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DIETARY EXPOSURE TO INORGANIC ARSENIC IN KENYA

BISONG LOVELYN AGBOROJONG

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Orientador: Doutora Ana Catarina Moreira de Carvalho

- Instituto de Saúde Pública da Universidade do Porto

- Faculdade de Ciências da Nutrição e Alimentação da Universidade do Porto

Co-Orientador: Doutora Sofia Almeida Costa

Instituto de Saúde Pública da Universidade do Porto

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ABBREVIATIONS

EFSA: European Food Safety Authority

IARC: International Agency for Research on Cancer

GDD: Global Dietary Database

BMR: Benchmark response

BMDLs: Low benchmark dose lower confidence limits

$BMDL_{05}$: Low benchmark dose lower confidence limits of 5%

RP: Reference Point

LB: Lower Bound

UB: Upper Bound

MOE: Margin of Exposure

WHO: World Health Organization

DMA: Dimethylarsinic

ROS: Reactive Oxygen Species

DDR: DNA damage response

CA: Chromosomal aberrations

MN: Micronuclei

KNMS: Kenya National Micronutrient Survey

LOQ: Limit of quantification

LOD: Limit of detection

ABSTRACT

Inorganic arsenic exposure, mainly resulting from dietary sources, has been associated with a higher risk of cancer due to its genotoxic effects. This study aims to estimate the dietary exposure to inorganic arsenic among the Kenyan population and its associated factors. Consumption data were collected through 24-hour recalls from a convenience sample of the Kenyan population from the Kenya National Micronutrient Survey (n=826; ages 6 months-49 years). Occurrence data on inorganic arsenic in food were obtained from EFSA publications. For the risk characterization, margins of exposure (MOE) for skin cancer outcomes were calculated. To compare inorganic arsenic exposure between groups, the Mann-Whitney U-Test and the Kruskal-Wallis Test were used. For the general study population, the median estimated daily dietary exposure per body weight to inorganic arsenic was 0.12 µg/kg/day, ranging from 0.06 to 0.22 µg/kg/day (25th to 75th percentile), with 1.33 µg/kg/day at the 99th percentile in the Lower Bound (LB) scenario, and 0.31 µg/kg/day, ranging from 0.20 to 0.51 µg/kg/day (25th to 75th percentile), with 2.15 µg/kg/day at the 99th percentile in the Upper Bound (UB) scenario. Children aged 6 months to 5 years had the highest inorganic arsenic exposure (median 0.17 µg/kg/day; 99th percentile 2.39 µg/kg/day in the LB, and 0.52 µg/kg/day; 99th percentile 3.23 µg/kg/day in the UB). For skin cancer outcomes, the median MOE estimated in the LB and UB was 2.48 and 0.67, respectively. In this study, according to the MOE estimates, 78.8% of the population presented a concerning exposure to inorganic arsenic in LB scenario and 97.4% in UB scenario. Rice and grains and grain-based products were the main sources of inorganic arsenic. The current dietary exposure to inorganic arsenic in the Kenyan population raises concerns regarding skin cancer outcomes, since the exposure exceeds the level considered safe. Our results highlight the need to reduce dietary inorganic arsenic exposure, especially among children, adolescents, rural residents, and pregnant and lactating women.

Keywords

Exposure assessment, inorganic arsenic, risk assessment, Survey, Kenya, food contaminants.

RESUMO

A exposição ao arsénico inorgânico, principalmente proveniente de fontes alimentares, tem sido associada a um risco mais elevado de cancro devido aos seus efeitos genotóxicos. Este estudo tem como objetivo estimar a exposição alimentar ao arsénico inorgânico entre a população queniana e os fatores associados. Os dados de consumo foram recolhidos através de questionários às 24 horas anteriores de uma amostra de conveniência da população queniana do Kenya National Micronutrient Survey (n = 826; idades entre 6 meses e 49 anos). Os dados de ocorrência de arsénio inorgânico nos alimentos foram obtidos a partir de publicações da EFSA. Para a caracterização do risco, foram calculadas as margens de exposição (MOE) para os resultados de cancro da pele. Para comparar a exposição ao arsénico inorgânico entre os grupos, foram utilizados o teste U de Mann-Whitney e o teste de Kruskal-Wallis. Para a população em geral, a mediana estimada da exposição diária alimentar por peso corporal ao arsénico inorgânico foi de 0,12 µg/kg/dia, variando de 0,06 a 0,22 µg/kg/dia (25º ao 75º percentil), com 1,33 µg/kg/dia no 99º percentil no cenário Lower Bound (LB) e 0,31 µg/kg/dia, variando de 0,20 a 0,51 µg/kg/dia (25º ao 75º percentil), com 2,15 µg/kg/dia no 99º percentil no cenário Upper Bound (UB). Crianças com idades entre 6 meses e 5 anos tiveram a maior exposição ao arsênico inorgânico (mediana de 0,17 µg/kg/dia; percentil 99 de 2,39 µg/kg/dia no LB e 0,52 µg/kg/dia; percentil 99 de 3,23 µg/kg/dia no UB). Para os resultados de cancro de pele, a mediana do MOE estimada no LB e no UB foi de 2,48 e 0,67, respetivamente. Neste estudo, de acordo com as estimativas do MOE, 78,8% da população apresentou uma exposição preocupante ao arsénio inorgânico no cenário LB e 97,4% no cenário UB. O arroz, os cereais e os produtos à base de cereais foram as principais fontes de arsénio inorgânico. A exposição alimentar atual ao arsénico inorgânico na população queniana suscita preocupações quanto aos resultados do cancro de pele, uma vez que a exposição excede o nível considerado seguro. Os nossos resultados destacam a necessidade de reduzir a exposição alimentar ao arsénico inorgânico, especialmente entre crianças, adolescentes, residentes rurais e mulheres grávidas e lactantes.

Palavras-chave

Avaliação da exposição, arsénico inorgânico, avaliação de risco, pesquisa, Kenya, contaminantes alimentares.

INTRODUCTION

Arsenic is a metalloid with atomic number 33, a relative atomic mass of 74.92, and occurs in group V of the periodic table. It is commonly found in the Earth's crust as well as in the soil, air, and groundwater (1, 2). It can be found combined with other elements such as sulfur, oxygen, carbon, and hydrogen. Inorganic arsenic (iAs) originates from its combination with sulfur and oxygen, while organic arsenic arises from its combination with carbon and hydrogen. In natural drinking water, arsenic appears in the inorganic form due to oxygenated conditions (3).

iAs are released into the environment by both natural and man-made processes, such as mining, coal and geothermal extraction, agricultural operations, industrial and municipal waste, fertilizers, pesticides, paints, and cosmetics. Volcanic emissions and the disintegration and dissolution of rocks and minerals are examples of natural sources. It could contaminate surface water, groundwater, soil, and air. The main way that humans are exposed is by consuming contaminated food and water (4, 5). However, geogenic mineralization and mining activity are the major sources of iAs pollution, which contribute to iAs contamination in groundwater and foods, especially grain-based products (6, 7). It has been predicted that all the earth's continents have high iAs concentrations, especially Asia, followed by Africa and America (8).

