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Worldwide arsenic levels in human breast milk and probabilistic health risk assessment: A systematic review and meta-analysis

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Abstract

Background: The exposure to toxic metals is a major global health concern due to their stability, bioaccumulation, and high toxicity. These metals can be transmitted to the fetus through the placenta and exposure can last throughout life. This systematic review focused on the potential risks of arsenic (As) in breast milk to newborns and infants.

Methods: Multiple keywords, such as "human milk" and "breast milk", associated with "toxic metal", "heavy metal" or "arsenic" were used to search related databases. Of the 151 articles found, 45 studies were eligible for qualitative review, and 34 were included in the meta-analysis.

Results: The lowest and highest levels of arsenic were found to be 0.04 ± 0.70 and 27.75 ± 28.30 µg/L, respectively. The overall pooled average concentration (95% CI) of arsenic in breast milk was 0.11 (95% CI: 0.11, 0.12). The results indicated that infants who consume breast milk are within a safe limit for cancer risk.

Conclusion: The exposure to significant metals is associated with disease development. Therefore, ongoing knowledge creation through mental acts and continuous observation is necessary to better understand the effects of heavy metals in future studies.

Keywords: Heavy metal poisoning, Arsenic, Human milk, Infant

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Introduction

Biological monitoring plays a critical role in toxicological research as it helps assess human health risks. Heavy metal pollution is a significant environmental problem that humans are exposed to through various pathways (1), including contaminated food such as vegetables (2), rice (3), and fish. Heavy metals can also be detected in biological samples such as hair (4) and breast milk. While some heavy metals like iron, manganese, zinc, and copper are essential for a healthy life, they can become harmful beyond permissible limits. Other metals like arsenic, cadmium, lead, and mercury are hazardous and toxic to humans and other living things, even in small amounts (5).

Breast milk is a highly beneficial and ideal food for human babies as it contains essential nutrients, antibodies, and other vital elements necessary for growth and development (6). It is a unique natural nutritional method with various properties. However, due to the transmission of contaminants through the food chain and breast milk, ensuring its safety and quality is imperative (7,8). Several studies have evaluated the health risks associated with various foods, infant formula, and breast milk, highlighting the need for attention and monitoring to ensure safety (9-11).

Arsenic is a metalloid that is found in many minerals and can occur in both organic and inorganic forms in the environment. The exposure to arsenic in the human body is mainly through water intake and seafood, especially shellfish (12). The gastrointestinal tract absorbs a significant amount of mineral arsenic, which is mostly excreted through urine (13). Inorganic arsenic is readily absorbed in the gastrointestinal tract and is also excreted mainly through urine. Arsenic is a toxic metal, and chronic exposure to inorganic arsenic has been linked to a range of health problems, including cancer of the bladder, lung, and skin, as well as cardiovascular disease, respiratory disease, and neurological effects. The International Agency for Research on Cancer (IARC) has classified inorganic arsenic as a group 1 carcinogen, which means it is carcinogenic to humans (14).

Childhood is a particularly vulnerable period for arsenic exposure (15). Arsenic is a known human carcinogen, and there is significant evidence of its damaging effects on various bodily systems, including the nervous, cardiovascular, respiratory, immune, and endocrine systems (16). Many studies have focused on populations with high exposure to arsenic in drinking water, particularly in regions such as Bangladesh, Chile, and Taiwan, where arsenic concentrations in drinking water have exceeded 50 µg/L. These studies have confirmed a relationship between exposure during early life and increased fetal mortality, reduced birth weight, and impaired cognitive function (17,18). However, the consistency of results between different studies has not always been observed. While scarce information is available on the short- and long-term consequences of exposure below the current maximum contamination level (MCL) of 10 µg/L, exposure to low doses of arsenic in utero has been found to be linked with an increased risk of respiratory tract infections in children and the severity of these infections. Reports from the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 2010 indicated that the previously adopted provisional tolerable weekly intake (PTWI) values for arsenic (15 mg/kg bw/day or 2.1 mg/kg bw/day) are no longer considered safe for humans (17). Instead, a benchmark dose of 3 mg/kg has been adopted as the reference point for risk assessment. Given the health effects of arsenic exposure among newborns (0-11 months) and toddlers (12-36 months), it is important to determine the extent of breast milk contamination and the associated risks of its intake. This systematic review aimed to report data on the concentration of arsenic in breast milk from research published worldwide between 1980 and 2021 (Figure 1) and its toxicology, with a particular focus on infants and children. In addition to collecting quantitative data, this review may be useful for assessing the international level of mother-infant exposure to arsenic for public health research.

Materials and Methods

This study was a systematic review and meta-analysis and was carried out based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Search strategy

The systematic search and review processes were based on the PRISMA guidelines. To collect incidence data, a query was conducted on the Scopus, PubMed, and Web of Science databases for studies published until September 25, 2021, using the keywords "human milk," "breastmilk," and "breast milk" in combination with "toxic metal," "heavy metal," or "arsenic".

Eligibility criteria

Inclusion criteria

The following criteria were used for studies included in the meta-analysis: 1) cross-sectional studies in lactating mothers reporting arsenic levels in their breast milk; 2) studies published in English; and 3) samples containing the mean arsenic level in breast milk.

