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Relative contribution of rice and fish consumption to bioaccessibility-corrected health risks for urban residents in eastern China

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ABSTRACT

There are global concerns about dietary exposure to metal(loid)s in foods. However, little is known about the relative contribution of rice versus fish to multiple metal(loid) exposure for the general population, especially in Asia where rice and fish are major food sources. We compared relative contributions of rice and fish consumption to multi-metal(loid) exposure on the city-scale (Nanjing) and province-scale in China. The effects of ingestion rate, metal(loid) level, and bioaccessibility were examined to calculate modeled risk from Cu, Zn, total As (TAs), inorganic As (iAs), Se, Cd, Pb, and methylmercury (MeHg). Metal(loid) levels in rice and fish samples collected from Nanjing City were generally low, except iAs. Metal(loid) bioaccessibilities in fish were higher than those in rice, except Se. Calculated carcinogenic risks induced by iAs intake (indicated by increased lifetime cancer risk, ILCR) were above the acceptable level ($1\ 0^{-4}$) in Nanjing City (median: 3×10^{-4} for female and 4×10^{-4} for male) and nine provinces (1.4×10^{-4} to 5.9×10^{-4}) in China. Rice consumption accounted for 85.0% to 99.8% of carcinogenic risk. The non-carcinogenic hazard quotients (HQ) for single metals and hazard index (HI) for multi-metal exposure were < 1 in all cases, indicating of their slight non-carcinogen health effects associated. In Guangdong and Jiangsu provinces, results showed that rice and fish intake contributed similarly to the HI (i.e., 42.6% vs 57.4% in Guangdong and 54.6% vs 45.4% in Jiangsu). Sensitivity analysis indicated that carcinogenic risk was most sensitive to rice ingestion rate and rice iAs levels, while non-carcinogenic hazard (i.e., HQ and HI) was most sensitive to ingestion rate of fish and rice, and Cu concentration in rice. Our results suggest that rice is more important than fish for human dietary metal(loid) exposure risk in China, and carcinogenic risk from iAs exposure in rice requires particular attention.

1. Introduction

There is increasing evidence indicating the key role of food consumption on the health risks of metal(loid)s (Eggers et al., 2018; Whyte et al., 2009; Yan et al., 2019). Both rice and fish are important in controlling dietary exposure to metal(loid)s, especially in Asian countries (Luo et al., 2018; Ullah et al., 2018; Wang et al., 2013). The global consumption of rice has increased from 448 million metric tons (MMT) in the 2008/2009 crop year to 497 MMT in the 2018/2019 crop year (USDA, 2012, 2021). As such, the possibility of carcinogenic and non-carcinogenic health effects due to dietary metal(loid) exposure, may occur. In risk assessment, non-carcinogenic hazard is estimated using hazard quotient (HQ, for a single metal) or hazard index (HI, for combined hazard due to multiple metals), while carcinogenic risk is

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quantified by increased lifetime cancer risk (ILCR) (USEPA, 2001). HQ/HI>1 or ILCR>10^{-4}, indicating possible risk, has been observed from rice or fish consumption in multiple studies (e.g., Islam et al., 2016, 2017a; Lei et al., 2015; Minh et al., 2012). For example, the Cd HQ was up to 2.7 from rice consumption in a Vietnam community (Minh et al., 2012), the As HQ ranged from 1.4 to 5.6 for 11 fish species in the Bogra district of Bangladesh (Islam et al., 2016), and the ILCR of inorganic As was 2.88×10^{-3} from rice consumption in Narayanganj district in central Bangladesh (Islam et al., 2017a). Among the many studies of metal(loid) exposure risks associated with rice or fish consumption, few have directly compared risk from rice versus fish, especially for multiple metal(loid)s or at regional scales (Chen et al., 2019; Gong et al. 2018; Mwakalapa et al., 2019; Wang et al., 2020a). This gap hinders the understanding, prioritization, and management of risks of metal(loid) exposure from food consumption, especially in Asian countries, where both rice and fish are staple foods (Barman et al., 2018; Rahman and Hasegawa, 2011).

There are growing concerns about the possible multi-metal(loid) contamination and associated food safety issues in China, but related studies have mainly focused on heavily contaminated areas (e.g., the mining areas). For instance, Lei et al. (2015) found that the accumulation of metal(loid)s in white rice around mining-affected areas in Hunan province led to high HI of 1.2–4.1, indicating of potential for health effects for the local population. Though metal(loid) exposure risk in non-contaminated areas has also been reported in China, most studies focused on the health risks of a single metal(loid) caused by consumption of one food type (Cai et al., 2015; Lin et al., 2015; Liu et al., 2018a), which may underestimate the risks of dietary exposure from multi-metal(loid) for the general population in these areas. For example, the ILCR of inorganic As in rice obtained from markets in Fuzhou province was 3.5×10^{-4} for adults (Fu et al., 2015), which exceeded the acceptable level (10^{-4}). Therefore, it is of particular significance to assess comprehensive multi-metal(loid) exposure via various food items such as rice and fish in non-contaminated areas in China.

Comparing effective metal(loid) exposure via rice and fish consumption is complicated by the fact that dietary exposure largely depends on metal(loid) bioaccessibility in food (He and Wang, 2013; Liu et al., 2018b). Bioaccessibility is defined as the fraction that is released from the food, which can exert potentially toxic effects. As such, bioaccessibility is often used as an indicator for contaminant oral bioavailability (Hu et al., 2012; Versantvoort et al., 2005). Bioaccessibilities of metal(loid)s in rice and fish are rarely measured or considered in previous studies, which could lead to bias in assessing the risks associated with different food items. Differences in metal(loid) bioaccessibilities between rice and fish have varied greatly in a few studies. For instance, the bioaccessibility of Cd in rice (74%) was 12 times higher than that in common carp (6%) (Wang et al., 2014a), whereas bioaccessibility of methylmercury (MeHg) in rice (40.5%) was lower than that in fish (61.4%) (Gong et al., 2018). Thus, it is important to consider the bioaccessibility of metal(loid)s in exposure and risk assessment, given that foods and metal(loid) types may have impacts on effective dietary exposure.

We hypothesized that, after being corrected for bioaccessibility, the risk of multi-metal(loid) exposure of the population would be greatly reduced. We also hypothesized varying contributions to the health risk from fish and rice consumption across different fish species and metal(loids) because the concentration and bioaccessibility of each metal(loid) vary greatly in different food matrices. To test these hypotheses, we quantified concentrations and bioaccessibilities of metal(loid)s in rice and fish samples and determined ingestion rates using a questionnaire survey, in Nanjing City, eastern China. We also performed a literature review to determine the metal(loid) concentrations and ingestion rates in other provinces in China. We then compared potential health risks (carcinogenic and non-carcinogenic) of effective metal(loid) intake from rice and fish consumption in Nanjing City and other 12 provinces, accounting for 47.6% of the Chinese population (NBS, 2012). These bioaccessibility-corrected and cross-regional dietary exposure and risk analysis help to characterize the health risks caused by common food consumption, with policy implications for reducing the multi-metal(loid) exposure burden in non-contaminated areas.