When assessing dietary exposure to iAs across all age groups, the primary sources of exposure were "rice", "rice-based products", "grains and grain-based products (not rice)", and "drinking water", according to the European Food Safety Authority (EFSA) report from 2021 (9).

Another study, conducted in Germany, identified that across all age categories, the food group "Grains and grain-based products" (including rice) had the greatest contribution on iAs dietary exposure. For the age categories 0.5–<5 years, 12–17 years, and ≥14 years, the main food group "Composite dishes" was identified as a significant contributor to iAs as well. Both major food groups include rice (Grains and grain-based products) and rice-based products like rice pudding, rice, vegetable and meat meals, or rice and vegetable meals (Composite dishes), which are among the foods that significantly influence dietary exposure to iAs in all age groups. Due to high consumption, the third major contributor for both infants and young children was food products for infants and toddlers. In contrast, for adolescents and adults, the main contributors are coffee, chocolate, tea, and infusions (12).

It is expected that for infants and toddlers "Cereal-based food for infants and young children" and "Children's biscuits, rusks, and cookies") contribute significantly to the dietary exposure to iAs due to the dietary patterns adopted during these early ages (9-11).

Information regarding dietary exposure to inorganic arsenic (iAs) in African countries has been notably scarce until present.

Arsenic, in its inorganic form, has been classified among the top ten chemicals that are a threat to human health by the World Health Organization (WHO) (12, 13). iAs toxicity to living organisms has raised significant concerns. The EFSA Panel on Contaminants in the Food Chain (CONTAM) used the benchmark dose lower confidence limit based on a benchmark response (BMR) of 5% of 0.06 µg iAs/kg bw per day as a Reference Point (RP) on skin cancer (14). A margin of exposure (MOE) approach for risk characterization is used for the different carcinogenic effects, and a value of 1 raises a public health concern in the case of dietary exposure to iAs (14).

This study aims to estimate the dietary exposure to inorganic arsenic in a sample of the Kenyan population, analyzing the contribution of specific food groups.

LITERATURE REVIEW

2.1 Toxicokinetic and Metabolism

Inorganic arsenic is readily absorbed after being ingested by humans. After ingestion and absorption, it is widely distributed to nearly all organs, and it can also cross the placental barrier. It is distributed between plasma and erythrocytes in blood (14).

In humans, it is metabolized through three different but linked pathways through a sequence of reduction and oxidation methylation steps in the classical pathway. The first step of metabolism after ingestion is the reduction of arsenic from +5 to +3 in the blood and the liver. Then, the +3 species is coupled with a methyl group as it undergoes a cycle of oxidative methylation and reductive reactions. Secondly, arsenic binds to specific proteins or bonds with glutathione and is later methylated by arsenite-methyltransferase. After a series of reactions, it is finally oxidized to the respective pentavalent form. Excretion through urine in the form of methylated species or inorganic arsenic occurs with a half-life of about 2-3 days (14, 15).

The extent of methylation is responsible for its toxicity, while vulnerability factors include sex, life stage, nutritional status, and genetic polymorphism (14, 16, 17).

2.2 Mode of genotoxic action

Exposure to iAs species induces oxidative stress, which likely contributes to various biological effects by disrupting signaling pathways, causing epigenetic modifications, and directly damaging cellular molecules.

2.2.1 Induction of oxidative stress

Arsenic species induce oxidative stress through multiple interconnected mechanisms. Inorganic arsenic disrupts mitochondrial function by inhibiting key enzymes in the electron transport chain, such as complexes I and III and succinic dehydrogenase, leading to the increased generation of reactive oxygen species (ROS), including superoxide anions (O_2^-) and hydrogen peroxide (H_2O_2) (18). Additionally, during the metabolic formation of intermediate arsenic compounds like dimethylarsinic (DMA), peroxy radicals are produced, causing oxidative damage to cellular components (19). The oxidation of arsenite (As^{3+}) to arsenate (As^{5+}) also contributes to ROS generation (20). Moreover, arsenic species interfere with cellular antioxidant defenses by binding

to thiol groups in enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, thereby inhibiting their activity and diminishing the cell's ability to neutralize ROS. Collectively, these processes result in the accumulation of oxidative damage and underlie the genotoxic potential of arsenic, particularly its capacity to damage DNA and other vital cellular structures (21).

2.2.2 Interference with the DNA damage response

Arsenic species disrupt the DNA damage response through multiple mechanisms, impacting both DNA repair processes and cell cycle regulation. At low concentrations, iAs and its metabolites inhibit DNA repair by interacting with redox-sensitive cysteine residues in zinc finger domains of key repair proteins. This interaction leads to the inactivation of enzymes such as poly (ADP-ribose) polymerase-1 (PARP-1), which is crucial for DNA repair. Additionally, arsenic exposure interferes with cell cycle checkpoints and apoptotic pathways, promoting cell proliferation and survival of cells with DNA damage. This interference allows the accumulation of genetic mutations and contributes to carcinogenesis. Collectively, disruptions in DNA damage response (DDR) mechanisms enhance the genotoxic potential of arsenic, leading to increased DNA damage and genomic instability(22, 23).

Inorganic arsenic species also influence cellular signaling pathways that regulate various processes, including cell proliferation, differentiation, and apoptosis. They can modulate cell cycle regulators at both transcriptional and post-translational levels, as well as affect specific protein-protein interactions. For instance, arsenic compounds have been shown to interfere with regulatory proteins such as cyclins, thereby playing a crucial role in cell cycle control. Additionally, inorganic arsenic exposure can activate both intrinsic and extrinsic apoptotic pathways through the caspase cascade, leading to programmed cell death (24).

2.2.3 Induction of clastogenic and aneugenic events

Inorganic arsenic is an inducer of chromosomal aberrations (CAs) and micronuclei (MN) in both in-vitro and in-vivo models, as well as in humans. A comparative analysis of occupational and environmental studies assessing MN frequency in lymphocytes of individuals exposed to various genotoxic agents, including pesticides, herbicides, polycyclic aromatic hydrocarbons (PAHs), and formaldehyde, revealed that metals induced the most significant fold increase in MN frequency over background levels. Among these, arsenic exposure was one of the most concerning contaminants, resulting in a 6.5-fold increase in MN frequency (1).

