Environmental Research 171 (2019) 185–192

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Global burden of cancer and coronary heart disease resulting from dietary exposure to arsenic, 2015

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ARTICLE INFO

Keywords:
Arsenic
Cancer
Coronary heart disease
Diet
Disability-Adjusted life year
Foodborne burden of disease

ABSTRACT

Arsenic is a ubiquitous, naturally occurring metalloid that poses a significant risk for human cancer and non-cancer diseases. It is now evident that arsenic contamination in food, especially rice and grains, presents a significant exposure to hundreds of millions of individuals worldwide. However, the disease risk from chronic exposure to the low amounts of arsenic found in food remains to be established. Thus, this research estimates the global burdens of disease expressed as Disability-Adjusted Life Years (DALYs) for lung, skin and bladder cancers, as well as coronary heart disease (CHD) attributable to inorganic arsenic in food. To determine foodborne inorganic arsenic exposures worldwide, we used the World Health Organization (WHO) estimates of food consumption in 17 country clusters, in conjunction with the reported measurements of total and inorganic arsenic in different foods. We estimated cancer potency factors for arsenic related bladder and lung cancers, and from US Environmental Protection Agency risk estimates for skin cancer to calculate the cancer incidence in males and females within each of the WHO member states. Summary relative risk estimates and population attributable fractions were developed to estimate the YLD, YLL, and DALYs for arsenic-induced CHD. The findings indicate that, globally, each year the combined DALYs for all cancers attributable to inorganic arsenic in food are approximately 1.4 million with variation in global distribution based on population and food consumption patterns. The global burden of CHD attributable to foodborne inorganic arsenic also varied with WHO region and may contribute as much as 49 million DALYs. However, in contrast to cancer burden, there is a threshold effect for arsenic-associated CHD with no increased risk of heart disease at the expected lower bound of arsenic consumption in food. These estimates indicate that foodborne arsenic exposure causes a significant yet avoidable global burden of human disease.

1. Introduction

Foodborne diseases are a serious public threat worldwide. In the efforts to control foodborne diseases, assessments of their public health impact serve as the scientific basis for risk-based management decisions and regulatory actions. However, the lack of a reliable estimate of foodborne burden of disease, as well as the need for better assessment of the content of arsenic and arsenicals in food, have impeded development of effective protective policies. In collaboration with multiple external and internal partners, the Department of Food Safety and Zoonoses at World Health Organization (WHO) launched the initiative to estimate the global burden of foodborne diseases. The Foodborne Disease Burden Epidemiology Reference Group (FERG) was convened to assist with this task. The FERG Chemicals and Toxins Task Force (CTTF) focused on estimation of the global burden of diseases from dietary exposure to chemical contaminants including arsenic,

Abbreviations: ASGM, Artisanal and small scale gold mining;; CHD, Coronary heart disease; CTTF, Chemicals and Toxins Task Force; DALY, Disability-adjusted life year; FERG, Foodborne Disease Burden Epidemiology Reference Group; GBD, Global burden of disease; GEMS, Global Environment Monitoring System; GHE, Global health estimates; IARC, International Agency for Research on Cancer; iAs, Inorganic arsenic; PAF, Population attributable fraction; RR, Relative risk; UI, Uncertainty interval; WHO, World Health Organization; YLD, Year lived with disability; YLL, Year of life lost

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https://doi.org/10.1016/j.envres.2019.01.025
Received 14 August 2018; Received in revised form 8 January 2019; Accepted 10 January 2019
Available online 11 January 2019
0013-9351/

cadmium, lead, and methylmercury and toxicants like dioxin, aflatoxin, cyanide in cassava, in food and peanut allergy (Gibb et al., 2015; Havelaar et al., 2015). The current study reports the global burden of diseases for dietary arsenic.

Inorganic arsenic is ubiquitous in the environment and exposure through water and food is a prominent global health problem (EFSA Panel on Contaminants in the Food Chain (CONTAM), 2009; Nachman et al., 2017, 2018). Arsenic is unique among metals and chemicals in that the majority of evidence of adverse health outcomes comes from a wealth of human epidemiological studies instead of relying on studies in animals (NRC, 2014). The weight of human evidence for lung, bladder, and non-melanoma skin cancer led the International Agency for Research on Cancer (IARC) to classify arsenic as a Group 1 carcinogen (IARC, 2017; NRC, 2014). In addition to cancer, exposure to low to moderate levels of arsenic increases risk of mortality from cardiovascular (Moon et al., 2017), as well as a number of other non-cancer diseases. The majority of the epidemiological evidence for arsenic disease risk comes from studies of drinking water exposures where water contamination is often orders of magnitude above expected levels of arsenic in food (NRC, 2014). However, several recent studies in the United States and Bangladesh found increased trends for cardiovascular disease, skin lesions, and possibly lung and bladder cancer risk in populations where water arsenic was low (Muraki et al., 2015; Melkonian et al., 2013; Gossai et al., 2017; Zhang et al., 2016). These studies suggest that disease risk from consuming low levels of arsenic in food mirrors that from low levels found in drinking water.

Vegetables, grains, meats, and fish are the prominent food sources that naturally contain levels of arsenic that can be a significant source of exposure (Davis et al., 2012; Kile et al., 2007; Nachman et al., 2017; Schoof et al., 1999). The arsenic comes from uptake by food crops from the soil and irrigation water (Biswas et al., 2012; Dittmar et al., 2010; Nachman et al., 2017; Schoof et al., 1999). Preparation and cooking of food with arsenic-contaminated water can also increase the arsenic content of food (e.g., in boiling rice, making breads or pasta; (Kile et al., 2007; Signes et al., 2008)). According to a recent WHO background document on global arsenic exposure (JECFA, 2011), arsenic in contaminated water is completely bioavailable and provides the majority of daily arsenic dose (NRC, 2014). However, as water arsenic concentrations decrease, the relative contribution of dietary sources becomes more significant to human arsenic exposures (Schoof et al., 1999; Davis et al., 2012; EFSA Panel on Contaminants in the Food Chain (CONTAM), 2009; Nachman et al., 2018). Fig. 1 depicts the influence diagram by which arsenic accumulates in foods and then contributes to adverse human health effects. It is difficult to assess the contribution of water contamination to food (Nachman et al., 2018), and consequently this analysis focuses only on potential risks only from the inorganic arsenic in the foodstuffs.

