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Key Points:

- Residents in exposed black shale areas consume excessive Se and Cd through local rice
- Human liver and kidney functions are not significantly damaged in exposed black shale areas
- The USEPA method may not accurately assess Cd risk in exposed black shale areas

Correspondence to:
M. Li, M. Peng and C. Huang,
leeminglong@126.com;
pmin@mail.cgs.gov.cn;
huangchuying2008@126.com

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Author Contributions:
Data curation: Liang Qiu, Keyuan Xu, Kai Zhang
Funding acquisition: Minglong Li, Min Peng, Chuying Huang
Investigation: Xunru Ai, Kai Zhang, Chuying Huang
Methodology: Guogen Sun
Project administration: Minglong Li, Chuying Huang
Resources: Xunru Ai
Software: Kai Zhang
Validation: Liang Qiu
Visualization: Guogen Sun
Writing – original draft: Minglong Li, Keyuan Xu, Min Peng, Chuying Huang

Effects of Selenium and Cadmium on Human Liver and Kidney Functions in Exposed Black Shale Areas

Minglong Li[1,2,3], Liang Qiu[4], Xunru Ai[3], Keyuan Xu[2], Min Peng[5,6], Guogen Sun[7], Kai Zhang[2], and Chuying Huang[7]

[1]Hubei Key Laboratory of Resources and Eco-environmental Geology, Hubei Geological Bureau, Wuhan, China, [2]Second Geological Brigade of Hubei Geological Bureau, Enshi, China, [3]School of Forestry and Horticulture, Hubei Minzu University, Enshi, China, [4]School of Earth Science and Resources, China University of Geosciences, Beijing, China, [5]Key Laboratory of Geochemical Cycling of Carbon and Mercury in the Earth's Critical Zone, Institute of Geophysical and Geochemical Exploration, Chinese Academy of Geological Sciences, Langfang, China, [6]Research Center of Geochemical Survey and Assessment on Land Quality, China Geological Survey, Langfang, China, [7]Central Hospital of Enshi Tujia and Miao Autonomous Prefecture, Enshi, China

Abstract Animal experiments suggest that selenium (Se) may alleviate cadmium (Cd) toxicity in animal liver and kidneys, but its effect on human liver and kidneys remains uncertain. In China, areas with black shale have shown elevated levels of Se and Cd. According to the USEPA (U.S. Environmental Protection Agency) evaluation method, the soil and rice in these areas pose significant risks. In black shale regions such as Enshi and Zhuxi County, residents who long-term consume local rice may surpass safe Se and Cd intake levels. Significantly high median blood Se (B-Se) and urine selenium (U-Se) levels were detected in these areas, measuring 416.977 μg/L and 352.690 μg/L and 104.527 μg/L and 51.820 μg/L, respectively. Additionally, the median blood Cd (B-Cd) and urine Cd (U-Cd) levels were markedly elevated at 4.821 μg/L and 3.848 μg/L and at 7.750 μg/L and 7.050 μg/L, respectively, indicating substantial Cd exposure. Nevertheless, sensitive liver and kidney biomarkers in these groups fall within healthy reference ranges, suggesting a potential antagonistic effect of Se on Cd in the human body. Therefore, the USEPA method may not accurately assess Cd risk in exposed black shale areas. However, within the healthy ranges, residents in the Enshi study area had significantly greater median levels of serum creatinine and cystatin C, measuring 67.3 μmol/L and 0.92 mg/L, respectively, than those in Zhuxi did (53.6 μmol/L and 0.86 mg/L). In cases of excessive Se and Cd exposure, high Se and Cd levels impact the filtration function of the human kidney to some extent.

Plain Language Summary Se is an essential trace element for humans. However, excessive intake of Se can harm humans. Cd is a carcinogen and a chronic potent nephrotoxin that mostly accumulates in the human liver and kidneys. Animal experiments suggest that Se may alleviate Cd toxicity in animal liver and kidneys, but its effect on human liver and kidneys remains uncertain. In China, areas with black shale exposure have shown elevated levels of Se and Cd. According to the USEPA (U.S. Environmental Protection Agency) evaluation method, the soil and rice in these areas pose significant risks. Our results suggested that the exposed black shale areas are simultaneously enriched with Se and Cd. However, residents in these areas were exposed to excessive Se and Cd long-term without significant damage to liver and kidney functions. Therefore, the USEPA method may not accurately assess Cd risk in exposed black shale areas. The risk assessment of heavy metals in high-Se geological background areas cannot be separated from human health surveys. Our study provides evidence for the antagonistic effects of Se and Cd on the human body.

1. Introduction

Selenium (Se) is a vital trace element for humans. However, the biological role of Se is dual, and excessive intake of Se can harm humans. Enshi County, a typical high-Se area in China, experienced a concentrated outbreak of human Se poisoning caused by excessive Se intake from 1961 to 1963, with hair loss and nail loss as the major symptoms. The total Se content of the surface soil in areas with excessive Se is greater than 3.0 μg/g (Tan et al., 2002; Yang et al., 1983). Cadmium (Cd) is a carcinogen and a chronic potent nephrotoxin (IARC, 1993) that mostly accumulates in the human liver and kidneys. Due to its longer half-life (10–40 years) and toxicity, long-term high exposure to Cd can seriously damage human liver and kidney functions (Satarug et al., 2017). As a staple food for Asians, rice is heavily contaminated with Cd (Khanam et al., 2020; Mao et al., 2019; Sebastian &

Prasad, 2014), which has become a major public health issue. Both the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) of the United Nations have set a safety limit of 3.0 μg/g for the total Cd content in surface soil used for growing food crops (Callan et al., 2014; Chen et al., 2020).

Due to the migration of elements in rock–soil–plant systems, the trace element levels in humans are closely related to the geological background. Some residents in areas with high geological backgrounds may be overexposed to certain elements (Nordberg et al., 2022). The natural high-Se areas in China are mostly related to the exposure and weathering of black shale in the middle Permian and low Cambrian. For example, Middle Permian black shale is exposed in Enshi County, Hubei Province (Li et al., 2020, 2022), while Lower Cambrian black shale is exposed in Ziyang County, Shaanxi Province (Jie & Luo, 2017), Longyou County, Zhejiang Province (Li, Yang, et al., 2023), and the Changde area, Hunan Province (Ni et al., 2016). However, black shale in China is also highly enriched in Cd, resulting in high Cd contents in soil, water, and crops in these high-Se areas (Li, Yang, et al., 2023).

At present, the ecological risk assessment method for Se and heavy metal elements in China is based on the U.S. Environmental Protection Agency (USEPA) (2001). Thus, to estimate whether human intake exceeds this limit, the contents of elements in environmental media (e.g., soil, surface water and crops) have been investigated (Du et al., 2018; Huang et al., 2013; Mao et al., 2019; Xie et al., 2021). These researchers have proposed risk warnings for exceeding Se and heavy metal standards. However, the health risk assessment model of the USEPA does not consider the bioavailability of elements (Lv et al., 2021). The circulation and metabolism of elements in the animal body are complex, and the levels of elements in the blood and urine are relatively intuitive indicators of internal exposure (Nordberg et al., 2022). In addition, animal experiments have shown that Se can alleviate Cd toxicity in animal liver and kidney tissue (Chen et al., 2021; Li et al., 2019; Zhang et al., 2023), and the levels of Se and Cd in environmental media in black shale areas and their relationships with human liver and kidney health need to be further revealed. Serum glutamic oxaloacetic transaminase (AST), alanine aminotransferase (ALT), and total bilirubin (TBIL) are sensitive liver biomarkers (Oh et al., 2017; Otto-Ślusarczyk et al., 2016), while serum creatinine (SCr), cystatin C (Cys C), urinary nitrogen (BUN) and uric acid (UA) are sensitive kidney function biomarkers (Chen et al., 2020; Khan et al., 2010; Sands, 2003). Long-term Cd exposure can cause kidney and liver functional damage, leading to abnormal levels of these sensitive kidney and liver biomarkers (Hyder et al., 2013; Kang et al., 2013; Kobayashi et al., 2008; Liang et al., 2021). When using the USEPA method to evaluate the risk of Se and Cd in environmental media in black shale-exposed areas, these biomarkers should be important evaluation indicators.