2. Materials and methods

2.1. Sampling of rice and fish in Nanjing City

Samples and questionnaire surveys in this study were the same as those in our previous study (Gong et al., 2018). In several comparisons among a range of food items within China, rice and fish have been identified as the predominant sources of dietary metal exposure and risk (Huang et al., 2018; Shao et al., 2013; Tang et al., 2015; Wang et al., 2018; Zheng et al., 2007). Therefore, rice (white rice only) and fish species were collected in Nanjing City, eastern China in 2016. Rice samples produced from northern Jiangsu (NJS) and northeastern China (NEC) were collected, because they are staple production areas of rice in China. Besides, as Nanjing is the capital city of Jiangsu province and many Chinese customers have shown a taste preference for rice grown in northeast China in comparison to rice grains in southern China (Hansen et al., 2001), the commercially available rice in Nanjing was mainly produced in the two rice production areas (i.e., NJS and NEC). We identified nine commonly consumed fish species according to the China Fishery Statistics Yearbooks (FAB, 2016), and included them in the survey questionnaire: crucian carp, Chinese bream, bighead carp, yellowhead catfish, silver carp, largehead hairtail, squid, silver pomfret, and yellow croaker. Based on the results of the survey, the top three consumed fish species in Nanjing City were collected: crucian carp (*Carassius carassius,* 60.8% of the respondents chose), yellow croaker (*Larimichthys polyactis,* 32.6%), and largehead hairtail (*Trichiurus lepturus,* 18.1%). Finally, we collected 40 rice samples and 60 fish samples from 25 farmer's markets and supermarkets in 8 districts (6 urban districts and 2 suburban districts, Fig. 1). We targeted relatively large markets and supermarkets in the districts, in order to represent the greatest number of residents. One to six samples of each rice or fish species were acquired from each district for analysis of metal(loid) concentration and bioaccessibility (Table S1).

2.2. Questionnaire survey

Dietary behaviors (e.g., average daily intake, purchase information of rice and fish, preference for fish species) and demographic characteristics (gender, body weight, age and residence information) were determined using a questionnaire survey (given in Text S1). The written survey and food sampling were conducted simultaneously in Nanjing City in 2016. The survey was distributed around the food sampling sites and completed by 227 residents. Each respondent signed an informed consent form after receiving a thorough explanation of the survey. The results of the survey, providing a basis for health risk assessment (Section 2.6), were summarized in Table S2. The survey was approved by the Ethics Committee of Institute of Dermatology, Chinese Academy of Medical Sciences and Peking Union Medical College.

2.3. Determining metal(loid) concentrations in rice and fish

To better indicate metal(loid) exposure associated with food consumption, all rice and fish samples were cooked, considering that cooking may affect concentrations and bioaccessibilities of metal(loid)s in food (Halder et al., 2014; Signes-Pastor et al., 2012). Rice samples were rinsed with ultrapure water and then steamed for 10 min. Similarly, fish samples were steamed for 30 min and dissected to obtain edible fish muscle (Gong et al., 2018; Peng et al., 2016, 2017). Then, these cooked samples were freeze-dried, ground into fine powder, sealed, and stored at −20 °C until further analysis. Nitric acid (HNO_3) was added in weighed samples for pre-digestion overnight and then

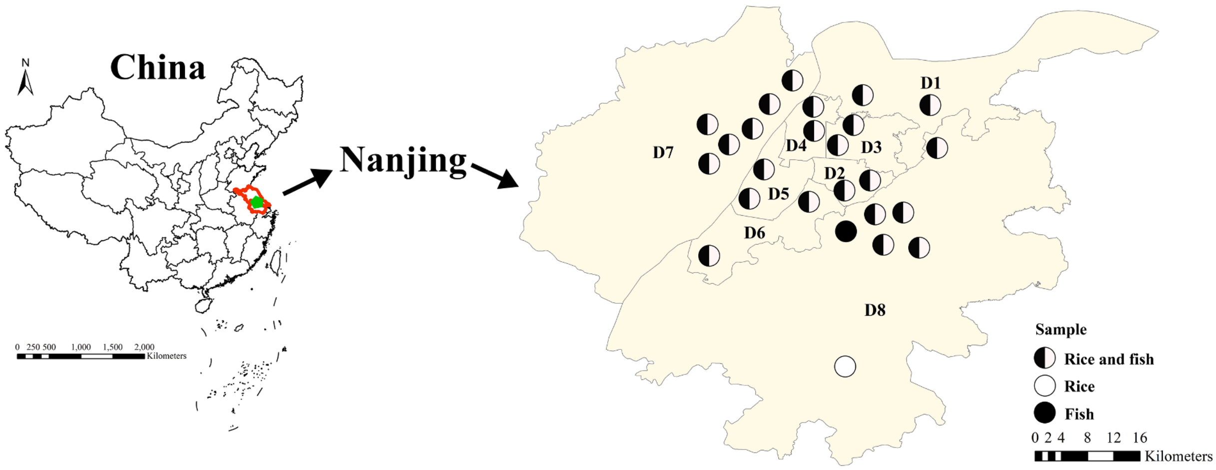

Fig. 1. Sampling sites of rice and fish samples in 8 districts of Nanjing City, eastern China. Six urban districts: D1 (Qixia District), D2 (Qinhuai District), D3 (Xuanwu District), D4 (Gulou District), D5 (Jianye District), D6 (Yuhuatai District); Two suburb districts: D7 (Pukou District), D8 (Jiangning District).

samples were heated in tubes using a graphite digestion system (Hanon SH230) at 120 °C for 4 h. All samples were then measured for metal (loid) concentrations with an ICP-MS (Perkin Elmer/NexION300). Cadmium (Cd), copper (Cu), lead (Pb), total arsenic (TAs), selenium (Se) and zinc (Zn) were quantified in this study, with detection limits of 0.08, 0.06, 0.07, 0.48, 0.50 and 0.63 ng/L, respectively. The essential micronutrients Zn and Se were included because excessive intake may lead to health problems (Arsenault and Brown, 2003; Wang et al., 2014b). Extraction and analysis were performed in duplicate for each sample. The recoveries of Cu, Zn, TAs, Se, Cd and Pb for rice in the certified reference material (CRM) of Liaoning rice (GBW10043) were 103.1 ± 5.2% (mean ± standard deviation), 109.6 ± 5.3%, 109.3 ± 8.2%, 111.9 ± 7.7%, 103.8 ± 5.9% and 94.5 ± 11.8%, respectively; and these recoveries for fish in CRM of scallop tissue (GBW10024) were 103.7 ± 6.5%, 111.1 ± 5.5%, 114.3 ± 9.0%, 98.0 ± 5.6%, 103.0 ± 4.0% and 104.8 ± 9.3%, respectively.

