of total products exceeding the interim reference level increased from 1.5% at 3 g to 33.8% at 25 g of kratom ingestion per day (Figure 3(C)).

Table 2 displays the median nickel concentrations per g and the amounts that would be delivered at kratom ingestion doses of 3, 6, 8, 9, 12, and 25 g daily for all products assessed ($n = 68$), non-extract products (powders, capsules, or tablets, $n = 55$), extract products ($n = 11$) and a soda preparation ($n = 1$). The nickel amounts delivered per day would be much greater for the non-extract products than the extract products because of the differences in median nickel concentrations ($3.68 \mu\text{g/g}$ versus $0.36 \mu\text{g/g}$).

Figure 2 displays the percentage of kratom products (non-extract, extract, and total) that exceeded the permissible daily exposure limit for nickel ($200 \mu\text{g/day}$) at kratom ingestion doses of 3–25 g daily. The percentage was much greater in non-extract products (Figure 2(A)) than in extract products (Figure 2(B)), especially at greater ingestion doses. The percentage of total products exceeding the permissible daily exposure limit increased from 0% at 3 g to 20.6% at 25 g of kratom ingestion daily (Figure 2(C)). None of the

Table 1. Concentrations of elemental impurities in 68 kratom products from three individual datasets.

Product	Lead concentration ($\mu\text{g/g}$) $n = 68$	Nickel concentration ($\mu\text{g/g}$) $n = 68$	Arsenic concentration ($\mu\text{g/g}$) $n = 32$	Cadmium concentration ($\mu\text{g/g}$) $n = 8$	Manganese concentration (mg/g) $n = 24$
1	0.477	1.07	NA	NA	NA
2	0.478	1.11	NA	NA	NA
3	0.615	3.8	NA	NA	NA
4	0.398	8.67	NA	NA	NA
5	0.904	1.78	NA	NA	NA
6	0.402	2.03	NA	NA	NA
7	0.382	2.21	NA	NA	NA
8	0.485	1.83	NA	NA	NA
9	0.574	1.57	NA	NA	NA
10	0.305	3.83	NA	NA	NA
11	0.332	2.57	NA	NA	NA
12	0.333	3.166	NA	NA	NA
13	0.847	9.02	NA	NA	NA
14	0.53	3.02	NA	NA	NA
15	0.584	4.7	NA	NA	NA
16	0.46	5.1	NA	NA	NA
17	0.79	4.4	NA	NA	NA
18	0.55	4.7	NA	NA	NA
19	2.7	2.89	NA	NA	NA
20	0.32	2.26	NA	NA	NA
21	0.51	10	NA	NA	NA
22	0.77	1.99	NA	NA	NA
23	1.4	2.68	NA	NA	NA
24	0.406	1.36	NA	NA	NA
25	0.49	2.39	NA	NA	NA
26	1.01	4.4	NA	NA	NA
27	0	0.69	NA	NA	NA
28	0	0.576	NA	NA	NA
29	0.352	10.7	NA	NA	NA
30	0.438	20.1	NA	NA	NA
31	0.687	22.6	NA	NA	NA
32	0.777	29	NA	NA	NA
33	0.307	3.68	NA	NA	NA
34	0.424	3.22	NA	NA	NA
35	0.252	5.72	NA	NA	NA
36	1.2	1.06	NA	NA	NA
37	0.36	2.6	0.24	0.036	NA
38	0.28	1.9	0.165	0.0355	NA
39	0.345	2	0.155	0.026	NA
40	0.435	2.8	0.21	0.026	NA
41	0.395	3.45	0.28	0.0265	NA
42	1.025	2.85	0.24	0.0265	NA
43	0.97	4.4	0.15	0.0455	NA
44	0.375	5	0.225	0.0475	NA
45	0.2	15	0.01	NA	0.38875
46	0	27.5	0	NA	0.4425
47	0.5	20	0.2	NA	0.44625
48	2.5	17.5	0.09	NA	0.53
49	0	17.5	0	NA	0.75
50	0.01	0	0	NA	0.002238
51	4.5625	0	0	NA	0.03125
52	0	3	0.01	NA	0.24
53	0.8	5	0	NA	0.38
54	3	8	0.2	NA	0.7375
55	0	0	0	NA	0.001205
56	0	3.75	2.875	NA	11.88
57	4.125	25	0	NA	35.59875
58	0	8.25	3.25	NA	7.0125
59	3	12.5	0.225	NA	0.835
60	0	0.9375	0	NA	0.009375
61	0	0.15	0	NA	0.000938
62	0	1.875	0	NA	0.0125
63	0	0.75	0	NA	0
64	0	0	0	NA	0.0015
65	0	1.125	0	NA	0.02875
66	0	3.125	0	NA	0.04375
67	0	0.8875	12.375	NA	0.44375
68	0	0.3	0	NA	0.0175
Overall [16,24,27], median (IQR)	0.40 (0–0.59)	3.07 (1.31–5.26)	0.01 (0–0.21)	0.03 (0.03–0.04)	0.31 (0.02–0.58)