Permian black shale is extensively exposed in Enshi County (Li, Qiu, et al., 2023; Li et al., 2020), and Cambrian black shale is extensively exposed in Zhuxi County. These two areas can serve as typical examples of two sets of high-Se black shale outcrops in China. In this study, the outcrops of black rock in Enshi County and Zhuxi County were taken as the study areas (Figure 1). Black shale, surface soil, drinking water, and rice samples, as well as human blood and urine samples, were collected in these two study areas. The Se and Cd concentrations were tested. In addition, we tested sensitive liver and kidney functional biomarkers. The results showed that, possibly due to the antagonistic effect of Se and Cd, residents in exposed black shale areas have experienced long-term excessive Se and Cd exposure, but their liver and kidney functions have not been significantly damaged. The USEPA method may not accurately assess Cd risk in exposed black shale areas.

2. Materials and Methods

2.1. Study Population

Both the Enshi and Zhuxi County study areas have completed a 1:50000 geochemical evaluation of land quality, accurately delineating the distribution range of high-Se soil, which is completely consistent with the black shale exposed area. Permian black shales are extensively exposed in Baoshuixi Village and Xiatangba Village in Xintang Town and Huabei Village in Shadi Town, Enshi County. The Cambrian black shale is extensively exposed in Maocaoping Village and Jinyuan Village in Tianbao Town, Zhuxi County. The surface soil of these five villages has high levels of Se and Cd (Figure 1). Due to the cumulative effects of Cd on human kidney damage (Satarug et al., 2017), the study population in this cross-sectional survey was mostly middle-aged and elderly people who had lived locally for more than 30 years. They had not colored their hair in the past 6 months, had no occupational exposure to Se and Cd, and had no long-term history of alcohol abuse. The women who participated in the survey were not pregnant. In this survey, some males smoked, while females did not smoke.

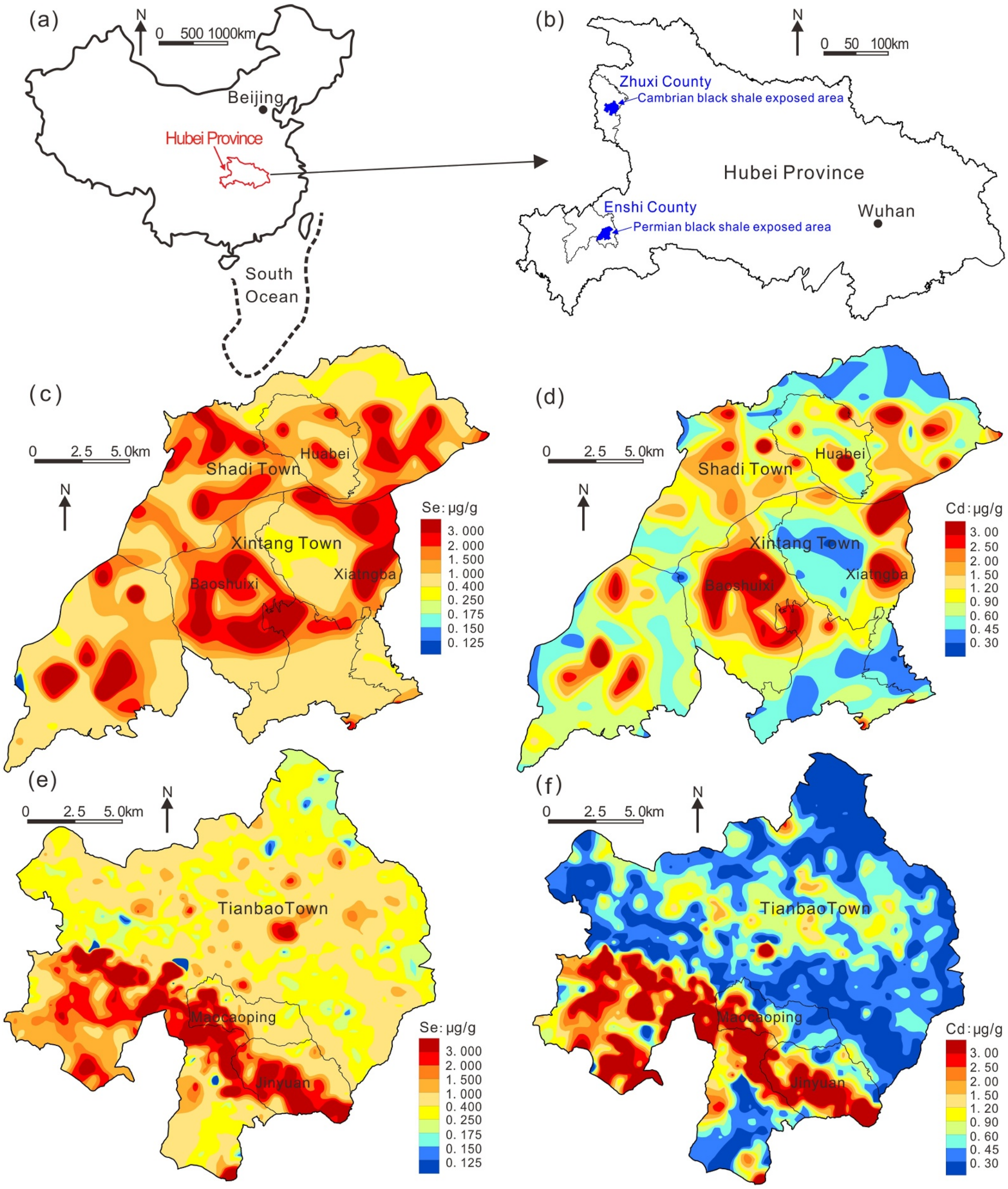

Figure 1. The location of the study area and the distribution of Se and Cd in the surface soil. (a, b) Location of the study area. (c) The distribution of total Se in the surface soil of the Enshi study area. (d) The distribution of total Cd in the surface soil of the Enshi study area. (e) The distribution of total Se in the surface soil of the Zhuxi study area. (f) The distribution of total Cd in the surface soil of the Zhuxi study area.

This survey was conducted in collaboration with Enshi Central Hospital, and 321 participants were recruited for the survey.

The survey population in the exposed area of the Permian black shale in Enshi County has always relied on local rice and vegetables as the major diet. There were 207 respondents in this area (108 men and 99 women, with a mean age of 62.92 ± 13.08 years). After discovering the issue of excessive Cd levels in locally grown rice in the exposed black shale area of Zhuxi County, the government no longer allowed rice to be planted and provided subsidies, which began in 2022. Therefore, some villagers have consumed ecdemic commercial rice for the past 1–2 years, while vegetables are still grown locally. There were 48 people in this category in this study. However, more than half of the villagers had rice left in their homes before 2022 and used it as their staple food. There were

Table 1
Detection Limits of Se and Cd in This Study

Elements	Methods	Blood and urine (μg/L)	Rock and soil (μg/g)	Rice (μg/g)
Se	AFS	0.002	0.01	0.003
Cd	ICP–MS	0.001	0.02	0.001

66 people included in this study. The total number of surveyed individuals in the study area of Zhuxi County was 114 (44 men and 70 women, with a mean age of 62.06 ± 9.30).

2.2. Sample Collection

In the study area of Enshi County, 21 Permian black shale samples and 81 arable land surface soil samples (0–20 cm) were collected. In the study area of Zhuxi County, 10 Cambrian black shale samples and 56 arable land surface soil samples (0–20 cm) were collected. Rice is the staple food of residents in southern China, and the Cd content in rice may be important for the daily total intake of residents in the area (Khanam et al., 2020; Li, Yang, et al., 2023; Mao et al., 2019). Ninety rice samples were collected in the Enshi study area, and 78 rice samples (41 local rice and 37 ecdemic rice) were collected in the Zhuxi study area. The rice sample was shelled by residents and used as a daily staple food (not heated or steamed). Xintang town and Sandi town in Enshi have built centralized drinking water reservoirs, and 1 drinking water sample was collected from each town. Two villages in Tianbao town, Zhuxi, received drinking water from the same drinking water reservoir, and 1 drinking water sample was collected.