Since As is carcinogenic and most toxic in its inorganic form (Nordberg et al., 2014), inorganic arsenic (iAs), rather than TAs, was considered in carcinogenic risk assessment. The following procedure was used for extraction and determination of iAs. Following Xu et al. (2008), 2 M trifluoroacetic acid (TFA) was used to extract iAs from freeze-dried rice samples. Mixtures of 0.25 g sample and 2 mL TFA in tubes were kept at room temperature overnight. The tubes were then moved to the graphite digestion system and heated at 100 °C for 5 h to evaporate the solution. Then the volume was diluted with ultrapure water to 10 mL. The contents of two species of iAs, i.e., As(III) and As(V), were determined by HPLC (Agilent/1260 Infinity II) coupled with ICP-MS (Agilent Technologies/7900). The detection limits were 0.049 ng/mL for As(III) and 0.021 ng/mL for As(V). The standard addition method was used as quality control, showing that in rice samples the recoveries of As(III) and As(V) were 87.0 ± 9.6% and 94.7 ± 13.0%, respectively. Arsenic species in fish samples were extracted with a mixture of methanol (CH_3OH) and water (1:1 v/v) (Zhang et al., 2015). The mixture of samples and digestion solution was homogenized with a tissue homogenizer (RA-35S) for 15 min, and then centrifuged at 10,000 rpm for 10 min. The supernatant was heated at 50 ℃ until evaporating to 1 mL, then diluted and filtered for the determination of As(III) and As(V). For fish samples, the standard addition recoveries of As(III) and As(V) were 114.8 ± 12.1% and 89.6 ± 10.4%, respectively.

For MeHg, the measurement and quality control were described in Gong et al. (2018). Briefly, 2 mL KOH-methanol was added in weighed samples, heated to 65 °C, and vibrated at 230 rpm for 4 h. Then MeHg measurement was conducted by the MERX Automated Mercury System (Brooks Rand Labs). The detection limit for MeHg was 0.05 ng/g. Certified reference material (DORM-3, fish muscle tissue) and matrix spikes were used as quality control, with MeHg recoveries of 93 ± 3% and 91 ± 13%, respectively.

2.4. *Determining metal(loid) bioaccessibilities in rice and fish*

To date, several methods have been developed for bioaccessibility measurement. These include the simulator of the human intestinal microbial ecosystem (SHIME, Van de Wiele et al., 2004), a method developed by the National Institute for Public Health and the Environment of Dutch (RIVM, Versantvoort et al., 2005), and the unified BARGE method (UBM, Li et al., 2015b). In addition to pollutant characteristics (e.g., metal(loid) type) and matrices (e.g., food item), digestion conditions also affect bioaccessibility (Lu et al., 2021). To compare the bioaccessibility results, we used the in vitro digestion model in this study (Versantvoort et al., 2005), which has been frequently used for metal (loid) bioaccessibility (e.g., He and Wang, 2013; Liu et al., 2018b).

The fresh digestive solution, including saliva, gastric juice, duodenal juice, and bile were prepared to mimic the human digestive environment. The digestive solution was pH adjusted with HCL and NaHCO3 (saliva: 6.8 ± 0.2; gastric juice: 1.3 ± 0.02; duodenal juice: 8.1 ± 0.2; bile: 8.2 ± 0.2), stored at 4 ℃ after configuration, and then heated to 37 ± 2 ℃ before using. Samples of rice and fish were weighed and then incubated with saliva for 5 min (incubation pH = 6.8). After 2 h of incubation with gastric juice (incubation pH = 2–3), duodenal juice and bile were added to the mixture and incubated for another 2 h (incubation pH = 6.5–7). During the whole digestion, the tubes were shaken (55 rpm) and kept at 37 °C in an incubator. Finally, the mixture was centrifuged (3000 rpm, 20 min) to separate the supernatant and pellet, both of which were determined for metal(loid) concentrations.

Bioaccessibilities of metal(loid)s in rice or fish were calculated as below (Gong et al., 2018; Wang et al., 2020a):

$$Bioaccessibility(\%) = \frac{Metal(loid)\ levels\ in\ supernatant\ (mg/kg)}{Metal(loid)\ levels\ in\ cooked\ fish\ and\ rice\ samples\ (mg/kg)} \times 100 \quad (1)$$

The recoveries of metal(loid) extraction, i.e., 100% × [metal(loid) in supernatant (mg/kg) + metal(loid) in pellet (mg/kg)] / [metal(loid) in samples before extraction (mg/kg)] in cooked rice samples, were 89.6 ± 8.7%, 95.6 ± 7.1%, 101.1 ± 1.4%, 91.6 ± 12.9%, 91.5 ± 3.1% and 102.5 ± 15.7% for Cu, Zn, TAs Se, Cd and Pb, respectively. The recoveries of metal(loid) extraction in cooked fish samples were 88.1 ± 9.4%, 81.2 ± 3.9%, 94.5 ± 7.8%, 90.8 ± 6.6%, 117.0 ± 3.7% and 89.4 ± 5.7% for Cu, Zn, TAs, Se, Cd and Pb, respectively.

2.5. Data sources and study selection

To describe dietary metal(loid) exposure from commercially available rice and fish in other provinces in China, metal(loid) levels in rice and fish were collected nationwide, through Web of Science and China National Knowledge Infrastructure (CNKI) (last accessed June 2020), using the search terms [China & market & (rice or fish) & metal] (Fig. S1). In order to focus on human general population exposure, only results of rice and fish samples obtained from markets or supermarkets were included. Studies in which samples were directly collected from paddy fields or aquatic ecosystems were excluded. Metal(loid) levels in rice and fish from screened literature (29 studies, valid from 2008 to 2018) are summarized in Table S3 and Table S4, covering 13 provinces in China. The selected literature survey areas were concentrated in the coastal areas whereas there were no suitable food data for inland areas. Se was excluded from the province scale risk assessment because there were too few selenium-related studies that met our screening criteria.

