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Review article

# The concentration of potentially toxic elements (PTEs) in human milk: A systematic review, meta-analysis, and health risk assessment

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ABSTRACT

Human milk has an important role in infants' psychological and immunological development. In addition to providing vital substances, some environmental contaminants, such as potentially toxic elements (PTEs), can be transmitted by human breast milk to infants. However, some studies monitored PTEs concentration in human breast milk; no metanalysis was conducted to estimate the concentration of PTEs in human breast milk. Therefore, this review aimed to determine PTEs concentrations in human breast milk and consumption-related health effects worldwide via meta-analysis and health risk assessment. After searching among Scopus, Web of Science, and PubMed databases, 32 studies were included in this work. Based on the results, the rank order of PTEs was Fe (258.44 μg/kg) > Zn (205.16 μg/kg) > Cu (32.29 μg/kg) > Mn (4.30 μg/kg) > Cr (2.62 μg/kg) > Hg (0.44 μg/kg) > As (0.21 μg/kg) > Cd (0.16 μg/kg) > Pb (0.03 μg/kg). Moreover, Egypt, Pakistan, Brazil, Jordan, and Turkey for non-carcinogenic risk (n-CR) and Egypt, Jordan, Brazil, and Romania for carcinogenic risk (CR) have shown unsafe levels, respectively. Since the lactating mothers' diet can directly affect their milk's content, monitoring the feeding behavior (especially supplements taken during pregnancy) and the quality of foods is recommended.

## 1. Introduction

Chemical and microbial pollution of the environment (Yang et al., 2021; Yu et al., 2022), followed by food (Ke et al., 2022; Lei et al., 2022; Sun et al., 2022), can endanger human health in the long term. Human breast milk contains numerous macro and micronutrients such as carbohydrates, fats, proteins, antibodies, and hormones (Kılıç Altun et al., 2018) which play a fundamental role in infants' psychological and immunological development (Salmani et al., 2016). The outstanding composition of breast milk makes it a unique source of nourishment for infants; hence, mothers are highly recommended to exclusively breastfeed their children for at least six months (Ecsedi-Angyal et al., 2020). Breast, due to containing lipophilic tissue and lipids (such as triacylglycerols, phospholipids, fatty acids, and sterols), is susceptible to the accumulation of compounds with lipophilic nature like potentially toxic elements (PTEs). In other words, humans are exposed to various types of environmental contaminants through several exposure routes such as inhalation, ingestion, and dermal absorption, resulting in the accumulation of PTEs in the fatty tissues and, consequently, different levels of health risks(Bounar et al., 2020; Chen et al., 2022; Gao et al., 2022; Heshmati et al., 2020; Khanjani et al., 2018; Salmani et al., 2018; Wongsasuluk et al., 2020).

Breast milk can transfer such substances from the mother to the infant, who is biologically more vulnerable to PTEs than adults (Salmani et al., 2016). High elemental absorption due to an immature intestinal system and undeveloped immune system and detoxification mechanisms

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**Table 1**
Meta-analysis concentration of Pb (µg/Kg-wet weight) in human milk based on country*.