Inorganic arsenic induces micronuclei formation through two primary mechanisms: clastogenic and aneugenic effects. Clastogenicity arises from DNA strand breaks leading to acentric chromatids or chromosome fragments, which are then encapsulated in MN. Aneugenicity results from interference with mitotic progression, causing whole chromatids or chromosomes to be mis-segregated into MN. Inorganic arsenic can disrupt the spindle assembly checkpoint, impairing the proper attachment of microtubules to kinetochores and leading to chromatid mis-segregation. Additionally, inorganic arsenic exposure has been shown to induce c-anaphase, a form of abnormal anaphase characterized by the mis segregation of whole chromatids, resulting in the formation of MN containing whole chromosomes. These mechanisms contribute to genomic instability and are implicated in arsenic-induced carcinogenesis (25, 26) .

2.2.4 Induction of gene mutations

Inorganic arsenic (iAs) is generally considered a weak inducer of gene mutations. It exhibits low mutagenic activity in standard bacterial and mammalian cell mutation assays. However, inorganic arsenic can enhance the mutagenic effects of other DNA-damaging agents, a phenomenon known as co-mutagenesis. For instance, inorganic arsenic has been shown to potentiate the mutagenic effects of ultraviolet (UV) radiation, leading to an increased mutational burden in skin cells. This co-mutagenic effect is attributed to inorganic arsenic's ability to interfere with DNA repair mechanisms, thereby increasing the persistence of DNA damage induced by UV radiation. These interactions highlight the complex role of inorganic arsenic in mutagenesis, where it may not directly cause mutations but can exacerbate the mutagenic effects of other agents (27).

2.3 Risk-assessment methodology and health effects

Risk assessment studies have been done to evaluate the effect of inorganic arsenic on human health by EFSA in the European context (14, 28).

Risk assessment is a four-step scientific process involving 1) hazard identification, 2) hazard characterisation, 3) exposure assessment, and 4) risk characterisation used in toxicological studies to protect the public and the environment from food-borne hazards. The first step (*Hazard identification*) involves identifying chemical hazards such as inorganic arsenic, residues of pesticides, and drugs, and biological hazards such as bacteria, and viruses present in food which can cause harm to living organisms. In the second step (*Hazard characterisation*), foodborne

hazards are associated with different health effects. These effects are studied, and the level of exposure which is safe for consumers is calculated. Then, step three (*Exposure assessment*) aims to assess the exposure to a certain contaminant, through the amount of the hazard present in food and the quantity consumed by different age groups. In the final step (*Risk characterisation*), risk assessors determine the extent of the risk. If the level of exposure exceeds the established safe limits, it could pose health concerns for the general public or certain vulnerable groups. A margin of exposure (MOE) approach is used to characterize the risk of the different genotoxic effects (29).

According to scientific reports from EFSA, that used a risk assessment methodology, iAs is a genotoxic carcinogen, associated with several adverse health effects, including skin cancer, lung cancer, respiratory disease, skin lesions, ischemic heart disease, and chronic kidney disease (14, 28). Particularly, the latest risk assessment conducted by EFSA focused primarily on skin cancer and used a benchmark dose approach. In this report, an exposure of 0.06 μg iAs/kg bw was defined as reference point that result in a 5% increase of the background incidence of skin cancer after adjustment for confounders (14).

Also, the International Agency for Research on Cancer (IARC) classified inorganic arsenic as carcinogenic to humans (Group 1), with sufficient evidence to result in cancer of the skin, lungs, urinary bladder, prostate, liver, and kidneys (30). Observations from human epidemiological studies indicate an association between dietary exposure to inorganic arsenic and several health effects (Table 1).

Table 1: Epidemiological studies and health outcomes concerning dietary exposure to inorganic arsenic

Type of study	Age group/sex	Country	Main food sources	Outcome
Total Diet Study (31)	Total population	Germany	Grains and rice	Cancer, low birth weight, neurotoxicity
HEAL Study (32, 33)	Adults	Bangladesh	Rice and drinking water	Skin cancer, lung, and bladder
Birth Cohort Study (34, 35)	Pregnant women & infants	New Hampshire (USA)	Rice, rice cereals, drinking water	Decreased birth weight, and neurotoxicity
Cohort study (36)	Pregnant women	Bangladesh	Tube well drinking water	Decreased birth weight, birth length, and head and chest circumference.
Survey (37)	Children	Italy	Rice and rice-based snacks	Increased oxidative stress biomarkers

2.4 Inorganic Arsenic – a public health concern

Inorganic arsenic occurs naturally in the earth's crust and is thus present globally and poses a significant global health concern due to its presence in groundwater, crops, and food sources (38). However, depending on several factors, such as the degree of anthropogenic activities, age, and food consumption patterns, the level of contamination differs from one country to another.

However, most regions in Africa, Central Asia, Southeast Asia, South America, and North America are highly exposed, with Africa being the 4th area most affected and the 2nd most affected population (Figure 1) (39). A reference point of 0.06 µg iAs/kg bw per day was chosen on skin cancer as well as lung cancer, bladder cancer, skin lesions, ischemic heart disease, chronic kidney disease, respiratory disease, spontaneous abortion, stillbirth, infant mortality and neurodevelopmental effects based on results from case-control studies on basal cell carcinoma from the US, Hungary, Romania, and Slovakia (40, 41). The EFSA Panel on Contaminants in the Food Chain concluded that a margin of exposure of 1 raises public health concern regarding skin cancer (14). The mean daily dietary exposure to inorganic arsenic in the European countries was estimated to be 0.03-0.15ug/kg bw for adults, 0.12-0.61 ug/kg bw for toddlers, and 0.09-0.61ug/kg bw for infants (14).

As a result of the global public health concern about the carcinogenicity of inorganic arsenic, the WHO prescribed a maximum permissible limit of 10ug/L inorganic arsenic in drinking water worldwide, which was the same as that adopted by the United States Environmental Protection Agency (42) , the European Union, and most countries(43).

However, based on a recent study, approximately 90-220 million people worldwide are probably at higher levels of exposure to groundwater inorganic arsenic (8, 39).