As indicated by its IARC classification, arsenic exposure increases the risk for a number of important cancers. Numerous epidemiologic studies indicate an association between arsenic exposure and an increased risk for lung cancer mortality (Gibb et al., 2011; IARC, 2017; NRC, 2014; Smith et al., 2009), and lung cancer may be the leading cause of arsenic-associated cancer deaths. A meta-analysis of available epidemiologic studies performed in Bangladesh, Chile, Argentina, Taiwan, and the United States (Begum et al., 2015), estimated about 4.51 additional lung cancer cases per 100,000 people for a maximum contamination level of 10 μg/L of arsenic in drinking water. An association between arsenic exposure and bladder cancer has been substantiated by multiple ecologic, as well as case–control and cohort studies (Christoforidou et al., 2013; Gibb et al., 2011; IARC, 2017).

In addition, an extensive body of literature definitively links the ingestion of arsenic to increased incidence of non-melanoma skin cancer (i.e., basal cell and squamous cell carcinoma (IARC, 2017; NRC, 2014)). Multiple ecologic studies based on mortality from skin cancer in Chile, Taiwan, and Bangladesh found consistent gradients of increasing risk with average level of arsenic in drinking water (IARC, 2017). Cohort studies from IARC reported risks of skin cancer to be related to average concentration of arsenic in drinking water and index for cumulative exposure to arsenic (IARC, 2017).

The risk for cardiovascular diseases increases in areas with high arsenic levels in drinking water (Moon et al., 2012, 2017). A recent prospective study, found an association between lifetime exposure to low levels of inorganic arsenic in drinking water (10–100 μg/L) and an increased risk for coronary heart disease (CHD) (James et al., 2015). Systematic review and meta-analysis of studies that include over 200,000 individuals provides strong evidence for an association between arsenic and CHD across low-moderate to high levels (Moon et al., 2017). Given the high burden of cardiovascular disease worldwide, it is likely that CHD is the most important non-cancer disease risk posed by environmental arsenic exposures (NRC, 2014). CHD refers to the disease of the coronary arteries and the resulting complications of myocardial infarction, angina, and ultimately cardiac death. Most clinical manifestations of CHD are caused by atherosclerosis. Early studies in areas contaminated with very high arsenic levels led to the common misperception that CHD, myocardial infarctions, and peripheral vascular disease occurred only in certain populations and when arsenic was present in levels not expected to be found in food. Comparable studies examining cardiovascular risk from arsenic in food rather than drinking water are very limited (Nachman et al., 2017). However, it is evident that the predicted level of inorganic arsenic consumption in foods is in the range of daily consumption that can pose a risk of cardiovascular disease (Moon et al., 2017)

The incidence and/or prevalence of morbidity, disability and mortality associated with acute and chronic manifestations of disease can be defined as burden of disease. Burden of disease assessments rely on use of all available mortality and health data by appropriate methods to confirm the comparability and consistency of estimates of demographic and epidemiological importance worldwide. A partial risk assessment of the global arsenic associated burden of disease was made previously by the JECFA who reviewed the provisional tolerable weekly intake of inorganic arsenic (iAs) with an emphasis on the speciation and occurrence of iAs in food (JECFA, 2011). In addition, the human health risks in European countries from foodborne arsenic was assessed by the European Food Safety Authority Panel on Contaminants in the Food Chain (EFSA Panel on Contaminants in the Food Chain (CONTAM) (2009)). However, the global burden of cancers and coronary heart disease caused by foodborne arsenic exposure has not been investigated, nor has the extent of iAs content in different diets worldwide. Thus, we focused our study's adverse effects on iAs exposure, as foodborne organic arsenical exposures pose little human health risk (Kile et al., 2007; Davis et al., 2012; Hughes et al., 2011; JECFA, 2011; EFSA Panel on Contaminants in the Food Chain (CONTAM), 2009). We estimated the DALYs for cancers and CHD in 2015 due to iAs through food in different diets worldwide, based on data adapted from WHO Global Environment Monitoring System (GEMS)/Food Consumption 17 group Cluster Diets database (Sy et al., 2013; https://extranet.who.int/gemsfood/).

2. Materials and methods

2.1. Incidence of arsenic-induced bladder, lung and skin cancer

The methodology to quantify the risk of developing bladder, lung and skin cancer due to exposure to arsenic is described in Oberoi et al. (2014). In order to estimate the global burden of a specific arsenic-induced cancer, dietary arsenic exposure was multiplied by a cancer potency factor and then summed across different populations. The cancer potency factors, analogous to cancer slope factors, were derived from dose-response curves that were driven through the point (0, 0) and linearized through the concentration of arsenic required to cause 1% of the population to develop a given cancer ([As], 0.01). Using data from Table 8 of Morales et al. (2000) who developed multiple models for