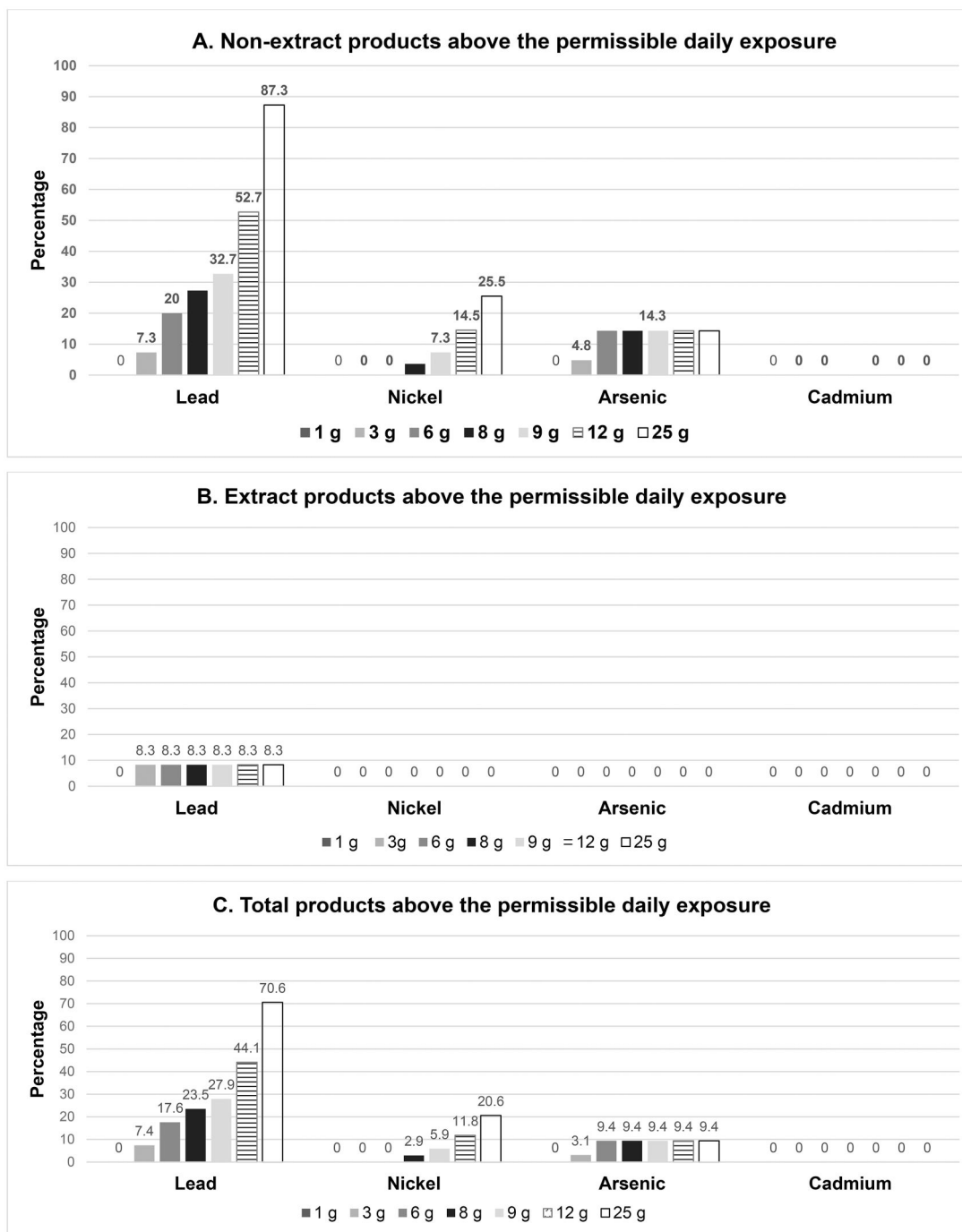
0 $\mu\text{g/g}$: below the limit of detection; NA: not analyzed.

