



A human health risk assessment of heavy metal ingestion among consumers of protein powder supplements

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ABSTRACT

Concerns have recently been raised about the presence of heavy metals in protein powder supplements following a Consumer Reports analysis of 15 protein powder products. The Consumer Reports study found that the average amounts of heavy metals in three servings of protein powder per day exceeded the maximum limits in dietary supplements proposed by U.S. Pharmacopeia. In a follow up to the Consumer Reports analysis, another study reported that 40 % of the 133 protein powder products they tested had elevated levels of heavy metals. The objective of this analysis was to determine whether the heavy metal concentrations reported in protein powder supplements posed any human health risks, based on the reported concentrations of arsenic (As), cadmium (Cd), mercury (Hg), and lead (Pb) in the protein powder. The US EPA reference doses (RfD) for As and Cd, and the EPA screening level for Hg were based on the most sensitive health endpoint which were used to calculate hazard quotients (HQs) for each metal. The ‘worse-case scenario’ assessment for each protein powder product was expressed as a cumulative hazard index (HI), which is the sum of HQs from each heavy metal. Additionally, we utilized the U.S. EPA’s Adult Lead Methodology (ALM) model to estimate adult blood lead levels (BLLs), which were compared to the CDC BLL guidance value of 5 µg/dL. All models assumed one or three servings of protein powder per day. Our results indicate that the exposure concentrations of the studied metals do not pose an increased health risk (Hazard Index < 1). We noted that the protein powder HI was mainly driven by the As or Cd content in each product. Interestingly, the highest HI levels (which approached 1) were found in ‘mass gain’ type protein powder supplements, whereas the lowest calculated HI levels were in whey protein powders. Moreover, background Pb exposure was the primary contributor to estimated BLLs in adults, and all modeled BLLs were below 5 µg/dL. Overall, our results suggest that the typical intake of dietary supplements would not result in adverse health effects due to heavy metals.

1. Introduction

Consumption of over the counter protein powder supplements has become increasingly popular among the United States (US) population, with an estimated revenue of \$4.7 billion in 2020 that is expected to increase to \$6.6 billion by 2025 [48]. Various protein powder supplements are marketed for different desired uses, including muscle building, weight loss, and/or meal replacement. Common supplements include ready to drink liquids, as well as dry powders that are mixed with milk or water prior to consumption.

Recently, there have been concerns regarding the safety of protein powder supplements due to the reported presence of heavy metals (arsenic [As], cadmium [Cd], mercury [Hg], and lead [Pb]) in tested products [1,2]. In 2010, the US Consumer Reports measured heavy

metal concentrations in 15 commercially available protein powder supplements, and reported that all of the examined products contained “detectable concentrations” of at least one heavy metal [2]. In a separate evaluation in 2018, the Clean Label Project tested 133 protein powder supplements, and found that all of the tested products similarly contained “detectable concentrations” of heavy metals [1]. Specifically, the Clean Label Project reported that 70 % and 74 % of the test products contained “measurable levels” of Pb and Cd, respectively [1]. These studies are cited by the media as evidence for possible adverse health effects following consumption of protein powder supplements.

When ingested in sufficient quantities, As, Cd, Hg, and Pb have been associated with adverse human health effects, potentially including carcinogenesis, neurotoxicity, nephrotoxicity and reproductive issues [3–9]. For example, chronic exposure to Cd is associated with renal

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disease, thyroid disruption, and weakened bones, while chronic exposure to As is associated with dermal lesions and carcinogenic effects [10–13]. Additionally, high doses of ingested Pb compete with calcium in the body, affecting neurotransmitter release and heme synthesis, which may result in nervous, hematological, reproductive, and renal effects [5,14,15]. Further, sufficient Hg exposure can elicit neurological, motor, renal, cardiovascular, immune and reproductive dysfunction [16].

Although studies have shown that heavy metals are present at detectable levels in protein powder supplements, to our knowledge, no quantitative exposure assessment has been conducted to evaluate the potential health risks following consumption of these products. Additionally, it is important to understand any potential health effects associated with consumption of the products, due to the fact that the US Food and Drug Administration (US FDA) does not regulate protein powder supplements. Therefore, the objective of this analysis was to determine the non-carcinogenic health risk for As, Cd, Hg, and Pb from consumption of protein powder supplements.

2. Methods

For this analysis, we relied on reported heavy metal concentrations in protein powder supplements from the US Consumer Reports [2] and the Clean Label Project [1]. Specifically, the US Consumer Reports tested 15 commonly consumed liquid and powder protein supplements. Protein powder supplements were classified as weight gainer or whey protein products. When unknown, products were classified based on the manufacturer label, the ingredients and/or based on professional judgement. Additionally, the reported serving size information for each product was used to characterize consumption rates in this analysis (1 serving/day and 3 servings/day).