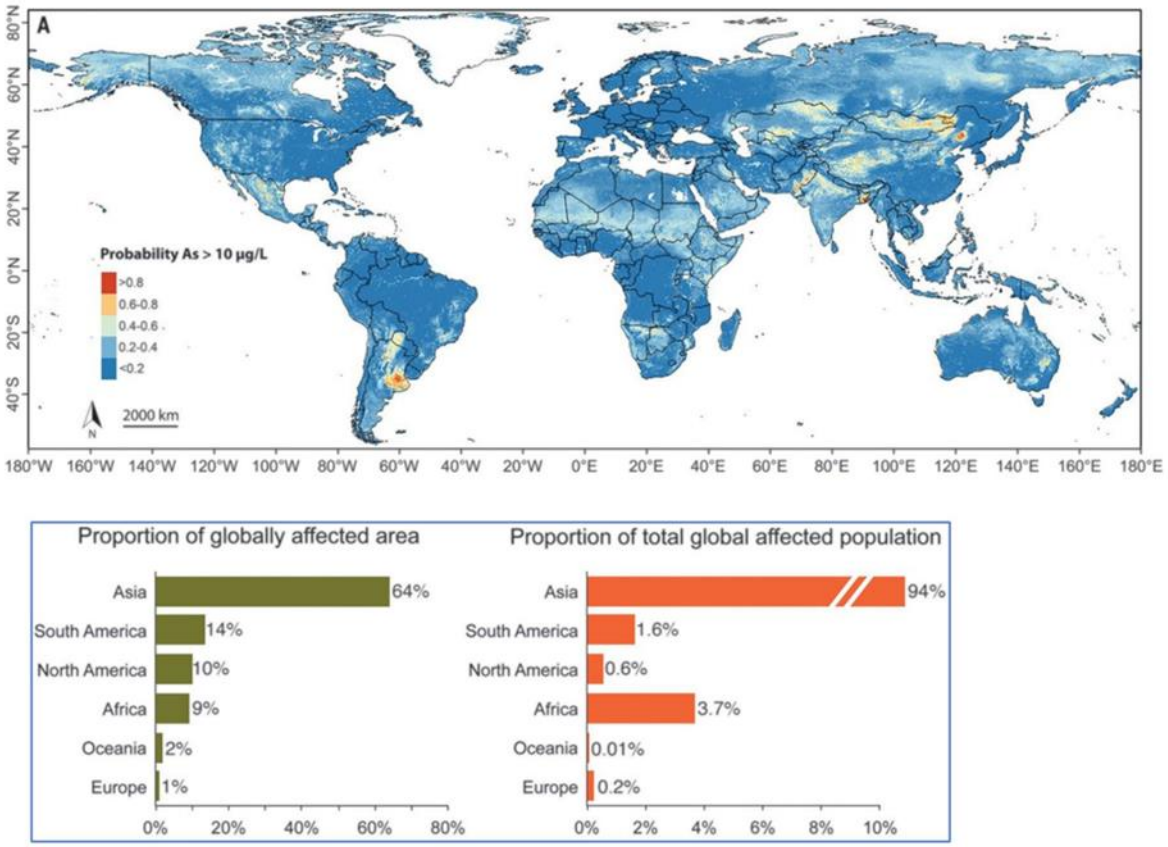

Figure 1: Inorganic arsenic global distribution in groundwater and population affected(39).

2.5 Focus on Kenya

Kenya is one of the countries highly affected by inorganic arsenic in Africa due to the many mining activities carried out in most regions, causing leakage and drainage of this contaminant into the water bodies (44, 45). An assessment carried out on the quality of water from eight major lakes in Kenya proved the presence of metal contaminants notably inorganic arsenic resulting from mine

tailings (46). Inorganic arsenic is expected to be on the rise in Africa due to an increase in human activities and natural occurrences (47). However, there is a lack of information on dietary exposure to inorganic arsenic in Kenya. Individuals residing in regions with significant inorganic arsenic contamination, especially in drinking water and food, are at increased risk and may need specific public health interventions.

The findings from this project will aid in the design and implementation of targeted interventions aimed at reducing inorganic arsenic exposure in Africa and, more broadly, at the global level. By understanding the extent of exposure, policymakers may provide effective strategies and initiatives for mitigating the health risks associated with arsenic contamination in food and water, ensuring that vulnerable populations are protected.

OBJECTIVE

This thesis aims to estimate the dietary exposure to iAs in a sample of the Kenyan population. Moreover, the contribution of specific food groups to inorganic arsenic dietary exposure will be analyzed.

METHODS

4.1 Study population - Kenya National Micronutrient Survey

The data used in the study were sourced from the Kenya National Micronutrient Survey (KNMS), conducted between 2011-2012 (48) available in the GDD platform(49) . In KNMS, participants aged between 6 months and 49 years were selected using a stratified two-stage cluster design made up of 296 clusters, 173 in the rural and 123 in urban areas. Urban areas were classified as Municipalities, Cities, Urban Councils, all District Headquarters, and Town Councils. Rural areas were classified as large, sparsely populated regions, primarily consisting of open fields, where farming was the predominant economic activity (48).

The KNMS 2011-2012 assessed different dimensions of a sample of the Kenyan population, such as socio-economic status, household characteristics, demographics, and dietary intake, by systematically collecting data at the household level. The data collection teams were trained, and piloting activities were done before the main fieldwork. The fieldwork for this survey was executed in 2011, spanning from September to December, applying a comprehensive suite of data collection instruments. These instruments encompassed:

- A household questionnaire
- Age-specific individual questionnaires
- Anthropometric assessment forms
- The Kenya Integrated Household Budget Survey (KIHBS) questionnaire
- A multiple-pass 24-hour dietary recall module

For this thesis, we used data on sex, age group, residence, pregnancy and lactation, weight and dietary information, collected through questionnaires. The household questionnaire was conducted to gather information about participants' sex, age group, and residency. Then, an age and sex-specific individual questionnaire was used to collect detailed information about the participants. One example of such a questionnaire was the women's questionnaire for ages 15 to 49, which addressed health issues concerning women of reproductive age, including inquiries about

pregnancy and lactation. With the aid of the anthropometric assessment forms, participants' body weight was either measured or self-reported (49).

4.2 Dietary assessment methods

In KNMS, trained interviewers collected information on dietary intake. Adults, as well as parents and guardians of children, were asked about a 24-hour recall. During the presential interview, the participants reported and quantified all food and beverages (overall diet) that they ate during a day, per occasion.

Food atlas and food photographs, household measures (cups, spoons, glasses, and bowls), standard units (such as slices and pieces), reference objects (tennis balls, matchboxes, mounds) or grids (rulers, rectangular pieces, and wedges), were all used for the quantification of food items.

4.3 Occurrence data of inorganic arsenic in foods

Data on the occurrence of inorganic arsenic in food groups were extracted from the EFSA scientific Opinion on inorganic arsenic in Food, published in 2021 (9). For each food group, the mean concentration of lower bound and upper bound inorganic arsenic reported by EFSA were used to estimate the inorganic arsenic levels in foods consumed by the population in Kenya.