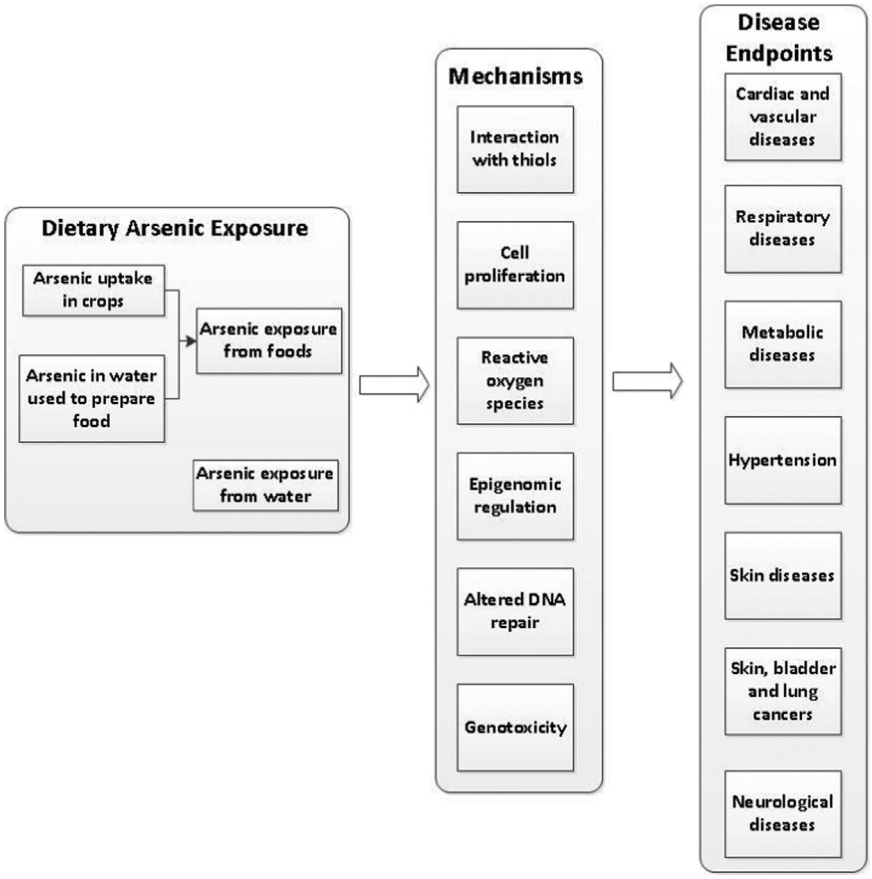

Fig. 1. Foodborne arsenic and disease pathways in humans.

estimating cancer potency factors for bladder cancer and lung cancer in a Taiwan population from water iAs exposure, we divided the risk at 1% by the dose (μg/L) that produced the 1% risk (i.e., the ED01), multiplied by 2 L/day:

$$Cancer\ risk\ per\ \mu g\ iAs/day = 0.01/(ED01\mu g/L \times 2\ L/day)$$

The factor of 2 L/day was based on conversion of the risk estimate assuming a consumption of 2 L of water containing the amount of iAs for 1% cancer risk per day. Thus, the converted cancer potency factor gave the risk per μg of iAs consumed per day regardless of source (Table 1). In this model, which best fit the data based on the Akaike information criterion, the relative risk (RR) of mortality at any time is assumed to increase exponentially, with a linear function of dose and a quadratic function of age; no external comparison population was used (Morales et al., 2000). For skin cancer risk, we used the EPA IRIS reported amount of arsenic in drinking water that caused a 1% increased risk of skin cancer (200 μg/L; IRIS, 1998) adjusted accordingly for food exposure (0.01/200 μg/L * 2 L/day = 0.000025 μg/day; Table 1).

Table 1
Cancer potency factors for incidence of each arsenic related cancer (adapted from Oberoi et al., 2014).

Cancer type	Slope factor (increased population risk per μg iAs/d)	
	Males	*Females*
Bladder[a]	0.0000127	0.0000198
Lung[a]	0.0000137	0.0000194
Skin[b]	0.0000250	0.0000250

[a] Cancer potency factors derived by using data adapted from Morales et al. (2000).
[b] Cancer potency factor was adapted from the U.S. EPA IRIS (1998).

Exposure assessment is informed by consumption rates of foods that have a higher tendency to accumulate arsenic (e.g. rice and grains) from the media in which they are grown. Global consumption rates of these foods was derived from the GEMS Food Cluster Diets database that divides the world into 17 clusters of countries with similar dietary consumption rates. Common ranges of arsenic content in these food cultivated worldwide was provided by data from JECFA (2011), these ranges allowed normalization of exposures to reveal the influence of consumption rates in given dietary clusters on the levels of arsenic exposure. However, the rates of arsenic incorporation into various foodstuffs (e.g. different rice cultivars) and the amounts of arsenic in local growing media can vary widely (Meharg et al., 2009; Halder et al., 2012). This underlies the range of arsenic content in the JECFA database and variability in the exposure estimates. We used literature values (JECFA, 2011; EFSA Panel on Contaminants in the Food Chain (CONTAM), 2009; Yost et al., 1998; Schoof et al., 1999) to determine the range of arsenic content in different food categories (Oberoi et al., 2014). The range of uncertainty for iAs content was created by multiplying the lower and upper boundaries of the reported range for iAs to total arsenic content for a given food group (Oberoi et al., 2014). Combining the GEMS consumption rates and the lower and upper boundaries of arsenic content in foodstuffs provided by JECFA allowed estimation of the influence of dietary consumption patterns in specific parts of the world on exposure. For risk characterization, the lifetime average daily dose estimates from the exposure assessment were multiplied by the selected cancer potency factors (Table 1) to produce quantified estimates of the burden of arsenic-related cancers worldwide.

2.2. Dose-response meta-analysis for coronary heart disease due to foodborne arsenic

The slope of the dose-response curve for ingested iAs and coronary heart disease due to foodborne arsenic comes from a recent meta-analysis (Moon et al., 2017). This analysis incorporated all of the prospective arsenic and cardiovascular disease epidemiological studies that determined dose-response relationships at the lower end of exposures in Bangladesh (GEMS cluster 9), India (GEMS cluster 5), United States and Italy (both in GEMS cluster 10). The analysis incorporates data from more than two hundred thousand individuals worldwide based in countries that fall in the three most populous GEMS clusters.