In contrast, the Clean Label Project tested 133 different protein powder supplements, but did not provide additional identifying information about the products. Therefore, descriptive statistics of heavy metal-specific concentrations for all 133 products were used in the Clean Label Project analysis. As the Clean Label Project did not disclose the protein powder supplement brand/product name, we were unable to ascertain the product specific serving size. Therefore, we assumed a serving size of 43 g (calculated average serving size from the US Consumer Reports). Additionally, we assumed that all 133 products were non-liquid protein powder supplements.

2.1. Exposure estimation

2.1.1. Heavy metal exposure estimate

The metal concentrations reported in the protein powder supplements (As, Cd, Hg, and Pb) were used to calculate the chronic daily intake (CDI), which characterizes the exposure to metals resulting from product consumption. The following equation was used to determine the CDI [17]:

$$CDI = C \times DI$$

Such that:

CDI = chronic daily intake ($\mu\text{g}/\text{day}$);

C = concentration of each metal found in the protein powder ($\mu\text{g}/\text{g}$ or $\mu\text{g}/\text{mL}$);

DI = average daily intake rate of protein powder (g/day or mL/day).

We assumed a minimum of 1 or a maximum of 3 servings of protein powder per day (consistent with the recommended serving size for the evaluated protein powder supplements).

2.2. Non-carcinogenic health-risk assessment

2.2.1. Hazard quotient determination

To estimate the non-carcinogenic risk of heavy metal ingestion resulting from protein powder supplement consumption, a hazard

quotient (HQ) for 3 of the 4 metals (As, Cd, and Hg) was determined using the standard US EPA methodology [18]. The EPA reference doses (RfDs) for inorganic As, Cd, and the screening level for Hg are 3×10^{-4} $\text{mg}/\text{kg}/\text{day}$ ($0.3 \mu\text{g}/\text{kg}/\text{day}$), 5×10^{-4} $\text{mg}/\text{kg}/\text{day}$ ($0.5 \mu\text{g}/\text{kg}/\text{day}$), and 3×10^{-4} $\text{mg}/\text{kg}/\text{day}$ ($0.3 \mu\text{g}/\text{kg}/\text{day}$), respectively [18, 45]. The RfD is an estimate of a daily oral exposure to the human population (including sensitive subgroups) that is likely to produce no appreciable risk of deleterious effects during a lifetime [44]. In this analysis, it was assumed that a 70 kg adult ingested the protein powder supplements. The following equation was used to calculate the HQ:

$$HQ = \frac{CDI}{RfD}$$

2.2.2. Hazard index determination

The cumulative risk of the evaluated heavy metals was expressed as a hazard index (HI), which is the sum of the HQs for As, Cd, and Hg [18].

$$HI = HQ_{As} + HQ_{Cd} + HQ_{Hg}$$

Since there is no RfD for Pb, it was not included in the HQ analysis. However, we characterized the risk of Pb exposure via changes in blood lead levels (BLLs). The EPA adult lead model (ALM) was selected to estimate adult BLLs, as the EPA recommended this model for assessments of non-residential Pb exposures that result in BLLs $<25 \mu\text{g}/\text{L}$ [43]. A baseline adult BLL of $1.27 \mu\text{g}/\text{dL}$ was used, which was the calculated weighted geometric mean of BLLs in adults aged 20 years or older during the 2005–2012 NHANES survey years [40]. We assumed that individuals consumed 1 or 3 servings of protein powder per day, for a total of 365 days per year.

Gastrointestinal absorption of Pb was conservatively assumed to be 20 % [39,47]. The BLL guidance value of $5 \mu\text{g}/\text{dL}$ from the Center for Disease Control (CDC) was used as the benchmark in this analysis. Additionally, the change in BLL from baseline was calculated for each exposure scenario.

2.3. Statistical analyses

The concentration of metals were compared using Kruskal-Wallis rank test with a post-hoc Dunn's pairwise comparison test. A two-sample Wilcoxon rank-sum (Mann-Whitney) test was used to compare the concentration of each metal and changes in BLLs between weight gainer and whey protein products. The limit of quantification (LOQ) was not reported in the US Consumer Reports data; therefore, for statistical analyses, a value of zero was assigned to all non-detect samples. For Clean Label Project data, non-detect samples were assigned a value of $\frac{1}{2}$ the LOQ (LOQs were $4.0 \mu\text{g}/\text{kg}$ for As, $2.0 \mu\text{g}/\text{kg}$ for Cd, $2.0 \mu\text{g}/\text{kg}$ for Hg, and $4.0 \mu\text{g}/\text{kg}$ for Pb). All analyses were performed using Stata version 14.2.

