

Quantification and Risk Assessment of Lead, Cadmium, Arsenic and Other Harmful Metals in Calcium Supplements in China

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Abstract Harmful metals are easily enriched in the human body and damage our health. The aim of this study was to conduct risk assessment on commercially available calcium supplements in China by analyzing the contents of 6 harmful metal elements, including arsenic, lead, cadmium, chromium, aluminum and mercury, and calcium according to Chinese National Standards and Joint Expert Committee on Food Additives. A total of 82 calcium supplements from China market was collected and analyzed for selected metal elements. The results showed the ranges of content of arsenic, lead, cadmium, chromium, aluminum, and mercury in calcium supplements were 0.01~15.34, 0.001~8.49, ND (not detected) ~1.104, 0.09~192.66, 3.32~761.11, and ND~0.036 mg/kg, respectively. Calcium supplements were more easily contaminated with lead, arsenic and chromium, but their contents were within the safe range. The exposure limits (MOE) of lead in calcium supplements for both children and adults was close to 1, which was close to the upper safe limit. Besides, the maximum daily exposure of chromium exceeded the maximum tolerable dose of chromium for children and adults, which should be taken seriously.

Keywords: calcium supplements, arsenic, lead, cadmium, harmful metal, risk assessment

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1. Introduction

Calcium is an essential element in the human body which distributes almost all over the body. It is the main inorganic component of bones and teeth and plays an important role in maintaining the normal function of muscles, nerves, body fluids and bones, etc [1]. Since calcium is essential for many metabolic processes, it must be supplemented daily to maintain the normal function of human body [2]. Insufficient or excessive calcium intake can cause harmful effect to human development and health [3]. When dietary calcium intake does not meet the nutritional requirements, people tend to choose calcium supplements to fill the gap.

Calcium supplements are prepared based on the physiological, biochemical and pharmacological effects of calcium, and its major component is calcium salt. In China, commercially available calcium supplements include tablets, soft capsules, granules, oral liquids and other dosage forms. The use of calcium supplements has

increased dramatically in recent decades. However, harmful metal elements residue in calcium supplements poses serious threats to consumers' health and this problem is becoming increasingly prominent. Zinn, G. M. [4] found that calcium supplements were contaminated with heavy metals such as lead, cadmium and arsenic in varying degrees by using microwave digestion and ICP-MS. Da Silva, E. [5] found that the content of aluminum in calcium supplements would vary depending on the source of calcium by wavelength-dispersive X-ray fluorescence spectrometry.

Exposure to harmful metals, including heavy metals such as arsenic (As), chromium (Cr), cadmium (Cd), lead (Pb), aluminum (Al), and mercury (Hg), can cause damage to organs or systems in human body, even at low levels [6,7]. Arsenic, lead and mercury ranks the top 3, and cadmium ranks 7th in the 2019 US ATSDR priority list which prioritizes substances based on their frequency, toxicity, and potential human exposure at sites on the National Priority List (NPL) [8]. Generally, harmful metals originate from bioconcentration of raw materials and cross-contamination during processing [9]. Public

health is constantly threatened by harmful metals. Even though most commercially available calcium supplements are of low safety risk, they should still be used with caution.

The present study aimed to detect the levels and assess the health risks of 6 harmful metal elements, including lead, cadmium, chromium, arsenic, aluminum and mercury in commercially available calcium supplements in China. Calcium supplements samples were collected and product information was recorded. Microwave ablation was used for pretreatment, ICP and cold atomic absorption mercury meter were used for the quantification of harmful metals and flame atomic absorption meter was employed to quantify calcium contents. Risk assessment was conducted by comparing the quantification results of harmful metals and calcium with the national standards to provide guidance for the public when choosing calcium supplements.

2. Materials and Methods

2.1. Sample Collection

A total of 82 calcium supplements samples was collected from pharmacy or online purchasing, factors including target population, dosage forms, brands, cost-performance ratio and sales volume were considered when making choices. The calcium supplements samples covered almost all the commonly seen Chinese brands, and several foreign brands were also chosen.

2.2. Reagents

Ultrapure water (18mΩ.cm) was provided by RephiLe company UP water purification system (RephiLe company, Shanghai, China). The suppliers of the reagents were: Except potassium dichromate as analytical pure (BEIJING HONGXING CHEMICAL PLANT, Beijing, China), the other reagents are of excellent grade or MOS grade, and the argon purity is 99.995%. The standard solutions of Pb, Cd, Cr, As, Hg, Al and Ca are all element standard solutions recognized by the state with the certification certificate of standard substances. All glassware were soaked for at least 24 h in 10% nitric acid (Tianjin Fengchuan Chemical Reagent Co., LTD, Tianjin, China) and then rinsed 3 times with tap water and 6 times with ultrapure water.