2.6. Health risk assessment

Health risk assessment models were used to assess carcinogenic risk from iAs and non-carcinogenic hazard from Cu, Zn, Se, Cd, Pb, and MeHg due to rice and fish consumption. We employed the risk assessment method, developed by the United States Environmental Protection Agency (USEPA, 1989, 2001); this method has been widely used in China (e.g., Huang et al., 2008; Li and Zhang, 2010; Wang et al., 2011; Xia et al., 2010), Europe (e.g., Atkinson et al., 2012), Japan (e.g., Tokumura et al., 2016) and Korea (e.g., Choi et al., 2008). Food ingestion rates and metal(loid) concentrations for Nanjing City were based on the measurement and survey results of our study, while these parameters for other provinces were summarized from the literature (Table S3, S4 and S5). Due to the importance of MeHg for dietary exposure risk (Li et al., 2010; Mahaffey et al., 2009), MeHg data in rice and fish samples (concentrations and bioaccessibilities) from Nanjing City, which have been reported before (Gong et al., 2018), were incorporated into the risk assessment.

The average daily dose (ADD) of metal(loid)s from food was calculated using the following equation, recommended by the USEPA (1989):

$$ADD_{i,j} = (C_{i,j} \times \varphi_{i,j} \times IR_j \times EF \times ED)/(BW \times AT) \tag{2}$$

where $ADD_{i,j}$ is the average daily dose of metal(loid) *i* from ingested food *j* (mg/(kg day)); $C_{i,j}$ is the metal(loid) *i* concentration in food *j* (mg/kg); $\varphi_{i,j}$ is the metal(loid) *i* bioaccessibility of food *j* (%); IR_j is the ingestion rate of food *j* (kg/day); EF is the exposure frequency (day/year); ED is the exposure duration (year); BW is the body weight (kg); and AT is the averaging time, set as 75 year × 365 days/year. For non-carcinogen and carcinogen effects, AT = ED × EF. When calculating ADD of fish, we weighted IR_j according to fish preferences indicated in the surveys (Table S6).

The carcinogenic risk of iAs exposure was assessed by calculating the value of increased lifetime cancer risk (ILCR), including cancer of the bladder, lung, skin and liver (Jiang et al., 2015; Nordberg et al., 2014):

$$ILCR = ADD_{iAs} \times CSF \tag{3}$$

where ILCR is the increased probability of an individual developing cancer over a lifetime (unitless) and CSF is the cancer slope factor (mg/(kg day))$^{-1}$. Following prior recommendations (Chen et al., 2020; USEPA, 1989, 2001), we treated ILCR below 10^{-6} as negligible, and ILCR over 10^{-4} as unacceptable.

The non-carcinogenic hazards vary depending on specific metals, and may affect cardiovascular, musculoskeletal, neurological, hepatic, immunological, reproductive, renal and other organ systems (Nordberg et al., 2014). They were quantified by calculating HQ or HI value (USEPA, 1989):

$$HQ_{i,j} = ADD_{i,j}/RfD_i \tag{4}$$

where $HQ_{i,j}$ is the hazard quotient of metal(loid) *i* from food *j* and RfD_i is the oral reference dose of metal(loid) *i* (mg/(kg day)).

Hazard index (HI) was obtained by summing the HQs of different metal(loid)s:

$$HI = \sum_{i,j}^{n} HQ_{i,j} \tag{5}$$

Following USEPA (1989, 2001), the exposed population is assumed to have no potential health risk (i.e., no hazard) when HQ or HI < 1.

2.7. Uncertainty and sensitivity analysis

Uncertainty analysis was conducted to characterize uncertainty regarding risks of metal(loid) exposure (i.e., ILCR and HI) through food consumption. The uncertainty propagation through the risk assessment models was made using Monte Carlo Simulations (MCS), combining effects of parameter uncertainty and variability. For the MCS, body weight, ingestion rate, metal concentration and bioaccessibility were varied according to theoretical statistical distributions developed based on data collected in Nanjing City for this study (Table S6). Sensitivity analysis was performed on the MCS to compare the sensitivity of results to each input parameter. Input parameters were compared based on their Spearman's rank order correlation coefficients with the MCS results.

2.8. Statistical and graphical analysis

One-way analysis of variance (ANOVA) test and Tukey's HSD test were performed using SPSS22.0 (SPSS Inc., Chicago, IL, USA) to determine the differences in metal(loid) concentrations and bioaccessibilities between rice and fish. The spatial patterns in health risks were visualized using ArcGIS10.2.2 (Environmental Systems Research Institute, Inc., Redlands, CA, USA). Vose Model Risk software (Vose Software Inc., Ghent, Belgium) with 10,000 iterations was employed for MCS and sensitivity analysis.

3. Results and discussion

3.1. Metal(loid) concentrations in rice and fish collected from Nanjing City

Metal(loid) concentrations in rice samples (Cu: 2.2 ± 0.4 mg/kg, Zn: 13.5 ± 2.2 mg/kg, TAs: 108.4 ± 42.3 μg/kg, iAs: 70.0 ± 20.4 μg/kg, Se: 51.2 ± 15.4 μg/kg, Cd: 25.6 ± 22.6 μg/kg and Pb: 14.0 ± 7.2 μg/kg, Table 1) in this study were generally low, comparable with those documented previously in non-contaminated areas in China (e.g., Dai et al., 2014). Concentrations of iAs, Cd and Pb in rice samples were all well below the national guidelines (i.e., 0.2 mg/kg for the three metal (loid)s, GB2762-2017). This could be attributed to the low levels of metal(loid)s in the agricultural soil of rice production areas, i.e., northern Jiangsu (NJS) and northeastern China (NEC) (Yang et al., 2018). Our results showed that iAs accounted for 71.1 ± 23.6% of TAs

Table 1
Concentrations of metal(loid)s (wet weight) in cooked rice and fish samples (mean ± SD).

Food Items	Samples	Cu (mg/kg)	Zn (mg/kg)	TAs (μg/kg)	iAs (μg/kg)	Se (μg/kg)	Cd (μg/kg)	Pb (μg/kg)	MeHg [d] (μg/kg)
Rice [a]	Safety Standard [b]	NA	NA	NA	200	NA	200	200	NA
N = 40	NEC-Rice [c]	2.1 ± 0.4	14.1 ± 2.4	119.4 ± 54.4	68.0 ± 22.6	58.0 ± 13.8	24.1 ± 25.1	14.3 ± 7.4	2.3 ± 1.0
	NJS-Rice [c]	2.3 ± 0.4	13.3 ± 1.3	98.3 ± 27.0	70.8 ± 18.8	47.4 ± 16.2	28.5 ± 21.3	13.2 ± 8.8	2.3 ± 0.8
	Average	2.2 ± 0.4	13.5 ± 2.2	108.4 ± 42.3	70.0 ± 20.4	51.2 ± 15.4	25.6 ± 22.6	14.0 ± 7.2	2.3 ± 0.9
Fish [a]	Safety Standard [b]	NA	NA	NA	100	NA	100	500	500 [e]/ 100[f]
N = 60	Crucian Carp	0.5 ± 0.3	12.1 ± 6.6	50.6 ± 41.3	0.4 ± 0.7	231.0 ± 158.3	0.7 ± 0.4	14.1 ± 7.0	14.2 ± 9.5
	Yellow Croaker	0.3 ± 0.1	5.5 ± 1.8	1635.3 ± 919.9	53.8 ± 102.9	521.9 ± 324.2	5.6 ± 11.4	16.5 ± 11.1	33.1 ± 17.5
	Largehead Hairtail	0.3 ± 0.1	4.8 ± 1.1	945.9 ± 711.7	19.9 ± 24.9	517.9 ± 176.3	16.9 ± 28.6	16.8 ± 11.1	31.0 ± 24.0

N, sample size.
NA, not available.
[a] Metal(loid) concentrations of rice and fish were converted to wet weight basis assuming 14% and 71% moisture, respectively (Gong et al., 2018). Wet weight results were presented to correspond to exposure and risk assessment calculations, because dietary consumption rates are obtained on a wet weight basis.

