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Dietary exposure to arsenic and human health risks in western Tibet

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HIGHLIGHTS

- A survey of As in foods in western Tibet discovered high dietary exposure.
- Highland barley contained elevated As and high proportions (83%) of inorganic As.
- A typical barley-rich Tibetan diet increased cancer risk to 5.4 in 10,000.

GRAPHICAL ABSTRACT

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ABSTRACT

The health effects of drinking water exposure to inorganic arsenic are well known but are less well defined for dietary exposure. The rising concerns of arsenic risks from diet motivated this study of arsenic concentrations in highland barley, vegetables, meat, and dairy products to evaluate arsenic exposure source and to assess health risks among rural residents of Ngari area, western Tibet. Total arsenic and arsenic speciation were measured by inductively coupled plasma mass spectrometry (ICP-MS) and high-performance liquid chromatography combined with ICP-MS (HPLC-ICP-MS) respectively. Average total arsenic concentrations of 0.18 ± 0.21 ($n = 45$, median: 0.07 $mg \cdot kg^{-1}$), 0.40 ± 0.57 ($n = 17$, median: 0.15 $mg \cdot kg^{-1}$), 0.21 ± 0.16 ($n = 12$, median: 0.17 $mg \cdot kg^{-1}$), and 0.18 ± 0.08 ($n = 11$, median: 0.22 $mg \cdot kg^{-1}$) were observed in highland barley, vegetables, meat, and dairy products, respectively. Inorganic arsenic was determined to be the main species of arsenic in highland barley, accounting for about 64.4 to 99.3% (average 83.3%) of total arsenic. Nearly half (44.4%) of the local residents had ingested $>3.0 \times 10^{-4}$ $mg \cdot kg^{-1} \cdot d^{-1}$ daily dose of arsenic from highland barley alone, above the maximum oral reference dose recommended by the United States Environmental Protection Agency (USEPA). The inorganic arsenic daily intake from highland barley was 3.6×10^{-4} $mg \cdot kg^{-1} \cdot d^{-1}$. Dietary exposure to inorganic arsenic

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alone increased the cancer risk probability to 5.4 in 10,000, assuming that the inorganic arsenic in highland barley has the same carcinogenic effects as that in water.

1. Introduction

Inorganic arsenic (iAs), one of the toxic metalloids, is ranked as a class one human carcinogen. Due to its toxicity, the World Health Organization (WHO) has a guideline value for As in drinking water of 10 $\mu g \cdot L^{-1}$ (WHO, 2004). >200 million people in over 70 countries have been estimated to expose to drinking water As beyond the WHO's provisional guideline value of 10 $\mu g \cdot L^{-1}$ (Naujokas et al., 2013). Chronic iAs exposure via drinking water can result in skin lesions (Ahsan et al., 2000), respiratory system diseases (Calderon et al., 2001; Milton and Rahman, 2002), cardiovascular disease (Lee et al., 2002; Rahman et al., 2015), nervous effects (Tsai et al., 2003), and carcinogenic disease, such as skin cancer (Luster and Simeonova, 2004), lung cancer (Ferreccio et al., 2000; Smith et al., 1998) and bladder cancer (Morales et al., 2000; Steinmaus et al., 2003). Health effects of chronic exposure to iAs through drinking water has been observed in America (Welch et al., 2000), Argentina (Tapia et al., 2019), Bangladesh (Horneman et al., 2004), Chile (Smith et al., 1998), China (He and Charlet, 2013). Although iAs is classified as a group I carcinogen by the International Agency for Research on Cancer, iAs is not considered to be directly genotoxic, and potential mechanisms of its toxicity include induction of oxidative stress and inflammation, inhibition of DNA repair, and epigenetic dysregulation (Chikara et al., 2009; Clarisse and Mats, 2015; Demanelis et al., 2019; Farzan et al., 2017; Singh et al., 2015).

Arsenic exposure via the food especially cereals cannot be ignored but has not been as widely investigated as the exposure via water (Kile et al., 2007). Especially relevant is As speciation assessment because numerous studies have demonstrated that the toxicity of inorganic species arsenite (AsIII) and arsenate (AsV) are higher than organic species monomethylarsonic acid (MMA) and dimethylarsonic acid (DMA) (Egbenda et al., 2015; Van Herreweghe et al., 2003). Rice has been widely regarded as a main pathway to iAs exposure (Batista et al., 2011; Rahman et al., 2009), with iAs and DMA as the main species of As in rice (Batista et al., 2011; Williams et al., 2006; Ma et al., 2016). Another cereal, wheat contained >20% of iAs with total As (tAs) concentrations ranging from below detection limit to 0.238 $mg \cdot kg^{-1}$ as revealed by several studies (D'Amato et al., 2011; Tong et al., 2014; Zhao et al., 2010). Zhao et al. (2010) measured As speciation of 5 wheat cultivars with below detection limit to 0.024 $mg \cdot kg^{-1}$ tAs from France, and found only iAs in the extracts, of which AsIII was the main species (64–90%). Williams et al. (2007) observed variable but sometimes high As concentration (0.01 to 0.54 $mg \cdot kg^{-1}$) in 35 barley samples of England, especially in As-contaminated areas.