2.3. Sample Digestion and Analysis

2.3.1. Sample Digestion

Tablets were first grinded into powder. Then, 0.2 g solid sample or 2 mL liquid sample were transferred to a centrifuge tube (Labserve, USA) for digestion using a microwave digestion apparatus (Anton Paar, Shanghai, China) according to the following steps. Samples were spiked with 5 mL nitric acid, then warmed up to 180°C in 30 min and hold for 20 min for microwave digestion. After cooling, the acid was driven at 100°C. 1% nitric acid solution was added to the digestion tube. Samples were filtered through quantitative filter paper, and the final volume was reconstituted to 50 mL using 1% nitric acid.

2.3.2. Instrumental Analysis

According to the methods of Chinese National Standards, 7 elements including Pb, Cd, Cr, As, Hg, Al and Ca in calcium supplements samples were analyzed. NexION 300D ICP-MS (PerkinElmer, USA) was used to analyze Pb, Cd, Cr and As, and ASX-560 automatic sampler (TELEDYNE, USA) was used to inject samples into the system. Al was analyzed by ICP-AES715 (Agilent, USA). Hg was analyzed by F732-V cold atomic absorption mercury meter (Shanghai instrument huabang factory, Shanghai, China). Ca was analyzed by flame atomic absorption meter (Beijing Rayleigh, Beijing, China).

2.4. Statistical Analysis

Data were processed using Statistical Package for Social Science (SPSS) 19.0 and Origin 9.1. Descriptive statistics including minimum, maximum, and mean values, and standard deviation (SD) were calculated. Pearson's chi-square test was used to compare differences of the exceedance rate and mean content of each element between different dosage forms. Risk assessment of harmful metals were conducted according to Chinese National Standards, and the maximum tolerated dose was determined according to Joint Expert Committee on Food Additives (JECFA) [10].

3. Results and Discussion

3.1. Concentration of Harmful Metals in Calcium Supplements

Harmful metals in calcium supplements may originate from raw materials and processing. Marine organisms, such as oysters and shellfish, have a strong adsorption capacity of heavy metals [11], and these harmful elements tend to accumulate in their bones [12]. So, inorganic calcium-based calcium supplements made from marine biological calcium and animal bone powder are vulnerable to contamination by harmful metals. Usually, inorganic calcium is used to make tablets and soft capsule in calcium supplements.

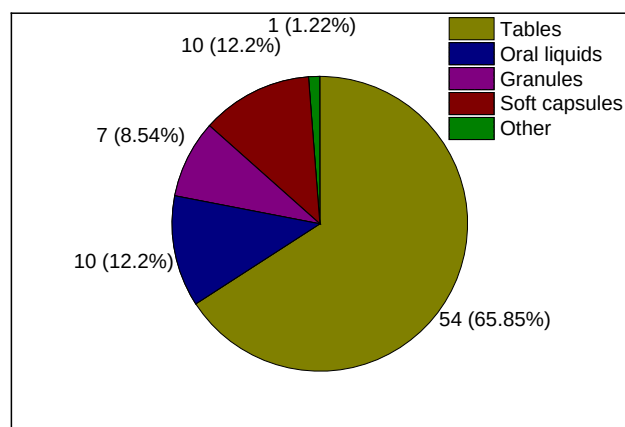


Figure 1. Classification and number of dosage forms in calcium supplements

Among the 82 kinds of calcium supplements collected, there were 54 types of tablets, 10 types of soft capsules, 7 types of granules, 10 types of oral liquids, and 1 type of other dosage form (Protein Drink). As shown in Figure 1.

The correlation coefficient (R^2) of the standard curve was between 0.998 and 1.000 in the quantification of each element. The internal standard of Rh (Rhodium) of 10 ng/mL was used in ICP-MS measurement. The results showed that the content of Ca in all calcium supplements was close to labeled values, except for soft capsules.