| Country | Number of studies | ES | Lower | Upper | Weight (%) | Heterogeneity statistic | df[1] | P value[2] | $I^2$ (%)[3] |
|---|---|---|---|---|---|---|---|---|---|
| Austria | 2 | 0.200 | 0.181 | 0.219 | 33.23 | 28.62 | 17 | 0.038 | 40.60% |
| Saudi Arabia | 1 | 4.018 | 2.474 | 5.562 | 0.19 | 6.78 | 1 | 0.009 | 85.30% |
| Pakistan | 1 | 11.391 | 5.956 | 16.827 | 0.39 | 336.84 | 2 | < 0.001 | 99.40% |
| Greece | 1 | 0.041 | 0.000 | 0.083 | 4.47 | 40.97 | 1 | < 0.001 | 97.60% |
| India | 1 | 0.328 | 0.250 | 0.405 | 13.45 | 224.86 | 11 | < 0.001 | 95.10% |
| Iran | 4 | 5.233 | 4.774 | 5.691 | 6.61 | 907.29 | 47 | < 0.001 | 94.80% |
| Turkey | 4 | 0.307 | 0.274 | 0.340 | 15.42 | 2339.08 | 28 | < 0.001 | 98.80% |
| Sweden | 1 | 0.195 | 0.165 | 0.225 | 2.17 | 0.00 | 0 | . | .% |
| Taiwan | 1 | 1.231 | 0.550 | 1.913 | 5.06 | 293.91 | 3 | < 0.001 | 99.00% |
| Egypt | 1 | 39.011 | 5.162 | 72.860 | 0 | 25.88 | 2 | < 0.001 | 92.30% |
| Iraq | 1 | 1.509 | 0.936 | 2.082 | 1.32 | 9.86 | 1 | 0.002 | 89.90% |
| Poland | 1 | 0.107 | 0.096 | 0.118 | 4.45 | 1.13 | 1 | 0.288 | 11.40% |
| Nigeria | 2 | 4.719 | 3.910 | 5.527 | 2.41 | 110.24 | 4 | < 0.001 | 96.40% |
| Cyprus | 1 | 0.155 | 0.100 | 0.210 | 2.02 | 0.00 | 0 | . | .% |
| Brazil | 2 | 35.155 | 0.000 | 101.174 | 0.53 | 176.07 | 1 | < 0.001 | 99.40% |
| Romania | 1 | 0.026 | 0.000 | 0.077 | 2.05 | 0.00 | 0 | . | .% |
| Hungary | 1 | 0.253 | 0.230 | 0.277 | 6.11 | 0.34 | 2 | 0.844 | 0.00% |
| USA | 1 | 1.123 | 0.406 | 1.840 | 0.11 | 0.00 | 0 | . | .% |
| Jordan | 1 | 10.062 | 8.069 | 12.055 | 0.02 | 0.00 | 0 | . | .% |
| **Overall** | **28** | **0.611** | **0.586** | **0.635** | **100** | **15,569.09** | **139** | **< 0.001** | **99.10%** |

Degrees of freedom
P value of heterogeneity
Estimates of heterogeneity
* WHO "normal condition levels" in human breast milk (µg/l): 2–5(1 g of human breast milk is equivalent to 0.970 mL) (Bansa et al., 2017; Parr et al., 1991)

by the kidney and liver make infants more susceptible to the adverse effects of these toxicants (Ekeanyanwu et al., 2020; Fakhri et al., 2019). Therefore, although the benefits of human breast milk make it the best nutrition for newborns and infants, it can be a route of exposure for infants to toxic substances (Al-Saleh et al., 2003; Tahboub et al., 2021).

PTEs are of considerable interest due to their toxicity and widespread use caused by fossil fuels, industrial by-products (Fakhri et al., 2021; Hu et al., 2022; Luo et al., 2022; Nematollahi et al., 2021; Xiao et al., 2010), atmospheric deposits (Malakootian et al., 2021), agricultural lands, pesticides, herbicides, insecticides, fertilizers applications, waste incinerators, and sewage sludge (Rezaei et al., 2020). Moreover, several studies identified them in human breast milk, suggesting the exposure of infants to these toxicants and consequent health effects during lactation (Ekeanyanwu et al., 2020; Kunter et al., 2017; Olszowski et al., 2016; Samiee et al., 2019). Additionally, some parameters can affect the level of PTEs in human milk, including place of residence (higher in industrial and urban areas), maternal age (higher in older mothers), stage of lactation (higher in colostrum), smoking habits, maternal dietary intakes, and parity (Cherkani-Hassani et al., 2019). A significant correlation between PTEs concentration in breastfeeding mothers and sociodemographic characteristics such as mother's age, educational level, fish, fruit and vegetable consumption, family income, lipstick use, employment status, and smoking habits was noted (Vahidinia et al., 2019).

Based on previous studies, heavy metals such as Cd, Pb, As, and Cr result in the incidence of autism, rickets, and anemia, affect neurological development and infants growth, and decrease the intelligence quotient (IQ) score (Ekeanyanwu et al., 2020; Szukalska et al., 2021; Wongsasuluk et al., 2020; Zoghi et al., 2022). Accordingly, exposure to PTEs can affect the mother's health, breast milk quality, and infant health status (Wongsasuluk et al., 2020).