3. Results

3.1. Heavy metal exposure estimate

The heavy metal concentrations in protein powder supplements (per serving), based on data from US Consumer Reports, are reported in Table 1. There was a statistically significantly higher concentration of As per serving when compared to all other evaluated metals ($p < 0.05$). The calculated CDI range for heavy metals in 1–3 servings of protein powder supplements identified by Consumer Reports were: 0.2 – $16.9 \mu\text{g}/\text{day}$ for As, 0 – $5.6 \mu\text{g}/\text{day}$ for Cd, 0 – $1.1 \mu\text{g}/\text{day}$ for Hg, and 0 – $13.5 \mu\text{g}/\text{day}$ for Pb (Table 2). Notably, weight gainer products had a statistically significantly higher concentration of As ($p < 0.05$), and a non-statistically significantly higher concentration of Pb, Cd, and Hg ($p > 0.05$), in comparison to whey protein products. Therefore, on average, the calculated CDIs for weight gainer products were higher than whey protein products.

Table 1

Heavy metal concentrations in protein powder supplements, per serving (adapted from the Consumer Reports).

Sample ID	Supplement Type	Amount of Protein Powder Per Serving	Heavy Metal Concentration Per Serving (μg)			
			Arsenic	Cadmium	Lead	Mercury
1	Whey protein	35 g	1.10	1.23	0.83	0.10
2		44 g	1.40	0.87	1.80	0.37
3		26 g	1.30	0.53	0.80	0.30
4		48 g	2.33	1.30	1.63	ND
5		79 g	1.80	0.83	0.83	ND
6		27 g	0.63	ND	0.40	ND
7		32 g	0.40	ND	0.13	0.30
8		32 g	0.83	0.57	0.33	0.07
9		39 g	0.50	ND	ND	ND
10		39 g	0.77	ND	ND	ND
11	20 g	0.20	ND	ND	ND	
12	Weight gainer	500 mL	5.63	1.70	ND	ND
13		70 g	4.07	1.87	4.50	0.23
14		330 mL	4.77	ND	2.27	ND
15		70 g	3.73	0.67	4.07	ND

Table 2

Range of potential exposure to heavy metals from ingesting 1 or 3 servings of protein powder supplements.

Sample ID	Supplement Type	Consumer Daily Intake ($\mu\text{g}/\text{day}$)							
		Arsenic		Cadmium		Lead		Mercury	
		1 serving/day	3 servings/day	1 serving/day	3 servings/day	1 serving/day	3 servings/day	1 serving/day	3 servings/day
1	Whey protein	1.10	3.30	1.23	3.70	0.83	2.50	0.10	0.30
2		1.40	4.20	0.87	2.60	1.80	5.40	0.37	1.10
3		1.30	3.90	0.53	1.60	0.80	2.40	0.30	0.90
4		2.33	7.00	1.30	3.90	1.63	4.90	0.00	0.00
5		1.80	5.40	0.83	2.50	0.83	2.50	0.00	0.00
6		0.63	1.90	0.00	0.00	0.40	1.20	0.00	0.00
7		0.40	1.20	0.00	0.00	0.13	0.40	0.30	0.90
8		0.83	2.50	0.57	1.70	0.33	1.00	0.07	0.20
9		0.50	1.50	0.00	0.00	0.00	0.00	0.00	0.00
10		0.77	2.30	0.00	0.00	0.00	0.00	0.00	0.00
11	0.20	0.60	0.00	0.00	0.00	0.00	0.00	0.00	
12	Weight gainer	5.63	16.90	1.70	5.10	0.00	0.00	0.00	0.00
13		4.07	12.20	1.87	5.60	4.50	13.50	0.23	0.70
14		4.77	14.30	0.00	0.00	2.27	6.80	0.00	0.00
15		3.73	11.20	0.67	2.00	4.07	12.20	0.00	0.00

Summary data on the heavy metal concentrations in protein powder supplements (per serving), based on data from the Clean Label Project, are reported in Table 3. Cd had the highest mean concentration per serving, followed by Hg, As and then Pb. There was a statistically significantly lower concentration of Hg per serving in comparison to all other evaluated metals ($p < 0.05$). The calculated CDI range for heavy metals in 1–3 servings of protein powder supplements identified by the Clean Label Project were: 0.09–10.3 $\mu\text{g}/\text{day}$ for As, 0.03–39.5 $\mu\text{g}/\text{day}$ for Cd, 0.04–2.92 $\mu\text{g}/\text{day}$ for Hg, and 0.09–15.9 $\mu\text{g}/\text{day}$ for Pb (Table 4).

3.2. Non-carcinogenic health risk assessment

3.2.1. Hazard quotient determination

Calculated hazard quotients from consumption of protein powder supplements are reported in Table 5 (Consumer Reports), and Table 6 (Clean Label Project). Metal exposure from consumption of protein powder supplements identified by US Consumer Reports were all below the RfD for each respective metal ($\text{HQ} < 1$). Regarding the Clean Label Project protein powder supplement data, all hazard quotients were below 1, except for a single exposure scenario. However, this was due to 3 servings per day of a single product with an exceedingly elevated Cd concentration (13.18 $\mu\text{g}/\text{serving}$), which may not be representative of

all protein powder supplement products. It is noteworthy that consumption of 3 servings per day of a protein powder supplement containing the 95th percentile concentration of Cd resulted in a calculated HQ of 0.59 (Table 6).