Tablets and soft capsules were more seriously contaminated with harmful metals. In tablet samples, the contents of As, Pb, Cd, Cr and Al exceeded the national Chinese standard, and Hg was also detected. Moreover,

the maximum concentration of Pb (8.49mg/kg), Cd (1.104mg/kg), As (15.34mg/kg), Cr (192.66mg/kg) and Al (761.11mg/kg) in calcium supplements samples were all found in tablets. In soft capsules, only Pb was within standard range, As, Cd, Cr and Al all exceeded the standard limits, and Hg was also detected. The highest average concentrations of As, Cd, Al and Hg were also found in soft capsules, which were 4.21 ± 3.80 mg/kg, 0.043 ± 0.084 mg/kg, 142.73 ± 34.29 mg/kg and 0.016 ± 0.013 mg/kg, respectively. In granules, As, Cr and Al also exceeded the standard limits. In liquids, only As was detected.

For the exceedance rate of each element, the top 3 were Cr (81.87%), As (35.36%) and Al (28.75%). The exceedance details of each element in different dosage forms are summarized in Table 1.

Table 1. Summary of Arsenic quantification result in calcium supplements (mg/kg)

Elements	Dosage forms	n	Number of detection	Detection rate (%)	Number of exceedance	Exceedance rate (%)	Mean $\pm$ SD	Range
As ^a	Tables	54	/	/	17	31.48	1.98 ± 3.36	0.09 ~ 15.34
	Oral liquids	10	/	/	0	0.00	0.28 ± 0.22	0.01 ~ 0.66
	Granules	7	/	/	3	42.86	1.11 ± 0.74	0.50 ~ 2.34
	Soft capsules	10	/	/	9	90.00	4.21 ± 3.80	0.58 ~ 12.24
	Other	1	/	/	0	0.00	0.60 ± 0.00	0.60 ~ 0.60
	Total	82	/	/	29	35.36	1.95 ± 3.18	0.10 ~ 15.34
Pb ^b	Tables	54	/	/	9	16.67	1.28 ± 1.71	0.14 ~ 8.49
	Oral liquids	10	/	/	0	0.00	0.02 ± 0.02	0.001 ~ 0.06
	Granules	7	/	/	0	0.00	0.17 ± 0.08	0.08 ~ 0.29
	Soft capsules	10	/	/	0	0.00	0.15 ± 0.16	0.04 ~ 0.59
	Other	1	/	/	0	0.00	0.17 ± 0.00	0.17 ~ 0.17
	Total	82	/	/	9	10.98	0.88 ± 1.50	0.001 ~ 8.49
Cd ^c	Tables	54	34	/	5	9.26	0.07 ± 0.19	ND ~ 1.10
	Oral liquids	10	10	/	0	0.00	0.001 ± 0.001	0.00 ~ 0.00
	Granules	7	1	/	0	0.00	0.03 ± 0.00	ND ~ 0.03
	Soft capsules	10	10	/	1	10.00	0.04 ± 0.08	0.00 ~ 0.28
	Other	1	1	/	0	0.00	0.004 ± 0.00	0.00 ~ 0.00
	Total	82	61	/	6	7.32	0.05 ± 0.15	ND ~ 1.10
Cr ^d	Tables	54	/	/	53	98.15	7.85 ± 27.80	0.72 ~ 192.66
	Oral liquids	10	/	/	0	0.00	0.30 ± 0.17	0.09 ~ 0.56
	Granules	7	/	/	7	100.00	2.12 ± 0.70	1.56 ~ 3.55
	Soft capsules	10	/	/	6	60.00	1.16 ± 0.61	0.45 ~ 2.44
	Other	1	/	/	1	100.00	1.43 ± 0.00	1.43 ~ 1.43
	Total	82	/	/	67	81.71	5.55 ± 22.72	0.09 ~ 192.66
Al ^e	Tables	54	/	/	14	25.93	111.86 ± 126.67	35.97 ~ 761.11
	Oral liquids	10	/	/	0	0.00	9.01 ± 9.27	3.32 ~ 34.73
	Granules	7	/	/	2	28.57	142.17 ± 245.92	22.98 ~ 695.68
	Soft capsules	8	/	/	7	87.50	142.73 ± 34.29	79.93 ~ 200.27
	Other	1	/	/	0	0.00	21.31 ± 0.00	21.31 ~ 21.31
	Total	80	/	/	23	28.75	103.61 ± 130.47	3.32 ~ 761.11
Hg ^f	Tables	54	7	12.96	/	/	0.01 ± 0.01	ND ~ 0.03
	Oral liquids	10	0	0.00	/	/	/	/
	Granules	7	0	0.00	/	/	/	/
	Soft capsules	8	4	50.00	/	/	0.02 ± 0.01	ND ~ 0.04
	Other	1	0	0.00	/	/	/	/
	Total	80	11	13.75	/	/	0.01 ± 0.01	ND ~ 0.04

a: exceeded the maximum limit of 1 mg/kg set for As by GB16740-2014.

b: exceeded the maximum limit of 2 mg/kg set for Pb by GB16740-2014.

c: exceeded the maximum limit of 0.1 mg/kg set for Cd by GB2762-2017.

d: exceeded the maximum limit of 1 mg/kg set for Cr by GB2762-2017.

e: exceeded the maximum limit of 100 mg/kg set for Al by GB2760-2014.

f: exceeded the maximum limit of 0.3 mg/kg set for Hg by GB16740-2014.

