

## Research Article

## The Global Burden of Disease for Skin, Lung, and Bladder Cancer Caused by Arsenic in Food

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## Abstract

**Background:** Arsenic is a ubiquitous, naturally occurring metalloid that poses a significant human cancer risk. While water consumption provides the majority of human exposure, millions of individuals worldwide are significantly exposed to arsenic through naturally occurring levels of arsenic in grains, vegetables, meats and fish, as well as through food processed with water containing arsenic. Thus, we estimated the global burdens of disease for bladder, lung, and skin cancers attributable to inorganic arsenic in food.

**Methods:** To determine foodborne inorganic arsenic exposures worldwide, we used World Health Organization estimates of food consumption in thirteen country clusters, in conjunction with reported measurements of total and inorganic arsenic in different foods. We estimated slope factors for arsenic-related bladder and lung cancers, and used the U.S. Environmental Protection Agency skin cancer slope factor, to calculate the annual risk of the cancer incidence in males and females within each country cluster.

**Results:** We estimated that each year 9,129 to 119,176 additional cases of bladder cancer, 11,844 to 121,442 of lung cancer, and 10,729 to 110,015 of skin cancer worldwide are attributable to inorganic arsenic in food.

**Conclusions:** These estimates indicate that foodborne arsenic exposure causes a significant global burden of human disease.

**Impact:** Estimating the global cancer burden caused by arsenic exposure in food will support policies that reduce exposure to disease-promoting environmental hazards. *Cancer Epidemiol Biomarkers Prev*; 23(7): 1187–94. ©2014 AACR.

## Introduction

Arsenic is a naturally occurring metalloid found in drinking water and certain foods. The International Agency for Research on Cancer (IARC) classifies arsenic as a Group 1 carcinogen based on evidence that inorganic arsenic (iAs) causes bladder, lung, and non-melanoma skin cancer in humans (1). In addition, arsenic exposure increases risk of mortality from cardiovascular (2, 3) and respiratory diseases (4, 5).

Naturally occurring levels of arsenic in vegetables, grains, meats, and fish present a significant source of arsenic exposure worldwide (6–8). The arsenic comes from uptake by food crops from the soil and irrigation water (6, 9–12). In addition, arsenic in water can contaminate food during processing and cooking (e.g., in boiling rice, making breads or pasta; refs. 7, 13). According to a recent World Health Organization (WHO) background

document on global arsenic exposure (14), arsenic in contaminated water is completely bioavailable and provides the majority of daily arsenic dose (15). However, as water arsenic concentrations decrease, the relative contribution of dietary sources becomes more significant to human arsenic exposures (7, 8, 16).

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 (1, 17–20), and lung cancer may be the leading cause of arsenic-associated cancer deaths. Meta-analysis of available epidemiologic studies performed in Bangladesh, Chile, Argentina, Taiwan, and the United States (21), 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 (reviewed in refs. 1, 17, 18, 22). 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 (1). 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 (1, 23). Cohort studies from IARC, 2012 reported risks of skin cancer to be

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significantly related to average concentration of arsenic in drinking water and index for cumulative exposure to arsenic (1, 23–25).

The objective of the current study was to use quantitative risk assessment to estimate the global burden of foodborne arsenic-induced bladder cancer, lung cancer, and skin cancers. Global burden of disease (GBD) is a widely accepted parameter that provides a frame of reference for comprehensive analysis of health gaps. It relies 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. This risk estimate was made as part of the WHO Foodborne Disease Burden Epidemiology Reference Group (FERG) efforts to estimate the GBD from foodborne chemical exposures, including dietary iAs exposure. A partial risk assessment was made previously by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) who reviewed the PTWI of iAs with an emphasis on the speciation and occurrence of iAs in food (26). In addition, the human health risks in European countries from foodborne arsenic was assessed by the EFSA Panel on Contaminants in the Food Chain (27). However, the global burden of cancers caused by foodborne arsenic exposure has not been investigated, nor the extent of iAs content in different diets worldwide.

Specifically, we focused on adverse effects associated with iAs exposure, as foodborne organic arsenical exposures pose little human health risk (7, 8, 23, 26, 27). We estimated the numbers of additional cases of cancers per year due to iAs through food in different diets worldwide, based on data adapted from WHO Global Environment Monitoring System (GEMS)/Food Consumption Cluster Diets database (28). GEMS/Food Consumption Cluster Diets database divides countries of the world into 13 groups based on diets.