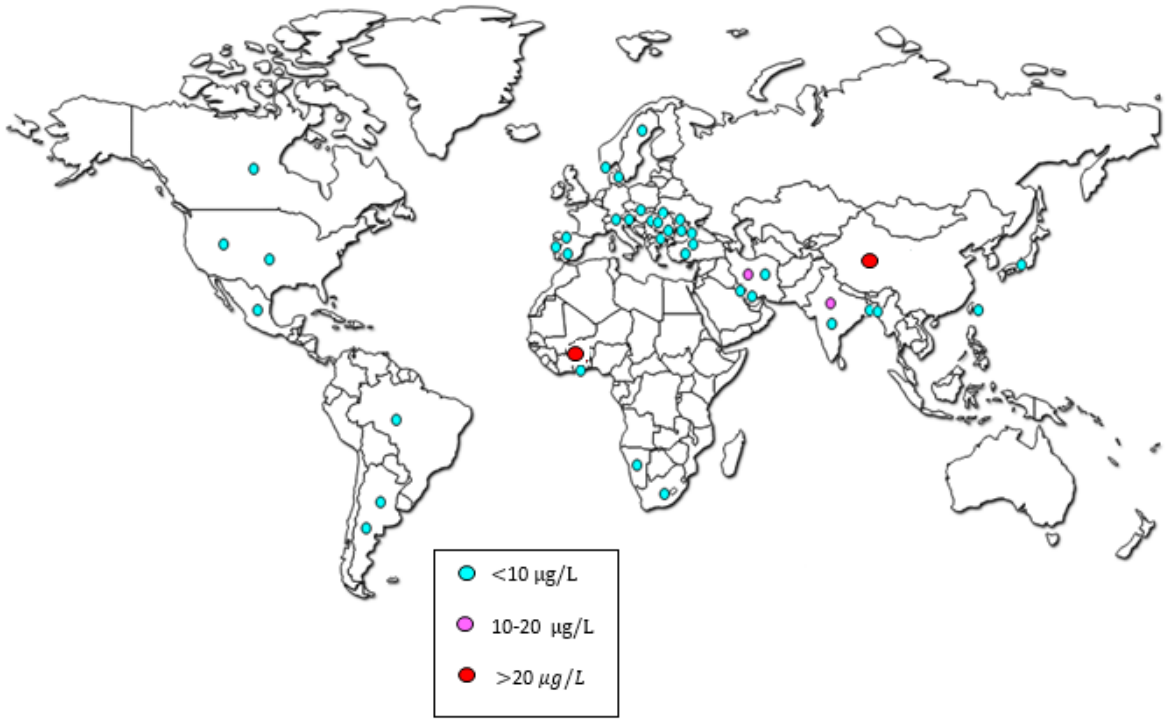

Figure 1. Location map of human breast milk samples collected from various countries across the world to determine arsenic levels worldwide over the last four decades (1980–2020)

Exclusion criteria

The following criteria were used to exclude studies from the meta-analysis: 1) studies without quantitative data on arsenic levels in breast milk of human subjects; 2) articles with unavailable information; 3) non-English articles; 4) articles reporting data from books, reports, theses, conferences, symposia, and poster abstracts from congresses; and 5) data from articles on the development or validation of analytical methods. There were no restrictions based on time or ethnicity.

Study selection criteria

Two reviewers independently reviewed the identified articles. Titles and abstracts were inspected to assess eligibility criteria, and full texts of potentially relevant studies were selected and reviewed. In cases where studies were conducted on the same population or had overlapping samples, only the study with the highest number of participants was selected. The selected articles were saved using Endnote Reference Management Software. After removing duplicate studies, each article was coded as "included," "excluded," or "uncertain." Figure 2 shows the search, screening, and eligibility strategies, as well as the included studies in a flow diagram of the literature search process.

Data extraction

Information was extracted from each paper using an adapted data extraction table. The main characteristics extracted included the first author, year of publication, geographical area (country and continent), sample size, maternal age, lactation time, ethnic distribution, type of milk, arsenic concentration (mean ± SD, range), percentage of positive samples, analytical technique used, limit of detection (LOD), and limit of quantification (LOQ).

Two researchers independently coded the study characteristics and analyzed the reliability of the data