Assessment of PTEs concentration in human breast milk was investigated in different studies. The study of Pb and Cd levels in the breast milk of lactating mothers in Lebanon showed a range of 0.87 ± 1.18 and 18.18 ± 13.31 µg/kg for Cd and Pb, respectively (Bassil et al., 2018). In another work in Slovak, results showed that the average Cd, Pb, and Hg concentrations in breast milk samples were 0.43, 4.7, and 0.94 mg/kg, respectively (Ursinyova and Masanova, 2005). Also, PTEs such as Se, Zn, Cu, and Mn have been detected in breast milk samples from Korea while the Mn concentration exceeds daily recommended requirements (Kim et al., 2012). The toxicological analysis resulting from the determination of breast milk levels from Jordanian mothers indicated high intakes of As and Pb than their provisional tolerable weekly intake (PTWI) (Tahboub et al., 2021).

Thus, Identification and quantification of these contaminants in the mother milk and systematic investigation of the correlation between sociodemographic characteristics and PTEs can be used to assess the mother's exposure as well as respective health risks in infants (Bastos et al., 2018; Olowoyo et al., 2021; Samiee et al., 2019). Prolonged contact with PTEs can cause adverse effects on infant health (Ecsedi-Angyal et al., 2020; Samiee et al., 2019). Safety and quality assurance of breast milk is of great importance and has been the subject of many surveys. However, no meta-analysis study regarding PTEs in human breast milk and following health risks of infants was published. Accordingly, the present work is conducted to review the concentration of potentially toxic elements in human milk and estimate the consequent health risk in the infant.

## 2. Methods

### *2.1. Study identification and selection*

According to the PRISMA protocol, a search was conducted on international databases, including Scopus, PubMed, and Wed of Sciences, for 1 January 2000–10 August 2021. The search was conducted using the following terms: "metal OR heavy metal OR elements OR trace element OR potential toxic element or potential hazard element" AND "breast milk OR human milk OR women's milk.".

### *2.2. Inclusion and exclusion criteria and extraction of data*

The inclusion criteria were English language articles and descriptive and cross-sectional studies that measured PTEs concentration in human milk. The studies with unclear data, systematic reviews, narrative reviews, clinical trials, experimental studies, and dissertations were excluded during the selection process. The data were extracted, including the year of publication, country, sample size, and concentration statistics (Mean, standard deviation/ standard error). The concentrations based on fresh weight were included in the meta-analysis. To convert the weights, Eq. 1 (Table 1S) was used. Studies on mother milk