For each GEMS cluster, we derived a cluster-specific RR estimate by applying the dose-response curves generated for CHD incidence and mortality by Moon et al. (2017) to the GEMS-specific iAs exposure levels.

2.3. Disability-adjusted life years

DALYs combine Years of Life Lost (YLLs) with Years Lived with Disability (YLDs) into an estimate of the total number of healthy life years lost due to mortality and morbidity, respectively (Devleesschauwer et al., 2014). For consistency with existing global health envelopes, we derived conversion factors to map our cancer incidence estimates into estimates of mortality, YLD and YLL. Specifically, we sought compatibility with the WHO/Global Health Estimates 2015 (WHO/GHE; (World Health Organization, 2017)).

For skin, lung and bladder cancer, we derived the number of deaths, YLLs and YLD per incident case by dividing country-specific WHO/GHE mortality, YLL and YLD rates, by the corresponding IARC incidence rates. For instance, if $Incidence_{LC,As}$ denotes the incidence rate of arsenic-associated lung cancer, as estimated by the current study, then we estimated $Mortality_{LC,As}$, $YLL_{LC,As}$, and $YLD_{LC,As}$ as follows:

$$Mortality_{LC,As} = Incidence_{LC,As}{}^{*}(Mortality_{LC,WHO}/Incidence_{LC,IARC})$$

$$YLL_{LC,As} = Incidence_{LC,As}{}^{*}(YLL_{LC,WHO}/Incidence_{LC,IARC})$$

$$YLD_{LC,As} = Incidence_{LC,As}{}^{*}(YLD_{LC,WHO}/Incidence_{LC,IARC})$$

where $Incidence_{LC,IARC}$ is the IARC incidence rate for all-cause lung cancer, and $Mortality_{LC,WHO}$, $YLL_{LC,WHO}$, $YLD_{LC,WHO}$ are the WHO/GHE mortality, YLL and YLD rates for all-cause lung cancer.

In the absence of age-specific arsenic-induced cancer estimates, we also adopted the age distributions estimated by WHO/GHE for the respective parameters. In other words, we assumed the age distribution of arsenic-induced cancer to be the same as the age distribution of the respective all-cause cancer.

For CHD, we converted our RR estimates into population attributable fractions (PAF):

$$PAF = (RR - 1)/RR$$

We then used this PAF to attribute the WHO/GHE CHD incidence, mortality, YLD and YLL envelopes to iAs.

We used 2015 population estimates from the United Nations World Population Prospects 2017 Revision to calculate the absolute number of incident cases, deaths, YLDs, YLLs, and DALYs from the corresponding rates. The DALY calculations were implemented in a probabilistic framework, using 10,000 Monte Carlo simulations to propagate uncertainty (Devleesschauwer et al., 2015). Specifically, uncertainty in the arsenic-induced cancer estimates was represented using uniform distributions, uncertainty in the GEMS-specific As exposure levels, foodstuff-specific proportion iAs, and bioavailability levels using uniform distributions, and uncertainty in the WHO/GHE envelopes as gamma distributions. The resulting uncertainty distributions of incident cases, deaths, YLDs, YLLs, and DALYs, were summarized by their median and a 95% uncertainty interval (UI) defined as the distribution's 2.5th and 97.5th percentile.

Table 2
Range of foodborne total arsenic exposure at 50–100% bioavailability for 17 WHO/GEMS country clusters[a].

GEMS cluster	Total As[b], LB (μg/kg bw/day)[c]	Total As[b], UB (μg/kg bw/day)	iAs[d], LB (50% bioavailable) (μg/person/day)[f]	iAs[e], UB (100% bioavailable) (μg/person/day)[f]	Range of iAs exposure via cereal and cereal products (μg/day)
G1	0.76	1.04	4.82	46.67	0.06–0.54
G2	1.17	1.56	5.32	56.11	0.06–0.50
G3	0.94	1.18	3.08	36.11	0.04–0.30
G4	1.40	1.74	5.39	56.95	0.06–0.53
G5	0.96	1.22	4.76	46.98	0.06–0.52
G6	1.39	1.80	6.84	70.26	0.08–0.68
G7	1.65	2.01	4.42	51.38	0.04–0.35
G8	1.43	1.82	4.59	53.23	0.04–0.37
G9	2.23	2.54	6.00	62.88	0.07–0.56
G10	2.00	2.38	5.09	58.01	0.05–0.40
G11	1.41	1.82	4.28	52.64	0.03–0.28
G12	1.37	1.72	4.48	51.80	0.05–0.39
G13	0.78	1.01	4.18	41.68	0.06–0.47
G14	1.78	2.05	4.92	52.59	0.05–0.46
G15	1.27	1.66	4.74	99.70	0.05–0.40
G16	0.85	1.15	2.76	37.34	0.02–0.20
G17	2.52	2.87	4.57	57.19	0.03–0.28

[a] Listing of countries within each cluster is available at https://goo.gl/YY7uh2.
[b] Calculations based on Table 13, JECFA (2011) for range of total arsenic content in food items.
[c] Assuming 60 kg body weight per individual (Walpole et al., 2012).
[d] Lower bound for iAs content assumes non-detect equals zero (Table 18 in JECFA, 2011). Calculated as lower boundary of estimated food group iAs content percentage multiplied by the total arsenic measured.
[e] Upper bound for iAs content assumes non-detect equals the limit of detection (Table 18 in JECFA, 2011). Calculated as upper boundary of estimated food group iAs content percentage multiplied by the total arsenic measured.
[f] Calculations based on Tables 2 and 3 in Oberoi et al. (2014) for range of mean% inorganic arsenic content in food items.