IQR: interquartile range.

Table 2. Lead and nickel exposure doses based on the median concentrations per g in the types of kratom products (non-extract, extract, soda and total) and the dose of kratom (3–25 g) taken daily.

Dose of kratom taken daily	3 g	6 g	8 g	9 g	12 g	25 g
Lead (median)						
Non-extract products, <i>n</i> = 55 (0.46 µg/g)	1.38 µg	2.76 µg	3.68 µg	4.14 µg	5.52 µg	11.50 µg
Extract products, <i>n</i> = 11 (0 µg/g)	0 µg	0 µg	0 µg	0 µg	0 µg	0 µg
Soda product, <i>n</i> = 1 (0 µg/g)	0 µg	0 µg	0 µg	0 µg	0 µg	0 µg
Total products, <i>n</i> = 67 (0.40 µg/g)	1.19 µg	2.38 µg	3.17 µg	3.57 µg	4.76 µg	9.91 µg
Nickel (median)						
Non-extract products, <i>n</i> = 55 (3.68 µg/g)	11.04 µg	22.08 µg	29.44 µg	33.12 µg	44.16 µg	92.00 µg
Extract products, <i>n</i> = 11 (0.36 µg/g)	1.09 µg	2.18 µg	2.90 µg	3.27 µg	4.36 µg	9.08 µg
Soda product, <i>n</i> = 1 (3.13 µg/g)	9.38 µg	18.75 µg	25.00 µg	28.13 µg	37.50 µg	78.13 µg
Total products, <i>n</i> = 67 (3.07 µg/g)	9.22 µg	18.44 µg	24.58 µg	27.65 µg	36.87 µg	76.81 µg

0 µg/g = below the limit of detection.

**Figure 2.** The percentage of kratom products with elemental impurities (lead, arsenic, nickel, cadmium) exceeding the Permissible Daily Exposure (PDE) limits in relation to the types and doses (1–25 g) consumed daily.