Blood samples were collected from 207 participants in Enshi and 114 participants in Zhuxi. A total of 60 mL of venous blood was drawn from each participant and stored in 2 tubes, 30 mL each, containing an anticoagulant. One was tube was kept for elemental analyses, and the other was kept for biomarker analyses. The blood samples were stored in refrigerated containers below 4°C after collection and delivered to the laboratory within 8 hr. Due to inconvenient transportation and storage conditions, some samples were damaged. The numbers of samples for elemental analyses and biomarker analyses in Enshi and Zhuxi were 204 and 114, respectively. A total of 167 and 103 morning urine samples were collected in Enshi and Zhuxi, respectively, with 20 mL of each sample collected for Se and Cd analyses.

2.3. Sample Measurements and Data Statistics

Rock and soil samples were digested using an intelligent electric heating plate (SD46-1, Tianjin Tuozhiming Lab Equipment Co., Ltd., China) before testing. Rice, blood, urine, and drinking water samples were digested with 65% HNO_3 in a microwave digestion system (MARS6, CEM Corporation, United States) before testing. Inductively coupled plasma–mass spectrometry (ICP–MS, ICAP Qa, TMO. US) was used to measure the contents of Cd in the samples. Atomic fluorescence spectroscopy (AFS, AFS-230E, Beijing Haiguang Instrument Co., Ltd., China) was used to measure the contents of Se in the samples. Table 1 lists the detection limits of Se and Cd. The detailed analytical data are shown in Tables A1–A3.

The accuracy of Se and Cd in rice, drinking water, blood and urine samples was determined by calculating the recovery rate of added standard substances. A certified standard solution (BW30026-100-N-50 and GSB04-1767-2004) was used for the contents of the target substances, and the spiked recovery rate of Se and Cd was 90%–110%. National standard substances (GBW07127 and GBW07130) were used for the determination of accuracy in rock samples, while GBW007978 and GBW007980 were used for the determination of accuracy in soil samples. After logarithmic difference and standard deviation testing, the accuracy rate was 100%.

The biochemical analysis of blood samples was carried out using an automatic biochemical analyzer (AU5800, Beckman Coulter, Inc., US), and the reagent kit was produced by Roche Diagnostics Co., Ltd. AST, and ALT were measured using the rate method, while BUN, UA, TBIL, and SCr were measured using colorimetry. Cys C was measured by immune turbidimetry. The testing accuracy of various biomarkers met the study requirements.

Half of the detection limit was used to replace data that were below the detection limit, referring to the methods of the WHO. IBM SPSS Statistics 20.0 was used to construct the boxplots. Figure 1c–1f are geochemical maps plotted using the kriging interpolation method. The total Se and Cd contents of approximately 2200 surface soil

Table 2
Characteristic Value Statistics of Se and Cd in Environmental Media Samples From Two Black Shale-Exposed Areas

Sample type		Black shale		Surface soil			Rice				Drinking water	
Unit		μg/g		μg/g			μg/g				μg/L	
n		21		81			90 (loacl)		Ecdemic		2	
Parameter		Se	Cd	Se	Cd	pH	Se	Cd	Se	Cd	Se	Cd
Enshi	Max	177.01	41.97	14.87	17.29	8.21	4.623	2.488	-	-	0.214	0.012
	Min	0.75	0.24	1.05	0.84	4.31	0.014	0.003			0.020	0.003
	Median	28.24	2.58	3.85	2.59	5.83	0.648	0.171			0.117	0.007
	Mean	39.48	5.31	4.32	3.13	6.18	0.956	0.372			0.117	0.007
	SD	44.04	8.81	2.84	2.38	1.15	0.900	0.477			0.137	0.007
n		10		56			41 (loacl)		37 (ecdemic)		1	
Zhuxi	Max	30.30	12.71	10.98	8.67	8.20	0.856	1.190	0.114	0.215	4.271	0.163
	Min	1.75	0.34	1.04	0.96	4.59	0.074	0.054	0.031	0.008		
	Median	5.41	3.67	2.73	2.98	7.61	0.307	0.229	0.050	0.073		
	Mean	7.17	4.48	3.30	3.09	7.17	0.346	0.384	0.051	0.065		
	SD	8.32	3.83	2.32	1.75	0.98	0.155	0.348	0.015	0.045		

Note. SD = arithmetic standard deviation. pH Dimensionless.

samples were used. The element contents in the environmental media samples (i.e., black shale, surface soil, drinking water, and rice) were expressed using arithmetic means and standard deviations. The median describes the distribution of indicator concentrations in blood and urine. The populations that relied on local rice as a staple food of the exposed Cambrian black shale area in Zhuxi were the control group. The differences between the indicators in blood and urine samples of residents who relied on local rice as a staple food of the exposed Permian black shale area in Enshi and the control group were compared using the Mann–Whitney test. The differences between the residents of the exposed Cambrian black shale area in Zhuxi who relied on ecdemic rice as a staple food within the last 1–2 years and those in the control group were compared using the Mann–Whitney test. Spearman correlation coefficients between serum liver and kidney biomarkers and between Se and Cd in blood, rice, and urine were calculated, and a P value < 0.05 was considered to indicate statistical significance. All the statistical analyses were completed using IBM SPSS Statistics 20.0.

3. Results and Discussion

3.1. Risk Assessment of Se and Cd in Environmental Media Using the USEPA Method

The results of the elemental analysis of the rock, soil, rice and drinking water samples are shown in Table 2.

The Se and Cd concentrations in the upper continental crust (UCC) were 0.05 and 0.098 μg/g, respectively (Taylor & McLennan, 1985). The Se contents in the black shales of the Gufeng Formation in Enshi County and the Lujiaping Formation in Zhuxi County were 39.84 ± 44.04 μg/g ($n = 21$) and 7.81 ± 8.32 μg/g ($n = 10$), with averages of 790 and 143 times greater than those of the UCC, respectively. The Cd contents of the two sets of black shale were 5.31 ± 8.81 μg/g ($n = 21$) and 4.48 ± 3.83 μg/g ($n = 10$), respectively, with averages of 106 and 90 times the UCC, respectively. These two sets of black shale are abnormally rich in Se and Cd, and their exposure and weathering pose extremely high risks to the supergene environment.

The safety limits for Se and Cd in cultivated soil are both 3.0 μg/g (Callan et al., 2014; Chen et al., 2020; Tan et al., 2002). The Se contents of the surface soil in the exposed areas of the Permian and Cambrian black shales in Enshi County and Zhuxi County were 4.32 ± 2.84 μg/g ($n = 81$) and 3.30 ± 2.32 μg/g ($n = 56$), respectively, corresponding to Cd contents of 3.13 ± 2.38 μg/g ($n = 81$) and 3.09 ± 1.75 μg/g ($n = 56$), respectively. Therefore, there is a high risk of Se and Cd exceeding the standard for crops planted in the two exposed black shale areas.

These survey results showed that the daily consumption of rice by residents in the Enshi and Zhuxi study areas was roughly equivalent, approximately 400 g. Their formula for estimating Se and Cd intake through rice consumption can be expressed as I = (0.4 × M) × 1,000, where M represents the average concentration of Se (Cd) in rice (μg/g) and I represents the intake of Se or Cd (μg). The daily tolerable upper intake level (UL) and recommended intake (RNI) of Se for adults are 400 and 60 μg, respectively (NHFPC, 2017). The UL of Cd for adults is 1 μg/kg/d (WHO, 2011), and the average weight of adults in the study areas was approximately 65 kg, with a UL of 65 μg/d. The Se intake of adults in the Enshi study area through local rice consumption was 382 μg/d, close to the UL, combined with other food sources, which could easily cause Se intake to exceed the UL. The Cd intake through rice consumption was 149 μg/d, far exceeding the UL. The Se intake for residents in the study area of Zhuxi through local rice consumption was 138 μg/d, exceeding twice the RNI but below the UL. The Cd intake through local rice consumption was 154 μg/d, far exceeding the UL. The Se and Cd intakes of adults in Zhuxi through ecdemic rice consumption were 21 and 26 μg/d, respectively, which are far below the safety limits. Smoking is one of the sources of human Cd intake, and smoking 20 cigarettes a day can result in the absorption of 1–2 μg of Cd (WHO, 1992). Compared to the intake of rice by residents in the study area, this can be ignored.