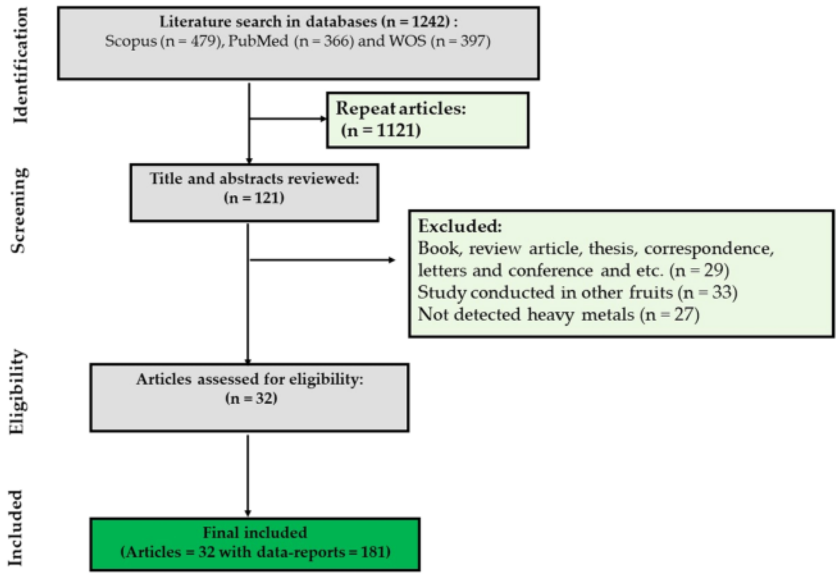


**Fig. 1.** Flow chart for searching process.

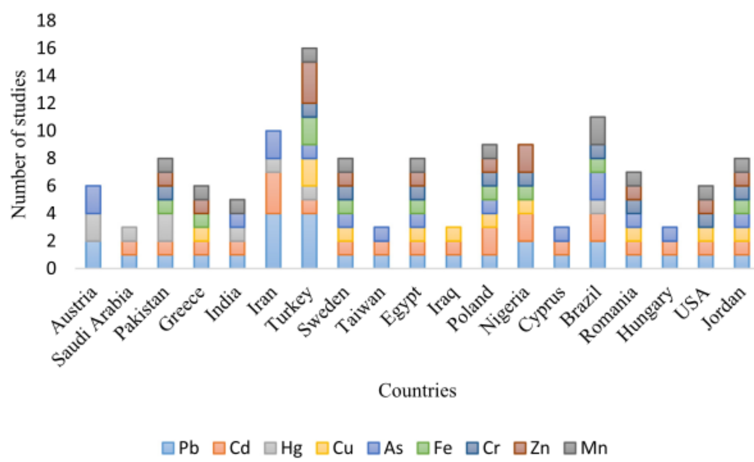


**Fig. 2.** statistics of investigated PTEs among countries.

with positive smoking were excluded.Table 1.

### 2.3. Meta-analysis

The data was extracted using concentration statistics (mean and SE), and STATA 14.00 software was used for the meta-analysis (Aranega and Oliveira, 2022; De Souza et al., 2021). The parameter of SE was calculated according to Eq. 2 (Table 1S). The heterogeneity of data is a crucial parameter for determining the used model. Depending on the $I^2$ index, random effect model (> 50%) or fixed-effect model (< 50%) for meta-analysis are used. The fixed-effect model assumes the same effect size for all studies, while the random effect model assumes various effect sizes among studies using Cochrane's Q-test and $I^2$ statistical analysis (Atamaleki et al., 2021; Borenstein et al., 2011; Higgins et al., 2019).

### 2.4. Health risk assessment

In the current study, non-carcinogenic and carcinogenic risks due to PTEs in human milk were estimated in infants according to the equation in Table 1s.

## 3. Results and discussion

### 3.1. Selection process and characteristics of studies

From those databases (Scopus, Web of Science, and PubMed) searched systematically between 2000 and 2021, 32 articles with 181 data reports were included. The study selection process is illustrated in Fig. 1. The number of studies conducted on of PTEs in human milk are shown in Fig. 2. Accordingly, the percentage of countries based on number of study was: Turkey (12.12%) > Brazil (8.33%) > Iran > (7.58%) > Poland (6.82%) ~ Nigeria (6.82%) > Sweden (6.06%) ~