As concentration in calcium supplements ranged from 0.01 to 15.34 mg/kg and the maximum value appeared in tablets. The mean value of As concentration was 1.95 ± 3.18 mg/kg, with the highest found in soft capsule (4.21 ± 3.80 mg/kg). As in 35.36% of calcium supplements samples exceeded the maximum residual amount of As in dietary supplements (1.0 mg/kg). Portugal, Ó. B. et al [13] tested the concentration of As by graphite furnace atomic absorption spectroscopy for four commercial brands sold in Tacna, Peru. He discovered that the maximum content of arsenic was 0.294 mg/kg, which was smaller than the results of our study and within the safe content range.

Pb concentration in calcium supplements ranged from 0.001 to 8.490 mg/kg, with the maximum value in tablets. The mean value of lead concentration was 0.88 ± 1.50 mg/kg, with the highest also found in tablets (1.28 ± 1.71 mg/kg). 10.98% of the calcium supplements contained Pb exceeding the maximum residue level (2mg/kg). The mean value in our study (0.88 mg/kg) was lower than that reported by Mustatea, G. et al [14], who tested 41 food supplements in Romania market and found the maximum value of Pb was 1.274 mg/kg, which was still within the limits of the current legislation.

Cd concentration in calcium supplements ranged from ND (not detected) to 1.104 mg/kg, with the maximum value in tablets. The mean value of Cd concentration was 0.048 ± 0.153 mg/kg, also with the highest found in tablets (0.065 ± 0.190 mg/kg). There were 7.32% of calcium supplements containing Cd exceeding the maximum residue level (0.1mg/kg). This result was lower than that of Ćwieląg-Drabek, M. et al [15], who tested 41 dietary supplements for Cd and found that their maximum Cd concentration was 0.94 mg/kg. Among the 41 supplements, 4 brands contained more than 0.1 mg/kg of Cd and the exceedance rate was 9.76%.

Cr concentration in calcium supplements ranged from 0.09 to 192.66 mg/kg and the maximum value appeared in tablets. The mean Cr concentration was 5.55 ± 22.72 mg/kg, with the highest also found in tablets (7.85 ± 27.80 mg/kg). Cr in 81.71% of calcium supplements exceeded the standard (1mg/kg). Araujo-Barbosa, U. et al [16] tested 15 commercial iron supplements in several cities in Brazil and Spain. Their Cr concentration ranged from 0.4 to 61.2 mg/kg, and 7 supplements contained more than 1 mg/kg of Cr, accounting for 46.67% of total samples.

Al concentration in calcium supplements ranged from 3.32 to 761.11 mg/kg, with the maximum value found in tablets. The mean value of Al concentration was $103.61 \pm$

130.47 mg/kg, with the highest in the soft capsules (142.73 ± 34.29 mg/kg). There were 28.75% of calcium supplements exceeding the Al standard (100mg/kg). Barrella, M. V. et al [17] tested the concentration of Al in herbal supplements collected from Brazil and China, and found the range was 11.76–342.4 mg/kg, with only 1 sample exceeding the limit. Marín-Martínez, R. et al [18] tested 263 samples from 12 types of candies widely consumed in Spain for Al concentration, and found it ranged from 21.28 to 62.91 µg/g, which was within the safety range.

The Hg concentration of calcium supplements ranged from ND to 0.036 mg/kg, with the maximum value in soft capsules. The mean value of Hg content was 0.013 ± 0.009 mg/kg, with the highest also found in soft capsules (0.016 ± 0.013 mg/kg). No calcium supplements exceeded the maximum residue of Hg (0.3mg/kg). Brodziak-Dopierała, B. et al [19] reported the mean concentration of mercury in 24 herbal dietary supplements commercially available in Poland was 0.194 mg/kg, and Hg concentration in 2 herbal dietary supplements exceeded the standard.