3. Results

Oberoi et al. (2014) provided a detailed assessment of foodborne arsenic-induced cancers based on the previous GEMS classification of 13 clusters. The analysis was updated by using the current 17 GEMS cluster classification and GEMS Food contamination monitoring and assessment program with 2015 cancer demographic data. Table 1 presents the cancer potency factors for arsenic related bladder and lung cancer developed using data from Morales et al. (2000); and for arsenic induced skin cancer that were adapted from US EPA IRIS database (IRIS, 1998).

The data in Table 2 present the range of arsenic exposures for 17 GEMS clusters of countries. For each GEMS cluster the bioavailability of consumed inorganic arsenic has been estimated at the lower and upper bounds of inorganic arsenic found in the food. The consumption pattern for major food categories including fruits, vegetables, nuts, meat, beverages and cereals was obtained from the GEMS food consumption database. Rice is generally considered the major source of inorganic arsenic in foodstuffs and thus we separated cereals from the GEMS cluster diets for illustrative purposes. Unfortunately, the new GEMS clustering does not segregate the cereals and a true estimate of the contribution of arsenic in rice to the disease risk is not possible.

The risk of additional cases of cancers was then characterized by taking the product of the cancer potency factors (Table 1) with the estimated exposure to arsenic for all WHO member states within the respective GEMS cluster of countries (Table 2). Note that the exposure data were corrected for body weight using a global average body

Table 3
Incidence of iAs-associated bladder, lung and skin cancer, 2015.

Region	Bladder cancer	Lung cancer	Skin cancer	Total
Africa (AFR)	6722 (1472–12,077)	6849 (1500–12,306)	10,337 (2263–18,573)	23,908 (5235–42,956)
AFR D	3288 (727–5901)	3352 (741–6014)	5064 (1120–9087)	11,704 (2588–21,001)
AFR E	3434 (745–6177)	3498 (758–6291)	5273 (1144–9486)	12,205 (2646–21,954)
America (AMR)	8528 (1875–15,314)	8686 (1910–15,597)	13,090 (2879–23,505)	30,303 (6664–54,416)
AMR A	3333 (724–5993)	3394 (738–6104)	5116 (1112–9200)	11,843 (2574–21,297)
AMR B	4430 (977–7953)	4512 (995–8100)	6798 (1499–12,204)	15,740 (3470–28,256)
AMR D	765 (174–1368)	779 (178–1393)	1176 (268–2102)	2720 (620–4863)
Middle East (EMR)	6288 (1470–11,202)	6419 (1501–11,436)	9750 (2280–17,370)	22,457 (5252–40,008)
EMR B	1793 (422–3191)	1835 (432–3265)	2809 (661–4999)	6436 (1515–11,456)
EMR D	4495 (1048–8011)	4585 (1069–8170)	6942 (1619–12,371)	16,021 (3737–28,552)
Europe (EUR)	8764 (1908–15,756)	8917 (1942–16,032)	13,396 (2917–24,085)	31,077 (6767–55,874)
EUR A	4385 (922–7916)	4464 (939–8059)	6719 (1413–12,130)	15,567 (3275–28,106)
EUR B	2381 (529–4271)	2424 (539–4348)	3649 (811–6545)	8455 (1878–15,163)
EUR C	1998 (457–3569)	2029 (464–3625)	3028 (693–5411)	7055 (1614–12,605)
Southeast Asia (SEAR)	18,986 (4376–33,889)	19,371 (4465–34,575)	29,368 (6769–52,420)	67,725 (15,610–120,884)
SEAR B	3444 (794–6148)	3510 (809–6264)	5298 (1221–9456)	12,252 (2824–21,868)
SEAR D	15,542 (3582–27,741)	15,861 (3656–28,311)	24,070 (5548–42,963)	55,473 (12,786–99,015)
Western Pacific (WPR)	18,431 (4245–32,901)	18,802 (4330–33,563)	28,492 (6562–50,861)	65,725 (15,137–117,326)
WPR A	1592 (363–2844)	1620 (370–2896)	2438 (557–4358)	5650 (1290–10,098)
WPR B	16,839 (3881–30,057)	17,182 (3960–30,668)	26,053 (6005–46,503)	60,074 (13,847–107,228)
World	**67,719 (15,347–121,140)**	**69,044 (15,648–123,509)**	**104,433 (23,670–186,814)**	**241,195 (54,665–431,463)**

weight (Walpole et al., 2012). As this is a conservative estimate, it may overestimate bodyweight-adjusted dose in countries where body weight averages are higher. The resulting estimates of the incidence of iAs-associated bladder, lung and non-melanoma skin cancers by WHO region and sub-region are presented in Table 3.

We next mapped the cancer incidence estimates as estimates of mortality, YLD and YLL. The data were converted to compatibility with the WHO/GHE (World Health Organization, 2017) to derive the number of skin, lung and bladder cancer deaths, as well as YLLs and YLDs per incident case by dividing country-specific WHO/GHE mortality, YLL and YLL rates, and by the corresponding IARC incidence rates. We also adopted the age distributions estimated by WHO/GHE for the respective parameters. DALYs derived for cancer attributed to iAs consumption are presented in Table 4. The results indicate a significant global impact of arsenic associated cancers that varies with region.

We derived the “extra CHD cases” for each WHO member state within the respective GEMS clusters using the cluster-specific RR derived from applying the GEMS-specific lower and upper bounds of iAs exposures to the dose-response curves generated for CHD incidence and mortality by Moon et al. (2017). There was no evidence of risk for CHD incidence or mortality when consumption is at the lower bound of iAs content as the RR values across all GEMS clusters were below 1.0 (Table 5). In contrast, RR for both CHD incidence and mortality were appreciable at the upper bound of arsenic consumption in all of the GEMS clusters.