**Table 2**
Meta-analysis concentration of Cd (μg/Kg-wet weight) in human milk based on country*.

| Country | Number of studies | ES | Lower | Upper | Weight (%) | Heterogeneity statistic | df[1] | P value[2] | $I^2$ (%)[3] |
|---|---|---|---|---|---|---|---|---|---|
| Saudi Arabia | 1 | 0.216 | 0.092 | 0.34 | 5.19 | 34.11 | 1 | < 0.001 | 97.10% |
| Pakistan | 1 | 6.886 | 3.589 | 10.183 | 0.06 | 53.02 | 2 | < 0.001 | 96.20% |
| Greece | 1 | 0.022 | 0.016 | 0.028 | 5.92 | 8.16 | 1 | 0.004 | 87.70% |
| India | 1 | 0.113 | 0.084 | 0.142 | 20.06 | 153.1 | 11 | < 0.001 | 92.80% |
| Iran | 3 | 0.299 | 0.258 | 0.34 | 12.37 | 18.94 | 7 | 0.008 | 63.00% |
| Turkey | 1 | 3.484 | 2.102 | 4.867 | 0.01 | 2.40 | 2 | 0.301 | 16.60% |
| Sweden | 1 | 0.011 | 0.01 | 0.013 | 2.96 | 0.00 | 0 | . | .% |
| Taiwan | 1 | 0.083 | 0.061 | 0.104 | 22.11 | 135.76 | 7 | < 0.001 | 94.80% |
| Egypt | 1 | 1.638 | 0.785 | 2.492 | 0.06 | 3.93 | 2 | 0.14 | 49.10% |
| Iraq | 1 | 0.998 | 0.349 | 1.647 | 0.52 | 11.98 | 1 | 0.001 | 91.70% |
| Poland | 2 | 0.011 | 0.005 | 0.017 | 5.93 | 31.82 | 1 | < 0.001 | 96.90% |
| Nigeria | 2 | 2.953 | 0.835 | 5.070 | 3.13 | 805.85 | 4 | < 0.001 | 99.50% |
| Cyprus | 1 | 0.058 | 0.050 | 0.067 | 2.93 | 0.00 | 0 | . | .% |
| Brazil | 2 | 4.833 | 0.000 | 14.213 | 3.21 | 5688.05 | 1 | < 0.001 | 100.00% |
| Romania | 1 | 0.052 | 0.016 | 0.088 | 4.27 | 1.18E+ 00 | 1 | 0.277 | 15.30% |
| Hungary | 1 | 0.025 | 0.023 | 0.028 | 8.88 | 3.53 | 2 | 0.171 | 43.30% |
| USA | 1 | 0.040 | 0.000 | 0.095 | 1.99 | 0.00 | 0 | . | .% |
| Jordan | 1 | 0.820 | 0.616 | 1.025 | 0.38 | 0.00 | 0 | . | .% |
| **Overall** | **23** | **0.161** | **0.147** | **0.174** | **100** | 11,182.75 | 60 | < 0.001 | 99.50% |

Degrees of freedom
P value of heterogeneity
Estimates of heterogeneity
* WHO "normal condition levels" in human breast milk (μg/l): < 1 (1 g of human breast milk is equivalent to 0.970 mL) (Bansa et al., 2017; Parr et al., 1991)

**Table 3**
Meta-analysis concentration of Hg (μg/Kg-wet weight) in human milk based on country*.

| Country | Number of studies | ES | Lower | Upper | Weight (%) | Heterogeneity statistic | df[1] | P value[2] | $I^2$ (%)[3] |
|---|---|---|---|---|---|---|---|---|---|
| Austria | 2 | 0.212 | 0.190 | 0.234 | 26.34 | 55.08 | 17 | < 0.001 | 69.10% |
| Saudi Arabia | 1 | 0.408 | 0.159 | 0.658 | 2.89 | 20.96 | 1 | < 0.001 | 95.20% |
| Pakistan | 2 | 1.003 | 0.945 | 1.061 | 27.01 | 5468.54 | 25 | < 0.001 | 99.50% |
| India | 1 | 0.244 | 0.183 | 0.305 | 11.24 | 202.37 | 11 | < 0.001 | 94.60% |
| Iran | 1 | 0.120 | 0.097 | 0.142 | 1.64 | 0.00 | 0 | . | .% |
| Turkey | 1 | 0.237 | 0.198 | 0.276 | 28.61 | 473.72 | 19 | < 0.001 | 96.00% |
| Brazil | 1 | 0.669 | 0.000 | 1.893 | 2.28 | 96.84 | 1 | < 0.001 | 99.00% |
| **Overall** | **9** | **0.444** | **0.419** | **0.468** | **100** | **7488.04** | **80** | **< 0.001** | **98.90%** |

Degrees of freedom
P value of heterogeneity
Estimates of heterogeneity
* WHO "normal condition levels" in human breast milk (μg/l): 1.4–1.7 (1 g of human breast milk is equivalent to 0.970 mL) (Bansa et al., 2017; Parr et al., 1991)