The left-censored occurrence data (results below the limit of detection (LOD) or limit of quantification (LOQ)) was treated by the substitution method as recommended in Principles and Methods for the Risk Assessment of Chemicals in Food (50) and in the EFSA scientific report on Management of left-censored data in dietary exposure assessment of chemical substances (51). The guide suggests that the LB (lower bound) and UB (upper bound) approach should be used for chemicals that are likely to be present in food (e.g., naturally occurring contaminants and nutrients). The LB is obtained by assigning a value of zero (the minimum possible value) to all samples reported as lower than the LOD/LOQ. The UB is obtained by assigning the numerical value of LOD/LOQ to values reported as < LOD/LOQ (the maximum possible value), depending on whether the data provider reported the LOD/LOQ. The outcome of this approach will generate two exposure assessments under the LB and the UB scenarios (52).

4.4 Assessment of dietary exposure to inorganic arsenic and risk characterisation

Food consumption data were merged with the occurrence data using the FoodEx2 base-term codes, as foods from both datasets were coded using this food classification system. For some food items, for which contamination with inorganic arsenic was expected but no occurrence data were available, some assumptions were made:

- For meat soup, mean concentration of inorganic arsenic for drinking water was considered because it is composed mainly of water;
- Vegetables without inorganic arsenic concentration on occurrence data were attributed the code as garlic since they are aggregated within a hierarchical parent-child structure (53);
- Preserved vegetables or canned vegetables were attributed the same code as the main ingredient or vegetable, and the brine was considered disregarded;
- Fried dough sweet were considered biscuits since they are aggregated within a hierarchical parent-child structure;
- Other kinds of sources of meat, such as chicken and goat meat, were all considered as beef meat since they are aggregated within a hierarchical parent-child structure;
- For vol or vent, the standard recipe was used to estimate the proportion of the meat in the recipe and assumed that value for the occurrence;
- For ice cream, the code for milk was considered, which is the main ingredient;
- In some cases where no exact match was found in the *Occurrence values of inorganic arsenic in food* database, but for which analytical data on inorganic arsenic were available on EFSA publication (9) , the latter were considered for the assessment;

For dried tea, milk powder and fruit juices powder, a dilution factor of 75, 8 and 12.5 was applied respectively, in accordance with *Technical report on handling occurrence data for dietary exposure assessments*, published by EFSA in 2021, to revert them to their liquid forms after being converted for harmonization with the occurrence data (54).

For garlic powder, the concentration factor of 1/4 was applied given the difference in water content of fresh garlic versus dried garlic.

The daily dietary exposure to inorganic arsenic in the population, in µg/kg of body weight/day, was calculated by merging the dietary information with occurrence data. For the risk characterisation, the margins of exposure (MOE) were calculated for each participant, using the lower confidence limit of the benchmark dose for a 5% extra risk ($BMDL_{05}$) for skin cancer ($BMDL_{05}$=0.06 µg/kg of body weight/day). For skin cancer outcomes, a MOE higher than 1 is considered sufficient to conclude that there is no health concern (14).

4.5 Statistical analysis

Statistical analyses were conducted using SPSS and Excel software. Descriptive statistics and analysis of exposure assessment to dietary iAs and risk characterisation were performed for the entire sample and also stratified by sex, residence, age group, and pregnant or lactating status. The results are presented by percentiles.

The normality of the distribution was tested using the skewness and kurtosis coefficients. To compare the inorganic arsenic exposure between groups, the Mann-Whitney U-Test and the Kruskal-Wallis Test were applied. A significance level of 0.05 was considered.

The main food group contributors to dietary exposure to inorganic arsenic in the population were obtained by summing the concentration in each food group and dividing by the total concentration from all food groups, then multiplying by 100 to get the percentages of iAs from each food group.

RESULTS

5.1 Sample characteristics

The final sample consisted of 826 participants, including 672 females (81%) (Table 2). Based on the different age groups, 277 participants were children between 6 months and 5 years, 27 were adolescents aged 15 to 17 years, and 522 were adults between 18 and 49 years. Most participants were from rural areas (59.6%), and the remaining were from urban areas (40.4%). According to the household member questionnaire, 44 women were pregnant, 186 were lactating, and 5 were both pregnant and lactating.

Table 2: Socio-demographic characteristics of participants (n=826) in the Kenya survey (KNMS 2011-2012)

	N	%
Sex		
Female	672	81.4
Male	154	18.6
Age group		
Children (≤5years)	277	33.5
Adolescence (15-17years)	27	3.3
Adult (18- 49years)	522	63.2
Residence		
Rural	492	59.6
Urban	334	40.4
Pregnant or lactating status		
Not pregnant/lactating	314	38.0
Pregnant	44	5.3
Lactating	186	22.5
Pregnant Lactating	5	0.6

5.2 Daily dietary iAs exposure

Table 3 shows the overall daily dietary exposure to iAs in a sample of the population in Kenya, as well as by the different groups. In the LB scenario the overall median of daily dietary exposure to iAs in this sample was 0.12 µg/kg/day , ranging from 0.06 to 0.22 µg/kg/day (25^{th} and 75^{th}

percentile, respectively) with 1.33 µg/kg/day in the 99th percentile (Table 3). In the UB scenario, an overall median of 0.31 µg/kg/day, ranging from 0.20 to 0.51µg/kg/day (25th and 75th percentile respectively) with 2.15 µg/kg/day in the 99th percentile.

Concerning the age groups, the daily median was 0.17 µg/kg/day (99th percentile: 2.39 µg/kg) in children and 0.10 µg/kg/day (99th percentile: 0.72 µg/kg) in adults in the LB. In the UB scenario, it was 0.52 µg/kg/day (99th percentile: 3.23 µg/kg/day) in children and 0.27 µg/kg/day (99th percentile: 1.05 µg/kg/day) in adults. Generally, from 6 months of age, the median value of inorganic arsenic daily exposure decreased with increasing age.

Comparing individuals from rural and urban areas, the daily median of exposure was 0.12 µg/kg/day (99th percentile: 1.62 µg/kg/day) in rural areas and 0.11 µg/kg/day (99th percentile: 1.03 µg/kg/day) in the urban areas in the LB and 0.31 µg/kg/day (99th percentile: 2.29 µg/kg/day) in rural areas with 0.30 µg/kg/day (99th percentile: 2.01 µg/kg/day) in the urban areas in the UB.

The daily median of exposure was 0.10 µg/kg/day (99th percentile: 0.72 µg/kg/day) for non-pregnant women and 0.11 µg/kg/day (99th percentile: 0.70 µg/kg/day) for pregnant or lactating women in the LB, while in the UB, 0.26 µg/kg/day (99th percentile: 1.05 µg/kg/day) for non-pregnant women and 0.28 µg/kg/day (99th percentile: 1.07 µg/kg/day) for non-pregnant or lactating women was the median of exposure obtained.