The RR estimates were converted to PAF to attribute the WHO/GHE CHD incidence, mortality, YLD and YLL envelopes to iAs. Population estimates for the year 2015 from the United Nations World Population Prospects 2017 Revision were used to calculate the absolute number of incident cases, deaths, YLDs, YLLs, and DALYs from the corresponding rates. The DALY calculations were implemented in a probabilistic framework, using 10,000 Monte Carlo simulations to propagate uncertainty (Devleesschauwer et al., 2015). The resulting uncertainty distributions were summarized by their median and a 95% uncertainty interval (UI) defined as the distribution's 2.5th and 97.5th percentile (Table 6). The DALYs derived from the YLD and YLL calculations are presented in Table 6. Similar to the cancer burden, the global

Table 4
Disability-Adjusted Life Years due to iAs-associated bladder, lung and skin cancer, 2015.

Region	Bladder cancer	Lung cancer	Skin cancer	Total	Total per 100,000
Africa (AFR)	48,707 (10,677–87,499)	61,911 (13,600–111,190)	14,126 (3089–25,383)	124,744 (27,366–224,073)	13 (3–23)
AFR D	21,067 (4682–37,780)	25,173 (5657–45,080)	6870 (1514–12,334)	53,110 (11,853–95,194)	11 (2–20)
AFR E	27,640 (5995–49,719)	36,738 (7943–66,110)	7255 (1575–13,049)	71,633 (15,513–128,879)	14 (3–25)
America (AMR)	30,077 (6619–54,006)	79,113 (17,413–142,050)	11,310 (2522–20,274)	120,501 (26,554–216,330)	12 (3–22)
AMR A	8675 (1885–15,600)	23,288 (5061–41,881)	961 (209–1728)	32,924 (7155–59,209)	9 (2–16)
AMR B	18,078 (3976–32,464)	46,886 (10,310–84,195)	7592 (1688–13,615)	72,556 (15,973–130,273)	14 (3–25)
AMR D	3324 (758–5942)	8939 (2041–15,974)	2757 (626–4931)	15,020 (3426–26,847)	16 (4–29)
Middle East (EMR)	44,560 (10,504–79,298)	66,307 (15,635–117,995)	17,793 (4152–31,707)	128,660 (30,291–229,000)	20 (5–35)
EMR B	15,626 (3704–27,787)	24,152 (5723–42,951)	3003 (708–5344)	42,782 (10,136–76,082)	23 (6–42)
EMR D	28,934 (6800–51,511)	42,155 (9911–75,044)	14,790 (3444–26,362)	85,878 (20,155–152,918)	18 (4–33)
Europe (EUR)	45,614 (9995–81,946)	102,800 (22,521–184,688)	10,336 (2290–18,543)	158,750 (34,806–285,177)	17 (4–31)
EUR A	15,735 (3287–28,433)	42,338 (8913–76,432)	3078 (652–5553)	61,151 (12,851–110,418)	14 (3–25)
EUR B	18,942 (4206–33,973)	35,738 (7947–64,087)	3436 (761–6164)	58,116 (12,913–104,224)	25 (6–44)
EUR C	10,937 (2502–19,540)	24,724 (5661–44,169)	3822 (878–6826)	39,483 (9041–70,535)	17 (4–30)
Southeast Asia (SEAR)	82,806 (19,087–147,803)	377,818 (87,086–674,375)	69,556 (16,033–124,153)	530,181 (122,205–946,330)	28 (6–49)
SEAR B	17,740 (4089–31,664)	127,566 (29,404–227,695)	16,232 (3741–28,972)	161,537 (37,234–288,331)	46 (11–83)
SEAR D	65,067 (14,998–116,139)	250,252 (57,682–446,680)	53,325 (12,291–95,180)	368,643 (84,971–657,999)	23 (5–42)
Western Pacific (WPR)	67,098 (15,455–119,776)	211,035 (48,618–376,707)	78,598 (18,115–140,293)	356,731 (82,187–636,776)	19 (4–34)
WPR A	5348 (1222–9557)	8935 (2034–15,974)	1670 (383–2983)	15,953 (3639–28,513)	10 (2–18)
WPR B	61,750 (14,233–110,219)	202,101 (46,584–360,733)	76,928 (17,732–137,310)	340,778 (78,549–608,262)	20 (5–36)
World	**318,862 (72,336–570,328)**	**898,985 (204,872–1607,005)**	**201,719 (46,201–360,353)**	**1419,566 (323,409–2537,685)**	**19 (4–35)**

Table 5
Relative risk (RR) estimates for incidence and mortality of coronary heart disease (CHD) in GEMS cluster of countries induced by foodborne arsenic.

GEMS cluster	CHD incidence RR at lower exposure boundary	CHD incidence RR at upper exposure boundary	CHD mortality RR at lower exposure boundary	CHD mortality RR at upper exposure boundary
G1	0.90	1.39	0.78	1.66
G2	0.93	1.42	0.82	1.73
G3	0.81	1.33	0.62	1.56
G4	0.93	1.43	0.83	1.74
G5	0.90	1.39	0.78	1.66
G6	0.98	1.47	0.92	1.82
G7	0.89	1.41	0.75	1.70
G8	0.89	1.41	0.77	1.71
G9	0.95	1.45	0.87	1.77
G10	0.92	1.43	0.81	1.74
G11	0.88	1.41	0.74	1.70
G12	0.89	1.41	0.76	1.70
G13	0.87	1.36	0.73	1.62
G14	0.91	1.41	0.79	1.70
G15	0.90	1.55	0.78	1.95
G16	0.79	1.34	0.57	1.57
G17	0.89	1.43	0.76	1.74

distribution of CHD DALYs per 100,000 varies greatly with WHO region. In contrast to the cancer burden, the greatest burden of arsenic-associated CHD DALYs was found in the European region, where the general burden of CHD is high.

4. Discussion

Exposure to arsenic is a serious global health problem. While the primary concern is arsenic in drinking water, consideration of exposure from foodborne contamination has become increasingly important. Accordingly, we used quantitative risk assessment and dose-response meta-analysis to estimate the increased global burden of cancers and coronary heart disease due to arsenic in food.