## Materials and Methods

### Quantitative cancer risk assessment

To assess the quantitative cancer risk for a given population, the dietary arsenic exposure was multiplied by the cancer potency factor (slope factor) for a given cancer end point. The global estimate for burden of a particular arsenic-induced cancer was then obtained by summing across different populations.

### Dose–response assessment

Cancer potency factors for bladder cancer and lung cancer were derived using data adapted from Morales et al. (Table 8: Model 1), in which the relative risk 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 (29). EPA has used the same model for the development of arsenic water standard (2001) as it best fit the data based on the Akaike information criterion.

This study was selected as the best estimates of the cancer potency factor despite concerns that it may not be

representative of risk worldwide. However, a recent review found that there are no other currently published studies that provide a more powerful estimate (17). This table provides the concentration of arsenic in drinking water ( $\mu\text{g}/\text{L}$ ) estimated to cause bladder or lung cancer in 1% of males and females in a cohort in southwestern Taiwan. The cancer potency factor was transformed to be relevant to human doses by assuming a daily consumption of 2 liters of water per adult. For skin cancer caused by iAs, the slope factor was adapted from the United States EPA IRIS database (30). The EPA developed dose–response for skin cancer using data from Taiwan on about 40,000 persons exposed to arsenic in drinking water and 7,500 relatively unexposed controls (31, 32).

The dose–response assessment included the following assumptions: (i) that the southwestern Taiwanese population that provides the dose–response data (29) used for estimation of the cancer potency factors are reasonably representative of global populations in terms of adverse effects of arsenic [based on IARC 2012 (1)]; this allowed the same cancer potency factor to be applied in other parts of the world; (ii) that dose–response curves for arsenic-induced cancers can be linearized and driven through (0, 0); (iii) that the average human consumption of water is 2 liters per day (28); (iv) that iAs in food and water has the same potency and efficacy for cancer promotion; and (v) that the slope factors for arsenic-related bladder cancer and lung cancer would not change appreciably as a result of infections or coexposures in the Taiwanese population from which Morales and colleagues (28) derived the data.

### Exposure assessment

Exposure to arsenic via food depends on the concentration of arsenic in individual foods and the rate of consumption of these food items. The range of iAs content including a range of uncertainty for different food groups that represents content in crops worldwide was adapted from literature values (26, 27, 33) to derive the mean portion of iAs relative to the total food arsenic. Using a common range of arsenic content for food crops grown in different parts of the world has the advantages of demonstrating the effect of dietary patterns on arsenic exposure via food and allowing uniformity in calculations across all nations. For each cluster of countries, a lower and an upper bound value of iAs content was modeled at 50% and 100% bioavailability, respectively, to take into account a factor of uncertainty. JECFA noted the need for improved data on occurrence of different species of arsenic in, and their bioavailability from, different foods to improve the estimates of dietary and systemic exposure (26).

To estimate the total bioavailable iAs in the diet worldwide, these exposure assessment calculations were then consolidated for each relevant population, across all of the different foods consumed in different proportions. The GEMS Food Consumption Cluster Diets database (28) was used to gather information on the dietary patterns (amounts of specific foods consumed) in different parts

of the world, as it divides the world into 13 clusters of countries based on dietary similarities. The GEMS database uses data from the FAOSTAT to divide the countries of the world into thirteen clusters on the basis of similarities in dietary pattern. In the final step, the populations of individual nations across each of the GEMS cluster were summed to estimate the global population.

The primary assumption in the exposure assessment was that the values reported in literature for total foodborne exposure to arsenic and the proportion of iAs in different foodstuffs (6, 26, 30) are reasonably accurate. In addition, it was assumed that the rough upper and lower bounds for bioavailability of iAs in foods is 50% to 100% (26), with beverages being 100% as seen with drinking water. For calculations based on populations within each GEMS cluster, it was assumed that (i) roughly an equal number of men and women comprise each GEMS dietary cluster of nations; and (ii) that the individuals within each GEMS cluster consume roughly comparable amounts of the foodstuffs that are presented in the GEMS database, including across age groups and genders.

### Risk characterization

To characterize the risk of bladder, lung, and skin cancer due to foodborne arsenic, the data from dose-response and exposure assessment were integrated to quantify the burden of arsenic-related cancers across the world. For each cancer type, the respective slope factor was multiplied with the estimated range of daily dietary iAs exposure, and the population size of the individual GEMS cluster to obtain an annual gender-specific estimate of the additional number of foodborne arsenic-related cancers. The life span per individual was assumed to be 70 years.