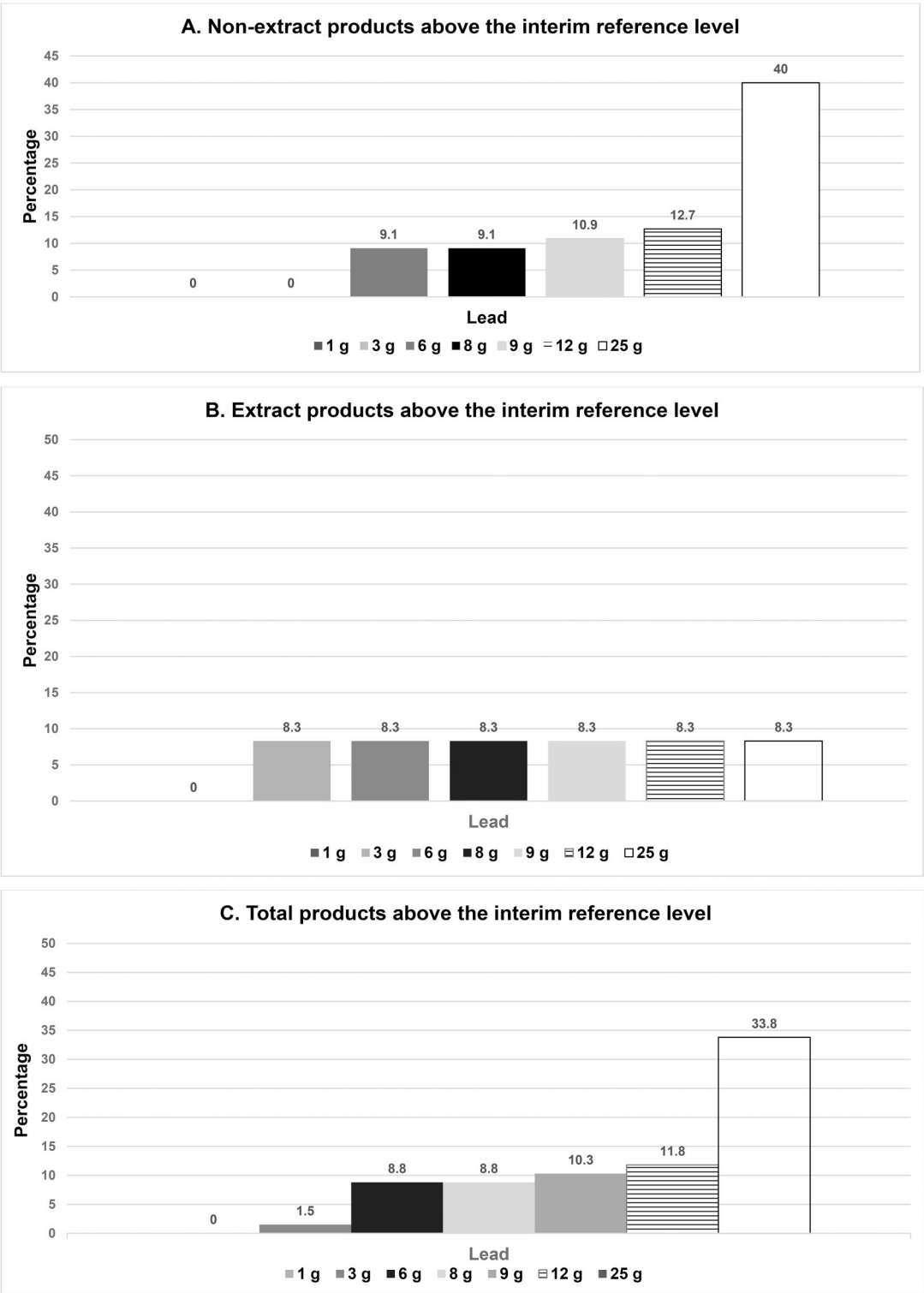


Figure 3. The percentage of kratom products with lead levels exceeding the interim reference limit in relation to the types and doses (1–25 g) consumed daily.

products assessed exceeded the tolerable upper intake level for nickel at any kratom dosage (Figure 4).

Table 3 displays the median arsenic concentrations per g and the amounts that would be delivered at kratom ingestion doses of 3, 6, 8, 9, 12, and 25 g daily for all products assessed ($n=32$), non-extract products (powders, capsules, or tablets, $n=21$), extract products ($n=10$) and a soda preparation ($n=1$). The arsenic amounts delivered per day would be much greater for the non-extract products than the

extract products because of the differences in median arsenic concentrations ($0.16\text{ }\mu\text{g/g}$ versus $0\text{ }\mu\text{g/g}$).

Figure 2 displays the percentage of kratom products (non-extract, extract, and total) that exceeded the permissible daily exposure limit for arsenic ($15\text{ }\mu\text{g/day}$) at ingestion doses of 3–25 g daily. The percentage was much greater in non-extract products (Figure 2(A)) than in extract products (Figure 2(B)), especially at greater ingestion doses. The percentage of total products exceeding the permissible daily