The safety limits for Se and Cd in drinking water are 10 μg/L and 5 μg/L, respectively (WHO, 1984). The mean concentrations of Se and Cd in two drinking water samples from the study area of Enshi were 0.117 and 0.007 μg/L, respectively, while those in one drinking water sample from the study area of Zhuxi were 4.271 and 0.163 μg/L, respectively. The drinking water quality met the standards in both exposed black shale areas. However, it is worth noting that the Se concentration in drinking water in the study area of Zhuxi was 4.271 μg/L, which was 21 times the average concentration of Se in freshwater in China of 0.2 μg/L (Wang & Gao, 2001). The Cd content in unpolluted water was very low. The Cd concentration in the drinking water in the study area of Zhuxi was 0.163 μg/L, which was within the range of 0.15–0.70 μg/L in the Asano River in Japan after Cd pollution (Kobayashi & Kizu, 2001). The large amount of Se and Cd in the drinking water may have come from leaching of the Cambrian black shale in the study area of Zhuxi. Therefore, it is necessary to monitor the levels of Se and Cd in drinking water in the study area of Zhuxi.

3.2. Cd in Residents' Blood and Urine

As mentioned earlier, residents in the study areas of Enshi and Zhuxi have high levels of Se and Cd intake through local rice consumption. Furthermore, whole blood Cd (B-Cd) is an important internal exposure biomarker (Elinder & Barregard, 2022). In most countries, nonsmokers have normal or reference levels in their blood below 1 μg/L (Elinder & Barregard, 2022; Friberg & Vahter, 1983), for example, in the United States (0.30 μg/L) and Germany (0.38 μg/L) (Heitland & Koster, 2006). However, in Japan in the 1990s, environmental Cd levels were high, and the reference value for B-Cd in the general population who did not smoke was 2 μg/L (Watanabe et al., 2000). The B-Cd concentration is also high in East China (Nie et al., 2016), with a median value of 1.70 μg/L ($n = 5{,}544$). Blood cadmium levels can also be used for occupational biological monitoring of Cd exposure, and a B-Cd level of 5.0 μg/L is recommended as the level of action (WHO, 1992).

The median B-Cd concentration in the residents in the study area of Enshi was 4.821 μg/L (Table 3), which is close to the warning value of occupational biological monitoring. The median B-Cd concentrations of residents who relied on local rice and ecdemic rice (within the last 1–2 years) as their main food in the study area of Zhuxi were 3.848 μg/L and 3.510 μg/L, respectively, which were much higher than the B-Cd levels of the general population in the 1990s in Japan and the general population in East China. In human blood, the biological half-lives are 100 days for the fast component and 7–16 years for the slow component (Järup et al., 1983). The residents in Zhuxi County stopped consuming local rice with excessive Cd for 1–2 years, and the B-Cd content did not significantly decrease ($P = 0.911$), indicating that slow components in the blood may need time to metabolize.

In the human renal cortex, Cd has a very long half-life (10–40 years) (Friberg et al., 1986). Due to the good consistency between urinary cadmium (U-Cd) and renal Cd, U-Cd is currently widely accepted as an indicator of physical burden and renal Cd accumulation (Kido et al., 2004; Nordberg et al., 2002). The U-Cd concentration is generally adjusted by the addition of creatinine (Elinder & Barregard, 2022; Vacchi-Suzzi et al., 2016). However, Akerstrom et al. (2013) reported that creatinine or specific gravity in urine cannot fully regulate diuretic changes, and the regulation of U-Cd by creatinine is not entirely consistent with Cd toxicity. Furthermore, because villagers in the study area worked outside during the day, we could not collect urine continuously from each participant for 24 hr. The following parameters were evaluated using measured U-Cd concentrations.

The median U-Cd concentration of residents in the study area of Enshi was 7.750 μg/L. The median U-Cd concentrations of residents who relied on local rice and ecdemic rice within the last 1–2 years as their main

Table 3
Se and Cd Levels in Human Blood and Urine in the Enshi- and Zhuxi-Exposed Black Shale Areas

Group	*n*	Parameter	Mean	Median	P_{25}	P_{75}	*P* value
ESLR	204	B-Se	596.008	416.977	275.891	764.002	0.018
		B-Cd	5.896	4.821	3.117	8.224	0.033
	167	U-Se	177.930	104.527	45.023	240.395	<0.001
		U-Cd	8.660	7.750	4.025	12.300	0.238
ZXLR	66	B-Se	398.690	352.690	283.063	445.063	
		B-Cd	4.557	3.848	2.870	5.5670	
	59	U-Se	62.565	51.820	33.390	89.580	
		U-Cd	8.875	7.050	4.280	12.810	
ZXER	48	B-Se	245.604	218.798	183.856	284.710	<0.001
		B-Cd	4.553	3.510	2.782	5.991	0.911
	44	U-Se	37.663	33.46	20.670	44.400	0.007
		U-Cd	8.721	7.240	5.110	10.470	0.858

Note. ESLR = People in the Enshi exposed black shale area who rely on local rice as their staple food, ZXLR= People in the Zhuxi exposed black shale area who rely on local rice as their staple food, ZXER = People in the Zhuxi exposed black shale area who rely on ecdemic rice as their staple food within the last 1–2 years.

food in the study area of Zhuxi were 7.050 µg/L and 7.240 µg/L, respectively, which were much higher than the B-Cd levels of the general population in China. For example, the median U-Cd concentrations of healthy individuals without occupational exposure to Cd in Lichuan County, Hubei Province, Hunan Province, and Xinxiang area, Henan Province, were 2.243 µg/L ($n = 91$), 2.180 µg/L ($n = 1{,}168$), and 2.260 µg/L ($n = 651$), respectively (Li, Yang, et al., 2023; Wang et al., 2015). Consistent with B-Cd, although some residents in the exposed black shale areas in Zhuxi County stopped consuming local rice within the last 1–2 years, the U-Cd content did not significantly decrease ($P = 0.858$), indicating that they experienced long-term internal exposure to Cd.

3.3. Se in Residents' Blood and Urine

In China, the average blood Se (B-Se) concentrations in individuals with and without symptoms of Se poisoning in high-Se areas were 3,200 and 440 µg/L, respectively, and the average B-Se concentration in areas with sufficient Se was 95 µg/L. The corresponding average levels of Se in urine (U-Se) were 2,700 µg/L, 140 µg/L and 26 µg/L (Yang et al., 1983). The average B-Se levels of the populations in the study areas of Enshi and Zhuxi, which rely on local rice as a staple food, were 596.008 µg/L and 398.690 µg/L, respectively, which are close to the level without symptoms of Se poisoning in high-Se areas but higher than that (319.5 µg/L) of Inuit in Canada who are overloaded with Se by consuming marine mammals and fish (Hu et al., 2017). The average B-Se level of the population that relies on ecdemic rice as a staple food within the last 1–2 years in Zhuxi was 245.604 µg/L. There was a significant decrease compared to the population in Zhuxi, which relies on local rice as a staple food ($P < 0.001$), but it was greater than that (228.4 µg/L) of residents in the Tapajós River region of the Brazilian Amazon who were overloaded in Se by consuming *Bertholletia excelsa*, game meat and certain fish (Mélanie et al., 2012). The average U-Se level of the population in the study area of Enshi was 177.930 µg/L, close to the level of the asymptomatic population in high-Se areas. The average U-Se values of residents who relied on local rice and ecdemic rice within the last 1–2 years as their main food in the study area of Zhuxi were 62.565 µg/L and 37.663 µg/L, respectively. Compared to the population that relies on local rice in the study area of Zhuxi, the population that stopped consuming local rice within the last 1–2 years experienced a significant decrease in U-Se ($P < 0.001$), but this value was higher than the reference U-Se content of 30 µg/L (Robberecht & Deelstra, 1984).