### Results

The essential steps of risk assessment are hazard identification, dose-response relationship, exposure assessment, and risk characterization. For the present work, we relied on the hazard identification by IARC 2012 (1) that clearly identifies arsenic as a human carcinogen with increased risk for bladder, lung, and non-melanoma skin cancers. To establish the dose-response relationship, we converted the dose response estimates for water exposure to human dose and the data in Table 1 include the imputed slope factors for each of the cancers. For bladder and lung cancers, gender-specific slope factors are reported on the basis of the data adapted from Morales and colleagues (29). However, for skin cancer, the slope factors are the same for both the genders (30). The total increased risk in the population of each of the cancers for every incremental unit of foodborne arsenic was estimated on the basis of the slope factors.

For exposure estimation, the data in Table 2 provide the mean adjusted total arsenic content of foods used in the EFSA (27) dietary exposure estimates along with the conversion factors from total arsenic to iAs in each of the different foodstuffs provided in JECFA (26). In contrast to

**Table 1.** Slope factors, or cancer potency factors, for incidence of each arsenic-related cancer

Cancer type	Slope factor (increased population risk per $\mu\text{g}$ iAs/d)	
	Males	Females
Bladder <sup>a</sup>	0.0000127	0.0000198
Lung <sup>a</sup>	0.0000137	0.0000194
Skin <sup>b</sup>	0.000015	0.000015

<sup>a</sup>Slope factor derived by using data adapted from Morales et al. (2000).

<sup>b</sup>Slope factor was adapted from the United States EPA IRIS database (2001).

water exposures, not all of the arsenic in food is bioavailable and Table 3 presents the estimated levels of bioavailable iAs for the 13 GEMS food consumption clusters as well as the population size for each cluster. For each of these clusters, the GEMS food consumption database provides an estimate of the amount of cereals, vegetables, fruits, beverages, meat, nuts, and oilseeds consumed. Rice and rice products appear to be a major source of exposure to iAs, especially in GEMS cluster G composed of Asian countries.

Risk characterization of the total estimated cases of bladder, lung, and skin cancers attributable to foodborne arsenic annually, worldwide was calculated from the slope factors in Table 1 and the exposure data in Tables 2 and 3. These estimates are listed in Table 4 and further resolved by GEMS cluster and gender to yield the number of expected additional cases of bladder, lung, and skin cancer from foodborne iAs exposures per year in Table 5 with the assumption of 70 years life span per individual. Overall, the data indicate that arsenic in food causes a small, but significant burden of the three major cancers that is distributed throughout the world.

### Discussion

Using quantitative risk assessment, we estimated the increased incidence of cancers that can be attributed to arsenic in food. The most difficult aspect of this risk assessment was estimating the highly variable levels of iAs in the varied foods consumed by the different populations contained in the GEMS clusters. There is uncertainty in whether arsenic in food is equivalent to arsenic in water for disease promotion given the many other food constituents, such as folate (34) and selenium (35) that may modulate arsenic pathogenesis. In addition, the assumption of linear dose-response relationships of arsenic-related cancers is controversial, particularly regarding the mode of carcinogenicity of skin cancer, despite the EPA IRIS derivation of a single slope factor for arsenic-related skin cancer (30). There are no studies that present the effects of low-dose arsenic exposures on skin cancer,

**Table 2.** Mean adjusted total arsenic content of foods and the reported conversion factors from total arsenic to iAs used in the dietary exposure estimates

Food group	Total arsenic lower bound mean level (mg/kg)	Total arsenic upper bound mean level (mg/kg)	Mean% iAs
All cereal and cereal products	0.0671	0.0848	30–100 <sup>a</sup>
Cereal-based dishes	0.0157	0.0283	
Cereal and cereal products	0.0825	0.1017	
Sugar products and chocolate	0.0135	0.0320	30–100 <sup>a</sup>
Fats (vegetable and animal)	0.0063	0.0245	30–100 <sup>a</sup>
All vegetables, nuts, pulses	0.0121	0.0212	30–100 <sup>a</sup>
Vegetable soups	0.0050	0.0110	
Vegetables, nuts, pulses	0.0122	0.0213	
Starchy roots and tubers	0.0031	0.0142	30–100 <sup>a</sup>
Fruits	0.0051	0.0155	30–100 <sup>a</sup>
Juices, soft drinks, and bottled water	0.0030	0.0068	30–100 <sup>a</sup>
Fruit and vegetable juices	0.0048	0.0129	
Soft drinks	0.0044	0.0132	
Bottled water	0.0023	0.0041	
Coffee, tea, cocoa	0.0034	0.0051	30–100 <sup>a</sup>
Alcoholic beverages	0.0055	0.0151	30–100 <sup>a</sup> (this category not detailed in GEMS diets database and hence was not used for calculations)
Beer and substitutes	0.0054	0.0161	
Wine and substitutes	0.0061	0.0110	
Other alcoholic beverages	0.0085	0.0155	
All meat and meat products, offal	0.0044	0.0138	100 <sup>b</sup>
Meat and meat products	0.0042	0.0137	
Edible offal and offal products	0.0044	0.0139	
Meat-based preparations	0.0121	0.0185	
All fish and seafood	1.6136	1.6159	Standard ratio
Seafood and seafood products	5.5537	5.5545	0.015 – 0.10 mg/kg <sup>a</sup>
Fish and fish products	1.4426	1.4549	
Fish-based preparations	1.1524	1.1573	
Eggs	0.0042	0.0117	41 <sup>b</sup>
Milk and milk-based products	0.0044	0.0139	26 <sup>b</sup>
Milk and dairy-based drinks	0.0026	0.0104	
Dairy-based products	0.0068	0.0184	
Cheese	0.0065	0.0188	
Miscellaneous/special dietary products	0.3993	0.4187	30–100 <sup>a</sup> (Category not detailed in GEMS)
Miscellaneous products	0.2449	0.2658	
Foods for special dietary uses	0.4383	0.4573	