Likewise, arsenic exposure from other food items are also gaining attention. Several studies have investigated the accumulation of As in vegetables in south-eastern Sweden (Uddh-Soderberg et al., 2015), Pakistan (Rehman et al., 2016), northern Chile (Munoz et al., 2001), Bangladesh (Das et al., 2004) and southern China (Ma et al., 2017). High As has been found in vegetable in As-contaminated area. Halder et al. (2013) found tAs concentration ranged from 0.11 to 0.35 $mg \cdot kg^{-1}$ in 26 leafy vegetable samples in rural Bengal. Inorganic As is almost the only speciation in chard, radish, lettuce and mung beans (Halder et al., 2013; Juhasz et al., 2008). For a vegetarian diet, these vegetables may contribute considerably to the intake of As. In meat, tAs was lower than vegetables with the average concentration of 0.157 ± 0.0119 $mg \cdot kg^{-1}$; the only speciation detected was organic As (Polatajko and Szpunar, 2004). There is also the issue of bioavailability (sorbed by human body in vivo) and bioaccessibiliity (solubilized by gastric fluids in vitro) of iAs from rice and foods because only a few studies tackled this problem (He and Zheng, 2010; Pizarro et al., 2016; Signes-Pastor et al., 2012).

Ngari, located in the drainage basin of Singe Tsangpo (upstream of the Indus River) where high As water fed by geothermal water has been reported in a previous study (Li et al., 2013), is chosen because we are concerned about As risks associated with dietary exposure in this area given its high geogenic As background levels. Further, prior knowledge of As concentration and speciation of the Tibetan staple food highland barley (*Hordeum vulgare* L. *var. nudum HK. f.*) is limited, which is a traditional food and has always been a mainstay in the Tibetan diet (Newman and Newman, 2006; Zhu et al., 2015). This study therefore sought to determine the extent of As exposure via foods and to assess the health risks associated with a typical Tibetan diet. Such understanding As risks from foods can help guide policy regarding food safety.

2. Materials and methods

2.1. Food sample collection and preparation

Food samples were collected from 11 Tibetan villages in Ngari district in the Singe Tsangpo drainage basin with an average altitude of ~4350 m (upstream of the Indus River). The villages are all along the Singe Tsangpo and its tributaries, and are all located near roads, with a traditional nomadic life style. Food samples were collected from the homes of villagers or purchased from local markets, which included 45 highland barley and 4 rice samples of cereals, 6 yak (*Bos grunniens*) and 6 mutton samples of meat, 4 Chinese cabbage, 3 white radish, 4 potato, 2 bok choy and 4 onion samples of vegetables, and 11 dairy samples (Table S1). The highland barley, meat and dairy (as milk residual evaporates after the butter is churned from the milk) samples were all from the homes of local residents. All of the highland barley samples were produced in Ngari or other places of Tibet while the output of highland barley in Tibet was sufficient to meet the consumption needs of the Tibetan people (Feng et al., 2008) (Table S1). The meat and dairy samples were all produced in Ngari. Vegetables from local markets were leafy (Chinese cabbage and bok choy) and non-leafy (white radish, potato and onion) vegetables according to the common edible part. The meats and dairy were collected in the dried form to facilitate the transportation to laboratory. Vegetables were air dried under the sun in the field.

The food samples were cleaned and processed in the laboratory before analysis. The edible portions of vegetables were separated from the visible soil by a soft plastic brush. Potatoes and white radishes were peeled and cut into slices. The food samples were washed several times with deionized water, followed by freeze-drying. Then, dried samples were grounded by a food mill until they passed through a 74 μm mesh, and were stored in the dry and clean polyethylene bags at room temperature before analysis.

All food samples were weighed when wet and after drying to obtain water content.