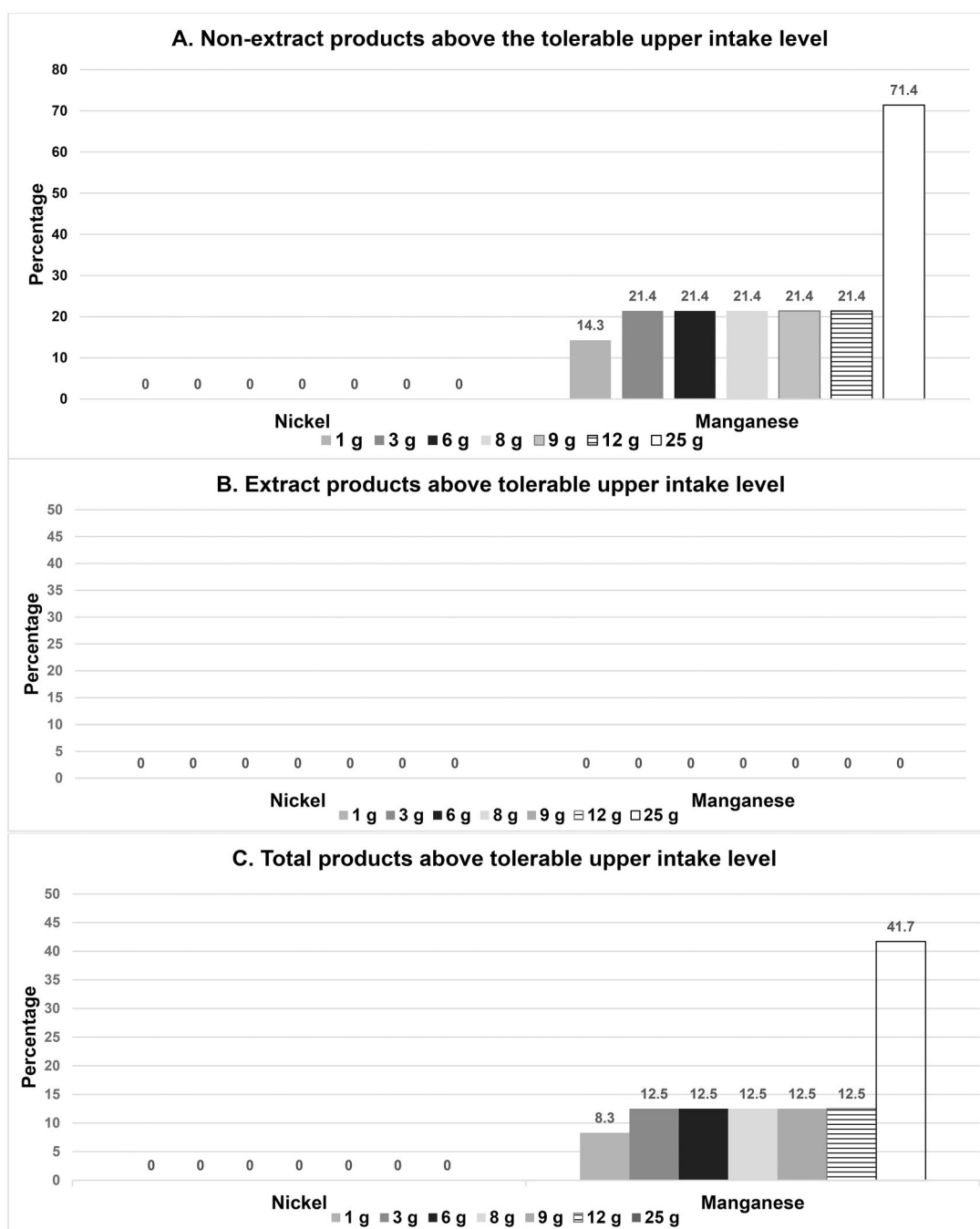


Figure 4. The percentage of kratom products with elemental impurity (nickel, manganese) concentrations exceeding the tolerable upper intake level in relation to the types and doses (1–25 g) consumed daily.

exposure limit increased from 3.1% at 3 g to 9.4% at 25 g of kratom ingestion daily (Figure 2(C)). It was not possible to determine the fraction of inorganic arsenic on which the permissible daily exposure limit is based.

Table 3 displays the median manganese concentrations per g and the amounts that would be delivered at kratom ingestion doses of 3, 6, 8, 9, 12, and 25 g daily for all products assessed ($n=24$), non-extract products (powders, capsules, or tablets, $n=14$), extract products ($n=9$) and a soda preparation ($n=1$). The manganese amounts delivered per day would be much greater for the non-extract products than the extract products because of the

differences in median manganese concentrations (0.49 mg/g versus 0.01 mg/g). Figure 4 displays the percentage of kratom products (non-extract, extract, and total) that exceeded the tolerable upper intake level limit for manganese (11 mg/daily) at ingestion doses of 3–25 g daily. The percentage was much greater in non-extract products (Figure 4(A)) than in extract products (Figure 4(B)), especially at greater ingestion doses. The percentage of total products exceeding the tolerable upper intake level limit increased from 12.5% at 3 g to 41.7% at 25 g of kratom ingestion daily (Figure 4(C)).