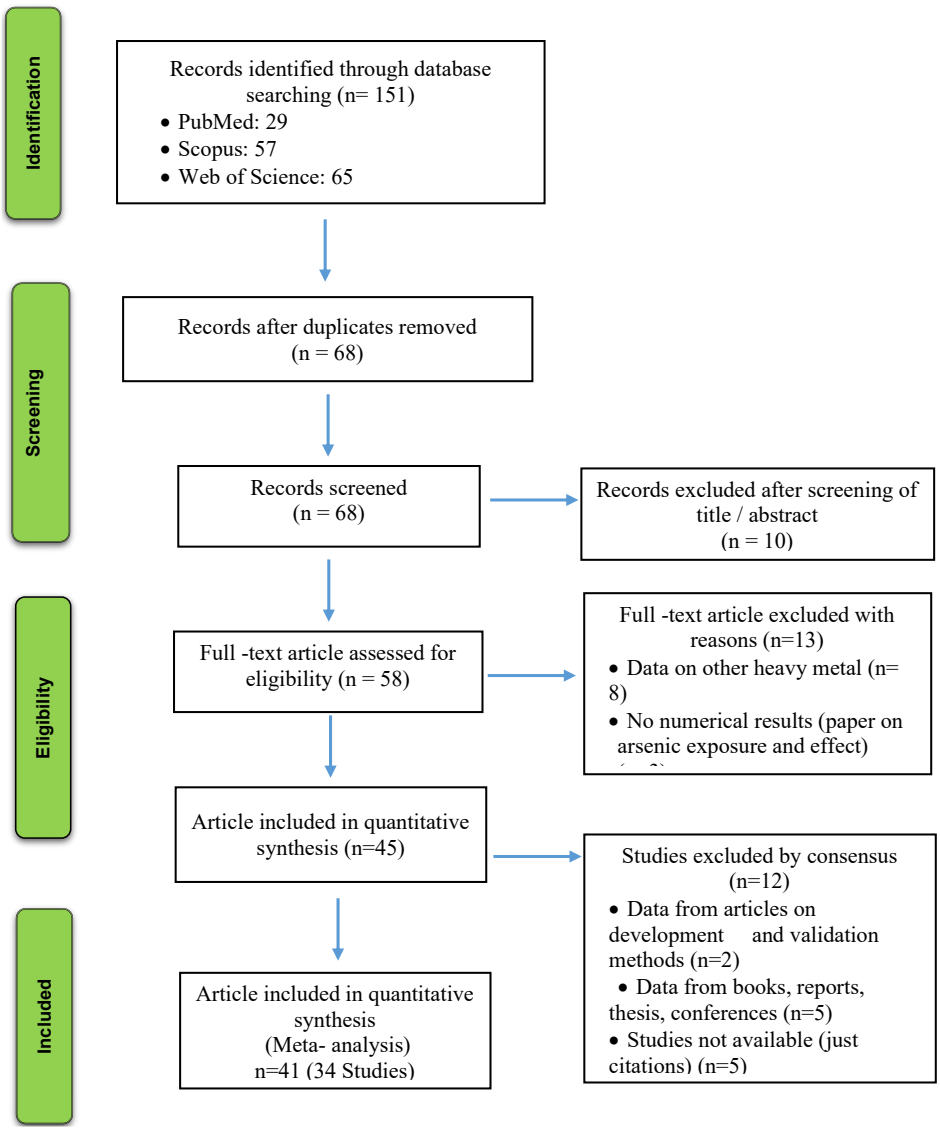

Figure 2. Flow diagram of the study selection process following the PRISMA guidelines

extraction process. The inter-rater agreement between the two researchers was calculated using kappa coefficients for categorical variables and intraclass correlation coefficients for continuous variables. Inconsistencies between the two reviewers were resolved by consensus or the involvement of a third researcher.

Risk of bias

Assessing the methodological quality of the incorporated studies was carried out based on the modified Newcastle–Ottawa Scale (NOS) for cross-sectional studies (18). A score of >7 on the NOS scale for each study was representative of a low risk of bias and a brilliant methodological domain. Last, the classification of study quality was introduced as 'high' (6 stars), 'medium' (3 to 5 stars), or 'low' (< 3 stars).

Probabilistic risk assessment

Estimated daily intake

Health risk assessment is a process used to estimate the risk associated with exposure to a potentially toxic substance for a population. Health risk assessments for potentially toxic metals generally involve quantifying the level of risk and reporting it as either a carcinogenic or non-carcinogenic health risk. The two main factors used to calculate toxicity risk are the reference dose (RfD) for non-carcinogenic risk characterization and the slope factor for carcinogenic risk characterization. Daily intake (DI) of arsenic for the newborns was estimated using Eq. (1) (19):

$$\text{Daily intake } (\mu g = kg\text{–}bw = day) = \frac{C_{MILK} \times IR_{MILK}}{bw} \quad (1)$$

Where C_{milk}, IR_{milk}, and bw are representative of the arsenic level in breast milk (μg/L), the daily average consumption of milk (L/day), and body weight, respectively.

Estimation of non-carcinogenic risk

The non-carcinogenic risk is calculated using the hazard quotient (HQ), which is obtained by dividing the estimated DI by an RfD. An HQ greater than 1 indicates an unacceptable risk of adverse non-carcinogenic effects on health, while an HQ less than 1 is considered an acceptable level of risk. The RfD for arsenic was determined to be 0.3 mg/kg BW/day. Since calculating the daily intake of milk for a breastfed infant can be difficult, the results of other studies were used as a reference value to estimate the daily intake of toxic metals based on the mean infant.

Estimation of carcinogenic risk

Incremental lifetime cancer risk (ILCR) was estimated to determine the possible cancer risk of As in adults and children by consuming milk (20,21) and calculated by Eq. (2):

$$ILCR = EDI \times CSF \quad (2)$$

The cancer slope factor (CSF) is the risk produced by a lifetime mean dose of 1 mg kg^{-1} bw day^{-1} (20). CSF for As was 1.5 mg kg^{-1} day (22,23).

Statistical analyses and data synthesis

Following data extraction, Comprehensive Meta-Analysis version 15.0 (CMA) was used for meta-analysis. Means and standard deviations (SDs) were reported for eligible papers. The pooled level of arsenic was obtained by combining the data from included studies using the inverse variance of each effect-size estimate. Additionally, the random-effects model was used to report the pooled prevalence and 95% confidence interval. To check for heterogeneity between studies, Cochran's Q-statistic and the I^2 index were used. I^2 values of 25%, 50%, and 75% were used as approximations for low, moderate, and high degrees of heterogeneity, respectively.

Results

Processing the systematic review

In this study, the PRISMA flow chart was followed to summarize our search process, as shown in Figure 2. Initially, we searched the Scopus, PubMed, and Web of Science databases (ISI) for primary literature, and identified 151 articles, with 29, 57, and 65 from each database, respectively. After removing duplicates, 68 articles were left. Then, the title, abstract, and full text of each article were screened, and 10 articles that did not meet our inclusion and exclusion criteria were removed. Ultimately, 45 studies that met our criteria described above were identified, and a meta-analysis of 34 of these studies was conducted. These studies were conducted in 28 countries worldwide between 1980 and 2021, and aimed to assess the level of arsenic in breast milk.