3.2. Risk Assessment of Exposure to Elements

Exposure to elements was calculated based on the maximum recommended daily intake on the label. The risk assessment of exposure to elements was conducted using the maximum tolerated dose established by JECFA as reference. As and Pb were evaluated using margin of exposure (MOE) because the maximum tolerated dose was eliminated in JECFA.

Calcium supplements were divided into children's and adults' calcium supplements according to the target population on their labels. There were 35 types of calcium supplements for children and 64 types of calcium supplements for adults. The body weight of children was calculated at 30kg and the weight of adults was calculated at 60kg.

3.2.1. Ca

The maximum tolerated daily dose of Ca set by the Chinese Nutrition Society is 2000 mg/d. And hence the daily exposure to Ca should be less than 2000 mg/d even if a person takes the maximum recommended daily intake on the label. However, according to our analysis, several types of oral liquids and soft capsules for adults contained Ca exceeding the 2000 mg/d limit (Table 2).

Table 2. Daily exposure to Ca in calcium supplements

Dosage forms	Target population	Detected value (mg/d)		Labeling value (mg/d)	
		Mean $\pm$ SD	Range	Mean $\pm$ SD	Range
Tablets	Children	388.8 ± 245.0	8.7 ~ 1061.2	428.7 ± 224.4	30.7 ~ 900.1
	Adults	428.9 ± 316.0	1.2 ~ 1202.3	495.5 ± 313.6	30.3 ~ 1200.2
Oral liquids	Children	53.5 ± 9.0	47.1 ~ 59.9	285.9 ± 22.5	270.0 ~ 301.8
	Adults	404.9 ± 771.1	59.9 ~ 2152.1	319.0 ± 162.9	39.3 ~ 540.0
Granules	Children	290.7 ± 228.8	0.9 ~ 612.3	381.6 ± 406.9	47.2 ~ 1115.4
	Adults	556.7 ± 641.6	0.9 ~ 1224.5	534.7 ± 701.1	47.2 ~ 1560.0
Soft capsules	Children	1293.9 ± 461.0	968.0 ~ 1619.8	500.0 ± 0.0	500.0 ~ 500.0
	Adults	1501.7 ± 464.9	856.0 ~ 2039.5	421.7 ± 142.9	198.0 ~ 654.0
Total	Children	400.7 ± 329.3	0.9 ~ 1619.8	414.8 ± 254.3	30.7 ~ 1115.4
	Adults	574.3 ± 559.3	0.9 ~ 2152.1	460.5 ± 312.2	30.3 ~ 1560.0

3.2.2. As

In our study, As in all calcium supplements was within the safety range. Since MOE method was employed, the smaller the MOE, the higher the risk. When MOE is less than 1, it is assumed the risk exists, when MOE is over 100, it is assumed no risk exists, and when MOE is between 1 to 100, it is assumed the risk low.

As shown in Table 3, the mean MOE values for As were all greater than 1, and hence the risk of exposure to As was low. The lowest MOE for As exposure was found in oral liquids and soft capsules in both calcium supplements for children and adults. Núñez, R. et al [20] performed a risk assessment of As in 110 samples of fresh or processed tuna sold in Galicia using the THQ method. When THQ is less than 1, it is considered that there may be no health risk, and when THQ is no less than 1, it is considered to there may be potential risks [21]. He found that the THQ was less than 1 for both children and adults and concluded that the sample tested did not pose a health risk.

3.2.3. Pb

In our study, Pb was within the safety range in all calcium supplements. The lowest risk MOE was found in tablets and soft capsules in calcium supplements for children and adults, respectively. One calcium supplement indicated for both children and adults had the minimum MOE values of 1.07 and 2.33 for children and adults, respectively, which were close to 1, the margin of risk. Mustatea, G. et al [14] used the THQ method to assess the risk of Pb in 41 food supplements in Romania market, and

3 food supplements had THQ greater than 1 and were at risk (Table 4).

3.2.4. Cd

Our study showed Cd was within the safety range in all calcium supplements. The maximum monthly exposure to Cd for children was 0.552 $\mu\text{g}/\text{kg}\cdot\text{BW}$ in calcium supplements for children and 1.380 $\mu\text{g}/\text{kg}\cdot\text{BW}$ in calcium supplements for adults, both of which were less than the maximum tolerated monthly dose of 25 $\mu\text{g}/\text{kg}\cdot\text{BW}$ for Cd (Table 5). Hensawang, S. et al [22] conducted a health risk assessment of Cd in rice in Bangkok, Thailand and found that the mean daily exposure to Cd in adult population was 4.7×10^{-5} $\text{mg}/\text{kg}\cdot\text{BW}$. The maximum daily exposure to Cd was 1.63×10^{-4} $\text{mg}/\text{kg}\cdot\text{BW}$ and 1.01×10^{-4} $\text{mg}/\text{kg}\cdot\text{BW}$ in children and adults, respectively, and hence all rice samples were within the safety limits.