2.2. Standards and reagents

Arsenic standards of AsIII, AsV, MMA and DMA ($NaAsO_2$, $Na_2HAsO_4 \cdot 7H_2O$, CH_4AsNaO_3 and $C_2H_6AsNaO_2 \cdot 3H_2O$) were purchased from the National Institute of Metrology of China. Stock solutions were prepared by dissolving the chemicals in ultrapure water (18.2 MΩ cm, Direct-Q 3, Millipore SAS, France) and stored in the dark at 4 °C. Nitric acid (ultrapure grade), hydrochloric acid (ultrapure grade), ammonium hydroxide (ultrapure grade), hydrogen peroxide (guaranteed reagent grade) and malonic acid (ultrapure grade) were obtained from China National Pharmaceutical Industry Corporation (CNPIC). During the experiment, nitric acid was purified twice through distillation.

2.3. Total As concentration analysis

To determine tAs concentrations, the food samples were digested by a closed pressured technique following the procedure below (Zhang et al., 2017). All concentrations reported are of dry weight. For each sample, 0.05 ($\pm$0.01) g was weighed accurately and put into dry and clean Teflon digestion vessels. Three milliliters of twice-distilled HNO_3 were added into the vessels to be closed tightly. Then, the samples were put in an oven at 140 °C for 8 h. After cooling, the vessels were opened and 2 ml of concentrated H_2O_2 (30%) were added. Finally, digested solutions were brought to near dryness at 100 °C then re-dissolved with 2% HNO_3 for analysis. Dissolved As concentrations were measured using Inductively Coupled Plasma Mass Spectrometry (ICP-MS, NexION 300×, PerkinElmer, USA). For each digestion batch, two samples of certified reference material (CRM) of rice (GBW 100348 for tAs concentration $= 0.23 \pm 0.03$ mg·kg^{-1}) from the National Research Center for Certified Reference Materials (NRCCRM, Beijing, China) were also digested and analyzed and about 10% of samples were analyzed in duplicate or triplicate for quality control purposes. The results were comparable with reported value of As in CRM within 89.9% to 101.1%.

2.4. Extraction procedure and As speciation analysis of highland barley

From the sampling sites, 24 random samples of highland barley were chosen to analyze As speciation. The extraction method mostly followed Foster et al. (2007). In this study, samples were extracted by a heat-shaking method instead of the microwave-assisted extraction, while the buffer was a malonic acid solution instead of a phosphate solution. For each sample, ~1.0 g homogenized powder was weighed precisely into a 50 ml polypropylene centrifuge tube of and then 10 ml 2% v/v HNO_3 was added. The sample was then heated and shaken in a water bath at 90 °C for 1 h at 200 rpm. After cooling to room temperature, the sample was centrifuged at 7000 rpm for 15 min. Then, 1 ml of the supernatant was transferred to a polyethylene centrifuge tube and centrifuged again at 10,000 rpm for 15 min before analysis. For each batch of samples, a blank and a CRM of GBW 100348 were simultaneously extracted and selected samples were analyzed in duplicate or triplicate for quality control purposes. Arsenic speciation in the extracts was analyzed by a high-performance liquid chromatography (HPLC) coupled with an Agilent 7700× ICP-MS (Agilent Corp, USA). HPLC separation was performed under anion-exchange conditions at room temperature with a PRP-X100 (250 mm × 4.1 mm × 10 μm) column (Hamilton Company, Reno, Nevada, USA) and a mobile phase of 5 mM malonic acid at pH 5.6 adjusted with aqueous ammonia. The flow rate was 1.2 ml·min^{-1} and injection volume was 20 μl. A typical chromatogram was showed in Fig. S1. AsIII, AsV and DMA were determined in GBW 100348 with the average values of 0.14 ± 0.01, 0.04 ± 0.00 and 0.04 ± 0.01 mg·kg^{-1} and the recovery rate was $101 \pm 7\%$ ($n = 4$). The sum of AsIII and AsV is reported as iAs concentration (Table 1).

2.5. Dietary As exposure estimation

The estimated daily intake (EDI, mg·kg^{-1}·d^{-1}) was used to evaluate the total and inorganic As exposure (Ma et al., 2016; Munoz et al., 2017. The EDI from food was calculated according to the following equation:

$$EDI = C_w \times M/1000/BW \tag{1}$$

where C_w is the tAs or iAs concentration for highland barley, meat, vegetables and dairy (mg·kg^{-1}), M is the daily intake of food based on dried weight (g) and BW is the body weight (kg). Dietary consumption pattern of adults in Ngari was based on Liu et al. (2004). The daily intake of highland barley is 222.6 g in dry weight. Daily intake of meat, dairy, vegetable was 308.1, 422.6, and 112.3 g of wet weight (Liu et al., 2004). Based on the measured moisture contents of dairy (87%), the daily intake of dairy in dry weight were estimated to be 42.6 g. For with 60% moisture content, the average daily intake of mutton and yak meat in dry weight was estimated to be 123.2 g, and the average daily intake of vegetables for leafy vegetable, onion, potato and white radish was estimated to be 16.57 g based on their respective moisture content of 90%, 90%,76% and 85%. According to the National Physical Fitness Monitoring Report for Tibet Autonomous Region, the average BW of Tibetan adults (>16 years old) is 68.7 kg.