Study characteristics

Table 1 summarizes the main characteristics of the studies collected for this analysis. The studies were conducted in various regions around the world, with the majority of studies conducted in Europe (14). These studies were conducted in Denmark, Germany, Sweden, Croatia, Slovenia, Italy, Portugal, Poland, Turkey, Slovakia, Spain, Cyprus, Greece, and Hungary. Additionally, 11 studies were conducted in Asia, including in China, India, and the United Arab Emirates. In the Americas, two studies were conducted, with one study each in Mexico, Brazil, and Argentina. Finally, four studies were conducted in Africa, including in Namibia, Ghana (two studies), and South Africa. Two of the studies conducted surveys in multiple countries simultaneously: one reported levels from four countries (the United States, Namibia, Poland, and Argentina), and the other reported levels from four European countries (Croatia, Slovenia, Italy, and Greece).

Table 1. Arsenic levels in human breast milk reported in research articles published since 1980

Author, Country	Sample size	Lactation time	Maternal age mean±SD (range)	Population/area/ type of milk (N)	Arsenic concentration (μg/L)		Analytical technique	LOD (μg/L)
					Mean±SD	Median (range)		
Grandjean et al (1995), Denmark (24)	23	Few days after deliver	(16–40)			1.60 (0.10 – 4.40)	UV absorptiometry	
Concha et al (1998), Argentina (25)	10	T & M	(18–32)	Rural	3.20±1.10	(0.83 –7.20)	AAS	
Krachler et al (2000), Austria (26)	27					6.70±7.20 (1.30–30)	ICP	
Sternowsky et al (2002), Germany (27)	187	2- 90 Dpp			0.15±0.60	0.15 (0.30–2.80)	ICP	
Yang et al (2003), China (28)	32	T	(22–33)		20.8±8.30	11.20 (1.10–204)	ICP	
Sharm and Perve (2005), India (29)	120				2.43±1.50	(0.60–5.20)	AAS	
Samanta et al (2007), India (30)	226	3 Mpp			170±11.8	17 (2 – 49)	ICP	
Almeida et al. (2008), Portugal (31)	34	C	(18–40)		7.80±2.20		ICP	
Fängström (2008), Bangladesh (32)	79				1.80±4.70	(0.25–19)	ICP	
Kosanovic (2008), United Arab Emirates (33)	120				0.19±0.03	(0.02– 0.65)	ICP	
Abdulrazzaq (2008), United Arab Emirates (34)	205		(18–50)		0.89±0.07	(0.001– 0.28)	ICP	
Bentum et al (2010), Ghana (35)	20				1.54±1.94	(0.001– 6.22)	ICP	0.001
Sakamoto et al (2012), Japan (36)	9	3 Mpp	(22–36)		0.73±0.60	(0.40–1.80)	ICP	
Björklund et al (2012), Sweden (37)	60	M			0.55±0.70	(0.04– 4.60)	ICP	0.007
Gürbay et al (2012), Turkey (38)	64	2–5 Dpp			5.00±1.90	(<LOQ –7.60)	ASS	2.50
Miklavčič et al (2013), Croatia, Slovenia, Greece, Italy (39)	123	1 Mpp	(18 - ≥40)	Croatia	0.20±2.87	(0.40 –11.90)	ICP	0.04
	287	3–8 Mpp		Slovenia	0.04±0.71	(0.04 –2.90)		
	30	1 Mpp		Greece	0.80±1.12	(0.30 – 4.80)		
	602	1 Mpp		Italy	0.30±2.99	(0.04 –12.00)		
Chao et al (2014), Taiwan (40)	45	1–4 Dpp	(22–39)		1.50±1.50	(0.30 –2.30)	ASS	
Islam et al (2014), Bangladesh (41)	29	30 Dpp	(18–40)		1.12±2.10	(0.50 –8.90)	ASS	
Gaxiola-Robles et al (2014), Mexico (42)	108	7 Dpp			0.01±3.40	0.01 (0.01–13.8)	ASS	
Carignan et al (2015), United States (43)	9	1.7–7 Mpp	(19–45)		0.31±0.10	(<0.22–0.62)	ICP	0.22
Kunter et al (2016), Cyprus (57)	50				0.73±0.58	(0.12–0.08)	ICP	
Klein et al (2017), United States, Namibia, Poland, Argentina (45)	20			United States	3.47±0.80	(2.40 –6.02)	ICP	
	6			Namibia	6.66±2.50	(4.08–11.20)		
	23			Poland	6.88±2.50	(3.03–7.90)		
	21			Argentina	3.86±1.00	(2.54 –9.08)		
Bansa (2017), Ghana (44)	57	3 MPP			27.75±28.30	(7.00–120)	ICP	
Bassil et al (2018), Lebanon (46)	74	3-8 Wpp	26.8±4.84		2.36±2.00	(0.08 – 11.32)	ASS	0.19
Kılıç Altun et al (2018), Turkey (47)	42	3–520 DPP	(17–44)		<1	(<1)	ICP	0.01