NOTE: Data adapted from references 14 and 26.

<sup>a</sup>Data adapted from reference 14.<sup>b</sup>Reference: 33.

which reduces certainty regarding the shape of the lower end of the dose–response curve. Thus, it is conservative to default to the linear model for determining the skin cancer potency factor. Accounting for these uncertainties, we provide estimates that levels of iAs found in food cause a low but significant increase in the burden of lung, bladder, and non-melanoma skin cancers worldwide.

There are a limited number of epidemiologic studies that examine the health effects of the levels of arsenic

commonly found in food. Much of the available data on disease risk come from studies of arsenic in drinking water and often the populations studied are exposed to higher levels of arsenic (>100 µg/L drinking water). However, as levels of arsenic in water decrease, the contribution of arsenic from food to total arsenic exposure becomes greater and more significant (7, 36). While human biomarkers for arsenic exposure, such as arsenic and metabolite levels in urine, blood, hair, or nails are available (36), it is not possible to determine

**Table 3.** Range of foodborne total and inorganic arsenic exposure at 50% to 100% bioavailability for 13 WHO-GEMS clusters of countries<sup>a</sup>

GEMS Cluster	Lower boundary of total As <sup>b</sup> ( $\mu\text{g}/\text{kg bw}/\text{day}$ ) <sup>c</sup>	Upper boundary of total As <sup>b</sup> ( $\mu\text{g}/\text{kg bw}/\text{day}$ )	Lowest boundary of iAs <sup>d</sup> (50% bioavailable) ( $\mu\text{g}/\text{day}$ ) <sup>f</sup>	Upper boundary of iAs <sup>e</sup> (100% bioavailable) ( $\mu\text{g}/\text{day}$ ) <sup>f</sup>	Range of iAs exposure via rice and rice products ( $\mu\text{g}/\text{day}$ )	Population mid-2012 (millions) <sup>g</sup>
A	0.91	1.26	4.8	53.4	0.92–6.95	302.5
B	2.87	3.47	10.37	108.35	0.32–2.41	224.9
C	1.38	1.79	9.09	85.46	0.95–7.22	263.7
D	1.32	1.72	6.71	66.95	0.33–2.53	408
E	1.41	1.83	5.75	63.45	0.13–0.97	339.2
F	1.84	2.19	5.25	57.27	0.13–0.97	26.7
G	2.08	2.42	7.82	75.14	3.79–28.78	3544.5
H	1.15	1.55	6.44	66.54	0.65–4.9	213.5
I	0.87	1.18	5.02	52.2	0.38–2.9	256.8
J	0.97	1.28	5.01	51.88	0.75–5.67	357
K	1.04	1.48	6.6	66.13	2.39–18.19	335.7
L	2.69	3.05	7.88	79.1	3.84–29.1	307.4
M	1.35	1.83	6.44	70.56	0.35–2.64	436.8

NOTE: Data are adapted from reference 28.