2.6. Health risk assessment

Hazard quotient (HQ) for risks of non-carcinogenic diseases including highland barley based on tAs was estimated according to the following equation:

$$HQ = EDI_{tAs}/RfD \tag{2}$$

where RfD is the oral reference dose of 3.0×10^{-4} mg·kg^{-1}·d^{-1} as recommended by United States Environmental Protection Agency (USEPA) (USEPA, 2013).

Cancer risk (R) was assessed based on iAs according to the following equation:

$$R = 1 - \exp.(-SF \times EDI_{iAs}) \tag{3}$$

where SF is the slope factor of 1.5 kg·day·mg^{-1} for adults as recommended by USEPA (USEPA, 2013).

3. Results and discussion

3.1. Arsenic in meat, vegetables and dairy

Average tAs concentrations of 0.40 ± 0.57 ($n = 17$, median: 0.15 mg·kg^{-1}), 0.21 ± 0.16 ($n = 12$, median: 0.17 mg·kg^{-1}), and 0.18 ± 0.08 ($n = 11$, median: 0.22 mg·kg^{-1}) were observed in vegetables, meat, and dairy, respectively.

Total As concentrations varied in different vegetables. Total As in leafy vegetables was 0.72 ± 0.73 ($n = 6$, median 0.49 mg·kg^{-1}) higher than other non-leafy vegetables such as potato and onion that had only 0.06 ± 0.03 ($n = 8$, median: 0.06 mg·kg^{-1}) of As (Fig. 1). Although sample size is small, a non-leafy vegetable, white radish contained also high As, at 0.39 ± 0.57 ($n = 3$, median: 0.70 mg·kg^{-1}). Leafy vegetables like Chinese cabbage and bok choy have been shown to be more likely to accumulate As (Halder et al., 2013). High As concentration has been found in spinach, arum leaf, potatoes, carrot, radish, garlic in areas with high As groundwater or soil (Das et al., 2004; Munoz et al., 2001; Rahman et al., 2009), influenced by irrigation water As and soil properties (Amaral et al., 2013; Das et al., 2004). Further studies are needed to investigate irrigation water - soil - plant linkages in the study area and are beyond the scope of this study.

As concentrations in the meat samples (dried yak and mutton) were also high compared to meat from elsewhere. Average As concentration in meat was only 0.064 mg·kg^{-1} ($n = 39$) based on data from 11 cities of China, taken to be representative of Chinese cities (Zhou et al., 2016), or 3 times less than the average concentration in Ngari area. Arsenic concentration in chickens can be high with an average value of 0.157 mg·kg^{-1} due to organoarsenic drugs used for poultry (Hu et al., 2017; Silbergeld and Nachman, 2008). However, to the best of our

Table 1
Percentages of inorganic As of meat and vegetables in other areas.

Food types	Sample site	tAs (mg·kg^{-1})	%iAs	Reference
Meat				
Chicken and chicken products		<0.0017–0.16	Range of concentration: <0.0004–0.04 mg·kg^{-1}	Lynch et al. (2014)
Meat (excluding chicken)		<0.005–0.075		Lynch et al. (2014)
Cooked chicken meat	U.S.	GM[d]: 0.003	GM: 0.0018 mg·kg^{-1}	Nachman et al. (2013)
Chicken muscle	Guangzhou, China	GM: 0.0271	1–66	Hu et al. (2017)
Chicken giblet	Guangzhou, China	GM: 0.0417	1–66	Hu et al. (2017)
Beef[a]	Hongkong, China	GM: 0.022	50–56	Wong et al. (2013)
Ham[b]	Hongkong, China	GM: 0.010	8–12	Wong et al. (2013)
Chicken meat[a]	Hongkong, China	GM: 0.006	0–10	Wong et al. (2013)
Vegetables				
Vegetables	Bangladesh	0.02–2.33	96	M. Smith et al. (2006)
Bottle gourds	Bangladesh	0.32–0.47	100	Williams et al. (2006)
Green banana	Bangladesh	0.05–0.50	100	Williams et al. (2006)
Arum stolon	Bangladesh	0.05–1.93	100	Williams et al. (2006)
Arum tuber	Bangladesh	0.09–0.31	100	Williams et al. (2006)
Radish	West Bengal		61	Signes-Pastor et al. (2008)
Brinjal	West Bengal		100	Signes-Pastor et al. (2008)
Potato	West Bengal		58	Signes-Pastor et al. (2008)
Vegetables	Pakistan	0.03–1.4		Rehman et al. (2016)
Vegetables[c]	Northern Chile	0.008–0.604	28–114	Munoz et al. (2001)
Leafy vegetables	Southern China		>97	Ma et al. (2017)
Vegetables and legumes		<0.0014–19.00	Range of concentration: <0.0008–0.61 mg·kg^{-1}	Lynch et al. (2014)
Vegetables and their products[c]	Hongkong, China	n.d. - 0.14	68	Wong et al. (2013)
Dairy				
Milk[c]		0.0018–0.0079	Range of concentration: <0.00005–0.00094 mg·kg^{-1}	Lynch et al. (2014)
Dairy products	Hongkong, China	n.d. - 0.010	no iAs	Wong et al. (2013)