[b] It refers to the food safety national standard: Contaminant limits in food (GB2762-2017).

[c] NEC refers to northeastern China, while NJS refers to northern Jiangsu, both of which are the production areas of the rice samples collected in this study.

[d] Data of MeHg were adopted from our previous study (Gong et al., 2018). These MeHg concentrations were later incorporated into the health risk assessment of metal(loid) exposure.

[e] This standard value is for herbivorous and omnivorous fish.

[f] This standard value is for carnivorous fish.

content in measured rice samples, similar to the values (73% − 100%) reported by Islam et al. (2017b).

Levels of TAs were relatively high in the two marine fish species (yellow croaker: 1635.3 ± 919.9 μg/kg, largehead hairtail: 945.9 ± 711.7 μg/kg), but low in the freshwater crucian carp (50.6 ± 41.3 μg/kg). Other metals showed lower concentrations in fish samples (Table 1). Fish concentrations were far below the national guideline values (GB2762-2017) for Cd (100 μg/kg) and Pb (500 μg/kg), although 10% of yellow croaker showed higher iAs levels than the national guideline (iAs: 100 μg/kg). In addition to TAs, Se and Cd were lower in crucian carp, whereas Zn and Cu were higher in carp compared to the two marine species sampled. These differences could be attributed to species-specific variations in diet, habitat, mobility and other characteristic behaviors (Gale et al., 2004; Jonathan et al., 2015; Lyu et al., 2010), and general differences in Se bioaccumulation between marine and freshwater environments (Ohlendorf, 2003).

3.2. Metal(loid) bioaccessibilities in rice and fish collected from Nanjing City

The bioaccessibilities of the metal(loid)s in fish samples were significantly higher than those in rice samples ($p < 0.05$), with the exception of Se. The metal(loid) bioaccessibilities varied widely in rice (Cu: 52.7 ± 12.1%, Zn: 26.6 ± 10.2%, TAs: 27.4 ± 6.9%, Se: 71.5 ±

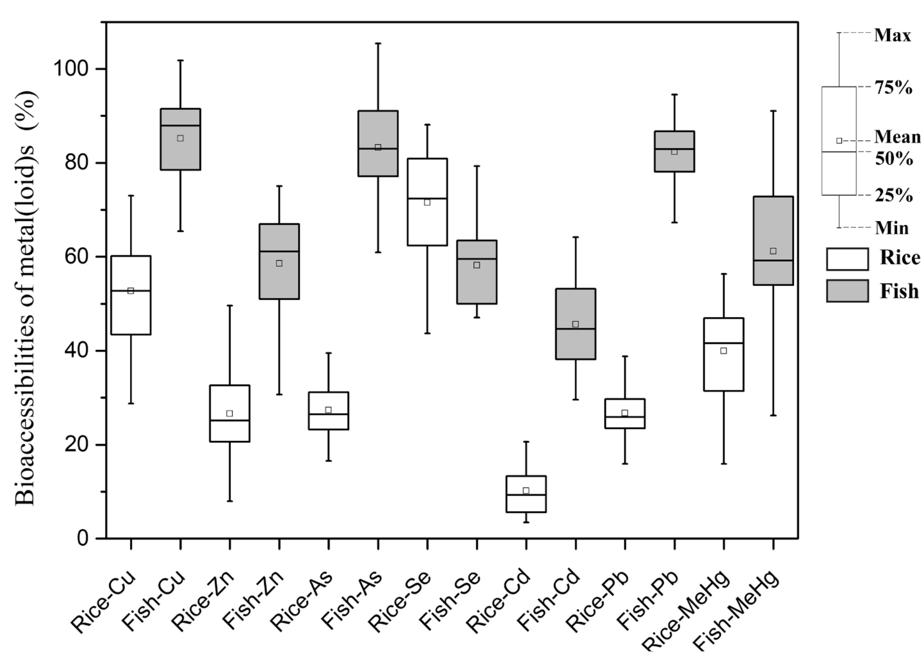

Fig. 2. Bioaccessibilities of metal(loid)s in rice and fish using the in vitro extraction model. The MeHg bioaccessibilities in rice and fish samples were adopted from Gong et al. (2018).

11.2%, Cd: 10.2 ± 5.8%, Pb: 26.7 ± 7.5%) and fish (Cu: 85.2 ± 8.8%, Zn: 58.6 ± 10.9%, TAs: 83.2 ± 10.0%, Se: 58.2 ± 8.2%, Cd: 45.6 ± 9.6%, Pb: 82.3 ± 6.8%) (Fig. 2). In the same samples, Gong et al. (2018) also reported higher MeHg bioaccessibility in fish than rice (Fig. 2).

The large differences we observed indicate that effective dietary exposure depends on both specific metal(loid) and food type (Erdemir and Gucer, 2018; Peng et al., 2017). Although ours is the first comparison of seafood vs rice bioaccessibility across multiple metal(loid)s in the same study design, prior studies using the same *in vitro* extraction method have also observed widely varying bioaccessibilities within these food types. For example, Liu et al. (2018a) demonstrated that between Cd, Cu, Pb, Zn, Cr and Ni, the mean bioaccessibilities ranged from 18.5% to 88.0% in grains from the upper Yellow River, Baiyin District, Northwest China. In 11 marine mollusk species (e.g. clams, scallops and abalones), collected in Chinese coastal waters, He and Wang (2013) observed bioaccessibilities of 42.5%, 56.5%, 48.0%, 90.7%, 80.8%, 85.9% and 88.7% for Fe, Co, Pb, As, Cu, Ni, and Se respectively.