Table 3 displays the median cadmium concentrations per g and the amounts that would be delivered at kratom

Table 3. Arsenic (μg), manganese (mg), and cadmium (μg) exposure doses based on the median concentrations per g in the types of kratom products (non-extract, extract, soda and total) and the doses of kratom (3–25 g) taken daily.

	Dose of kratom taken daily					
	3 g	6 g	8 g	9 g	12 g	25 g
Arsenic (median)						
Non-extract products, $n = 10$ (0.16 $\mu\text{g}/\text{g}$)	0.47 μg	0.93 μg	1.24 μg	1.40 μg	1.86 μg	3.88 μg
Extract products, $n = 21$ (0 $\mu\text{g}/\text{g}$)	0 μg	0 μg	0 μg	0 μg	0 μg	0 μg
Soda product, $n = 1$ (0 $\mu\text{g}/\text{g}$)	0 μg	0 μg	0 μg	0 μg	0 μg	0 μg
Total products, $n = 32$ (0.01 $\mu\text{g}/\text{g}$)	0.02 μg	0.03 μg	0.04 μg	0.05 μg	0.06 μg	0.13 μg
Manganese (median)						
Non-extract products, $n = 14$ (0.49 mg/g)	1.46 mg	2.93 mg	3.91 mg	4.39 mg	5.86 mg	12.20 mg
Extract products, $n = 9$ (0.01 mg/g)	0.03 mg	0.06 mg	0.08 mg	0.08 mg	0.11 mg	0.23 mg
Soda product, $n = 1$ (0.04 mg/g)	0.13 mg	0.26 mg	0.35 mg	0.39 mg	0.53 mg	1.09 mg
Total products, $n = 24$ (0.31 mg/g)	0.93 mg	1.86 mg	2.48 mg	2.79 mg	3.72 mg	7.75 mg
Cadmium (median)						
Non-extract products, $n = 7$ (0.03 $\mu\text{g}/\text{g}$)	0.10 μg	0.20 μg	0.27 μg	0.30 μg	0.40 μg	0.84 μg
Extract products, $n = 1$ (0 $\mu\text{g}/\text{g}$)	0 μg	0 μg	0 μg	0 μg	0 μg	0 μg
Total products, $n = 8$ (0.03 $\mu\text{g}/\text{g}$)	0.09 μg	0.18 μg	0.24 μg	0.27 μg	0.36 μg	0.75 μg

0 $\mu\text{g}/\text{g}$ = below the limit of detection.

ingestion doses of 3, 6, 8, 9, 12, and 25 g daily for all products assessed ($n = 8$), non-extract products (powders, capsules, or tablets, $n = 7$), and extract products ($n = 1$). The cadmium amounts delivered per day would be greater for the non-extract products than the extract products because of the differences in median cadmium concentrations (0.03 $\mu\text{g}/\text{g}$ versus 0 $\mu\text{g}/\text{g}$). No individual product had a cadmium amount that exceeded the permissible daily exposure (5 μg) at kratom dosing concentrations from 3 g to 25 g (Figure 2).

Discussion

Patients consuming kratom products may be exposed to elemental impurities exceeding the permissible daily exposure limits. For lead, the percentage of kratom products exceeding the permissible daily exposure limit progressively increased with the daily dose, from 7.4% at 3 g to 70.6% at 25 g. For nickel, the percentage of kratom products exceeding the permissible daily exposure limit increased with daily dose, from 2.9% at 8 g to 20.6% at 25 g. While we assessed arsenic exposure, it was in the inorganic form, based on which the permissible daily exposure is derived. As such, the significance of exceeding the permissible daily exposure limit (Figure 3) is not known. We did not find any kratom products that had cadmium concentrations exceeding the permissible daily exposure limit, based on a daily dose of 1 g to 25 g [16–18,24,27].