[a] Stir-fried.
[b] Pan-fried.
[c] Wet weight.
[d] GM was the abbreviation of geometric mean.

knowledge, organoarsenic drugs were not fed to the local livestock in Ngari. Therefore, the high As in the local meat might be related to high As in local environment (Li et al., 2013).

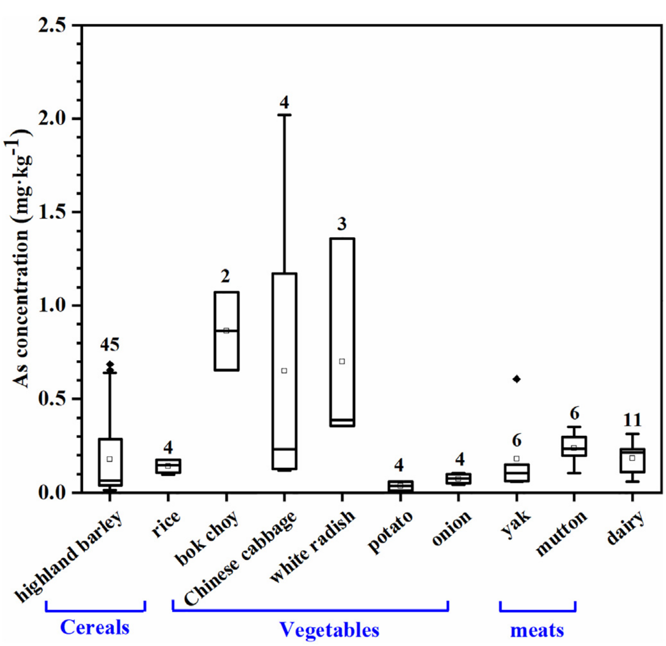

Fig. 1. Boxplot of total As concentrations in the food samples for Ngari area, western Tibet. The box represents the data between the 25th and 75th percentiles. The horizontal line and square inside the box indicate the median and mean value, respectively. Error bars represent the 5th and 95th percentiles. The rhombus represents outliers >1.5 times of 75th percentile. The number on each bar is the number of samples.

Arsenic concentrations in milk residual evaporates were also high compared to elsewhere (Table 1). The average As milk from dairy farms of Córdoba province, Chile with low-As shallow well water was significantly ($p = .001$) lower than that of farms with higher-As deep well water (Perez-Carrera et al., 2009). Rosas et al. (1999) also found As concentrations of milk (<0.0009–0.027 mg·kg^{-1}) and groundwater (7–740 μg·L^{-1}) in Comarca Lagunera, Mexico showed a good positive correlation with the coefficients of 0.507, indicating that water was a source of As to milk. Therefore, elevated As concentration in dairy from western Tibet may be attributed to the high As in natural water as drinking water for local livestock, with forage grass an additional possible source of dietary As for livestock (Rosas et al., 1999), though the bioaccessible As in forage grass was extreme low (Hwang et al., 1997). Besides, As is preferentially linked to casein (mainly due to presence of thiol groups) after the elimination of water during evaporation, causing the increased As concentration in cheese or milk residue (Vahter and Concha, 2001).

Because we did not measure As speciation in meat (beef and mutton), dairy products and vegetables, a literature review is conducted to illustrate the proportion of iAs in such food items (Table 1). Arsenic in vegetables appears to be mostly iAs (Table 1). In meat, iAs accounted for a variable fraction of tAs (Table 1), although most studies evaluated chicken. For beef, about half of As is iAs (Wong et al., 2013). In dairy, % iAs appears to be very low, with iAs below detection limit in some cases (Table 1; Wong et al., 2013). However, %iAs of vegetable is high in certain regions of the world, ranging from 28 to 114% (Table 1), with all As found to be iAs in some vegetables (Williams et al., 2006; Signes-Pastor et al., 2008). In summary, arsenic is likely to be of inorganic species in vegetables whereas meat is likely to contain more forms of organic As, with substantial iAs as well. Not knowing the speciation is a clear a challenge thus the cancer risk assessment is restricted to barley alone (see next section).