3.2.2. Hazard index determination

To estimate the cumulative non-carcinogenic risk from As, Cd, and Hg, a hazard index (HI) was calculated. The estimated HIs for all

Table 3

Heavy metal concentrations in protein powder supplements, per serving (Clean Label Project).

Value	Heavy Metal Concentration Per Serving ^{1,2} (μg)			
	Arsenic	Cadmium	Lead	Mercury
Min	0.09	0.03	0.04	0.09
Median	0.55	1.44	0.08	0.61
Mean	0.37	0.58	0.04	0.42
95th percentile	2.17	6.84	0.21	2.26
Max	3.42	13.18	0.97	5.31

¹ Assumed 43 g per serving.² Non detect samples were assigned a value of LOQ/2.

Table 4

Range of potential exposure to heavy metals from ingesting 1 or 3 servings of protein powder supplements.

Value	Consumer Daily Intake ($\mu\text{g}/\text{day}$)							
	Arsenic		Cadmium		Lead		Mercury	
	1 serving/day	3 servings/day	1 serving/day	3 servings/day	1 serving/day	3 servings/day	1 serving/day	3 servings/day
Min	0.09	0.26	0.03	0.10	0.04	0.13	0.09	0.26
Median	0.55	1.65	1.44	4.32	0.08	0.23	0.61	1.82
Mean	0.37	1.11	0.58	1.75	0.04	0.13	0.42	1.26
95th percentile	2.17	6.51	6.84	20.53	0.21	0.64	2.26	6.78
Max	3.42	10.27	13.18	39.54	0.97	2.92	5.31	15.93

Table 5

Hazard quotients from consumption of protein power supplements reported in Consumer Reports.

Sample ID	Supplement Type	Hazard Quotient					
		Arsenic		Cadmium		Mercury	
		1 serving/day	3 servings/day	1 serving/day	3 servings/day	1 serving/day	3 servings/day
1	Whey protein	0.052	0.157	0.035	0.106	0.005	0.014
2		0.067	0.200	0.025	0.074	0.017	0.052
3		0.062	0.186	0.015	0.046	0.014	0.043
4		0.111	0.333	0.037	0.111	0.000	0.000
5		0.086	0.257	0.024	0.071	0.000	0.000
6		0.030	0.090	0.000	0.000	0.000	0.000
7		0.019	0.057	0.000	0.000	0.014	0.043
8		0.040	0.119	0.016	0.049	0.003	0.010
9		0.024	0.071	0.000	0.000	0.000	0.000
10		0.037	0.110	0.000	0.000	0.000	0.000
11	0.010	0.029	0.000	0.000	0.000	0.000	
12	Weight gainer	0.268	0.805	0.049	0.146	0.000	0.000
13		0.194	0.581	0.053	0.160	0.011	0.033
14		0.227	0.681	0.000	0.000	0.000	0.000
15		0.178	0.533	0.019	0.057	0.000	0.000

Table 6

Hazard quotients from consumption of protein powder supplements reported in the Clean Label Project.

Value	Hazard Quotient					
	Arsenic		Cadmium		Mercury	
	1 serving/day	3 servings/day	1 serving/day	3 servings/day	1 serving/day	3 servings/day
Min	0.004	0.012	0.001	0.003	0.002	0.006
Median	0.026	0.079	0.041	0.123	0.004	0.011
Mean	0.018	0.053	0.017	0.050	0.002	0.006
95th percentile	0.103	0.310	0.196	0.587	0.010	0.030
Max	0.163	0.489	0.377	1.130	0.046	0.139

Table 7

Descriptive statistics for the hazard index of protein powder supplements reported in the Consumer Reports.

Sample ID	Supplement Type	Hazard Index	
		1 serving/day	3 servings/day
1	Whey protein	0.092	0.277
2		0.109	0.327
3		0.091	0.274
4		0.148	0.445
5		0.110	0.329
6		0.030	0.090
7		0.033	0.100
8		0.059	0.177
9		0.024	0.071
10		0.037	0.110
11	Weight gainer	0.010	0.029
12		0.317	0.950
13		0.258	0.774
14		0.227	0.681
15		0.197	0.590

products identified by US Consumer Reports were below 1 (Table 7). For the Clean Label Project data, HIs were calculated based on multiple concentration parameters (Table 8). Similarly to discussed above, consumption of a single product with the highest reported Cd concentration (13.18 $\mu\text{g}/\text{serving}$; 3 servings/day) resulted in an HI > 1 (HI was <1 in the 95th percentile Cd model).