Table 1. Continued

Author, Country	Sample size	Lactation time	Maternal age mean±SD (range)	Population/area/ type of milk (N)	Arsenic concentration (µg/L)		Analytical technique	LOD (µg/L)
					Mean±SD	Median (range)		
Samiee (2019), Iran (48)	20		(20–37)	Rural	10.75±7.62	(3.01–30.10)	ICP	
Samiee (2019), Iran (49)	100	2 Mpp			0.85±0.56	0.50 (0.50 –4.00)	ICP	0.50
		6 Mpp			1.60±0.92	0.50 (0.50 –5.80)		
		8 Mpp			0.69±0.12	0.50 (0.50 –2.40)		
		12 Mpp			1.30±0.88	0.50 (0.50 –5.80)		
Ecsedi-Angyal et al (2020), Hungary (50)	27	Different stages of lactation	(25–41)		0.41±0.20	(0.27–0.59)	ICP	
Jagodic et al (2020), Slovenia (51)	74		(19–39)	area with more frequent consumption of seafood	0.57±0.85		ICP	
Oliveira et al (2020), Brazil (52)	50	≥15 Dpp	30±6.00		0.29±0.10	(<LOQ – 0.80)	ICP	0.05
Mandiá et al (2021), Spain (53)	170	C	(23–46)		0.93±1.54	(0.52–1.34)	ICP	
Motas et al (2021), Spain (54)	35		32.57±4.25	Industrial/Mining Area	1.40±2.60	(≤15.30)	ICP	
	15		33.93±3.43	Agricultural rea	0.60±2.80			
Olowoyo et al (2021), South Africa (55)	54				0.664±0.729	5.131±0.488 <LOD –2.298	ICP	0.06
Szukalska et al (2021), Poland (56)	51	C	(18–40)	Passive smoker	2.61±1.31		ICP	0.32
	47			Tobacco smoker	2.53±1.36			
	52	M (1 month±7 days after giving birth)		Nonsmokers	1.37±0.56			

C: Colostrum; T: Transition milk; Preterm milk M: mature milk; Dpp: Day postpartum; Mpp: Month postpartum; Wpp: Week postpartum; W: Women; LOD: Limit of detection; AAS: Atomic absorption spectrometry; ICP: Inductively coupled plasma.

Estimations of the arsenic concentrations in the breast milk

Analyzing the levels of metals in breast milk can provide valuable information on how to protect both mothers and infants from the harmful effects of contamination. Breast milk is the best source of nutrition for infants during their first six months of life, and the World Health Organization (WHO) recommends that mothers breastfeed their infants exclusively during this time (23). In our analysis, a subgroup analysis based on the type of metal and country of origin was conducted (see Table 1). The mean concentration of arsenic in breast milk was found to be 0.11 µg/L (95% CI: 0.11–0.12, I2: 76.03%, *P*: 0.00), and the results are presented in a forest plot in Figure 3. As the WHO has not established "normal condition levels" for arsenic in breast milk, we compared our findings to the WHO limits for arsenic in drinking water (10 µg/L). Thirty of the studies analyzed in this study reported arsenic levels below the WHO's limit for drinking water (<10 µg/L). However, As shown in Table 1, the lowest and highest reported levels of arsenic in breast milk were 0.99±3.40 µg/L (28) and 27.75±28.30 µg/L (29), respectively, and the majority of studies exceeded the WHO's tolerable limits.

Health risk assessment

Table 2 presents the carcinogenic and non-carcinogenic arsenic risk associated with breast milk consumption in infants based on the estimates of daily intake in different countries. In terms of non-carcinogenic risk, the following countries ranked: Ghana > China > India > Iran > Portugal > Namibia > Austria > Turkey > Poland > USA > Argentina > Lebanon > Spain > Bangladesh > Denmark > Canada > UAE > Taiwan > Greece> Cyprus > Japan> South Africa > Sweden > Italy > Brazil> Croatia > Germany > Slovenia > Mexico. The results showed that TTHQ accounted for infants in all countries was lower than 1, indicating there are no potential risks from breast milk consumption in all countries.