3.2. Total As and As speciation in highland barley

An average As concentration of 0.18 ± 0.20 $mg \cdot kg^{-1}$ (0.01 to 0.69 $mg \cdot kg^{-1}$, median 0.07 $mg \cdot kg^{-1}$) was found for a total of 49 cereals (Fig. 1). As concentration in the 4 rice samples that are transported from other areas of China to Tibet ranged from 0.10 to 0.18 $mg \cdot kg^{-1}$ with a mean value of 0.14 ± 0.04 $mg \cdot kg^{-1}$. In the following, results of 45 highland barley samples are reported in detail.

Average As concentration in highland barley is 0.18 ± 0.21 $mg \cdot kg^{-1}$ ($n = 45$, ranging from 0.01 to 0.69 with a median of 0.07 $mg \cdot kg^{-1}$). In contrast, barley grains from Scotland and England showed much lower average concentrations (0.04 and 0.03 $mg \cdot kg^{-1}$) (Williams et al., 2007) than the Tibetan barley did. Furthermore, arsenic concentrations in barley and wheat grain were <0.55 $mg \cdot kg^{-1}$ even when they were grown in soils with 200 $mg \cdot kg^{-1}$ As, but rice had As level over 0.60 $mg \cdot kg^{-1}$ with a much lower soil As concentration of 10 $mg \cdot kg^{-1}$ (Williams et al., 2007). In Tibet, average As concentration in soils sampled from Singe Tsangpo and Yarlung Tsangpo was 38 $mg \cdot kg^{-1}$, ranging from 6 to 173 $mg \cdot kg^{-1}$ (Li et al., 2013). Of the 45 Tibetan barley samples analyzed, 13 samples or 28.9% exceeded the Chinese maximum contaminant level of 0.20 $mg \cdot kg^{-1}$ for rice (Table S1, red color). Again, why highland barley in Tibet contains elevated levels of As warrants further investigations, although it is likely to depend on available As concentration of soil and irrigated water As (Takahashi et al., 2004; Tong et al., 2014). Unlike rice, highland barley was previously believed to be unable to accumulate large amounts of As with the low effective bioavailability of AsIII in the aerobic environment (Su et al., 2009; Takahashi et al., 2004). Williams et al. (2007) found that As concentration in highland barley was below 0.54 $mg \cdot kg^{-1}$ even when As concentration in soil was above 200 $mg \cdot kg^{-1}$.

Table 2
The concentrations and percentages of different As species in highland barley samples ($n = 24$).

	As species concentration ($mg \cdot kg^{-1}$)			As species percentage (%)		
	Mean ± SD	Median	Range	Mean ± SD	Median	Range
tAs	0.15 ± 0.16	0.02	0.02–0.61			
DMA	0.03 ± 0.03	0.01	0.002–0.12	21.8 ± 15.2	20.6	0.7–55.1
iAs	0.10 ± 0.10	0.06	0.02–0.37	83.3 ± 9.9	82.7	64.4–99.3

Note: The sum of AsIII and AsV is reported as iAs.

The main species of As in a subset of barley samples ($n = 24$) was iAs (Table 2 and Table S1), with %iAs averaging 83.3 ± 9.9%. In our literature search, only one study or one report have reported inorganic As data for processed food containing barley such as flour and mixed cereal (Table S2). The concentrations of iAs are both low, and are <0.003 $mg \cdot kg^{-1}$ for organic barley flour, 0.006 and 0.012 $mg \cdot kg^{-1}$ for pearl barley flour with wheat, and range from 0.010–0.055 $mg \cdot kg^{-1}$ for a mixed grain cereal (Table S2). To the best of our knowledge, our study reports for the first time not only higher than expected total As concentration in Tibetan highland barley but also that the As speciation is mostly inorganic with DMA. Previously, it was of thought that As speciation in barley should be comparable to other cereals, such as wheat (D'Amato et al., 2011; Rasheed et al., 2018; Tong et al., 2014; Zhao et al., 2010) and rice (Chen et al., 2018), both of them contained substantial fractions of iAs (36.9–100% and 35–92%) with the rest being mostly DMA. This is now confirmed.