**Table 4**
Meta-analysis concentration of Cu (μg/Kg-wet weight) in human milk based on country*.

| Country | Number of studies | ES | Lower | Upper | Weight (%) | Heterogeneity statistic | df[1] | P value[2] | $I^2$ (%)[3] |
|---|---|---|---|---|---|---|---|---|---|
| Greece | 1 | 50.490 | 47.930 | 53.040 | 10.97 | 0.12 | 1 | 0.729 | 0.00% |
| Turkey | 2 | 60.566 | 51.259 | 69.874 | 12.19 | 7.87 | 3 | 0.049 | 61.90% |
| Sweden | 1 | 61.230 | 58.763 | 63.697 | 6.11 | 0.00 | 0 | . | .% |
| Egypt | 1 | 31.580 | 21.420 | 41.739 | 11.94 | 11.19 | 2 | 0.004 | 82.10% |
| Iraq | 1 | 13.293 | 5.153 | 21.434 | 12.53 | 45.01 | 1 | < 0.001 | 97.80% |
| Poland | 1 | 54.790 | 44.459 | 65.121 | 9.39 | 4.46 | 1 | 0.035 | 77.60% |
| Nigeria | 1 | 4.747 | 3.857 | 5.637 | 25.63 | 72.34 | 3 | < 0.001 | 95.90% |
| Romania | 1 | 76.267 | 61.101 | 91.433 | 4.17 | 1.76 | 1 | 0.184 | 43.30% |
| USA | 1 | 1.299 | 1.122 | 1.475 | 6.42 | 0.00 | 0 | . | .% |
| Jordan | 1 | 122.200 | 89.173 | 155.227 | 0.64 | 0.00 | 0 | . | .% |
| **Overall** | **11** | **32.287** | **29.502** | **35.071** | **100** | **6321.88** | **21** | **< 0.001** | **99.70%** |

Degrees of freedom
P value of heterogeneity
Estimates of heterogeneity
* WHO "normal condition levels" in human breast milk (μg/l): 180–310 (1 g of human breast milk is equivalent to 0.970 mL) (Bansa et al., 2017; Parr et al., 1991)

Pakistan (6.06%) ~ Jordan (6.06%) ~ Egypt (6.06%) > Romania (5.30%) > USA (4.55%) ~ Austria (4.55%) ~ Greece (4.55%) > India (3.79%) > Taiwan (2.27%) ~ Saudi Arabia (2.27%) ~ Iraq (2.27%) ~ Hungary (2.27%) ~ Cyprus (2.27%).

### 3.2. *Meta-analysis finding*

#### 3.2.1. *The concentration of PTEs based on the countries*

According to meta-analysis results (Tables 1–9), the concentrations of each PTE in human milk varied widely from one country to another, which can be correlated with the difference in the sources of these pollutants in different countries (Guo et al., 2022). PTEs contamination

**Table 5**
Meta-analysis concentration of As (μg/Kg-wet weight) in human milk based on country*.

| Country | Number of studies | ES | Lower | Upper | Weight (%) | Heterogeneity statistic | df[1] | P value[2] | $I^2$ (%)[3] |
|---|---|---|---|---|---|---|---|---|---|
| Pakistan | 2 | 0.261 | 0.220 | 0.302 | 44.95 | 4171.5 | 25 | < 0.001 | 99.40% |
| India | 1 | 0.181 | 0.139 | 0.224 | 15.08 | 311.97 | 11 | < 0.001 | 96.50% |
| Iran | 2 | 0.114 | 0.098 | 0.130 | 15.6 | 39.90 | 9 | < 0.001 | 77.40% |
| Turkey | 1 | 0.130 | 0.091 | 0.169 | 1.68 | 0.00 | 0 | . | .% |
| Sweden | 1 | 0.072 | 0.048 | 0.095 | 1.75 | 0.00 | 0 | . | .% |
| Taiwan | 1 | 0.079 | 0.009 | 0.148 | 6.15 | 21.24 | 3 | < 0.001 | 85.90% |
| Egypt | 1 | 22.818 | 0.794 | 44.842 | 0.02 | 19.40 | 2 | < 0.001 | 89.70% |
| Poland | 1 | 0.227 | 0.129 | 0.325 | 3.45 | 21.77 | 1 | < 0.001 | 95.40% |
| Cyprus | 1 | 0.095 | 0.074 | 0.116 | 1.76 | 0.00 | 0 | . | .% |
| Brazil | 2 | 4.016 | 0.000 | 12.018 | 1.8 | 41.29 | 1 | < 0.001 | 97.60% |
| Romania | 1 | 0.595 | 0.379 | 0.811 | 2.35 | 6.80 | 1 | 0.009 | 85.30% |
| Hungary | 1 | 0.054 | 0.043 | 0.064 | 5.35 | 6.66 | 2 | 0.036 | 70.00% |
| Jordan | 1 | 4.082 | 3.381 | 4.783 | 0.08 | 0.00 | 0 | . | .% |
| **Overall** | **16** | **0.207** | **0.186** | **0.227** | **100** | 6053.96 | 67 | **< 0.001** | 98.90% |