3.2.5. Al

Al in all calcium supplements was within the safety range. The maximum weekly exposure to Al was 0.69 $\text{mg}/\text{kg}\cdot\text{BW}$ for children and 0.35 $\text{mg}/\text{kg}\cdot\text{BW}$ for adults, both less than the maximum tolerated weekly dose (2 $\text{mg}/\text{kg}\cdot\text{BW}$) (Table 6). Antoine, J. M. et al [23] conducted an Al health risk assessment of 13 food crops in Jamaica and estimated daily intake to calculate the daily exposure to Al. Their study showed that the food crop with the highest daily exposure to Al was banana (46.17 $\mu\text{g}/\text{kg}\cdot\text{BW}$), which was within the safety range. He also used THQ for risk assessment of Al and found that the THQ of all food crops was less than 1, and concluded that these foods did not pose a health risk to consumers.

Table 3. MOE of As in calcium supplements^g

Dosage forms	Children		Adult	
	Mean $\pm$ SD	Range	Mean $\pm$ SD	Range
Tablets	107.51 $\pm$ 153.89	3.49 ~ 683.29	227.62 $\pm$ 279.11	3.49 ~ 1366.59
Oral liquids	19.19 $\pm$ 10.98	12.21 ~ 27.74	51.46 $\pm$ 73.78	4.54 ~ 241.07
Granules	107.63 $\pm$ 156.67	15.72 ~ 437.74	317.77 $\pm$ 405.96	10.48 ~ 875.53
Soft capsules	7.98 $\pm$ 6.09	3.68 ~ 12.29	66.23 $\pm$ 102.26	7.35 ~ 350.77
Total	96.84 $\pm$ 145.86	3.49 ~ 683.29	179.80 $\pm$ 256.51	3.49 ~ 1366.59

g: When MOE is less than 1, it is assumed the risk exists, when MOE is over 100, it is assumed no risk exists, and when MOE is between 1 to 100, it is assumed the risk low.

Table 4. MOE of Pb in calcium supplements^h

Dosage forms	Children		Adult	
	Mean $\pm$ SD	Range	Mean $\pm$ SD	Range
Tablets	7.72 $\pm$ 6.37	1.07 ~ 24.36	47.26 $\pm$ 45.30	2.33 ~ 197.57
Oral liquids	125.64 $\pm$ 170.13	5.34 ~ 245.94	292.73 $\pm$ 216.46	37.82 ~ 600.00
Granules	42.19 $\pm$ 32.19	5.17 ~ 97.26	369.91 $\pm$ 365.17	20.68 ~ 778.07
Soft capsules	36.73 $\pm$ 10.11	29.58 ~ 43.87	421.67 $\pm$ 194.38	101.32 ~ 653.26
Total	23.01 $\pm$ 44.00	1.07 ~ 245.94	222.40 $\pm$ 439.75	2.33 ~ 778.07

h: When MOE is less than 1, it is assumed the risk exists, when MOE is over 100, it is assumed no risk exists, and when MOE is between 1 to 100, it is assumed the risk low.

Table 5. Monthly exposure to Cd in calcium supplementsⁱ ($\mu\text{g}/\text{kg}\cdot\text{BW}$)

Dosage forms	Children		Adult	
	Mean $\pm$ SD	Range	Mean $\pm$ SD	Range
Tablets	0.108 $\pm$ 0.121	0.005 ~ 0.029	0.056 $\pm$ 0.221	0.000 ~ 1.380
Oral liquids	/	/	0.017 $\pm$ 0.012	0.000 ~ 0.040
Granules	0.186 $\pm$ 0.000	0.186 ~ 0.186	0.048 $\pm$ 0.092	0.000 ~ 0.190
Soft capsules	0.277 $\pm$ 0.389	0.002 ~ 0.552	0.041 $\pm$ 0.085	0.000 ~ 0.280
Total	0.134 $\pm$ 0.159	0.002 ~ 0.552	0.049 $\pm$ 0.179	0.000 ~ 1.380

i: According to JECFA, the maximum tolerated dose is 25 $\mu\text{g}/\text{kg}\cdot\text{BW}$.