For food safety analyses, exposure estimation generally uses a combination of the consumption patterns of various populations and the variable content of the contaminating hazard in foods available to the populations (Sy et al., 2013). For this estimation, we used the WHO/GEMS cluster database that consists of 17 clusters classifying 179 countries according to their apparent food consumption patterns. The GEMS cluster data are a powerful means to compare average consumption among countries, which is crucial for international risk assessment (Sy et al., 2013). Our earlier work estimated cancer burden from arsenic using the food consumption estimates in the 13 GEMS clusters (Oberoi et al., 2014). The new 17 clusters were created to address dietary exposure mischaracterization that arose from the earlier grouping of countries. The new clustering used advanced mathematical and statistical modeling, as well as more recent FAO food consumption databases to more accurately cluster countries according to their consumption system profiles (Sy et al., 2013). Despite these improvements, certain limitations of the GEMS cluster approach remain. For instance, certain foods included in the major food groups of a cluster are not consumed equally by all individuals or individual countries within a cluster (Sy et al., 2013), with wide variability of possible consumption patterns within clusters. Nonetheless, in the absence of individual food consumption surveys, the use of GEMS food clustering allows developing countries to better implement regional food safety measures and perform basic dietary exposure assessments for various food hazards (Sy et al., 2013). It is interesting that readjusting the risk estimates to accommodate the 17 new GEMS clusters relative to the earlier 13 GEMS clusters (Oberoi et al., 2014) reduced the estimated burden of lung, skin, or bladder cancers (both in males and females) associated with arsenic in food. This is most likely due to splitting India and China into separate clusters, which reduced an amplification effect from a very large population in the earlier cluster G and a different approximation of the consumption patterns in the two countries.

We found the estimated global burden for arsenic-associated bladder and lung cancers to be highest in clusters G5 (India, South Africa, South America) and G9 (China, Southeast Asia, Indonesia). This may be due to the fact that the countries within these clusters have among the highest arsenic bedrock content in the world and the highest consumption of rice-based products that are often enriched in arsenic. For the population residing in these clusters, this leads to a potentially high overall rate of exposure to arsenic through more than one route of exposure, a higher likelihood for arsenic content in food, and a consistent basis for extended exposures. This chronic exposure would predispose these populations to developing arsenic-associated cancers (Oberoi et al., 2014). In addition, these are the most populous clusters and the estimates may be affected by the same population amplification effects seen in our earlier estimates (Oberoi et al., 2014).

Assuming a linear dose-response relationship for cancers induced by arsenic is often controversial (Gibb et al., 2011; Lynch et al., 2017;

Table 6
Disease burden (median and 95% uncertainty interval) of iAs-associated coronary heart disease, 2015.

Region	Incidence	Deaths	DALYs	DALYs per 100,000
Africa (AFR)	225,122 (134,163–305,457)	84,755 (47,216–119,616)	2157,159 (1174,233–3060,288)	217 (118–308)
AFR D	98,210 (57,840–135,232)	45,002 (24,244–66,177)	1155,179 (605,437–1713,899)	243 (127–360)
AFR E	126,845 (73,987–173,341)	39,182 (21,990–56,980)	987,712 (546,477–1431,166)	191 (106–277)
America (AMR)	443,795 (305,156–560,590)	268,251 (186,588–333,199)	5350,215 (3658,947–6681,438)	544 (372–680)
AMR A	205,411 (141,659–255,763)	150,328 (101,159–186,081)	2731,646 (1840,898–3379,498)	744 (501–920)
AMR B	218,865 (104,114–310,286)	106,544 (44,848–148,181)	2349,795 (987,705–3268,605)	448 (188–623)
AMR D	21,488 (10,808–30,365)	13,627 (6555–18,705)	312,766 (152,746–430,943)	343 (167–472)
Middle East (EMR)	321,144 (218,107–407,762)	193,294 (124,181–246,418)	4578,500 (2940,319–5880,713)	703 (451–903)
EMR B	94,022 (70,737–115,645)	52,501 (39,165–64,668)	1183,891 (881,967–1473,036)	646 (481–804)
EMR D	227,422 (139,808–298,065)	140,707 (81,911–185,370)	3386,311 (1972,717–4490,248)	723 (421–959)
Europe (EUR)	1028,792 (871,361–1180,219)	648,311 (536,990–745,640)	11,620,041 (9589,097–13,383,968)	1273 (1050–1466)
EUR A	410,310 (339,641–479,622)	181,913 (149,361–211,169)	2671,279 (2200,307–3098,909)	603 (497–700)
EUR B	235,236 (195,186–275,500)	133,723 (110,435–155,474)	2599,841 (2125,335–3035,269)	1109 (906–1294)
EUR C	383,879 (285,620–471,299)	333,894 (250,866–402,171)	6365,211 (4757,558–7674,656)	2699 (2017–3254)
Southeast Asia (SEAR)	1064,638 (661,490–1406,714)	504,249 (298,190–655,519)	13,448,383 (7774,338–17,558,011)	698 (404–911)
SEAR B	202,330 (133,349–263,667)	102,757 (67,477–132,581)	2627,723 (1693,405–3462,574)	756 (487–996)
SEAR D	863,614 (472,888–1188,820)	402,872 (199,147–543,157)	10,847,823 (5291,381–14,712,306)	687 (335–932)
Western Pacific (WPR)	1205,522 (810,955–1529,112)	603,646 (408,686–742,601)	12,308,294 (8247,336–15,163,855)	658 (441–810)
WPR A	83,165 (59,043–104,493)	52,024 (36,375–63,488)	778,836 (547,754–949,199)	480 (337–585)
WPR B	1122,210 (733,010–1439,044)	552,604 (357,905–688,216)	11,547,540 (7491,957–14,372,851)	676 (438–841)
World	**4266,244 (3489,216–5024,679)**	**2287,465 (1873,826–2650,995)**	**49,125,808 (39,537,868–57,324,339)**	**669 (539–781)**

NRC, 2014). Both Morales et al. (2000) and the US EPA IRIS (IRIS, 1998) modeled arsenic associated cancer risks with a fixed linear dose-response relationship and a single slope factor. More recent modeling of the dose-response relationships for arsenic-induced lung and bladder cancer that include assessment of the risks at lower exposure levels suggested a non-linear relationship with a threshold effect (Lynch et al., 2017). However, these new estimates relied on data from a number of studies that may be of questionable value and may not have the same strength as those used for the original studies (Gibb et al., 2011). If there is a threshold for cancer risk, then our global cancer burden estimates would be reduced and may look similar to the estimates for CHD with no risk at consumption below approximately 3.5 μg/day for a 70 kg individual.