In this study, the estimates of inorganic arsenic exposure differed in both LB and UB among the age groups ($p < 0.001$ (LB), < 0.001 (UB)). No significant differences were observed for exposure values stratified by residents, pregnancy, and lactating status.

The results were, however, not comparable by sex because the males were all children between 6 months and 5 years old, meanwhile, women were up to 49 years old.

Table 3: Daily dietary exposure to inorganic arsenic in μg/kg of body weight

	LB						UB					
	P25	P50	P75	P95	P99	p-value	P25	P50	P75	P95	P99	p-value
General population	0.06	0.12	0.22	0.57	1.33		0.20	0.31	0.51	1.06	2.15	
Sex						0.007						<0.001
Female	0.06	0.11	0.20	0.51	0.89		0.19	0.29	0.45	0.93	1.58	
Male	0.07	0.15	0.30	1.07	3.83		0.28	0.50	0.86	2.04	5.12	
Age groups						<0.001						<0.001
Children (≤5years)	0.08	0.17	0.33	0.90	2.39		0.29	0.52	0.84	1.69	3.23	
Adolescence (15-17years)	0.06	0.11	0.20	0.52	0.62*		0.24	0.29	0.46	0.83	0.87*	
Adult (18-49years)	0.06	0.10	0.17	0.37	0.72		0.17	0.27	0.38	0.64	1.05	
Residence						0.082						0.364
Rural	0.07	0.12	0.23	0.61	1.62		0.20	0.31	0.51	1.12	2.29	
Urban	0.06	0.11	0.21	0.56	1.03		0.19	0.30	0.51	1.00	2.01	
Pregnant or lactating						0.084						0.530
No	0.06	0.10	0.16	0.37	0.72		0.18	0.26	0.38	0.70	1.05	
Yes	0.07	0.11	0.18	0.38	0.70		0.18	0.28	0.39	0.62	1.07	

* This value represents the maximum observed value.

5.3 Risk characterisation

Table 4 expresses the MOE values for carcinogenic effects resulting from iAs exposure in a sample of the Kenyan population. The MOE was 0.51 at the 50th percentile, with 0.27 and 0.92 at the 25th and 75th percentiles, respectively (134.64 at the 99th percentile) in the LB. The median consumers in the UB had a MOE of 0.19 with 0.12 to 0.30 in the 25th and 75th percentiles, respectively (1.53 at the 99th percentile).

In the LB, the MOE at the 50th percentile was 0.34, with 660.58 at the 99th percentile in children, and 0.11 with 6.71 at the 99th percentile in the UB. In adolescents and adults, the MOE at the 50th percentile was 0.56 (99th percentile: 2.73) and 0.59 (99th percentile: 6.45), respectively, in the LB, and 0.21 (99th percentile: 1.09) and 0.22 (99th percentile: 1.29), respectively, in the UB.

In urban areas, the MOE was 0.52 with a 99th percentile of 229.86, and 0.52 with a 99th percentile of 168.87 in rural areas. In the UB, the MOE was 0.20 (99th percentile: 1.43) in urban areas and 0.19 (99th percentile: 1.65) in rural areas.

At the 50th percentile, non-pregnant women had a MOE of 0.62 (99th percentile: 8.62) and 0.23 (99th percentile: 1.18) in the LB and UB, respectively. Meanwhile, pregnant and lactating women had 0.56 (99th percentile: 3.33) and 0.22 (99th percentile: 1.43) in the LB and UB, respectively.

As described in the methodology, an MOE lower than 1 represents a public health concern for skin cancer outcomes. In this study, according to the MOE estimates, 78.8% of the population presented a concerning exposure to inorganic arsenic in LB scenario and 97.4% in UB scenario.

Among children, 80.7% were at risk in the LB and 96.6% in the UB. The proportion of individuals at risk was 81.3% in the LB and 99.2% in the UB for adolescents, and 77.7% in LB and 98.1% in UB for adults.

The estimates of MOE also presented a public health concern in 81.5% of individuals in the rural residents in the LB and 97.9% in the UB. In the urban residents 75.0% and 97.0% were at risk in the LB and UB respectively.

Non-pregnant women, pregnant and lactating women presented a health concern in the LB of 75.2% and 81.5%, respectively, and in the UB, 98.2% of non-pregnant women and 97.9% of pregnant and lactating women were at risk.

Table 4: Margins of exposure values for skin cancer from inorganic arsenic dietary exposure.

	LB						UB					
	P25	P50	P75	P95	P99	p-value	P25	P50	P75	P95	P99	p-value
General population	0.27	0.51	0.92	2.48	134.6		0.12	0.19	0.30	0.67	1.53	
Sex						0.005						<0.001
Female	0.30	0.54	0.93	2.33	9.00		0.13	0.21	0.32	0.67	1.38	
Male	0.20	0.40	0.88	39.93	768.0		0.07	0.12	0.21	0.88	21.16	
Age groups						<0.001						<0.001
Children (≤5years)	0.18	0.34	0.76	7.78	660.6		0.07	0.11	0.21	0.87	6.71	
Adolescence (15-17years)	0.30	0.56	0.94	2.56	2.73*		0.13	0.21	0.26	0.90	1.09*	
Adult (18-49years)	0.36	0.59	0.95	2.35	6.45		0.16	0.22	0.34	0.64	1.29	
Residence						0.085						0.374
Rural	0.26	0.52	0.87	2.34	168.9		0.12	0.19	0.29	0.62	1.65	
Urban	0.29	0.52	1.00	2.89	229.9		0.12	0.20	0.32	0.77	1.43	
Pregnant or lactating						0.069						0.474
No	0.38	0.62	1.00	2.48	8.62		0.16	0.23	0.34	0.65	1.18	
Yes	0.34	0.56	0.88	1.82	3.33		0.15	0.22	0.34	0.62	1.43	

* This represents the maximum observed value.

5.4 Food contributors to iAs exposure

The most relevant food contributors to inorganic arsenic exposure in population expressed in percentages at the LB and UB are presented in Figures 2 and 3, respectively. The results showed that rice was the highest contributor to inorganic arsenic exposure in the LB (34.92%) while grains and grain-based products (not including rice) were the highest in the UB (27.77%). Other important contributors were seasoning, sauces and condiments, vegetables and vegetable products, starchy roots or tubers and products thereof, sugar plants, and milk and dairy products. (see annex).