<sup>a</sup>Listing of countries within each cluster is available at <http://www.who.int/foodsafety/chem/gems/en/index1.html>.<sup>b</sup>Calculations based on Table 13, reference 26 for range of total arsenic content in food items.<sup>c</sup>Assuming 60 kg body weight per individual.<sup>d</sup>Lower bound for iAs content assumes non-detect equals zero.<sup>e</sup>Upper bound for iAs content assumes non-detect equals the limit of detection.<sup>f</sup>Calculations based on Table 15, reference 26 for range of mean% inorganic arsenic content in food items.<sup>g</sup>Data source: "Population Data sheet 2012" by the Population Reference Bureau ([www.prb.org](http://www.prb.org)). PRB has derived the data from International Programs Center of the U.S. Census Bureau, the United Nations (UN) Population Division, the Institut national d'etudes démographiques (INED), Paris, and the World Bank.

**Table 4.** Global burden of cancers caused by foodborne arsenic

Cancer	Male	Female	Total burden (global) by foodborne arsenic
Bladder	4,527–46,420	7,096–72,756	9,129–119,176
Lung	4,913–50,373	6,931–71,069	11,844–121,442
Skin (non-melanoma)	5,365–55,007	5,365–55,007	10,730–110,014

the proportion of the measurements attributable to arsenic in drinking water or food. For the purposes of estimating human health consequences associated with arsenic consumption, knowing the overall population arsenic exposure matters more than knowing the relative contribution from different routes of exposure. However, for the purpose of recommending interventions, it can be helpful to understand the separate contributions.

There are several additional unavoidable constraints with estimating health risks from arsenic in food. The bioavailability of arsenic in different foods varies with the food group or method of processing and the complexity of influence of other food constituents on arsenic toxicity and adverse health effects. We focused our exposure estimates and risk characterization on both the range of iAs content and the range of predicted bioavailability of iAs in different foods. This approach is limited by using the GEMS cluster data for food consumption, as it contains an inherently broad range of dietary variation between the countries within each cluster (37). For example, the daily consumption of rice in Bangladesh (GEMS cluster G

country) was reported as 445 gm/day (38); however, for GEMS cluster G the average rice consumed daily is 380 gm. Using the cluster values may underestimate arsenic exposure via rice in Bangladesh. On the other hand, for the USA (GEMS cluster M country) the actual daily consumption is 18 gm (38), whereas overall for cluster M, it is almost double that level at 35 gm/day. Moreover, one of the major assumptions in the current analysis is that the speciation and arsenic content of rice cultivated in different regions of the world would be the same. However, there are conflicting reports indicating a large range in the levels of iAs in rice from developing and developed countries (38, 39). To overcome these limitations and obtain a realistic estimate for iAs levels, we used data from studies that provide actual measured levels (27) in different categories of food items (6, 12, 40).

The GEMS cluster data also does not provide specific details of the consumption of certain miscellaneous food items with reported high levels of iAs (e.g., seaweed hijiki and edible algae; ref. 27; Table 2, miscellaneous items). In certain Asian countries, such as Japan, the consumption of seaweed is a relatively important part

**Table 5.** Annual expected burden of cancers caused by foodborne arsenic, by GEMS cluster and gender, LB and UB<sup>a</sup>

GEMS Cluster	Bladder cancer				Lung cancer				Skin cancer			
	Male		Female		Male		Female		Male		Female	
	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
A	195	2,001	306	3,137	212	2,172	299	3,064	231	2,371	231	2,371
B	145	1,488	227	2,332	157	1,614	222	2,278	172	1,763	172	1,763
C	170	1,744	267	2,734	185	1,893	260	2,671	202	2,067	202	2,067
D	263	2,699	413	4,230	286	2,929	403	4,132	312	3,199	312	3,199
E	219	2,244	343	3,517	237	2,435	335	3,436	259	2,659	259	2,659
F	17	177	27	277	19	192	26	270	21	209	21	209
G	2,287	23,449	3,584	36,753	2,482	25,446	3,502	35,901	2,710	27,787	2,710	27,787
H	138	1,412	216	2,214	149	1,533	211	2,162	163	1,674	163	1,674
I	166	1,699	260	2,663	180	1,843	254	2,601	196	2,013	196	2,013
J	230	2,362	361	3,702	250	2,563	353	3,616	273	2,799	273	2,799
K	217	2,221	339	3,481	235	2,410	332	3,400	257	2,632	257	2,632
L	198	2,034	311	3,187	215	2,207	304	3,114	235	2,410	235	2,410
M	282	2,890	442	4,529	306	3,136	431	4,424	334	3,424	334	3,424
Total	4,527	46,420	7,097	72,756	4,913	50,373	6,932	71,069	5,365	55,007	5,365	55,007

Abbreviations: LB, lower bounds; UB, upper bounds.

<sup>a</sup>Assuming 70 years life span per individual.

of diet and can add substantially to the daily exposure levels of iAs (26, 41).