The populations in the Enshi and Zhuxi study areas that rely on local rice as their staple food had high Se exposure levels, while those in Zhuxi County that rely on ecdemic rice as their staple food within the last 1–2 years have higher Se exposure levels than those in sufficient Se areas.

3.4. Liver and Kidney Health Status of Residents

AST, ALT, and TBIL are commonly used liver biomarkers in blood biochemical tests. The liver biomarkers in all three groups were within the reference range (Table 4), indicating that liver function is generally normal and that long-term exposure to large amounts of Se and Cd does not significantly impair liver function. The clinical chemical symptoms of Se exposure are nonspecific. Liver toxicity symptoms, including elevated levels of serum AST and ALT, are observed in Se-exposed individuals, reflecting the inhibition of protein synthesis in the liver (Wang et al., 2021). This study did not observe a relationship between B-Se, U-Se, or ALT (Figure 2), but there was a weak positive correlation between B-Se and AST ($r = 0.161$, $P < 0.01$), indicating that excessive exposure to Se in black shale areas partially impacted the livers of residents. Comparatively, the correlation coefficients between liver biomarkers and B-Cd and U-Cd were lower (Figure 2), and the impact was weaker.

SCr, BUN, and UA are renal biomarkers in blood biochemical tests. The renal biomarkers of the populations in the Enshi and Zhuxi study areas, which rely on local and ecdemic rice, were generally within the reference range (Table 4), indicating that long-term exposure to large amounts of Se and Cd did not significantly damage renal function. Among the three renal biomarkers mentioned above, SCr is the most sensitive Cd exposure biomarker.

Table 4
Statistical Analysis of Blood Biochemical Indicators

Group	n	Parameter	Median	P_{25}	P_{75}	Reference range	*P* value
ESLR	190	Age	64	55	72		0.615
		AST	27	24	32	0–40	0.298
		ALT	17	13	21	0–40	0.110
		TBIL	10.3	8.1	12.7	3.4–20.5	0.804
		SCr	67.3	57.4	76.2	44–133	<0.001
		BUN	5.60	4.57	7.17	2.1–8.5	0.425
		UA	305.13	255.77	364.87	154–420	0.151
		Cys C	0.92	0.72	1.00	0.54–1.25	<0.001
ZXLR	66	Age	62	55	69		
		AST	28	24	33	0–40	
		ALT	19	14	24	0–40	
		TBIL	10.0	7.5	14.4	3.4–20.5	
		SCr	53.6	48.3	64.2	44–133	
		BUN	5.90	5.03	6.90	2.1–8.5	
		UA	320.50	278.25	367.75	154–420	
		Cys C	0.86	0.74	0.98	0.54–1.25	
ZXER	48	Age	60	54	71		0.849
		AST	25	21	30	0–40	0.014
		ALT	17	13	21	0–40	0.192
		TBIL	10.2	8.4	13.2	3.4–20.5	0.872
		SCr	50.5	44.9	62.3	44–133	0.265
		BUN	5.65	4.40	6.58	2.1–8.5	0.683
		UA	295.00	243.75	332.00	154–420	0.018
		Cys C	0.82	0.72	0.94	0.54–1.25	0.486

Note. Units of biomarkers, SCr, UA and TBIL (μmol/L). AST and ALT (U/L). BUN (mmol/L). Cys C (mg/L). ESLR = People in the Enshi exposed black shale area who rely on local rice as their staple food, ZXLR = People in the Zhuxi exposed black shale area who rely on local rice as their staple food, ZXER= People in the Zhuxi exposed black shale area who have relied on ecdemic rice as their staple food within the last 1–2 years.

In 21 villages in the Kakehashi River basin, Japan, the mean Cd concentration in rice before the completion of soil replacement was 0.38 mg/kg. After replacement, the mean Cd concentration in the rice plants was less than 0.1 mg/kg. The villagers (aged 50–70) had not consumed rice with excessive Cd for 5 years, but their SCr (ca. 100–120 μmol/L) approached the upper limit and tended to exceed it (Kobayashi et al., 2008). The residents of black shale-exposed areas in Enshi and Zhuxi were exposed to high Se and Cd simultaneously, and their SCr levels were much lower than those of Japanese villagers exposed to Cd alone. The median levels of SCr in residents of the Enshi study area (67.3 μmol/L) were significantly greater than those in residents who had relied on local rice (53.6 μmol/L) or ecdemic rice in the past 1–2 years (50.5 μmol/L) as their staple food in Zhuxi ($P < 0.001$) (Table 4, Figure 3). This may be related to the greater internal exposure to Cd currently experienced by the Enshi population (Table 3), with a median B-Cd value of 4.821 μg/L, which was significantly greater than that of the same population in Zhuxi (3.848 μg/L for B-Cd) ($P < 0.05$). However, the positive correlations between SCr and B-Cd and U-Cd were not significant ($r < 0.15$) but were rather weak positive correlations with U-Se ($r = 0.294$, $P < 0.01$) and B-Se ($r = 0.231$, $P < 0.01$) (Figure 2). In other words, as exposure to Se in human's increases in the case of excessive Se intake, the filtration function of the kidneys gradually deteriorates.

Analysis of variance (Table 4) revealed no significant differences in age among the three groups ($P > 0.05$), indicating that age was not the main factor affecting liver and kidney biomarkers in this study population. Furthermore, we measured the serum Cys C concentration of the subjects, which can more sensitively reflect early impairment of kidney filtration function and is not affected by factors such as height, weight, age, or race. The

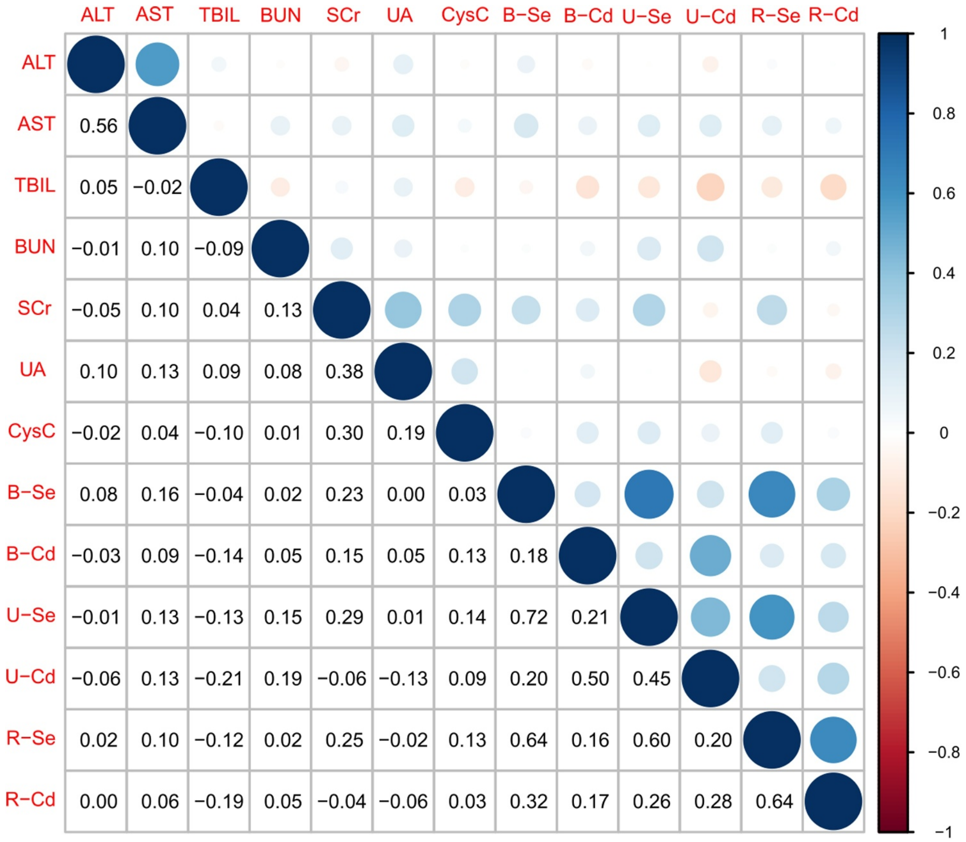

Figure 2. Correlation analysis for Se and Cd content in rice, blood, urine, and sensitive liver and kidney biomarkers (*n* = 249).