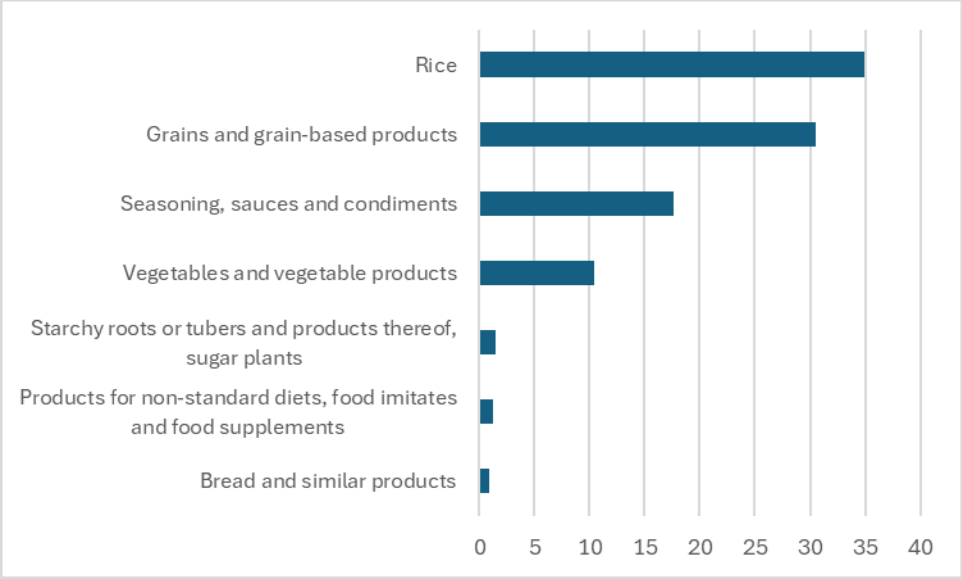

Figure 2: Percentual contribution (%) of food groups to dietary exposure to inorganic Arsenic (iAs) in the Population – Lower Bound (LB) scenario.

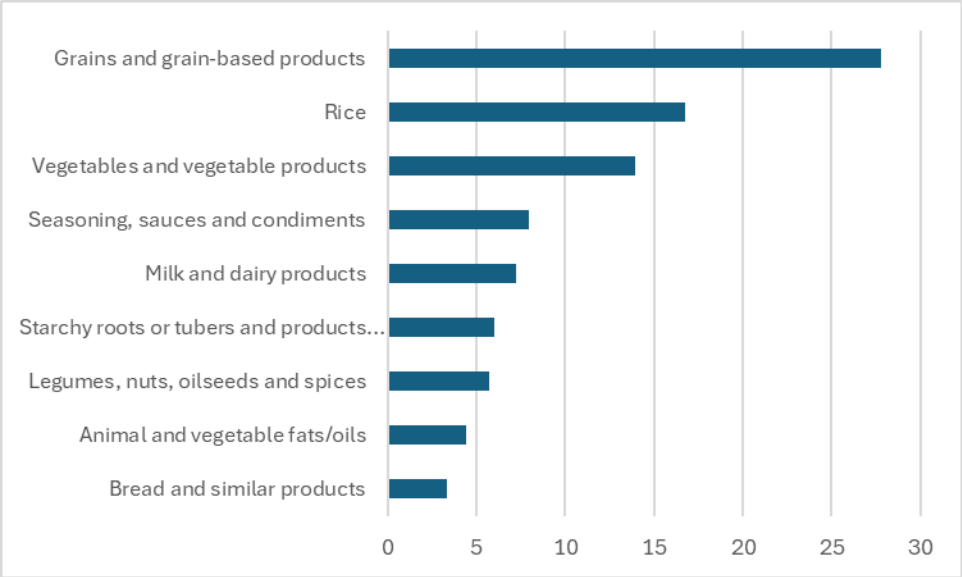

Figure 3: Percentual contribution (%) of food groups to dietary exposure to inorganic Arsenic (iAs) in the Population – Upper Bound (UB) scenario.

DISCUSSION

The present study estimated the dietary exposure to inorganic arsenic in a sample of the Kenyan population. For the population, the estimated median dietary exposure to iAs was 0.12 µg/kg/day in the LB and 0.31 µg/kg/day in the UB.The comparison of these results with other studies was difficult due to considerable differences observed in the occurrence databases and dietary assessment methodologies. Despite some methodological differences, the results observed were in accordance with other studies and reports. Data collected from the German total diet study showed some similarities regarding age groups. The mean estimated dietary exposure to inorganic arsenic in children was 0.10 µg/kg/day, with a 95th percentile of 0.24 µg/kg/day in the LB and 0.31 µg/kg/day in the UB, with a 95th percentile of 0.60 µg/kg/day. For adolescents, the mean estimated exposure was 0.08 µg/kg/day, with the 95th percentile of 0.17 µg/kg/day in the LB and 0.22µg/kg/day, with the 95th percentile of 0.44µg/kg/day in the UB. The estimated values for the mean inorganic arsenic in adults were 0.04 µg/kg/ day, with the 95th percentile of 0.13 µg/kg/day in the LB and 0.14µg/kg/ day, with the 95th percentile of 0.33 µg/kg/day in the UB (31).

Other studies had similar results as well, such as the diet study on inorganic arsenic in the Italian population (mean exposure of inorganic arsenic of 2.4 and 1.4 µg/kg/day times higher in children and adolescents compared to adults) (55). The Swedish study concluded that the median dietary exposure to inorganic arsenic in children was 0.095µg/kg/day and 0.047µg/kg/day in adults, which was similar to the dietary exposure in similar groups in the present study, with children more exposed than adults (56).

Data collected from 22 dietary surveys conducted throughout Europe showed similar dietary exposures in pregnant and lactating women as those found in the current study. The mean estimates in pregnant women ranged from 0.04 to 0.14 µg/kg/day, and for lactating women, between 0.03 and 0.06 µg/kg/day in the LB and UB, respectively. The 95th percentile dietary exposure estimates were between 0.09 and 0.28 µg/kg/day in pregnant women, and between 0.08 and 0.25 µg/kg/day in lactating women in the LB and UB, respectively (9).

The dietary exposure to inorganic arsenic calculated for a sample of the Kenyan population was different from the estimates from other countries. The estimated distribution of the mean daily exposure of inorganic arsenic in China's rural population was 0.88 µg/kg/day in rural areas, and a

mean of 0.71 µg/kg/day in urban areas (57). In Bangladesh, each district had a daily intake of inorganic As from rice that varied from 0.38 to 1.92 µg/kg bw (58). An important point is that in China and Bangladesh, the consumption of rice is much higher due to their specific dietary patterns (49). Thus, it is expected that their results should be much higher.