Despite the complexity of assessing foodborne arsenic exposures, the estimates for global burden of cancers caused by the estimated range of exposures appear feasible. We found that human exposures to iAs through food is substantial (see Table 2) and can be roughly comparable with lower levels of arsenic in drinking water. It was reasonable to convert the data from that of Morales and colleagues (29) to dietary consumption and calculate slope factors for lung and bladder cancer to estimate risk of foodborne iAs. Using this dataset reduces the concern about issues of low-dose extrapolations of arsenic's carcinogenic effects; although, the estimates would be improved by including additional epidemiologic studies that focus on low dose consumption. A recent review (17) emphasized the need for such studies on bladder and lung cancer that address adequacy of the sample size, as well as the synergistic relationship of arsenic and smoking, duration of arsenic exposure, age when exposure began and ended, and histologic subtype of cancer (17). This review observed that many recent studies that examine the risk ratio of bladder cancer from low arsenic concentration (<100 µg/L) drew cases and controls from arsenic-endemic areas that may reduce the difference in arsenic exposure, requiring a larger sample size to determine whether an excess risk exists for a given exposure. The potential for arsenic from smoking and the different patterns for smoking worldwide to confound the risk estimates attributable to food consumption would likely be true for lung cancer estimates as well. In addition, exposure misclassification probably further reduced the difference between groups and epidemiologic studies focused on low-arsenic levels have a greater need to control for confounders (17).

The estimated global burden for arsenic induced bladder and lung cancers is highest for both males and females in cluster G for several possible reasons. First, cluster G comprises of countries in Asia where the arsenic content in the bedrock ranks among the highest in the world. This translates into high overall rate of exposure to arsenic through more than one route of exposure and on a consistent basis for an extended period- thus predisposing this population to develop arsenic induced cancers. Second, rice is the main food consumed in most of the countries in Cluster G. As depicted in Table 3, rice contributes up to 68.1% of iAs exposure in cluster G countries.

Perhaps related to the first reason or type of cultivar, rice grown in cluster G may contain higher levels of arsenic than rice grown elsewhere (38, 39). Finally, the population size is a chief component in our model for the estimation of the disease burden. Cluster G comprises nearly 50% of the world population with inclusion of China and India. For this reason, although the percentage of arsenic via rice is high in cluster L countries as well (up to 65.8%), this does not reflect in a high global burden of disease for this cluster owing to its small population size. Moreover, other recent studies have also reported rapidly rising cancer incidence and high cancer mortality rates in China and India contributing to a major portion of global cancer burden (42, 43).

In conclusion, the results of this quantitative risk assessment indicate that consumption of arsenic in food increases the incidence of bladder, lung, and skin cancer. There are limitations with the estimates that are derived from the ranges of arsenic content in food and the interactions of arsenic with other foodborne constituents. Nonetheless, the risk estimates are valuable for informing policies to reduce the global burden of disease from arsenic exposures in food.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

#### Authors' Contributions

**Conception and design:** S. Oberoi, A. Barchowsky, F. Wu  
**Development of methodology:** A. Barchowsky, F. Wu  
**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** S. Oberoi, F. Wu  
**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** S. Oberoi, A. Barchowsky, F. Wu  
**Writing, review, and/or revision of the manuscript:** S. Oberoi, A. Barchowsky, F. Wu  
**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** S. Oberoi, A. Barchowsky  
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#### References

1. International Agency for Research on Cancer. A review of human carcinogens. Part C: arsenic, metals, fibres, and dusts/IARC working group on the evaluation of carcinogenic risks to humans (2009). IARC monographs on the evaluation of carcinogenic risks to humans; v. 100C. (Lyon, France); 2012. Available from: <http://monographs.iarc.fr/ENG/Monographs/vol100C/index.php>.
2. Chen Y, Graziano JH, Parvez F, Liu M, Slavkovich V, Kalra T, et al. Arsenic exposure from drinking water and mortality from cardiovascular disease in Bangladesh: prospective cohort study. *Br Med J* 2011;342:d2431.
3. Moon K, Guallar E, Navas-Acien A. Arsenic exposure and cardiovascular disease: an updated systematic review. *Curr Atheroscler Rep* 2012;14:542-55.
4. Parvez F, Chen Y, Brandt-Rauf PW, Slavkovich V, Islam T, Ahmed A, et al. A prospective study of respiratory symptoms associated with chronic arsenic exposure in Bangladesh: findings from the Health