3.3. The daily total and inorganic As intake from foods

The Tibetan staple, highland barley, is as important exposure pathway for As, comparable to areas with known water As exposure. The EDI_{tAs}, or total As estimated daily intake, was significantly higher from ingestion of highland barley (6.22×10^{-4} $mg \cdot kg^{-1} \cdot d^{-1}$) than that from meat ($3.75 \times 10^{-4}$ $mg \cdot kg^{-1} \cdot d^{-1}$), vegetables ($0.98 \times 10^{-4}$ $mg \cdot kg^{-1} \cdot d^{-1}$), and dairy ($1.14 \times 10^{-4}$ $mg \cdot kg^{-1} \cdot d^{-1}$), due to the large daily amount consumed and variable but can be high As concentration of barley (Fig. 2a). In comparison, average EDI_{tAs} from vegetables and dairy were all below the RfD or the maximum oral daily dose of 3.0×10^{-4} $mg \cdot kg^{-1} \cdot d^{-1}$ recommended by USEPA. To put this in perspective, Shanxi, an As endemic disease affected province of China, where As exposure was primarily from drinking water, with some from consumption of vegetables (Cui et al., 2013), has an EDI_{tAs} of 2.6×10^{-3} $mg \cdot kg^{-1} \cdot d^{-1}$. Based on the cumulative frequency distribution of EDI_{tAs}, from 45 highland barley samples, 44.4% of the residents consumed above the RfD of 3.0×10^{-4} $mg \cdot kg^{-1} \cdot d^{-1}$ (Fig. 3).

The EDI_{iAs} was also estimated (Fig. 2b). The EDI_{iAs} of dairy was not estimated and likely to be extremely low, because few iAs was detected by previous studies (Stiboller et al., 2017; Wong et al., 2013). The EDI_{iAs}

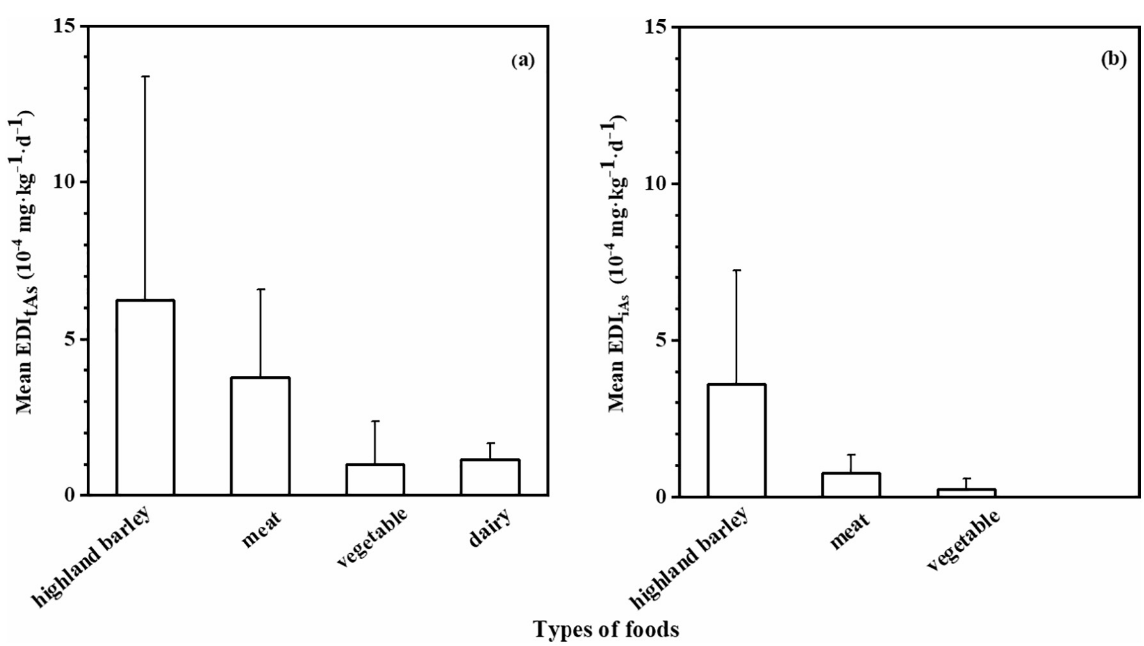

Fig. 2. Average (a) EDI_{tAs} and (b) EDI_{iAs} from highland barley, meat, vegetable and dairy. Error bars represent the standard deviation.