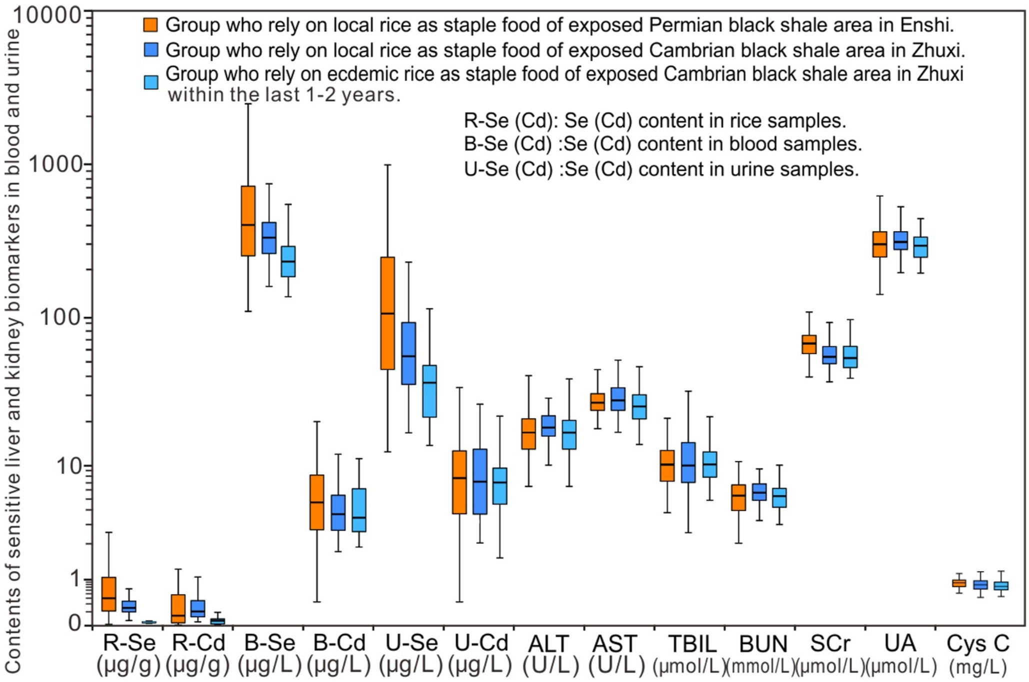

Figure 3. Boxplots of Se and Cd in rice, blood and urine and of ALT, AST, TBIL, BUN, SCr, Cys C, and UA in serum. Each box represents the interquartile range (25th and 75th percentile), the band near the middle of the box represents the 50th percentile (the median), and the whiskers represent the 5th and 95th percentiles.

serum Cys C levels of the population in the black shale-exposed areas of both Enshi County and Zhuxi County were generally within the healthy reference range (Table 4, Figure 3), indicating that their kidney filtration function was generally normal. However, the serum Cys C levels of the population in the black shale-exposed areas of Enshi were significantly greater than those of the population in Zhuxi ($P < 0.05$), indicating that greater exposure to Se and Cd affected kidney filtration to some extent. This finding is consistent with the results obtained for SCr (Cys C is positively correlated with SCr, $r = 0.304$). In summary, although the liver and kidney functions of the population in exposed black shale areas are generally normal, with increasing exposure to Se and Cd, the liver and kidney are partially affected.

Notably, Chen et al. (2020) reported that although the blood and urine Se and Cd levels of residents in the exposed black shale areas of Enshi were significantly greater than those of residents living in normal areas, they did not experience early kidney damage caused by Cd. The levels of N-acetyl-β-D-glucosaminidase, β2-microglobulin and albumin in the urine and superoxide dismutaseurine in the serum were not different from those in the control population ($p < 0.01$), possibly because Se can reduce the biological toxicity of Cd. However, the median levels of B-Se and B-Cd in the population exposed to high Se concentrations reported by Chen et al. (2020) were 238.90 and 2.60 μg/L, respectively, which were significantly lower than those (416.977 and 4.821 μg/L, respectively) in this study. Due to precise soil geochemical surveys conducted in the early stage, the exposure levels of the subjects of Enshi in this study were much greater than those reported by Chen et al. (2020). Under such long-term Se and Cd exposure, the liver and kidney functions of the human body are normal, further indicating that Se may have a potential antagonistic effect on Cd.

In recent years, animal experiments have further explained the mechanism by which Se can alleviate Cd toxicity in organisms. Cd ingested by *Caenorhabditis elegans* mostly binds sequentially with glutathione (GSH) and plant chelating elements (PCs) and then further interacts with selenocysteine to form tetrahedral PC2-Cd2-Sec2 complexes, which eventually become CdSe NPs (Li et al., 2019, 2021). Se can alleviate the toxicity of Cd to chicken kidneys by regulating the miR-26a-5p/PTEN/PI3K/AKT signaling pathway (Chen et al., 2021). In addition, Se reduces the toxicity of Cd to grass carp hepatocytes by activating the Keap1-Nrf2 signaling pathway (Zhang et al., 2023). Further research is needed to determine whether these mechanisms are the reason why residents in exposed black shale areas maintain normal liver and kidney functions despite long-term intake of large amounts of Se and Cd. In addition, we demonstrated that the investigation of relevant biomarkers is imperative when the USEPA method is used to assess Cd risk in exposed black shale areas.

4. Conclusions

1. The Se contents of the surface soil in the exposed areas of the Permian and Cambrian black shales in Enshi County and Zhuxi County were 4.32 ± 2.84 μg/g ($n = 81$) and 3.30 ± 2.32 μg/g ($n = 56$), respectively, corresponding to Cd contents of 3.13 ± 2.38 μg/g and 3.09 ± 1.75 μg/g, respectively. The Se contents of locally grown rice in the Enshi and Zhuxi study areas were 0.956 ± 0.900 μg/g ($n = 90$) and 0.346 ± 0.155 μg/g ($n = 41$), respectively, and the Cd contents were 0.372 ± 0.477 μg/g and 0.384 ± 0.348 μg/g, respectively. According to USEPA evaluations, soils and rice pose significant ecological risks.
2. The median B-Se and U-Se levels of residents who predominantly consume local rice in the Enshi ($n = 190$) and Zhuxi ($n = 66$) study areas were extremely high, measuring 416.977 and 352.690 μg/L, 104.527 and 51.820 μg/L, respectively. The median B-Cd and U-Cd levels in these populations were also markedly elevated at 4.821 μg/L and 3.848 μg/L and at 7.750 μg/L and 7.050 μg/L, respectively, indicating substantial Se and Cd exposure. Compared to those who consumed local rice, there was a significant decrease ($P < 0.01$) in B-Se (245.604 μg/L) and U-Se (37.663 μg/L) levels among people ($n = 48$) who consumed ecdemic rice in the past 1–2 years in Zhuxi. However, there was no significant difference ($P > 0.05$) in the B-Cd (3.510 μg/L) or U-Cd (7.240 μg/L) concentration. Therefore, Cd accumulates in the human body for a long time, but Se metabolism is faster.
3. The median levels of blood biochemical kidney and liver biomarkers in the groups that consumed local rice as a staple food in both the exposed black shale areas of Enshi and Zhuxi were within the healthy reference ranges. Because Se can antagonize Cd in the human body, the USEPA method cannot accurately assess the ecological risk of Cd in exposed black shale areas.
4. In areas exposed to black shale, the greater the population's exposure to Se and Cd is, the greater the serum levels of Cys C and SCr are. A weak positive correlation was found between SCr and U-Se and B-Se. Excessive Se exposure may impact human renal filtration to some extent.

Conflict of Interest

The authors declare no conflicts of interest relevant to this study.

Data Availability Statement

Data created and used for this paper are available at the Mendeley Data repository (Li, 2024), where it is free to access and use with no registration required.