3.2.3. Blood lead level (BLL) determination

Calculated BLLs are shown in Table 9 (US Consumer Reports) and Table 10 (Clean Label Project). None of the estimated BLLs exceeded the CDC guidance value of 5 $\mu\text{g}/\text{dL}$, for all examined exposure scenarios. The highest estimated BLLs were 2.24 (+0.97 from baseline) $\mu\text{g}/\text{dL}$ and 1.50 (+0.23 from baseline) $\mu\text{g}/\text{dL}$, using data from the US Consumer Reports and Clean Label Project, respectively. Weight gainer products generally had higher increases in BLLs when compared to whey protein products, but this difference was not statistically significant.

4. Discussion

Although the health concerns associated with heavy metal ingestion from protein powder supplements has gained media attention, to date,

Table 8

Descriptive statistics for the hazard index of protein powder supplements reported in the Clean Label Project.

Value	Hazard Index	
	1 serving/day	3 servings/day
Min	0.007	0.021
Median	0.071	0.213
Mean	0.036	0.109
95th percentile	0.309	0.927
Max	0.586	1.757

Table 9

Blood lead levels from consumption of protein powder supplements reported in Consumer Reports.

Sample ID	Supplement Type	Blood Lead Level ($\mu\text{g}/\text{dL}$)	
		1 serving/day	3 servings/day
1	Whey protein	1.34	1.47
2		1.41	1.70
3		1.33	1.46
4		1.40	1.66
5		1.34	1.48
6		1.30	1.37
7		1.28	1.30
8		1.30	1.35
9		1.27	1.27
10		1.27	1.27
11	1.27	1.27	
12	1.27	1.27	
13	Weight gainer	1.63	2.35
14		1.45	1.82
15		1.59	2.24

no systematic analysis have been performed to determine the potential human health risks. Here, we utilized publicly available quantitative data for heavy metal concentrations in a large collection of protein powder supplements and performed a human health risk assessment. Overall, findings from this analysis suggest that consumption of protein powder supplements containing As, Cd, Pb, and Hg is not associated with an increased risk of non-carcinogenic health effects due to heavy metal exposure.

4.1. Background dietary heavy metal exposures compared to heavy metal exposures from protein powder supplement ingestion

Heavy metals, including As, Cd, Pb, and Hg, are ubiquitous in the environment, and contamination of food can occur through a variety of anthropogenic and non-anthropogenic sources. Arsenic in surface freshwater sources, including in rivers and lakes is usually detected at concentrations of $<10 \mu\text{g}/\text{L}$, however, high concentrations (up to $5 \text{ mg}/\text{L}$) have been reported near anthropogenic sources. Foods that contain As include marine fish, mussels, and certain crustaceans (which may contain concentrations of up to $100 \text{ mg}/\text{kg}$) [19,20]. Other food sources that contain inorganic As include meats, poultry, dairy products and

Table 10

Blood lead levels from consumption of protein powder supplements reported in the Clean Label Project.

Value	Blood Lead Levels ($\mu\text{g}/\text{dL}$)	
	1 serving/day	3 servings/day
Min	1.27	1.28
Median	1.28	1.29
Mean	1.27	1.28
95th percentile	1.29	1.32
Max	1.35	1.50

cereal. Organic As is found in fruits and vegetables, but at much lower concentrations [19]. According to the World Health Organization (WHO), the estimated typical dietary intake of As in adult men aged 25–30 years was $9.9 \mu\text{g}/\text{day}$ [21]. It was noted that compared to men, women and children had a higher dietary As intake, and that intake also increased with aging. Comparing heavy metal exposure resulting from protein powder supplement ingestion to dietary background exposures is helpful in providing context to exposure from various sources. For comparison, in this analysis, the mean concentration of As ingested from three servings of protein powder supplements (calculated based on the reported As content in the 15 protein powder supplements provided by Consumer Reports) was $5.9 \mu\text{g}/\text{day}$, which was appreciably less than the average dietary As intake of $9.9 \mu\text{g}/\text{day}$ reported by WHO. The highest As intake from protein powder supplement ingestion was $16.9 \mu\text{g}/\text{day}$ for an individual ingesting 3 servings of this product per day, which is still significantly lower than an individual ingesting a seafood rich meal, once per day.

Cadmium on the other hand is found in most foodstuffs, but at ‘lower’ concentrations (the average reported concentration $<0.02 \mu\text{g}/\text{g}$) [22,23]. Higher concentrations of Cd are found in leafy vegetables, starchy roots, cereals, grains, and nuts compared to concentration in meats or dairy. The estimated weekly dietary Cd intake for adults is approximately $2.3 \mu\text{g}/\text{kg}$ body weight [22], or for a 70 kg adult $\sim 23 \mu\text{g}/\text{day}$. Of note, on a body weight basis, Cd intake in infants and children is generally higher than in adults [22]. In this analysis, ingestion of three servings of protein powder supplements was associated with a mean daily intake of $1.91 \mu\text{g}/\text{day}$ Cd (calculated based on Consumer Reports data). The highest Cd intake was $5.6 \mu\text{g}/\text{day}$, which is significantly lower than the estimated daily dietary intake of Cd for adults.