Some kratom products even exceeded the interim reference level for lead or the tolerable upper intake level for nickel and manganese [21–23]. There was a manganese product that exceeded the tolerable upper intake level when only 1 g of kratom was used daily. We found 34% of kratom products will deliver more than the interim reference level for lead (12.5 $\mu\text{g}/\text{day}$) when kratom 25 g is ingested [21]. The interim reference level has been lowered in women of child-bearing age (8.8 $\mu\text{g}/\text{day}$), given the negative impact of lead on the developing fetus and the percentage of kratom products exceeding this limit would be greater [21].

Importantly, we found that kratom extract products had lower concentrations of elemental impurities than powders, capsules, or tablets. We only had access to one soda preparation, which showed similar results to the extract products.

It is important to remember that kratom is one of many potential sources of elemental impurities that consumers are exposed to. Some consumers might have greater basal exposure, and the contribution of additional elemental impurities from kratom could become more significant. In adults, the interim reference level for lead (12.5 $\mu\text{g}/\text{day}$) corresponds to a blood lead concentration of 5 $\mu\text{g}/\text{L}$ [28]. There is sufficient evidence that blood lead concentrations (<100 $\mu\text{g}/\text{L}$ and 50 $\mu\text{g}/\text{L}$) are associated with adverse health effects [29]. Adverse health effects at higher blood lead concentrations are well established and have been associated with bone softening, the loss of mental acuity and dementia, hypertension, hepatotoxicity, and reduced renal function [28].

Nickel poisoning has been associated with generalized neurotoxicity, teratogenicity, and cancer formation [30]. Arsenicosis begins with gastroenteritis and hypotension and can progress over time to include dyesthesias, headaches, confusion, memory loss, seizures, delirium, anemia, leukopenia, and thrombocytopenia [31]. Left untreated, diffuse or spotted hyperpigmentation, basal cell and squamous cell carcinoma, ascites, and hepatomegaly have occurred [31]. Manganese is associated with early onset mood changes such as anxiety and depression, and in later stages patients can develop reduced cognition, psychosis, parkinsonian-like tremors, gait abnormalities, and dystonic movements [32].

An important question is why there are elemental impurities in kratom products, or any naturally derived product, to begin with? There are several potential sources of lead that need to be considered but to what extent each is, or is part of, the culprit is not yet known [25]. The country or origin for the kratom trees may play some role in the greater concentrations of elemental impurities [25,26]. One of the studies that we excluded, because it lacked individual product data, did assess kratom products that were reportedly cultivated in different countries [26]. For lead, Indonesia and Thailand had greater concentrations than Vietnam, Borneo, or Malaysia. For nickel, Borneo and Indonesia had greater doses than Thailand, Vietnam, and Malaysia. Manganese was greater in Thailand and Indonesia than Vietnam, Malaysia, and Borneo [26].

Volcanic rock can have high lead and other elemental impurity concentrations and as it wears away, it leeches into the soil and water [26]. These elemental impurities, naturally

found in both soil and water, can be enhanced by elemental impurities billowed into the air from fossil fuel based industrial pollution. The kratom trees growing in the elemental impurity laden soil can incorporate them into the leaves that are harvested for commercial use [26]. The local water used to wash the leaves can also cause elemental impurity contamination and when dried, elemental impurities are retained on the dried plant material [25]. Elemental impurities can be introduced into kratom products via the use of machinery that leeches them out during the harvesting, grinding, storage, and shipping of the leaves [25]. Finally, arsenic is included in some older pesticides and herbicides where it can leech into the water supply [25,26].

Our review has several limitations. First, we found three different laboratory studies assessing elemental impurity concentrations, one from the US Food and Drug Administration that gathered products via the internet and others that gathered products locally from either Chicago, IL or Richmond, VA [16,24,27]. These results might not be applicable to other parts of the country or other countries. While we have results in up to 68 different products for lead and nickel, the number of products evaluated for other elemental impurities is smaller and may not be as generalizable. The elemental impurity concentrations in kratom varied from study to study, and bigger studies of products from different sources would be needed.

Conclusions

Excessive concentrations of elemental impurities of toxicological concern, such as lead and arsenic, are present in several kratom products and daily use of these products can result in exposures exceeding the regulatory thresholds and adverse health effects.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

The authors reported there was no funding associated with the work featured in this article.

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Data availability statement

All of the original third-party laboratory data per product that we used to make our assessments have already been published and are referenced in our paper.

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