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References

Akerstrom, M., Sallsten, G., Lundh, T., & Barregard, L. (2013). Associations between urinary excretion of cadmium and proteins in a nonsmoking population: Renal toxicity or normal physiology? *Environmental Health Perspectives*, *121*(2), 187–191. https://doi.org/10.1289/ehp.1205418

Callan, A., Hinwood, A., & Devine, A. (2014). Metals in commonly eaten groceries in Western Australia: A market basket survey and dietary assessment. *Food Additives & Contaminants*, *31*(12), 1968–1981. https://doi.org/10.1080/19440049.2014.973457

Chen, H., Li, P., Shen, Z., Wang, J., & Diao, L. (2021). Protective effects of selenium yeast against cadmium-induced necroptosis through miR-26a-5p/PTEN/PI3K/AKT signaling pathway in chicken kidney. *Ecotoxicology and Environmental Safety*, *220*, 112387. https://doi.org/10.1016/j.ecoenv.2021.112387

Chen, J., He, W., Zhu, X., Yang, S., Yu, T., & Ma, W. (2020). Epidemiological study of kidney health in an area with high levels of soil cadmium and selenium: Does selenium protect against cadmium-induced kidney injury? *Science of the Total Environment*, *698*, 134106. https://doi.org/10.1016/j.scitotenv.2019.134106

Du, Y., Luo, K., Ni, R., & Rahib, H. (2018). Selenium and hazardous elements distribution in plant–soil–water system and human health risk assessment of Lower Cambrian, Southern Shaanxi, China. *Environmental Geochemistry and Health*, *40*(5), 2049–2069. https://doi.org/10.1007/s10653-018-0082-3

Elinder, C., & Barregard, L. (2022). Renal effects of exposure to metals. *Handbook on the Toxicology of Metals*, *1*, 485–502. https://doi.org/10.1016/B978-0-12-823292-7.00013-9

Friberg, L., Elinder, C. G., Kjellstrom, T., & Nordberg, G. F. (1986). *Cadmium and health: A toxicological and epidemiological appraisal: Volume 2: Effects and response* (1st ed.). CRC Press. https://doi.org/10.1201/9780429260599

Friberg, L., & Vahter, M. (1983). Assessment of exposure to lead and cadmium through biological monitoring: Results of a UNEP/WHO global study. *Environmental Research*, *30*(1), 95–128. https://doi.org/10.1016/0013-9351(83)90171-8

Heitland, P., & Koster, H. D. (2006). Biomonitoring of 37 trace elements in blood samples from inhabitants of Northern Germany by ICP-MS. *Journal of Trace Elements in Medicine & Biology*, *20*(4), 253–262. https://doi.org/10.1016/j.jtemb.2006.08.001

Hu, X., Eccles, K. M., & Chan, H. M. (2017). High selenium exposure lowers the odds ratios for hypertension, stroke, and myocardial infarction associated with mercury exposure among Inuit in Canada. *Environment International*, *102*, 200–206. https://doi.org/10.1016/j.envint.2017.03.002

Huang, Y., Wang, Q., Gao, J., Lin, Z., Bañuelos, G. S., Yuan, L., & Yin, X. (2013). Daily dietary selenium intake in a high selenium area of Enshi, China. *Nutrients*, *5*(3), 700–710. https://doi.org/10.3390/nu5030700

Hyder, O., Chung, M., Cosgrove, D., Herman, J. M., Li, Z., Firoozmand, A., et al. (2013). Cadmium exposure and liver disease among US adults. *Journal of Gastrointestinal Surgery*, *17*(7), 1265–1273. https://doi.org/10.1007/s11605-013-2210-9

IARC (International Agency for Research on Cancer). (1993). Cadmium. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, *58*, 119–238.

Järup, L., Rogenfelt, A., Elinder, C. G., Nogawa, K., & Kjellstrom, T. (1983). Biologicahalf-time of cadmium in the blood of workers after cessation of exposure. *Scandinavian Journal of Work, Environment & Health*, *9*(4), 327–331. https://doi.org/10.5271/sjweh.2404

Jie, L., & Luo, K. (2017). Trace element distribution and enrichment patterns of Ediacaran-early Cambrian, Ziyang selenosis area, Central China: Constraints for the origin of selenium. *Journal of Geochemical Exploration*, *172*, 211–230. https://doi.org/10.1016/j.gexplo.2016.11.010

Kang, M. Y., Cho, S. H., Lim, Y. H., Seo, J. C., & Hong, Y. C. (2013). Effects of environmental cadmium exposure on liver function in adults. *Occupational and Environmental Medicine*, *70*(4), 268–273. https://doi.org/10.1136/oemed-2012-101063

Khan, E., Batuman, V., & Lertora, J. J. (2010). Emergence of biomarkers in nephron pharmacology. *Biomarkers in Medicine*, *4*(6), 805–814. https://doi.org/10.2217/bmm.10.115

Khanam, R., Kumar, A., Nayak, A. K., Shahid, M., Tripathi, R., Vijayakumar, S., et al. (2020). Metal(loid)s (As, Hg, Se, Pb and Cd) in paddy soil: Bioavailability and potential risk to human health. *Science of the Total Environment*, *699*, 134330. https://doi.org/10.1016/j.scitotenv.2019.134330

Kido, T., Sunaga, K., Nishijo, M., Nakagawa, H., Kobayashi, E., & Nogawa, K. (2004). The relation of individual cadmium concentration in urine with total cadmium intake in Kakehashi River basin, Japan. *Toxicology Letters*, *152*(1), 57–61. https://doi.org/10.1016/j.toxlet.2004.04.001

Kobayashi, E., Suwazono, Y., Honda, R., Dochi, M., Nishijo, M., Kido, T., & Nakagawa, H. (2008). Changes in renal tubular and glomerular functions and biological acid-base balance after soil replacement in Cd-polluted rice paddies calculated with a general linear mixed model. *Biol. Biological Trace Element Research*, *124*(2), 164–172. https://doi.org/10.1007/s12011-008-8125-8

Kobayashi, J., & Kizu, R. (2001). Evaluation of metal contents in river water using a simple fractionation method. *Journal of Health Science*, *47*(5), 460–463. https://doi.org/10.1248/jhs.47.460

Li, L., Cui, Y., Lu, L. Y., Zhu, C., Tian, L., Li, W., et al. (2019). Selenium stimulates Cadmium detoxification in Caenorhabditis elegans through thiols-mediated nanoparticles formation and secretion. *Environmental Science & Technology*, *53*(5), 2344–2352. https://doi.org/10.1021/acs.est.8b04200

Li, L., Wu, Q., Chen, J., Cui, Y., Zhu, C., Li, B., et al. (2021). Mechanical insights into thiol-mediated synergetic biotransformation of cadmium and selenium in nematodes. *Environmental Science & Technology*, *55*(11), 7531–7540. https://doi.org/10.1021/acs.est.1c00686

Li, M. (2024). Analytical results of rock, soil, drinking water, human blood and urine samples of exposed black shale areas from Enshi and Zhuxi, China [Dataset]. *Mendeley Data, V1*. Retrieved from https://data.mendeley.com/datasets/kmp2vppc8y/1

Li, M., Qiu, L., Zheng, D., Yan, D. P., Zhang, Y., Yang, B., et al. (2023). Age and origin of a Guadalupian tuff in the E'Xi rift basin in South China: Evidence for the Emeishan continental hotspot track? *Terra Nova*, *35*(6), 514–523. https://doi.org/10.1111/ter.12674

Li, M., Yang, B., Ju, Z., Qiu, L., Xu, K., Wang, M., et al. (2023). Do high soil geochemical backgrounds of selenium and associated heavy metals affect human hepatic and renal health? Evidence from Enshi county, China. *Science of the Total Environment*, *883*, 163717. https://doi.org/10.1016/j.scitotenv.2023.163717

Li, M., Yang, B., Qiu, L., Zhang, Y., Xu, H., Shi, X., et al. (2022). Emeishan felsic volcanism lasted until the changhsingian? New evidence from volcanic ash in the northern South China block. *Journal of Asian Earth Sciences*, *238*, 105390. https://doi.org/10.1016/j.jseaes.2022.105390