The amount of Pb an individual ingests via food is largely dependent on the Pb concentrations found in the soil, air, and water that the food was grown in Bolger et al. [24], Khandekar et al. [25] and Marin et al. [26]. Anthropogenic sources of Pb, such as the proximity to industries producing Pb emissions impact the levels of Pb in food. According to IARC [27], in the United States, the estimated daily dietary intake of Pb is $\sim 83 \mu\text{g}/\text{day}$ (based on a market basket survey) [27]. However, dietary intake of Pb can vary depending on geological location, for example, the daily dietary intake may range from $7 \mu\text{g}/\text{day}$ (in Malaysia) to $230 \mu\text{g}/\text{day}$ (in Belgium) [27]. For comparison, the mean Pb exposure from ingestion of three servings of protein powder supplements was $3.52 \mu\text{g}/\text{day}$; the highest daily exposure potential was $13.5 \mu\text{g}/\text{day}$ (calculated based on Consumer Reports data).

The dietary intake of Hg is mainly through aquatic organisms and contaminated drinking water [20,23,26,28,29]. It was noted that the estimated average daily intake of inorganic Hg compounds in the general population from food and drinking water were $4.2 \mu\text{g}/\text{day}$ and $0.05 \mu\text{g}/\text{day}$, respectively [28]. Due to the variability in fish consumption habits in the US population, and the variability in methyl Hg concentrations found in fish, an exact Hg exposure (non-occupational) estimation for the US general population is difficult to perform. However, comparatively, the mean Hg exposure potential from ingesting three servings of protein powder supplements was only $0.27 \mu\text{g}/\text{day}$, with a maximum exposure potential of $1.1 \mu\text{g}/\text{day}$.

Together, this analysis indicates that relative to the average daily human exposure potential reported for As, Cd, Pb, and Hg from food and drink, ingestion of protein powder supplements contributes to only a fraction of the heavy metal body burdens for each heavy metal. Further, even in individuals that ingest three servings of protein powder supplements per day (potentially in individuals ingesting protein powder supplements as meal replacements), daily heavy metal (As, Cd, Pb, and Hg) concentrations ingested are well below the reported average daily heavy metal concentrations ingested by the general population.

4.2. Sources of heavy metal contamination in protein powder supplements

As noted above, heavy metals are ubiquitous in the environment, and

As, Cd, Pb and Hg have been identified as food-chain contaminants, which is supported in this analysis, as these heavy metals had the highest reported concentrations in the protein powder supplements that were evaluated [30]. Natural factors that influence As, Cd, Hg, and Pb levels in food are the specific food type, growing conditions (soil type, and water), agricultural and cultivation practices, and meteorological conditions (i.e. rate of atmospheric deposition, areas with geological formations rich heavy in metals). Specific to protein powder supplements, plant and milk based ingredients may be the primary sources of heavy metal contamination. Plants readily uptake heavy metals through the air, water and soil, and these heavy metals may remain in the end product, even after processing [31–33]. Furthermore, milk whey (the main ingredient in whey protein powder supplements, and one of the main ingredients in weight gainer protein powder supplements) is a byproduct of cheese production, and although a direct link has not been established it is likely that contaminated milk is one of the primary contributors to heavy metal contaminated whey protein. For example, high concentrations of As, Cd, and Pb have all been detected in cow milk in different regions of the world [32,34]. Specifically, one study in Bangladesh reported As in cow milk at a concentration of 89.6 ± 6.5 $\mu\text{g/L}$, and noted that there was a statistically significant positive correlation between the As content in milk and the As content in the contaminated drinking water and/or straw that the cows ingested [32]. Subsequently, the location of raw material sourcing for the manufacture of protein powder supplements may impact the heavy metal content of the final product.

4.3. Heavy metal exposure from protein powder supplement ingestion, compared to various regulatory values for non-cancer health effects