- Effects of Arsenic Longitudinal Study (HEALS). *Thorax* 2010;65:528–33.
5. von Ehrenstein OS, Mazumder DN, Yuan Y, Samanta S, Balmes J, Si A, et al. Decrements in lung function related to arsenic in drinking water in west bengal, India. *Am J Epidemiol* 2005;162:533–41.
  6. Schoof RA, Yost LJ, Eickhoff J, Crecelius EA, Cragin DW, Meacher DM, et al. A market basket survey of inorganic arsenic in food. *Food Chem Toxicol* 1999;37:839–46.
  7. Kile ML, Houseman EA, Breton CV, Smith T, Quamruzzaman Q, Rahman M, et al. Dietary arsenic exposure in bangladesh. *Environ Health Perspect* 2007;115:889–93.
  8. Davis MA, Mackenzie TA, Cottingham KL, Gilbert-Diamond D, Punshon T, Karagas MR. Rice consumption and urinary arsenic concentrations in U.S. children. *Environ Health Perspect* 2012;120:1418–24.
  9. Samal AC, Kar S, Bhattacharya P, Santra SC. Human exposure to arsenic through foodstuffs cultivated using arsenic contaminated groundwater in areas of West Bengal, India. *J Environ Sci Health A* 2011;46:1259–65.
  10. Dittmar J, Voegelin A, Maurer F, Roberts LC, Hug SJ, Saha GC, et al. Arsenic in soil and irrigation water affects arsenic uptake by rice: Complementary insights from field and pot studies. *Environ Sci Technol* 2010;44:8842–48.
  11. Biswas A, Biswas S, Santra SC. Risk from winter vegetables and pulses produced in arsenic endemic areas of Nadia District: field study comparison with market basket survey. *Bull Environ Contam Toxicol* 2012;88:909–14.
  12. Muñoz O, Diaz OP, Leyton I, Nuñez N, Devesa V, Súñer MA, et al. Vegetables collected in the cultivated andean area of Northern Chile: total and inorganic arsenic contents in raw vegetables. *J Agric Food Chem* 2001;50:642–7.
  13. Signes A, Mitra K, Burló F, Carbonell-Barrachina AA. Effect of cooking method and rice type on arsenic concentration in cooked rice and the estimation of arsenic dietary intake in a rural village in West Bengal, India. *Food Addit Contam A* 2008;25:1345–52.
  14. World Health Organization. Arsenic in drinking water, background document for development of WHO guidelines for drinking water quality. Geneva, Switzerland: WHO; 2011. Available from: [http://www.who.int/water\\_sanitation\\_health/dwq/chemicals/arsenic.pdf](http://www.who.int/water_sanitation_health/dwq/chemicals/arsenic.pdf).
  15. Abernathy CO, Thomas DJ, Calderon RL. Health effects and risk assessment of arsenic. *Br J Nutr* 2003;133:1536S–8S.
  16. European Food Safety Association. EFSA panel on contaminants in the food chain (CONTAM): scientific opinion on arsenic in food. *EFSA J* 2009;7:60–71.
  17. Gibb H, Haver C, Gaylor D, Ramasamy S, Lee JS, Lobdell D, et al. Utility of recent studies to assess the National Research Council 2001 estimates of cancer risk from ingested arsenic. *Environ Health Perspect* 2011;119:284–90.
  18. Smith AH, Goycolea M, Haque R, Biggs ML. Marked increase in bladder and lung cancer mortality in a region of Northern Chile due to arsenic in drinking water. *Am J Epidemiol* 1998;147:660–9.
  19. Smith AH, Ercumen A, Yuan Y, Steinmaus CM. Increased lung cancer risks are similar whether arsenic is ingested or inhaled. *J Expo Sci Environ Epidemiol* 2009;19:343–8.
  20. Ferreccio C, Yuan Y, Calle J, Benitez H, Parra RL, Acevedo J, et al. Arsenic, tobacco smoke, and occupation: associations of multiple agents with lung and bladder cancer. *Epidemiology* 2013;24:898–905.
  21. Begum M, Horowitz J, Hossain MI. Low-dose risk assessment for arsenic: a meta-analysis approach. *Asia Pac J Public Health* 2012. DOI: 10.1177/1010539512466568.
  22. Christoforidou EP, Riza E, Kales SN, Hadjstavrou K, Stolidi M, Kastania AN, et al. Bladder cancer and arsenic through drinking water: a systematic review of epidemiologic evidence. *J Environ Sci Health A Tox Hazard Subst Environ Eng* 2013;48:1764–75.