Li, M., Yang, B., Xu, K., Zheng, D., & Tian, J. (2020). Distribution of se in the rocks, soil, water and crops in Enshi County, China. *Applied Geochemistry*, *122*, 104707. https://doi.org/10.1016/j.apgeochem.2020.104707

Liang, Y., Zeng, T., Tian, J., Yan, J., Lan, Z., Chen, J., et al. (2021). Long-term environmental cadmium exposure induced serum metabolic changes related to renal and liver dysfunctions in a female cohort from Southwest China. *Science of the Total Environment*, *798*, 149379. https://doi.org/10.1016/j.scitotenv.2021.149379

Lv, Q., Xiao, Q., Wang, Y., Wen, H., Han, B., Zheng, X., & Lin, R. (2021). Risk assessment and hotspots identification of heavy metals in rice: A case study in Longyan of Fujian province, China. *Chemosphere*, *70*, 128626. https://doi.org/10.1016/j.chemosphere.2020.128626

Mao, C., Song, Y., Chen, L., Ji, J., Li, J., Yuan, X., et al. (2019). Human health risks of heavy metals in paddy rice based on transfer characteristics of heavy metals from soil to rice. *Catena*, *175*, 339–348. https://doi.org/10.1016/j.catena.2018.12.029

Mélanie, L., Aline, P., Myriam, F., Carlos, J. S. P., Jean, R. D. G., Fernando, B. J., & Mergler, D. (2012). No evidence of selenosis from a selenium-rich diet in the Brazilian Amazon. *Environment International*, *40*, 128–136. https://doi.org/10.1016/j.envint.2011.07.005

NHFPC (National Health and Family Planning Commission of the People's Republic of China). (2017). Chinese dietary reference intakes—Part 3: Trace element (DRIs) (p. 4). WS/T 578.3.

Ni, R., Luo, K., Tian, X., Yan, S., Zhong, J., & Liu, M. (2016). Distribution and geological sources of Se in environmental materials in Taoyuan county, Hunan province, China. *Environmental Geochemistry and Health*, *38*(3), 927–938. https://doi.org/10.1007/s10653-015-9772-2

Nie, X., Wang, N., Chen, Y., Chen, C., Han, B., Zhu, C., et al. (2016). Blood cadmium in Chinese adults and its relationships with diabetes and obesity. *Environmental Science and Pollution Research*, *23*(18), 18714–18723. https://doi.org/10.1007/s11356-016-7078-2

Nordberg, G., Jin, T., Bernard, A., Fierens, S., Buchet, J., Ye, T., et al. (2002). Low bone density and renal dysfunction following environmental cadmium exposure in China. *Ambio*, *31*(6), 478–481. https://doi.org/10.1579/0044-7447-31.6.478

Nordberg, G. F., Nordberg, M., & Costa, M. (2022). Toxicology of metals: Overview, definitions, concepts, and trends. In *Handbook on the toxicology of metals* (5th ed., Vol. I, pp. 1–14). General Considerations. https://doi.org/10.1016/B978-0-12-823292-7.00029-2

Oh, R. C., Hustead, T. R., Ali, S. M., & Pantsari, M. W. (2017). *Mildly elevated liver transaminase levels: Causes and evaluation* (Vol. 96, pp. 709–715). American Family Physician.

Otto-Ślusarczyk, D., Graboń, W., & Mielczarek-Puta, M. (2016). Aspartate aminotransferase-key enzyme in the human systemic metabolism. *Postępy Higieny i Medycyny Doświadczalnej*, *70*, 219–230. https://doi.org/10.5604/17322693.1197373

Robberecht, H. J., & Deelstra, H. A. (1984). Selenium in human urine: Concentration levels and medical implications. *Clinica Chimica Acta*, *136*(2–3), 107–120. https://doi.org/10.1016/0009-8981(84)90282-1

Sands, J. M. (2003). Mammalian Urea Transporters. *Annual Review of Physiology*, *65*(1), 543–566. https://doi.org/10.1146/annurev.physiol.65.092101.142638

Satarug, S., Vesey, D. A., & Gobe, G. C. (2017). Health risk assessment of dietary cadmium intake: Do current guidelines indicate how much is safe? *Environmental Health Perspectives*, *125*(3), 284–288. https://doi.org/10.1289/EHP108

Sebastian, A., & Prasad, M. N. V. (2014). Cadmium minimization in rice. A review. *Agronomy for Sustainable Development*, *34*(1), 155–173. https://doi.org/10.1007/s13593-013-0152-y

Tan, J. A., Zhu, W. Y., Wang, W. Y., Li, R. B., Hou, S. F., Wang, D. C., & Yang, L. (2002). Selenium in soil and endemic diseases in China. *Science of the Total Environment*, *284*(1–3), 227–235. https://doi.org/10.1016/S0048-9697(01)00889-0

Taylor, S. R., & McLennan, S. M. (1985). *The continental crust: Its composition and evolution* (p. 312). Blackwell Scientific Publication.

U.S Environmental Protection Agency (USEPA). (2001). Risk assessment guidance for superfund: Volume III—Part A, process for conducting probabilistic risk assessment, Washington DC. Retrieved from https://www.epa.gov/sites/default/files/2015-09/documents/rags3adt_complete.pdf

Vacchi-Suzzi, C., Kruse, D., Harrington, J., Levine, K., & Meliker, J. R. (2016). Is urinary cadmium a biomarker of long-term exposure in humans? A review. *Current Environmental Health Reports*, *3*(4), 450–458. https://doi.org/10.1007/s40572-016-0107-y

Wang, X., Seo, Y. A., & Park, S. K. (2021). Serum selenium and non-alcoholic fatty liver disease (NAFLD) in U.S. adults: National Health and Nutrition Examination Survey (NHANES) 2011–2016. *Environmental Research*, *197*, 111190. https://doi.org/10.1016/j.envres.2021.111190

Wang, Y., Zhang, S., Wang, Y., & Zhuo, X. (2015). Normal range of 33 elements in blood samples from general population in Hunan province. *Journal of Forensic Medicine*, *31*(02), 117–122. (in Chinese with English abstract). https://doi.org/10.3969/j.issn.1004-5619.2015.02.010

Wang, Z. J., & Gao, Y. X. (2001). Biogeochemical cycling of selenium in Chinese environments. *Applied Geochemistry*, *16*(11–12), 1345–1351. https://doi.org/10.1016/S0883-2927(01)00046-4

Watanabe, T., Zhang, Z. W., Moon, C.-S., Shimbo, S., Nakatsuka, H., Matsuda-Inoguchi, N., et al. (2000). Cadmium exposure of women in general populations in Japan during 1991-1997 compared with 1977-1981. *International Archives of Occupational and Environmental Health*, *73*(1), 26–34. https://doi.org/10.1007/PL00007934

World Health Organization (WHO). (1984). *Guidelines for drinking-water quality: Health criteria and other supporting information* (Vol. 2, pp. 84–90). World Health Organization.

World Health Organization (WHO). (1992). *Cadmium. International programme on chemical safety: Environmental health criteria (EHC)* (Vol. 134). WHO.

World Health Organization (WHO). (2011). *Food additive series 64: Safety evalution of certaion food evalution and contaminants*. WHO Publishing.

Xie, T., Shi, Z., Yu, W., Lin, M., & Li, M. (2021). Modeling analysis of the characteristics of selenium-rich soil in heavy metal high background area and its impact on main crops. *Ecological Informatics*, *66*, 101420. https://doi.org/10.1016/j.ecoinf.2021.101420

Yang, G. Q., Wang, S. Z., Zhou, R. H., & Sun, S. Z. (1983). Endemic selenium intoxication of humans in China. *The American Journal of Clinical Nutrition*, *37*(5), 872–881. https://doi.org/10.1093/ajcn/37.5.872

Zhang, T., Sun, S., Gavrilović, A., Li, D., & Tang, R. (2023). Selenium alleviates cadmium-induced oxidative stress, endoplasmic reticulum stress, and apoptosis in L8824 cells. *Ecotoxicology and Environmental Safety*, *262*, 115337. https://doi.org/10.1016/j.ecoenv.2023.115337