Degrees of freedom
P value of heterogeneity
Estimates of heterogeneity
* WHO "normal condition levels" in human breast milk (μg/l): 0.2–0.6 (1 g of human breast milk is equivalent to 0.970 mL) (Bansa et al., 2017; Parr et al., 1991)

**Table 6**
Meta-analysis concentration of Fe (μg/Kg-wet weight) in human milk based on country*.

| Country | Number of studies | ES | Lower | Upper | Weight (%) | Heterogeneity statistic | df[1] | P value[2] | $I^2$ (%)[3] |
|---|---|---|---|---|---|---|---|---|---|
| Pakistan | 1 | 393.556 | 346.901 | 440.211 | 55.94 | 733.85 | 22 | < 0.001 | 97.00% |
| Greece | 1 | 65.411 | 54.469 | 76.353 | 7.45 | 4.31 | 1 | 0.038 | 76.80% |
| Turkey | 2 | 154.698 | 122.357 | 187.04 | 9.13 | 5.99 | 3 | 0.112 | 49.90% |
| Sweden | 1 | 44.070 | 39.662 | 48.478 | 3.77 | 0.00 | 0 | . | .% |
| Egypt | 1 | 3990.000 | 1096.800 | 6880.000 | 0.1 | 17.27 | 2 | < 0.001 | 88.40% |
| Poland | 1 | 708.000 | 86.710 | 1330.000 | 3.34 | 96.75 | 1 | < 0.001 | 99.00% |
| Nigeria | 1 | 6.128 | 4.434 | 7.823 | 15.15 | 27.61 | 3 | < 0.001 | 89.10% |
| Brazil | 1 | 87.562 | 77.950 | 97.173 | 3.69 | 0.00 | 0 | . | .% |
| Jordan | 1 | 421.200 | 348.425 | 493.975 | 1.43 | 0.00 | 0 | . | .% |
| **Overall** | **10** | **258.443** | **247.398** | **269.487** | **100** | 9387.37 | 40 | < 0.001 | 99.60% |

Degrees of freedom
P value of heterogeneity
Estimates of heterogeneity
* WHO "normal condition levels" in human breast milk (μg/l): 350–720 (1 g of human breast milk is equivalent to 0.970 mL) (Bansa et al., 2017; Parr et al., 1991)

**Table 7**
Meta-analysis concentration of Cr (μg/Kg-wet weight) in human milk based on country*.

| Country | Number of studies | ES | Lower | Upper | Weight (%) | Heterogeneity statistic | df[1] | P value[2] | $I^2$ (%)[3] |
|---|---|---|---|---|---|---|---|---|---|
| Pakistan | 1 | 2.874 | 2.623 | 3.125 | 69.12 | 325.65 | 22 | < 0.001 | 93.20% |
| Turkey | 1 | 17.393 | 9.552 | 25.234 | 1.11 | 6.92 | 2 | 0.031 | 71.10% |
| Sweden | 1 | 0.039 | 0.000 | 0.927 | 1.93 | 0.00 | 0 | . | .% |
| Egypt | 1 | 8.264 | 3.654 | 12.875 | 1.01 | 7.41 | 2 | 0.025 | 73.00% |
| Poland | 1 | 0.060 | 0.020 | 0.100 | 6.64 | 24.07 | 1 | < 0.001 | 95.80% |
| Nigeria | 1 | 2.690 | 2.060 | 3.330 | 9.21 | 17.06 | 3 | 0.001 | 82.40% |
| Brazil | 1 | 0.571 | 0.514 | 0.628 | 3.31 | 0.00 | 0 | . | .% |
| Romania | 1 | 0.705 | 0.565 | 0.845 | 6.4 | 0.00 | 1 | 0.949 | 0.00% |
| USA | 1 | 1.828 | 0.030 | 3.626 | 0.84 | 0.00 | 0 | . | .% |
| Jordan | 1 | 17.160 | 14.471 | 19.849 | 0.44 | 0.00 | 0 | . | .% |
| **Overall** | **10** | **2.620** | **2.430** | **2.811** | **100** | **8747.04** | **40** | **< 0.001** | **99.50%** |