Table 6. Weekly exposure to Al in calcium supplements^j (mg/kg•BW)

Dosage forms	Children		Adult	
	Mean ± SD	Range	Mean ± SD	Range
Tablets	0.11 ± 0.15	0.01 ~ 0.69	0.04 ± 0.06	0.00 ~ 0.35
Oral liquids	0.26 ± 0.04	0.23 ~ 0.28	0.01 ± 0.01	0.00 ~ 0.02
Granules	0.06 ± 0.07	0.00 ~ 0.16	0.05 ± 0.07	0.00 ~ 0.16
Soft capsules	0.06 ± 0.00	0.06 ~ 0.07	0.03 ± 0.01	0.01 ~ 0.05
Total	0.11 ± 0.14	0.00 ~ 0.69	0.04 ± 0.05	0.00 ~ 0.35

j: According to JECFA, the maximum tolerated dose is 2 mg/kg•BW.

Table 7. Weekly exposure to Hg in calcium supplements^k (μg/kg•BW)

Dosage forms	Children		Adult	
	Mean ± SD	Range	Mean ± SD	Range
Tablets	0.070 ± 0.077	0.016 ~ 0.125	0.005 ± 0.005	0.002 ~ 0.014
Oral liquids	/	/	/	/
Granules	/	/	/	/
Soft capsules	0.009 ± 0.018	0.018 ~ 0.018	0.003 ± 0.001	0.002 ~ 0.005
Total	0.053 ± 0.062	0.015 ~ 0.125	0.004 ± 0.002	0.002 ~ 0.014

k: According to JECFA, the maximum tolerated dose is 4 μg/kg•BW.

Table 8. Daily exposure to Cr in calcium supplements^l (μg/d)

Dosage forms	Children		Adult	
	Mean±SD	Range	Mean ± SD	Range
Tablets	39.42 ± 151.85	0.94 ~ 751.37	31.07 ± 118.50	0.94 ~ 751.37
Oral liquids	4.47 ± 2.55	2.67 ~ 6.27	15.34 ± 12.83	2.67 ~ 33.88
Granules	6.58 ± 7.12	0.86 ~ 21.29	15.26 ± 19.51	0.86 ~ 42.58
Soft capsules	2.17 ± 0.87	1.56 ~ 2.79	2.16 ± 1.40	0.54 ~ 5.65
Total	28.73 ± 125.96	0.86 ~ 751.37	23.98 ± 94.29	0.54 ~ 751.37

l: According to JECFA, the maximum tolerated doses for adults and children are 500μg/d and 200μg/d.

3.2.6. Hg

Hg in all calcium supplements was within the safety range. The maximum weekly exposure to Hg was 0.125 μg/kg•BW for children and 0.014 μg/kg•BW for adults, which was much less than the maximum tolerated weekly dose (4 μg/kg•BW) (Table 7). Jinadasa, B. K. et al [24] assessed the health risk of Hg in yellowfin tuna (n=65) and swordfish (n=75) collected from the Indian Ocean around Sri Lanka. The study showed that in yellowfin tuna, the weekly exposure to Hg was 0.43 and 0.19 mg/(kg•BW) for children and adults, respectively; in swordfish, the weekly exposure to Hg was 0.55 and 0.25 mg/kg•BW for children and adults, respectively. This result was higher than that obtained in this study, but was still within the safety range.

3.2.7. Cr

Cr exposure in calcium supplements was within the safety range except for 1 type of tablet. It was indicated for both children and adults and its Cr exposure was 751.37 μg/d, exceeding the maximum tolerated daily dose of Cr for adults (500 μg/d) and for children (200 μg/d) (Table 8). Figueiredo, A. et al [25] performed a risk assessment of Cr in 25 weight loss supplements purchased from 5 different suppliers in the EU. They found only 2 supplements exceeded the limit of quantification (LQ), and the daily Cr exposures were 116.3 and 59.9 μg/d, respectively, which were within the safety range.