Discussion

Search results and study characteristics

Table 1 provides detailed information on the studies

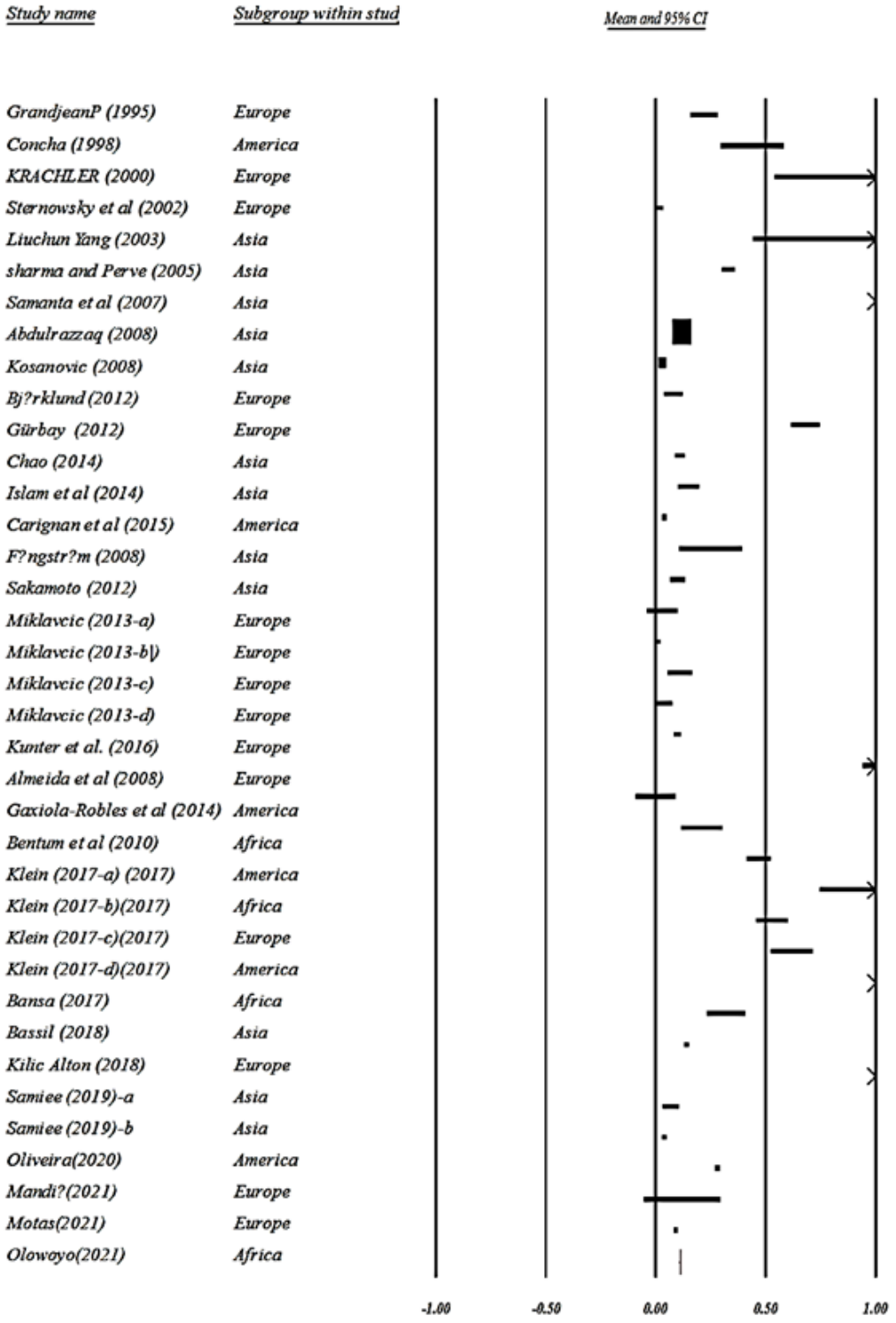

Figure 3. The forest plot of the mean breast milk arsenic concentrations (μg/L) of 42 studies. The dark blue squares represent the median As concentrations extracted from each study, while the lines represent the 95% confidence limits around them. The black diamond represents the average of the median BPA concentrations

Table 2. HQ values and ILCR values of infants through breast milk consumption

Indices	EDI (μg/ kg bw/week)		HQ		ILCR	
	Mean	Max.	Mean	Max.	Mean	Max.
Infants	3.456	19.35	1.647	12.60	329	5805

EDI, estimated daily intake; HQ, hazard quotient; ILCR, incremental lifetime cancer risk.

included in our meta-analysis, including sample specifications and other relevant data. The number of breast milk samples analyzed in the studies varied greatly, ranging from 9 to 1042, with 77% of studies including fewer than 100 samples. In terms of maternal age, over 64% of studies reported ages ranging from 16 to 50 years. The majority of studies analyzed mature or first milk,

with some also analyzing transitional milk. However, lactation status was not reported in eight of the studies. Inductively coupled plasma (ICP) was the most frequently used analytical technique for measuring arsenic levels (24 studies), followed by atomic absorption spectrometry (AAS) (9 studies) and UV absorption spectrometry (1 study).

Estimations of the arsenic concentrations

Biomethylation is a process that affects the body's susceptibility to arsenic. The main metabolites of arsenic found in urine are methylarsonic acid and dimethylarsinic acid, and increased levels of methylarsonic acid are a general risk factor that can easily cross the placenta and lead to a moderately increased risk of fetal growth retardation and mortality. The effective mechanisms and factors that influence the excretion of arsenic in human milk have not been entirely recognized, but it is believed that increased methylation of arsenic during pregnancy and breastfeeding may help protect fetuses and infants.

High mean concentrations of arsenic have been reported in Ghana (57). Our estimations suggest that the mean concentration of arsenic found in this study (27.75 ± 28.3) was approximately 2.5 times higher than the limit set by the WHO for drinking water. This is significantly higher than the reported values (with a mean value of 1.54 μg/L in the range of 0.00–6.22 μg/L) in non-mining communities in Ghana (57). The concentration of arsenic in breast milk ranged from 0.1 to 0.8 μg/L, which is well above the reported average for non-mining and mining communities in Indonesia, Bangladesh, Tanzania, and Zimbabwe (35,40,58). In a study by Yang et al (28), the highest and mean levels of arsenic in breast milk were 204 and 27.75 μg/L, respectively. In an area of India affected by high levels of arsenic in water (West Bengal, where levels in water were above 50 mg/L), the mean and median levels of arsenic in breast milk were 19.6 and 17.0 μg/L, respectively. Women with higher levels of arsenic in their hair, urine, and nails had higher concentrations of arsenic in their breast milk. In this population, when there was not enough accessible breast milk, newborns were given tube well water as early as the first month after birth, in addition to diluted cow/goat milk, which could increase their exposure to arsenic from an early age. The authors noted that the levels of arsenic in breast milk were much lower than the levels in urine (with a mean of 438 μg/L), which is a much more efficient route of arsenic excretion than lactation. According to a study by Fängström et al (32), the excretion of arsenic through breast milk is low, and exclusive breastfeeding can protect infants from arsenic exposure. This result is similar to the observations made by Carignan et al (43) in the United States, where levels of arsenic in water were low (less than 1 mg/L). Fängström et al (32) also found that the concentration of arsenic in urine was significantly lower in newborns who were exclusively breastfed compared to those who consumed other foods.