3.3. Risk characterizations concerning metal(loid) dietary exposure

3.3.1. Carcinogenic risk of iAs

The calculated carcinogenic risk from dietary exposure to iAs was above 10^{-4} for Nanjing City (MCS-derived ILCR: P50 = 3×10^{-4} (female), P50 = 4×10^{-4} (male), Table 2) and for 9 provinces in China (ILCR: 1.4×10^{-4} to 5.9×10^{-4}, Table S7). The major dietary exposure contribution to iAs carcinogenic risk was rice intake, averaging 87.5% in Nanjing City and 85.0% – 99.8% across different provinces (Fig. 3a). The high contribution of rice intake could be mainly attributed to its high ingestion rate instead of its iAs levels. On the province-scale, iAs levels in rice and fish were both well below the national limit of 0.2 mg/kg and 0.1 mg/kg in China (Table S3 and S4). However, ingestion rates of rice (51.1–244.6 g/d) were above 2 times of those of fish (9.4–74.7 g/d). Besides, Li et al. (2011) also emphasized that rice intake was the largest contributor (about 60%) of iAs exposure for consumers at the regional or national level in China.

The carcinogenic risks from fish intake were below the 10^{-4} threshold, at 6×10^{-6} for both genders in Nanjing (P50), and 9.8×10^{-7} to 7.6×10^{-5} in the studied provinces (Table 2 and Table S7). However, carcinogenic risks from fish were not negligible for consumers with high fish consumption rates, at either the city- or province-scale. The MCS-derived P95 ILCR from fish intake was 6×10^{-5} for female and male in Nanjing, just below the acceptable level (1 0 $^{-4}$). Among the 9 provinces, the contributions of fish intake to ILCR (Fig. 3a, Table S7) were highest in the coastal provinces of Guangdong (contributing 3.9×10^{-5} ILCR, which was 15.0% of total ILCR), Hainan (7.6×10^{-5}; 13.0%) and Jiangsu (1.6×10^{-5}; 6.2%). Interestingly, these higher fish contributions to ILCR resulted from both higher ingestion rates of fish (Table S5) and higher iAs levels in fish (Table S4) than other provinces, highlighting the regional geographic aspects of risk to seafood consumers (Gong et al., 2018; Mahaffey et al., 2009).

The finding of high carcinogenic risk from iAs confirms that major concern for health effects of iAs dietary exposure extends beyond geogenic arsenic hotspots such as regions of India and Bangladesh (Biswas et al., 2020; Halder et al., 2014; Rahman and Hasegawa, 2011) to regions throughout China (Fu et al., 2015; Jiang et al., 2015; Lei et al., 2015; Li et al., 2011; Li et al., 2015a; Lin et al., 2015). This supports continued and greater emphasis on national and international efforts to reduce iAs exposure from rice in China and elsewhere, employing agronomy, biotechnology, and public health education methods (e.g., Biswas et al., 2020; Chen et al., 2017; Linquist et al., 2015; Xu et al., 2008)

Table 2
Bioaccessibility-corrected hazard index (HI, unitless), and increased lifetime cancer risk (ILCR, unitless) from rice and fish consumption for residents in Nanjing City.

Food items	Percentile	Female		Male	
		HI[a]	ILCR[b]	HI[a]	ILCR[b]
Rice	P50	0.18	3×10^{-4}	0.19	3×10^{-4}
	P95	0.43	7×10^{-4}	0.43	7×10^{-4}
Fish	P50	0.10	6×10^{-6}	0.12	6×10^{-6}
	P95	0.42	6×10^{-5}	0.49	6×10^{-5}
Total	P50	0.28	3×10^{-4}	0.31	4×10^{-4}
	P95	0.85	7×10^{-4}	0.92	8×10^{-4}

[a] When HI < 1, it is assumed that the exposed population does not face a hazard of non-carcinogenic health effects (USEPA, 2001).

[b] When ILCR is within the acceptable range (10^{-6} to 10^{-4}), there is no carcinogenic health risk to the exposed population. When ILCR is over 10^{-4}, it is assumed that the exposed population has a certain carcinogenic risk (USEPA, 2001).

3.3.2. Non-carcinogenic hazard of metal(loid)s

Relative contributions of rice and fish consumption to HQ (for individual metals) were compared on a province-scale in China using all published available data (Table S3-S5). Given that concentration data of all examined metals were only available for Nanjing City (this study) and Jiangsu and Guangdong provinces (from the literature review, Table S3 and S4), the multi-metal HI and the contributions of rice and fish consumption thereof were assessed in this city and these two provinces.

For residents in Nanjing City, the MCS-derived P50 HI for overall dietary sources was 0.28 for female and 0.31 for male, while the P95 HI was 0.85 for female and 0.92 for male. More specifically, the MCS-derived P50 and P95 HI for rice consumption for female (male) were 0.18 (0.19) and 0.43 (0.43), while the P50 and P95 HI for fish consumption were 0.10 (0.12) and 0.42 (0.49) (Table 2). On the province-scale, the multi-metal HI (combining Cu, Zn, Cd, Pb, and MeHg) due to rice and fish consumption was 0.50 for Guangdong (0.21 for rice, and 0.29 for fish) and 0.20 for Jiangsu province (0.11 for rice and 0.09 for fish) (Table S7). All HI results were below 1, in consideration of metal (loid) bioaccessibilities, indicating the absence of non-carcinogenic hazard in these two provinces, regardless of exposure scenario.

In contrast to carcinogenic risk, which was almost entirely due to rice consumption (Fig. 3a), both rice and fish consumption contributed substantially to HI for Nanjing City (Fig. 4), and especially for Guangdong (42.6% for rice vs 57.4% for fish) and Jiangsu provinces (54.6% vs 45.4%) (Fig. 5).

The general descending order of single metal(loid) contribution to HI due to rice intake in Nanjing City was: Cu > Zn > MeHg > Se > Cd > Pb, while the order due to fish intake was: MeHg ≈ Zn > Cu > Se > Pb > Cd (Table S8). The descending order of single metal contribution to HI from rice intake in both Jiangsu and Guangdong provinces was the same as that in Nanjing (Cu > Zn > MeHg > Cd > Pb). However, the two provinces had slightly different descending orders of single metal exposure from eating fish, i.e., MeHg (78.9%) > Zn (11.2%) > Cu (6.7%) > Cd (2.8%) > Pb (0.5%) for Jiangsu; MeHg (90.5%) > Zn (4.3%) > Cu (2.1%) ≈ Pb (2.1%) > Cd (1.1%) for Guangdong. These findings were generally in line with the results of Wang et al. (2020b), who reported that the non-carcinogenic HQ from fish consumption were in the sequence of Hg > Pb > Cd in the rice-fish-farming system of China. In our study, the high contribution of fish MeHg to HI in Guangdong province attributes to both relatively high fish ingestion rates (Table S5) and elevated MeHg concentrations in fish (Table S4; data from Li et al., 2012) reported from this province. Overall, the predominant metal non-cancer exposure hazards induced by rice and fish consumption at province-scale were Cu (more than 60.7%) and MeHg (more than 78.9%), respectively (Fig. 5).