Currently, there are only limited exposure standards for heavy metals in protein powder supplements. Although the US FDA regulates the dietary supplement ingredients in the finished products, the scope of this regulation is limited to restricting the marketing of adulterated or misbranded products [49]. Conversely, the US Pharmacopeial (USP) Convention, a non-regulatory organization, published permissible daily exposures (PDE) for elemental contaminants in dietary supplements in 2012 [50]. According to the USP, the PDE is derived from the Provisional Tolerable Weekly Intake (PTWI) that is recommended by the Food and Agriculture Organization of the United Nations and World Health Organization (FAO/WHO) by subtracting the daily exposure ($\mu\text{g/day}$) to each elemental contaminant from air, food, and drinking water. Specifically, the USP's PDE for the heavy metals evaluated in this analysis are 15 $\mu\text{g/day}$ for As (inorganic), 5 $\mu\text{g/day}$ for Cd, 10 $\mu\text{g/day}$ for Pb and 15 $\mu\text{g/day}$ for Hg (total) [50]. It should be noted that the USP PDEs are determined based on a conservative average body weight of 50 kg and a composite safety factor (determined according to ICH Q3D guidelines). Based on the stringent limits set forth by the USP, 1 product out of the 15 products from the US Consumer reports was estimated to exceed the USP daily As limit of 15 $\mu\text{g/day}$; the reported As CDI for this product was 16.9 $\mu\text{g/day}$. No other exceedances were observed for the remaining evaluated metals. Based on the 95th percentile of heavy metal concentrations reported in the Clean Label Project, only Cd (two products, one with a maximum daily concentration of 20.53 $\mu\text{g/day}$) exceeded the USP PDE of 15 $\mu\text{g/day}$. Both of these exceedances assumed three servings of protein powder supplements per day. For comparison, based on the US EPA's RfDs and an assumed body weight of 70 kg, the daily exposure that is likely to be without an appreciable health risk during a lifetime is 21 $\mu\text{g/day}$, 35 $\mu\text{g/day}$, and 21 $\mu\text{g/day}$ for As, Cd, and Hg, respectively [18, 45]. No products from the US Consumer reports, nor the 95th percentile heavy metal concentrations from the Clean Label Project exceeded these EPA guideline values.

As previously discussed, no RfD has been derived for Pb. The human health risk for Pb is best characterized in terms of blood Pb concentrations as opposed to comparing exposure concentrations with an acceptable daily intake or permissible daily exposure value. Therefore,

the current analysis utilized the EPA ALM model to estimate changes in blood Pb concentration from exposure to reported Pb concentrations in protein powder supplements. Based on a baseline adult BLL of 1.27 $\mu\text{g/dL}$ (weighted geometric mean of BLLs in adults aged ≥ 20 years from NHANES 2005–2012), none of the estimated BLLs from any protein powder product under any exposure scenario assessed exceeded the CDC guidance value of 5 $\mu\text{g/dL}$. In fact, these results indicate that the total Pb body burden from ingesting protein powder supplements was within the normal variances found in the general population.

4.4. The hazard index (HI) for protein powder supplements is driven by the As and Cd concentrations in the products

It was interesting to note that the HI for protein powder supplements was largely driven by the As and Cd HQs for most protein powder supplements. As noted earlier, As and Cd contaminate foodstuffs, and these two heavy metals are commonly detected in a variety of plant, plant derived, and dairy products. Therefore, plant based protein powder supplements, or protein powder supplements that are intended for vegan consumers may contain a higher As and Cd content. Of note, according to the Clean Label Project, products that relied on a plant based protein tested “worst” for heavy metal content [1]. Further, the study reported that the sampled “organic” protein powder supplements contained “over 2X the heavy metals” content found in sampled “non-organic” protein powder supplements [1].

A comparison between whey protein powder supplements and weight gainer type protein powder supplements from the Consumer Reports data indicated that the HI for weight gainers was significantly higher than whey protein powder supplements. Specifically, we noted that the weight gainer type protein powder supplements contained a higher As content. Although it is unclear as to the source of As, it was noted that the weight gainer type protein powder supplements contained plant derived protein sources in addition to the whey protein. Similarly, 5/5 of the “top products” determined to contain the lowest heavy metal content by the Clean Label Project were either, “Pure,” “Pro,” or “100 %” whey protein powder supplements [1]. It can therefore be inferred that isolated whey proteins may contain the least amount of heavy metal contamination due to the lack of plant ingredients, or due to possibly the removal of heavy metals during whey protein processing.

4.5. Carcinogenic risk

Inorganic As is the only metal in the current study for which an oral cancer slope factor, and therefore, a carcinogenic risk could be estimated. The carcinogenic risk following ingestion of As has been investigated for decades. The International Agency for Research on Cancer (IARC) has long classified As as “carcinogenic to humans,” specifically, ingestion exposure of As has been associated with skin, lung, bladder, kidney, and possibly liver and prostate cancer ([19]: p. 85).