The observations of Fängström et alshowed a significant correlation between the total arsenic (TAs) levels in breast milk and the concentrations in the urine of infants aged 2-3 months ($rs = 0.64$, $P < 0.001$), as well as arsenic levels in maternal saliva and blood. This study was the only one to identify the forms of arsenic in breast milk, and it found that inorganic arsenic is the only form that poses a health risk to humans. In a study by Samiee et al (49), the levels of arsenic in breast milk were not significantly different between contaminated and non-contaminated areas (0.75 and 7.73 μg/L, respectively). The authors suggested that arsenic in breast milk may come from other sources, such as food crops. In a study conducted in Argentina, where levels of arsenic in water were high (200 μg/L), the average concentration of arsenic in the placenta was 34 μg/L, and in cord blood, it was 9 μg/L, with a significant correlation with arsenic levels in maternal blood (37). In studies conducted in the Mediterranean population, the levels of arsenic in breast milk in Italy and Croatia were almost the same, at 0.2 and 0.3 μg/L, respectively (39) (Table 1). The highest level l of As was found in Greece (0.8 μg/L), and the lowest level was found in Slovenia (0.04 μg/L). The authors noted that the lack of arsenic speciation analysis was a limitation of the study and that the higher levels of arsenic in samples collected in Greece might be due to other sources of arsenic, such as consuming food other than fish.

Exposure assessment

The chemical risk assessment process can be divided into four steps: 1) hazard identification, 2) hazard characterization, 3) exposure assessment, and 4) risk characterization. The results of the primary steps, i.e., 1 and 2, suggest the maximum vital unfavorable outcomes and establishing the health-primarily based guidance values, respectively. Ordinarily, they are completely based on laboratory animal data. However, human epidemiological studies may be also involved, particularly for metals. Since PTWI values of As do not protect human health, benchmark dose lower limit (BMDL) values were proposed to conclude the toxicology of this metal. In the step of exposure assessment, the concentration of the substance is multiplied by the amount of consumption of that substance and divided by the weight. In the step of risk characterization for As, by comparing the estimated intake with the health-based guidance value and expressing it as either a percentage or a hazard index (HI), there is the possibility of obtaining a conclusion regarding a potential risk to human health. The risk was observed for percentages higher than 100 or HI values greater than 1 (43).

Probabilistic health risk assessment

The uncertainties in risk evaluation depend on the quality

of the information used at each step of the process. For example, the quality of the toxicological database and the dose-response models used to estimate the PTWI, RfD, or BMDL can affect the resulting uncertainties. Uncertainty in exposure estimates is typically related to factors such as body weight, food intake, and concentration data used. This includes considerations such as whether the samples used are representative of the population, the number of samples examined, the analytical methods used, and how undetected samples are handled in the estimates.

Some of the studies listed in Table 1 also assessed the risk of arsenic exposure in breastfed infants. In cases where this information was not available, intake was estimated using incidence data from some studies, assuming a milk intake of 750 mL and a body weight of 5.5 kg. The objective was to evaluate the range of exposure levels to arsenic in different areas, from the lowest to the highest ones. The mean/median intakes of arsenic in infants and toddlers (six months old) are summarized in the table, expressed in µg/kg/day. The European Food Safety Authority (EFSA) and the UK Food Standards Agency (COT) Toxicological Commission also conducted as exposure assessments in their respective populations. If risk characterization was not available in the study, it was performed in connection with this review. Figure 4 summarizes the mean intakes of arsenic in infants from one to six months of age from different countries assessed in studies, ranging from 0.007 to 26.46 µg/kg bw/week. The figure also includes the BMDL for arsenic, which is a toxicological parameter used in the hazard characterization process.

According to Fängström et al (32), arsenic in breast milk is mainly present as inorganic arsenic (AI). Table 2 shows the total amount of arsenic in breast milk. In our review, only five studies estimated arsenic exposure through breast milk. Carignan et al (43) estimated the median exposure to be 0.04 µg/d for children aged 1-3 months (weight: 5.6 kg, milk intake: 810 mL/d). Even if the formula is prepared using water containing less than 1 µg/L of arsenic, the resulting exposure for breastfed infants (0.28 µ /kg/wk) is much lower than the value calculated for formula-fed infants (0.22 µg/kg/d). Sternowsky et al (27) found that the median arsenic intake for 3-month-old German infants (6 kg; 790 mL/d) was 0.02 µg/kg bw/day, or 0.14 µg/kg bw/wk. Based on the studies, since this exposure was much lower than the PTWI of 15 µg/kg bw/wk, it was considered safe. However, a much higher mean arsenic intake (5.5 µg/kg bw/wk) from milk consumption was estimated for Portuguese mothers. In the study by Samiee et al (49), the estimated median daily intake of arsenic was 0.70 µg/kg-bw/wk, and the 95th percentile value of daily intake was 0.61 µg/kg-bw/d.

As shown in Table 2, the highest levels of arsenic were reported in Africa by Bansa et al (57). Based on the consumption of 750 mL of milk and a weight of 5.5 kg for a 2- to 3-month-old baby, the estimated amount of arsenic absorption was 3.87 µg, which was higher than the values estimated in Europe and the United States and resulted in a hazard quotient (HQ) above 1, indicating a high concentration of arsenic in the drinking water of these regions. However, the absorption of arsenic in Bangladesh, a region with high arsenic content in water, was very low. In this study, the carcinogenic and non-carcinogenic health risks of infants due to consumption of mothers' breast milk were assessed. Exposure to