  23. Hughes MF, Beck BD, Chen Y, Lewis AS, Thomas DJ. Arsenic exposure and toxicology: a historical perspective. *Toxicol Sci* 2011;123:305–32.
  24. Wu MM, Kuo TL, Hwang YH, Chen CJ. Dose-response relation between arsenic concentration in well water and mortality from cancers and vascular diseases. *Am J Epidemiol* 1989;130:1123–32.
  25. Hsueh YM, Cheng GS, Wu MM, Yu HS, Kuo TL, Chen CJ. Multiple risk factors associated with arsenic-induced skin cancer: effects of chronic liver disease and malnutritional status. *Br J Cancer* 1995;71:109–14.
  26. Joint FAO/WHO Expert Committee on Food Additives (JECFA). Safety evaluation of certain contaminants in food. 63, FAO JECFA Monographs. Geneva, Switzerland: WHO Food Additives Series; 2011. Available from: [http://whqlibdoc.who.int/trs/who\\_trs\\_959\\_eng.pdf](http://whqlibdoc.who.int/trs/who_trs_959_eng.pdf).
  27. EFSA. EFSA panel on contaminants in the food chain (contam): Scientific opinion on arsenic in food. *EFSA J* 2009;7:60–71.
  28. World Health Organization. Global environment monitoring system-food contamination monitoring and assessment programme (GEMS/Food). Geneva, Switzerland: WHO; 2006. Available from: <http://www.who.int/foodsafety/chem/gems/en/index1.html>.
  29. Morales KH, Ryan L, Kuo TL, Wu MM, Chen CJ. Risk of internal cancers from arsenic in drinking water. *Environ Health Perspect* 2000;108:655–61.
  30. United States Environmental Protection Agency Integrated Risk Information System (IRIS). Arsenic, inorganic. Washington, DC; 1998. Available from: <http://www.epa.gov/iris/subst/0278.htm>.
  31. Tseng WP, Chu HM, How SW, Fong JM, Lin CS, Yeh S. Prevalence of skin cancer in an endemic area of chronic arsenicosis in Taiwan. *J Natl Cancer Inst* 1968;40:453–63.
  32. Tseng WP. Effects and dose-response relationships of skin cancer and blackfoot disease with arsenic. *Environ Health Perspect* 1977;19:109–19.
  33. Yost LJ, Schoof RA, Aucoin R. Intake of inorganic arsenic in the North American diet. *Hum Ecol Risk Assess* 1998;4:137–52.
  34. Hall MN, Gamble MV. Nutritional manipulation of one-carbon metabolism: effects on arsenic methylation and toxicity. *J Toxicol* 2012;2012:595307.
  35. Chen Y, Hall M, Graziano JH, Slavkovich V, van Geen A, Parvez F, et al. A prospective study of blood selenium levels and the risk of arsenic-related premalignant skin lesions. *Cancer Epidemiol Biomarkers Prev* 2007;16:207–13.
  36. Kurzius-Spencer M, Burgess JL, Harris RB, Hartz V, Roberge J, Huang S, et al. Contribution of diet to aggregate arsenic exposures-An analysis across populations. *J Expo Sci Environ Epidemiol* 2014;24:156–62.
  37. Liu Y, Wu F. Global burden of aflatoxin-induced hepatocellular carcinoma: a risk assessment. *Environ Health Perspect* 2010;118:818–24.
  38. Meharg AA, Williams PN, Adomako E, Lawgali YY, Deacon C, Villada A, et al. Geographical variation in total and inorganic arsenic content of polished (white) rice. *Environ Sci Technol* 2009;43:1612–17.
  39. Carey AM, Lombi E, Donner E, de Jonge MD, Punshon T, Jackson BP, et al. A review of recent developments in the speciation and location of arsenic and selenium in rice grain. *Anal Bioanal Chem* 2012;402:3275–86.
  40. Diaz OP, Leyton I, Munoz O, Nunez N, Devesa V, Suner MA, et al. Contribution of water, bread, and vegetables (raw and cooked) to dietary intake of inorganic arsenic in a rural village of Northern Chile. *J Agric Food Chem* 2004;52:1773–9.
  41. Uneyama C, Toda M, Yamamoto M, Morikawa K. Arsenic in various foods: cumulative data. *Food Addit Contam* 2007;24:447–534.
  42. Goss PE, Strasser-Weippl K, Lee-Bychkovskiy BL, Fan L, Li J, Chavarri-Guerra Y, et al. Challenges to effective cancer control in China, India, and Russia. *Lancet Oncol* 2014;15:489–538.
  43. Collingridge D. Three countries-half of the global cancer burden. *Lancet Oncol* 2014;15:483.

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