The relative contributions from rice and fish intake to HQ varied, depending on the metal(loid) and province. As depicted in Fig. 3b, rice

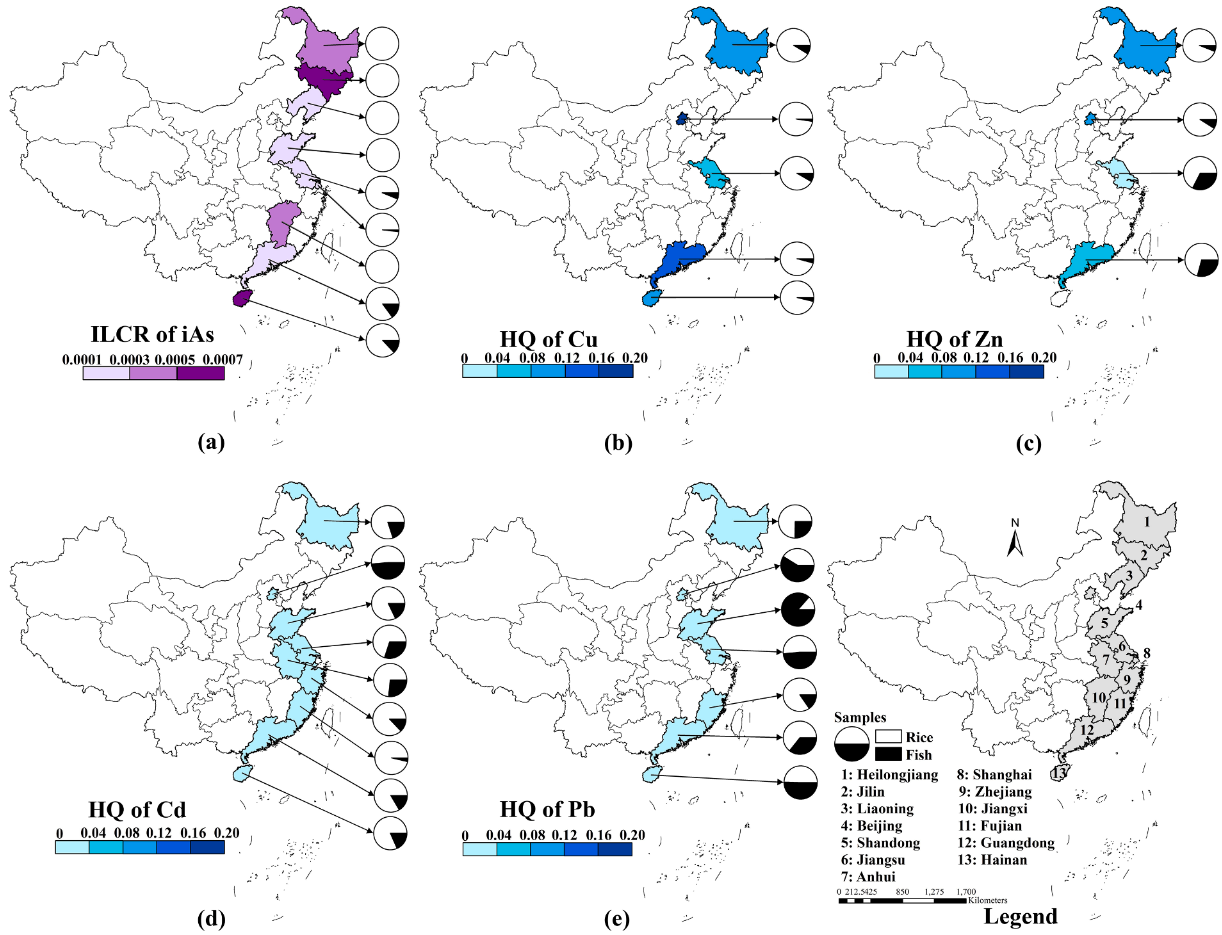

Fig. 3. Distribution of ILCR of iAs and bioaccessibility-corrected HQ of different metals for provinces in China.

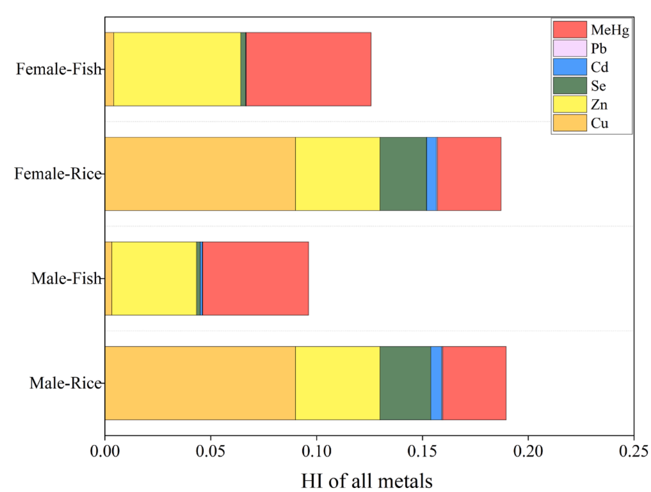

Fig. 4. Comparison of bioaccessibility-corrected HI for Nanjing City (based on P50 HQ of each metal).

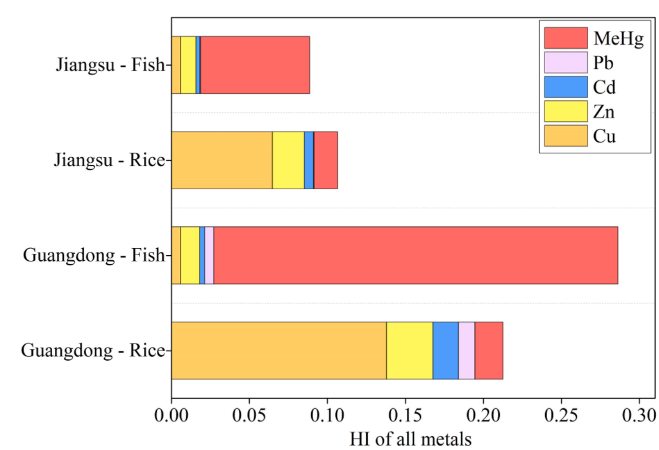

Fig. 5. Comparison of bioaccessibility-corrected HI for Guangdong and Jiangsu provinces.

intake accounted for 91.3% – 97.7% of Cu exposure while fish intake had a minor contribution. Yu et al. (2016) also reported that the contribution (0.4% – 0.6%) of fish intake to Cu dietary exposure was negligible in Jiangxi province, in comparison with the other four food items examined (vegetables, rice, meat and milk). Unlike Cu, the contribution of fish intake was found to be generally high in the coastal provinces for Zn exposure (i.e., 29.2% for Guangdong province and 32.5% for Jiangsu province, Fig. 3c). Although the HQ values of Cd and Pb were generally low among the selected provinces, the contribution ratios (rice versus fish) varied among provinces (Fig. 3d - e), due to variations among provinces in measured Cd and Pb levels in rice and fish (Tables S3 and S4), as well as dietary consumption patterns (Table S5). Our results suggest that rice and fish are of comparable importance for non-carcinogenic hazard from multiple metals (HI), while their relative contributions to the non-carcinogenic hazard from individual metals (HQ) vary among metal type and locality.