Several factors can also explain these differences: the different food items, the composition of the soil, and the growing conditions (59-61). Also, the use of a UB approach for left-censored data may overestimate the inorganic arsenic levels used as input to the exposure assessment.

The main food contributors identified for the population, being rice, grain and grain-based products, vegetables, and vegetable products, are in line with previous observations in other countries (31, 62). There is a lot of literature on the dietary exposure to inorganic arsenic through water intake (3, 63, 64). However, it was not found as a contributor in the current study because it was not reported in the KNMS data available in the GDD, used for this study. Thus, our results are probably underestimating the dietary exposure to iAs.

Skin cancer resulting from dietary exposure to inorganic arsenic has been well-defined, coupled with updates provided by EFSA (14), and the demonstration of carcinogenicity in humans by the IARC (30). In the present study, MOE values were substantially below 1 in 78.8% of the population in the LB, and 97.4 % in the UB , indicating a concern from a public health perspective, pointing to the need to mitigate dietary exposure to inorganic arsenic in Kenya.

To mitigate dietary exposure to iAs in Kenya, firstly and more importantly, long-term best agricultural and production practices should be implemented to achieve this goal. Moreover, thedaily dietary inorganic arsenic exposure is not only defined by its concentration, but also by the amount of food consumed. Combined efforts involving the different communities and the policy makers should be made to decrease the iAs levels in food and to change the dietary patterns of consumers, especially for the major food contributors (6, 65), such as rice, rice-based products, grains, and grain-based products (excluding rice) in the Kenyan population. Thus, another solution should be through risk communication of the entire population, especially among parents and guidance. They should be advised to diversify their diet with a variety of foods (66). This dual strategy addresses both the long-term goal of reducing iAs in the food supply and the short-term need to protect individuals through dietary advice. The plan also calls for a comprehensive public health campaign aimed at communicating the health risks associated with iAs exposure from excessive rice and grain consumption (67).

Study’s strengths and limitations

The methodology for the risk assessment was a strength, as it followed the principles of EFSA, and all assumptions were documented and reported in the methodology section. The use of the FoodEx2 classification system presents another significant strength. This system provided a standardized and detailed framework for categorizing food consumption data. This adoption enhanced the precision and clarity of the collected data, enabling a more accurate analysis of dietary patterns and exposure to various food components.

The study's use of a convenience sample from the Kenyan population means that its conclusions are not generalizable or statistically valid for the entire country. According to our results, Kenya population may be at risk, but a study with a representative sample is needed to verify this assumption.

The European Union's strict regulations on iAs in food, enforced by EFSA, ensure a degree of control over contamination. In contrast, Kenya has limited or no specific regulations and monitoring for iAs in food, which means that even if the source of contamination is similar, the final food product can have higher iAs levels in Kenya (14). A study on community health complications in Nairobi specifically identified high level of heavy metals, including iAs, in crops grown using wastewater near urban and industrial areas (68). This demonstrates the existence of these "hotspots" that would be missed by a broad, European-based assessment. Therefore, the use of occurrence data from EFSA in the current study would likely underestimate the dietary exposure to iAs in the population .

The assumptions that were made for this study, namely attributing values for foods that were not available on occurrence databases or using an UB approach might have overestimated the risk. However since this is risk assessment at the public health perspective it is better to have a conservative approach rather than to disregard risk.

Until now, there has been a lack of information about individual exposure to inorganic arsenic by the population of Kenya. This research represents the first step of the inorganic arsenic risk assessment in Kenya and allows the design of future investigations to assess the potential cumulative effect of inorganic arsenic exposure.

CONCLUSION

This study assessed and characterised the dietary exposure to inorganic arsenic in the Kenya population. Children aged 6 months to 5 years had the highest inorganic arsenic exposure (median 0.17 µg/kg/day; 99th percentile 2.39 µg/kg/day in the LB, and 0.52 µg/kg/day; 99th percentile 3.23 µg/kg/day in the UB) . This highlights that more focus should be directed towards children since the exposure values are higher than those for adolescents and adults, with a higher proportion of the sample presenting MOE values lower than 1.

To the best of our knowledge, this is the first study that estimated the dietary exposure to inorganic arsenic in a sample of the population of Kenya, analysed the associated factors, and identified the contribution of food groups. Our results suggest a public health concern regarding the dietary exposure to inorganic arsenic, mainly for the skin cancer effect in 78.8% of the overall sample in the LB, and 97.4 % in the UB. Thus, this information can be used to design effective public health interventions to reduce the exposure to inorganic arsenic in the Kenyan population, primarily by implementing long-term best agricultural and food production practices, public health campaigns on diet diversification, diet planning seminars, and communication of the health risks associated with iAs exposure from excessive rice and grain-based foods consumption.

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Annex: The food group contributions to inorganic Arsenic (iAs) exposure in the LB and UB scenarios.

Food Groups	LB	UB
Rice	34.920	16.719
Grains and grain-based products	30.557	27.772
Seasoning, sauces and condiments	17.616	7.958
Vegetables and vegetable products	10.370	13.926
Starchy roots or tubers and products thereof, sugar plants	1.506	5.966
Products for non-standard diets, food imitates and food supplements	1.250	0.620
Bread and similar products	0.960	3.357
Fish and seafood	0.954	1.328
Meat and meat products	0.632	1.534
Pasta, doughs and similar products	0.387	0.336
Coffee, cocoa, tea and infusions	0.301	0.172
Fruit and fruit products	0.195	0.218
Fruit and vegetable juices and nectars (including concentrates)	0.116	0.377
Herbs and edible flowers	0.072	0.040
Soups and salads	0.049	0.033
Legumes, nuts, oilseeds and spices	0.035	5.686
Milk and dairy products	0.027	7.230
Chips, crisps, fries and dough-based analogues	0.018	0.012
Unsweetened spirits and liqueurs	0.013	0.115
Food products for young population	0.010	0.005
Composite dishes	0.008	0.006
Dishes, incl. Ready to eat meals (excluding soups and salads)	0.002	0.005
Alcoholic beverages	0.002	0.015
Preserved or partly preserved sausages	0.000	0.001
Animal and vegetable fats/oils	0.000	4.439
Water and water-based beverages	0.000	1.769
Eggs and egg products	0.000	0.352
Sugar and similar, confectionery and water-based sweet desserts	0.000	0.010
Terrestrial invertebrates	0.000	0.000
Sugar and other sweetening ingredients (excluding intensive sweeteners)	0.000	0.000
Major isolated ingredients, additives, flavours, baking and processing aids	0.000	0.000
Confectionery including chocolate	0.000	0.000

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