In contrast to cancer risk estimates, a threshold is usually assumed for arsenic-associated non-cancer diseases. The meta-analysis of studies of CHD risk at low levels of arsenic that we used to derive RR for CHD incidence and mortality from arsenic in food indicated that there is indeed a threshold effect (Moon et al., 2017), although it may be at much lower than the threshold for cancer risk (Lynch et al., 2017). In addition, Moon et al. (2017) concluded that the combined data for dose-dependent arsenic-associated CHD from the most recent and highly powered prospective epidemiological studies are best modeled as a log-linear relationship that strengthens the evidence for an association between arsenic and CHD at low to moderate exposure levels. This included levels that can be found in common foods, especially in GEMS clusters with high rice and grain consumptions.

The data in Table 6 clearly show that the global burden of CHD incidence significantly increases by consumption of food with levels of arsenic at upper bounds of bioavailability; although there is much less attributable burden of CHD mortality. This most probably reflects a steeper and more significant dose-response relationship for arsenic-associated CHD incidence compared to mortality (Moon et al., 2017). The finding is of concern since being afflicted by CHD would have a greater impact on quality of life and DALYs than mortality that is usually from acute myocardial infarction. However, the concern is mitigated by the findings in Table 6 that indicate there is no RR of CHD incidence or mortality at the lower boundary of arsenic consumption. The estimates for attributable burden in Table 6 and the resultant estimated YLD, YLL, and DALYs assume that all individuals in a given cluster consume food with the same amount of arsenic content. This is clearly not the case as the uptake in different cultivars of foods, as well the arsenic in the media in which they grow can vary widely. It is important to note the unexpected, relatively high CHD incidence and mortality risk in Europe and especially EUR C (Table 6). This may have resulted from the new GEMS clustering not segregating consumption of rice from other grains and the higher consumption of grains that may not contain as much arsenic in this region. However, the data do suggest that the upper levels of arsenic found in food can increase CHD incidence in many individuals.

A final possible limitation in the risk estimates is uncertainty in the assumption that arsenic in food poses the same disease risk as arsenic in water. Bioavailability of inorganic arsenic in water is greater than 95% and water does not contain many mitigating factors found in food, such as micronutrients known to reduce arsenic pathogenesis (e.g. folate (Hall and Gamble, 2012)) and selenium (Chen et al., 2007). In addition, in most epidemiological studies it is often not possible to determine the proportion of exposure measurements attributable to arsenic in either drinking water or food, as the main biomarkers of exposure used are blood, urine, or toenail levels and these measurements cannot determine route of exposure. While it is critical to know the overall arsenic exposure in a population, the knowledge of route of exposure and arsenic source would be useful for optimizing interventions that reduce exposures (Nachman et al., 2017; Oberoi et al., 2014).

5. Conclusion

In summary, GEMS cluster data for global food consumption were used to estimate global exposures to arsenic in food and the consequent burdens of cancer and non-cancer CHD. These burdens are significant and suggest that global burden of disease can be reduced by consuming foods with less arsenic content. This is especially true for the burden of CHD as consuming foods containing the lower boundary of bioavailable, iAs pose little or no risk.

Acknowledgements

This study was conducted within the context of the Foodborne Disease Burden Epidemiology Reference Group (FERG) of the World Health Organization (WHO). The work was done through the in-kind support of the authors. Support to AB was also provided by grants from the National Institute of Environmental Health Sciences (R01ES023696 and R01ES013781). The authors acknowledge the funding provided to the FERG by the U.S. Food and Drug Administration, the U.S. Department of Agriculture, the U.S. Centers for Disease Control and Prevention, and the Governments of Japan and the Governments of Netherlands. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the views, decisions or policies of the World Health Organization or of the partners that have provided funding to the FERG.

The authors wish to acknowledge the support and guidance provided by the FERG chairman, Dr. Arie H. Havelaar, and by the Chemicals and Toxins Task Force (CTTF) of the FERG. Members of the CTTF include, in alphabetical order: Gabriel Adegoke, Reza Afshari, Janis Baines, Kalpana Balakrishnan, David Bellinger, Philip Michael Bolger, David Bellinger, Herman Gibb (Chairperson), John Pitt, and Rolaf van Leeuwen. The authors further wish to acknowledge the guidance of the FERG Core Group, in alphabetical order: Fred Angulo, David Bellinger, Nilanthi de Silva, Neyla Gargouri, Herman Gibb, Tine Hald, Arie Havelaar (Chairman), Martyn Kirk, Rob Lake, Nicolas Praet, Niko Speybroeck, and Paul Torgerson. Last, but certainly not least, we acknowledge the assistance of the WHO Secretariat over the course of the FERG initiative, particularly Claudia Stein, Tanja Kuchenmüller, Tim Corrigan, Danilo Lo-Fo-Wong, Amy Cawthorne, Yuki Minato, Natsumi Chiba, and Kurt Straif (International Agency for Research on Cancer, Lyon, France).

Competing interests

The authors declare they have no actual or potential competing financial interests.

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