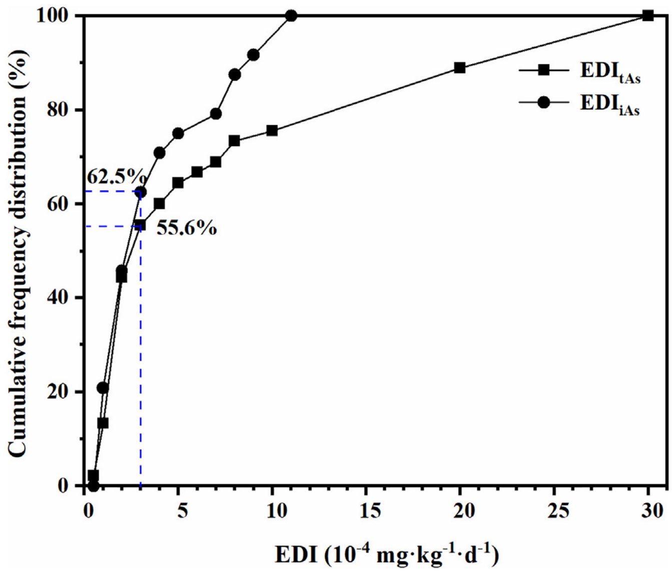

Fig. 3. Cumulative frequency distribution of EDI_{tAs} ($n = 45$) and EDI_{iAs} ($n = 24$) from highland barley. The blue dotted vertical line represents the RfD of 3.0×10^{-4} mg·kg^{-1}·d^{-1} recommended by the USEPA.

from meat and vegetable were both lower than that from highland barley, 2.1×10^{-4} mg·kg^{-1}·d^{-1} and 0.98×10^{-4} mg·kg^{-1}·d^{-1} assuming that the percentages of iAs in meat and vegetables are 56% and 100%, respectively (see Section 3.1 for justification). The EDI_{iAs} from 24 highland barley was 3.6×10^{-4} mg·kg^{-1}·d^{-1}, with 37.5% exceeding the USEPA's RfD of 3.0×10^{-4} mg·kg^{-1}·d^{-1} (Fig. 3). The main source of both total and iAs exposure from food was highland barley, followed by meat and vegetables.

3.4. Health impact assessment by the hazard quotient (HQ) and cancer risk (R)

The HQ was calculated based on the EDI_{tAs} values from highland barley, meat, dairy and vegetables (Table 3). Potential adverse impact on human health would occur when HQ ≥ 1 (Zeng et al., 2015). HQ exceeded 1.0 for 44.4%, 50.0% and 11.8% of residents from highland barley, meat and vegetable sourced exposure, respectively. The HQ from exposures due to dairy intake was below 1.0 (Table 3). Although epidemiological investigation has not been conducted in the study area, symptoms of chronic As poisoning including keratosis and depigmentation were notable on residents' skins in the study area, suggesting there is a need to further evaluate visible and invisible health effects.

The cancer risk probability over a lifetime was estimated and compared with the “acceptable” value of 1 in 10,000, in order to be consistent with water iAs risk assessment (USEPA, 1989). The R ranged from 0.91 in 10,000 to 19.1 in 10,000, with an average probability of 5.4 in 10,000 based on 24 highland barley samples' iAs speciation analysis

Table 3
Hazard Quotient (HQ) based on tAs in foods and Cancer Risk (R) based on iAs from highland barley, meat and vegetable.

Types of food	HQ[a]			R (10^{-4})[b]		
	Min	Mean	Max	Min	Mean	Max
Barley	0.16	2.07	7.94	0.91	5.42	19.10
Meat	0.36	1.25	3.63	0.91	3.21	9.15
Vegetable	0.01	0.34	1.62	0.05	1.46	7.36
Dairy	0.12	0.38	0.65			

[a] HQ > 1.00 suggests that toxic risk exists.
[b] 1 in 10,000 is the highest safe standard for cancer.

and distribution (Fig. 3 and Table 3). Although highly uncertain due to lack of iAs measurements in meat and vegetables, the average cancer risk probabilities from dietary meat and vegetable exposure at 3.2 and 1.4 in 10,000, were also higher than 1 in 10,000 (Table 3). Overall, iAs in highland barley presents a threat to human health for residents in Ngari, western Tibet.

4. Conclusion

High As content was detected in highland barley in western Tibet along Singe Tsangpo. Local rural residents were exposed to high As mainly via highland barley with high proportions of inorganic As, increasing the probability of cancer risk to 5.4 in 10,000. Together with symptoms of chronic As poisoning observed during our field work, it is recommended that multidisciplinary studies to further evaluate and reduce the sources of As exposure to be conducted in Tibet where geogenic As background levels are very high.

CRediT authorship contribution statement

Lili Xue: Resources, Formal analysis, Writing - original draft, Writing - review & editing. **Zhenjie Zhao:** Resources. **Yinfeng Zhang:** Resources, Formal analysis. **Jie Liao:** Formal analysis. **Mei Wu:** Formal analysis. **Mingguo Wang:** Resources. **Jing Sun:** Writing - original draft, Writing - review & editing. **Hongqiang Gong:** Resources. **Min Guo:** Resources. **Shehong Li:** Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing. **Yan Zheng:** Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no competing financial interests to this work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2020.138840.

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