Information related to As toxicity comes primarily from studies in populations exposed to high concentrations of inorganic As in the drinking water. In one study that evaluated 42-village cancer mortality datasets from the Blackfoot-disease endemic area of southwest Taiwan, a positive cancer slope factor was found with drinking water As concentrations above 200 $\mu\text{g/L}$, and a significant risk of cancer at concentrations at or above 400 $\mu\text{g/L}$ [35]. The authors also noted that no increased carcinogenic risk was found at exposure concentrations at or below 150 $\mu\text{g/L}$ [35]. Similar carcinogenic ‘threshold’ concentrations of <100 $\mu\text{g/L}$ for As in drinking water have also been reported by other researchers [36]. The European Food Safety Authority (EFSA) and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) have conducted human health risk assessment for cancers, including lung, urinary bladder, and skin, following As ingestion through food [41,46]. Both agencies derived reference doses based on modeling for the available epidemiological data on the occurrence of lung and urinary

tract cancers. EFSA noted that the BMDL₁ (lower confidence limit on the benchmark dose) for As was 0.3–8 µg/kg body weight/day for cancers of the lung, skin, and bladder. Assuming a 70 kg adult, this is approximately 21–560 µg inorganic As/day. JECFA noted that the inorganic BMDL for 0.5 % increased incidence of lung cancer was 3 µg/kg body weight/day; assuming a 70 kg adult, this is approximately 210 µg/day, which is consistent with the epidemiological data presented above. Conservatively, the current evidence indicates that inorganic As drinking concentrations below 100 µg/L (~200 µg/day assuming an adult water intake of 2 L/day) will not pose an increased carcinogenic risk. Therefore, the As concentrations detected in protein powder supplements (range: 0.2–16.9 µg/day) do not pose an increased carcinogenic risk to the consumer.

4.6. Strengths and limitations

For this risk assessment, we relied on heavy metal concentration data for protein powder supplements published by the US Consumer Reports [2], and the Clean Label Project [1]. The US Consumer Reports randomly selected 15 protein powder supplements from in-store purchases in the New York metro area and through online purchases, and the Clean Label Project relied on the ‘top-selling’ protein products as reported by Nielson and Amazon.com. Together, these two reports provided a good representative sample of the protein powder supplements available to the US consumer market. However, the underlying data relied upon for this risk assessment has some inherent limitations. For example, due to product ID blinding, a standard consumption rate per serving was assumed for the Clean Label Project data. Therefore, specific to the Clean Label Project dataset, it is possible that the calculated risks may be under- or overestimated depending on the actual product specific consumption rate. Further, while we believe that the data collected was based on standard techniques and is accurate, information pertaining to data validation was not provided in either report.

There are also several limitations in using the RfD and HI approach to estimating risk [37]. Specific to RfD, heavy metals that have the same RfD do not imply the same level of risk. For example, although the RfD for inorganic As and Hg are the same, they are based on divergent endpoints (e.g. RfD for inorganic As is based on a NOAEL for dermal effects in humans, whereas RfD for Hg is derived based on development of autoimmune effects in rats). While the application of uncertainty factors may account for some of the uncertainty in the data, they do not fully adjust for the lack of experimental confidence of individual studies relied upon when calculating RfDs. Therefore, RfDs derived for these metals may have varying degrees of confidence. Furthermore, the application of uncertainty factors may be subjective, and may not capture the true risk. Since the HI is calculated as a function of each metals’ RfD, some of the limitations inherent to the RfD are carried forward when using the HI approach to estimate non-carcinogenic risk. Specifically, the HI gives equal weight and combines each RfD (with varying levels of confidence, and with different uncertainty adjustments) to estimate non-carcinogenic risk. Further, the level of concern does not increase linearly as the HI approaches or exceeds one because the RfDs do not have equal accuracy or precision and are not based on the same severity of effect. Despite these limitations, the EPA has concluded that the HI approach is appropriate for a screening level risk assessment, as was performed in this study [42]. Additionally, RfDs are derived to be protective for the lifetime of the most sensitive subgroups in the population. Hence, the results generated from this approach are likely conservative estimates. Of note, there have been alternative approaches to the HQ/HI method of assessing risks to single compounds and mixtures of chemicals [38]. Specifically, aggregate exposure to chemicals has been a topic of interest in recent years. Future analyses could examine aggregate exposure to metals from various sources beyond background levels. In the current analysis, aggregate exposure was not examined for some of the metals, therefore, the conclusions of this analysis are specific

to the ingredient formulations of the protein powder supplements assessed.

5. Conclusion

This study presents a screening level risk assessment investigating whether protein powder supplement ingestion is likely a significant source of heavy metal exposure, and whether this exposure poses an increased risk to human health. The data in the current study suggest that heavy metal exposure via protein powder supplement ingestion does not pose an increased non-carcinogenic risk to human health. Further, no carcinogenic risk was expected from As via ingestion of protein powder supplements. This study demonstrates that health risks of heavy metals in protein powder supplements should be conducted within the context of relevant background exposures and established health based standards instead of the presence of hazardous substances alone.

CRedit authorship contribution statement

Suren B. Bandara: Conceptualization, Investigation, Methodology, Formal analysis, Writing - original draft, Visualization. **Kevin M. Towle:** Methodology, Formal analysis, Writing - review & editing. **Andrew D. Monnot:** Methodology, Writing - review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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