Rice provides an important source of carbohydrate, protein, fat and vitamin B complexes (Fresco, 2005), while fish is of high nutritional quality and rich in specific micronutrients, such as n-3 long-chain polyunsaturated fatty acid, selenium and essential amino acids (Li et al., 2010). Fish consumption has been shown to reduce diseases such as cardiovascular diseases, psychological disorders, and rheumatoid arthritis (Swanson et al., 2012), suggesting that it is biased to assess only the harmful effects of eating fish without considering its net effect on health (Li et al., 2010). However, to date, it seems that there are no appropriate risk assessment models considering nutrients and metal (loid)s in foods simultaneously. Future epidemiologic and clinical studies are needed to better compare the combined beneficial and adverse effects of multi-metal(loid) exposure induced by rice versus fish consumption.

3.4. Sensitivity analysis and study limitations

We performed sensitivity analysis to rank variables according to their relative contributions to health risks, further revealing which variables are more important in reducing risks from dietary exposure to metal(loid)s. For carcinogenic risk, rice ingestion rate and iAs concentrations in rice were the two most sensitive parameters, affecting ILCR more than body weight, fish ingestion rate and iAs concentrations in fish (Table S9). These findings were partly consistent with Li et al. (2011), who observed that ingestion rates of rice and aquatic products, together with iAs concentration in rice, were the most sensitive variables. For non-carcinogenic HI, the three most sensitive parameters were in the following order: ingestion rate of fish > ingestion rate of rice > Cu levels in rice (Table S9). Though bioaccessibilities showed significant variability among different food matrices and metal(loid) types (Fig. 2), sensitivity analysis showed that they generally had little impact on HI (Table S9). These results further suggest that rice ingestion could be the determinant for the carcinogenic risk of iAs, while both fish and rice consumption could contribute to the HI of multiple metal(loid)s. That said, rice rather than fish is the most sensitive food item.

The uncertainty and sensitivity analysis in this study were based on data collected from Nanjing City, including body weight, ingestion rate, and metal(loid) concentration and bioaccessibility (Table S6), given that only the statistical distributions from Nanjing data are available now. The 29 published literature sources that met our inclusion criteria were not sufficient to generate statistical parameter distributions for most parameters among other provinces. Therefore, point estimation was conducted for the risk assessment on the province-scale based on limited data. Cooking may also affect metal(loid) concentrations in foods (Perello et al., 2008; Zhuang et al., 2016), but because of the limited data on concentrations in foods, we did not distinguish between raw and cooked food concentrations. In future studies, more accurate and consistent collection and measurement of ingestion rate and metal(loid) concentration and better definition of their probability distributions across the country, would improve the accuracy of the national risk assessment.

There are additional limitations on this study approach and available data. Province-scale consumption rates were most recently available for most provinces in 2012 and 2013, and rates may have changed since that time. We were unable to measure the bioaccessibility data for iAs due to the precipitation of salts used for the digestive fluids. Therefore we conducted the MCS to estimate HQs of iAs exposure separately, without considering the bioaccessibility of iAs (Text S2). In addition, protein, fat, starch, phytic acid, and water content may vary considerably in different food matrices, resulting in significant differences in the interaction of metals with food components. For example, Hg, and Pb have been reported to bind dietary fiber (Ou et al., 1999). Cadmium has been shown to form complexes with protein, amino acid, and dietary fibers (Carballo et al., 2013). Methylmercury is attached to the thiol group of the cysteine residues in fish tissue (Li et al., 2012). Therefore, when using in vitro model to obtain the bioaccessibility data, we need to carefully consider the food matrix. As mentioned above, the study focused on risks from metal(loid) exposure and did not compare the nutritional benefits of fish (e.g., omega-3 fatty acids) versus those of rice. That said, the general risk assessment approach of the study is well established and has been widely employed for metal(loid)s and other compounds in fish, rice, and other foodstuffs (e.g., Gong et al., 2018; Jia et al., 2018; Jiang et al., 2015; Peng et al., 2016; Rahmani et al., 2018; Shaheen et al., 2016; USEPA, 1989; 2001; Wang et al., 2020b; Xia et al., 2010; Zeng et al., 2015; Zheng et al., 2007).

4. Conclusions

By calculating the carcinogenic risk and non-carcinogenic hazard of multi-metal(loid) associated with rice and fish consumption, we demonstrate that rice is most important for the carcinogenic risk of iAs exposure, while rice and fish consumption are both important for non-carcinogenic HI associated with multiple metal(loid)s. Our results also indicate that the risk from dietary exposure to metal(loid)s is food-specific. For instance, rice intake is the largest contributor to Cu exposure risk, while fish intake mainly contributes to MeHg exposure risk. Finally, our results incorporating metal bioaccessibilities into risk assessment do not indicate non-carcinogenic exposure hazard (HI < 1), but exposure to iAs poses elevated carcinogenic risks in China.

Considering that the consumption of rice and fish brings nutrients to the human body to different extents, the long-term goal should be to reduce their metal(loid) concentrations rather than to stop eating them directly. In addition to continuing efforts to reduce metal(loid) contamination in foods, we can also focus on diversifying the diets including food items and origins, and educating the public on preparation methods, to reduce the health risks while maintaining nutrition intake.

CRediT authorship contribution statement

Wenqin Wang: Formal analysis, Visualization, Writing - original draft. **Yu Gong:** Investigation, Project administration, Writing - original draft, Writing - review & editing. **Ben K. Greenfield:** Writing - original draft, Writing - review & editing. **Luís M. Nunes:** Formal analysis, Writing - original draft. **Qianqi Yang:** Formal analysis, Investigation. **Pei Lei:** Writing - original draft, Writing - review & editing. **Wenbo Bu:** Writing - original draft. **Bin Wang:** Writing - original draft. **Xiaomiao Zhao:** Writing - original draft. **Lei Huang:** Writing - original draft, Writing - review & editing, Funding acquisition. **Huan Zhong:** Writing - original draft, Writing - review & editing, Funding acquisition.

Declaration of Competing Interest

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

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2021.106682.

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