3.3. Current Status of Calcium Intake and Its Effect on Human Health

3.3.1. Intake of Calcium

According to the results of monitoring the nutrition and health status of Chinese residents, in 1992, the average daily intake of calcium per person in China was 405 mg, in 2002 it was 391 mg, and in 2012 it was 336.1 mg. The 2017 International Osteoporosis Foundation (IOF) study found that the national dietary calcium intake ranked the 6th from the end in the world, with only 338.1 mg, less than half of the recommended amount [26]. However, the IOF study used data from the 2002 National Nutrition and Health Survey conducted by Ma, G. et al [27], who reported the median value of national calcium intake was 338.1 mg. Therefore, in order to better reflect the current status of daily calcium intake in Chinese, results from the latest 2012 survey, which was 336.1 mg, was used as the reference mean daily dietary calcium intake.

Except for dietary intake of calcium, calcium supplements are commonly used to achieve the recommended daily intake of calcium set by the Chinese Nutrition Society. The value is 800-1000 mg/d for adults and 1000-1200 mg/d for children, and the maximum tolerated daily dose is 2000 mg/d. In our study, calcium supplements were classified into children and adult calcium supplements according to their labeled target population. 35 supplements were for children and 64 were for adults.

30 types of calcium supplements for children did not meet the standard concentration of calcium, accounting for 85.72% of total samples for children. Among them, 70.00% were tablets. All oral liquids and granules did not meet the standard. 2 types of calcium supplements meet the standard, accounting for 5.71%, all of which were tablets. 3 types of calcium supplements exceed the standard, accounting for 8.57%, including 1 type of tablets and 2 types of capsules. No calcium supplements exceeded the maximum tolerated dose.

37 types of calcium supplements for adults did not meet the standard concentration of calcium, accounting for 57.81% of total samples for adults. Among them, 62.16% were tablets. 8 types of oral liquids, 2 types of granules, 3 types of soft capsules and 1 types of other kind did not meet the standard. 12 types of supplements meet the standard, accounting for 18.75%, and they were all tablets. 11 types of supplements exceeded the standard, accounting for 17.19%, including 5 types of tablets, 2 types of granules and 4 types of soft capsules. 4 types of supplements exceeded the maximum tolerated dose, accounting for 6.25%, including 1 type of oral liquid and 3 types of soft capsules.

In general, the non-compliance rate of calcium concentration in tablets for children and adults was high. For oral liquids, 1 type for adults exceeded the maximum tolerated dose, and the rest types did not meet the standard. In granules, 2 types for adults exceeded the standard and the rest did not meet the standard. For soft capsules, all types for children exceeded the standard, 4 types for adults exceeded the standard and 3 exceeded the maximum tolerated dose.

3.3.2. Effect of Calcium Intake on Human Health

Optimal calcium intake can promote the development of teeth and skeleton in children and provide a good foundation for healthy bones in adults. It can also reduce the blood pressure in women during pregnancy, prevent osteoporosis and colorectal adenomas in adults, and lower cholesterol level [28].

Inadequate calcium intake in human increases the risk of diseases. Chronic inadequate calcium intake in children can lead to poor skeletal calcification, growth retardation, abnormal new bone structure, and in severe cases, skeletal deformities and rickets [29]. In addition, insufficient calcium intake is associated with obesity in healthy male adolescents [30]. In adults, insufficient calcium intake leads to osteoporosis and susceptibility to fractures [31]. According to current studies, except for bone health, calcium deficiency may be correlated to cardiovascular diseases and even heart failure [32]. It is suggested that an increase in calcium intake may reduce the risk of ovarian cancer. Although further studies are needed to confirm this conclusion [33].

Hypercalcemia caused by excessive calcium intake is rare, and its occurrence is associated with milk-alkali syndrome caused by concomitant administration of absorbable bases. Symptoms include muscle relaxation, constipation, polyuria, nausea, and in severe cases, confusion, coma, and even death [34]. When calcium intake exceeds the maximum tolerated dose, hypercalcemia and hypercalciuria can occur, leading to kidney stones, vascular calcification, and even renal failure [35].

4. Conclusion

Eighty-two commercially available calcium supplements were tested for harmful metals. According to the current national limit standards, the study found that the sequence of exceedance rate of harmful metals was: Cr (81.87%) > As (35.36%) > Al (28.75%) > Hg (13.75%) > Pb (11.68%) > Cd (7.32%).

The health risk assessment of hazardous metals revealed that As, Pb, Cd, Al and Hg were all within the safety range, and only 1 type of tablet exceeded the maximum tolerated daily dose of Cr. In conclusion, consumption of calcium supplements in China market can be considered safe, but continuous monitoring of harmful metals in calcium supplements is warranted.

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Statement of Competing Interests

The have no competing interests.

Practical Application

This paper may help the consumer in making calcium supplements choice to minimize the exposure risk to heavy metals.

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