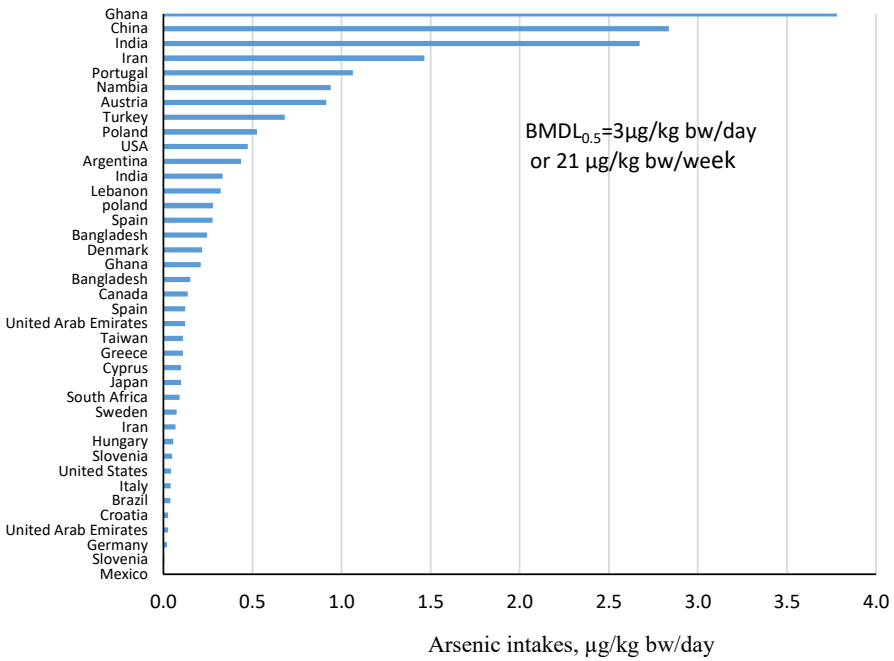

Figure 4. Mean intakes of arsenic by 1–6 months infants through breast milk; estimated from the concentration data provided (Table 2), assuming 750 mL daily consumption and 5.5 kg bw baby (24-56)

arsenic through breast milk consumption was evaluated by calculating the estimated daily intake (EDI) in two scenarios.

Non-carcinogenic risk

The non-carcinogenic risk of arsenic in breastfed infants was assessed by calculating the target hazard quotient (THQ) value. As presented in Table 2, the THQ for arsenic was determined based on the mean and maximum levels of arsenic from the current meta-analysis. The THQ values calculated for infant exposure to arsenic were greater than 1 in both scenarios, indicating a potential risk of adverse effects during infancy.

Carcinogenic risk

While various factors like race, sex, and age contribute to cancer development, exposure to environmental pollutants, including toxic elements, has been shown to increase cancer risk. Arsenic has been identified by the International Agency for Research on Cancer (IARC) as a substance that may contribute to the development of human cancer. In this study, the carcinogenic risk in breastfed infants was estimated using the ILCR value. The mean and maximum ILCRs of arsenic for infants were determined to be 329 and 5805, respectively. According to the United States Environmental Protection Agency (USEPA), an estimated ILCR of 1-in-100 000 ($\leq 1 \times 10^{-5}$) indicates "essentially negligible" cancer risks (8). When ILCR values greater than 1 x 10-5 are obtained, risk assessment should be revised, and/or risk management measures should be employed. The results of this study showed that infants consuming breast milk were within a safe limit for cancer risk.

Arsenic is a toxic metal that is widespread in nature, and exposure to it can pose a health concern for society. Arsenic can enter breast milk by passing through the placenta and the blood-brain barrier. Milk monitoring can be used as a non-invasive method to determine if a person is exposed to toxic metals and other contaminants. This review includes 42 studies evaluating the levels of arsenic in breast milk samples collected from around the world. However, a meta-analysis of data showed that the mean level of arsenic in breast milk was well below the limit of arsenic in drinking water declared by the WHO (<10 μg/L). The exposure assessment indicated that the exposure to arsenic in both children and adults was well below the risk values established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA).

The THQ values for arsenic were less than 1, indicating that there is a low non-carcinogenic risk for infants who consume breast milk. The carcinogenic risk assessment showed that the cancer risk for infants was within safe limits (ILCR > 10^{-6}). The measures to reduce the potential for exposure to toxic metals in pregnant and lactating women should be considered to decrease both intrauterine and postnatal exposure to breast milk. Based on the study findings, it is recommended to regularly monitor heavy metal food contamination to identify contributing factors and adopt strategies to reduce foodborne risks in infants.

The main strengths of the present study include the comprehensive search strategy used to identify relevant studies, the rigorous inclusion and exclusion criteria, and the use of meta-analysis to combine data from multiple studies. The main limitations of this study include the potential for publication bias due to the exclusion of studies not published in English, the limited number of studies included in the meta-analysis, and the difficulty in accurately estimating daily milk intake in breastfed infants, which could lead to imprecise estimates of arsenic exposure.

Conclusion

Breast milk is a valuable biological indicator of the nutritional status, environmental pollution, and arsenic exposure of both the mother and child. As has been identified as one of the most destructive environmental pollutants due to its bio-accumulative and environmentally sustainable properties. Additionally, exposure to this element, particularly in pregnant women and infants, has been linked to harmful effects, making it a major health concern.

To assess as concentrations in breast milk, this study reviewed available research and compared the observed concentrations to the standards set by the WHO. The review suggested that the mean total as levels in breast milk were lower than the As limits recommended by the WHO for drinking water (10 μg/L).

Furthermore, the study evaluated the non-carcinogenic and carcinogenic risks of toxic metals based on the concentrations of toxic metals in the breast milk of mothers from different countries. Infants who consume breast milk were found to be at no increased risk of cancer, but there was a non-carcinogenic effect. Given the high toxicity and dangers associated with exposure to As, it is crucial to manage and periodically monitor as levels in the environment and the human body. Identifying all potential risk factors for as exposure is also essential to mitigate the risks associated with this harmful substance.

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Competing interests

The authors declare that there is no conflict of interests.

Ethical issues

The authors certify that all data collected for the study described in the manuscript and the data obtained from the study have not been or will not be published separately elsewhere (Ethical code: IR.UMSHA.REC.1400.927).

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