Degrees of freedom
P value of heterogeneity
Estimates of heterogeneity
* WHO "normal condition levels" in human breast milk (μg/l): 0.8–1.5 (1 g of human breast milk is equivalent to 0.970 mL) (Bansa et al., 2017; Parr et al., 1991)

can be caused by natural (migration and redistribution of soil) and human activities (mining, abandoned mining, fertilizer and pesticide application, and sewage irrigation) (Atamaleki et al., 2021). For example, Egypt has the highest concentration of Pb, As, Fe, and Mn, which can be associated with their agricultural and mining activities, sewage wastes, the nature of sediments, and anthropogenic activities (paper, pulp, ferrosilicon factories, and phosphate mining) (Al Naggar et al., 2018; El-Amier et al., 2017; Hasballah and Behear, 2016). Waseem et al. (2014) reported that the concentrations of PTEs increased from the south to the north in Egypt along the Nile River. They also reported that industrial activities such as sand quarry, shale mining, the nitrogen fertilizer factory at Aswan, and toxic waste drain during seasonal flash floods are the primary sources of PTEs in Egypt. The highest concentrations for Cd, Hg, and Zn in Pakistan were directly associated with environmental challenges such as unbalanced economic and social development (Khalid et al., 2020; Nighat et al., 2016; Pe[illegible]o et al., 2019; Rehman et al., 2021). Accidental urban congestion is the main reason for the deterioration of air, water, and soil quality resources

**Table 8**
Meta-analysis concentration of Zn (μg/Kg-wet weight) in human milk based on country*.

| Country | Number of studies | ES | Lower | Upper | Weight (%) | Heterogeneity statistic | df[1] | P value[2] | $I^2$ (%)[3] |
|---|---|---|---|---|---|---|---|---|---|
| Pakistan | 1 | 7272.063 | 6796.897 | 7747.228 | 0.36 | 204.15 | 22 | < 0.001 | 89.20% |
| Greece | 1 | 512.916 | 268.950 | 756.882 | 9.64 | 144.15 | 1 | < 0.001 | 99.30% |
| Turkey | 3 | 410.252 | 355.928 | 464.577 | 18.16 | 57.39 | 6 | < 0.001 | 89.50% |
| Sweden | 1 | 451.230 | 419.027 | 483.433 | 4.24 | 0.00 | 0 | . | .% |
| Egypt | 1 | 132.000 | 62.810 | 200.000 | 11.32 | 18.79 | 2 | < 0.001 | 89.40% |
| Poland | 1 | 769.000 | 28.740 | 1510.000 | 3.36 | 181.61 | 1 | < 0.001 | 99.40% |
| Nigeria | 2 | 12.576 | 2.052 | 23.100 | 43.24 | 5858.57 | 4 | < 0.001 | 99.90% |
| Romania | 1 | 963.116 | 803.083 | 1123.149 | 0.33 | 0.96 | 1 | 0.328 | 0.00% |
| USA | 1 | 2.088 | 1.691 | 2.485 | 8.66 | 0.00 | 0 | . | .% |
| Jordan | 1 | 484.900 | 377.052 | 592.748 | 0.68 | 0.00 | 0 | . | .% |
| **Overall** | **13** | **205.156** | **195.875** | **214.436** | **100** | **20,892.84** | **46** | **< 0.001** | **99.80%** |

Degrees of freedom
P value of heterogeneity
Estimates of heterogeneity
* WHO "normal condition levels" in human breast milk (μg/l): 0.7–2 (1 g of human breast milk is equivalent to 0.970 mL) (Bansa et al., 2017; Parr et al., 1991)

**Table 9**
Meta-analysis concentration of Mn (μg/Kg-wet weight) in human milk based on country*.

| Country | Number of studies | ES | Lower | Upper | Weight (%) | Heterogeneity statistic | df[1] | P value[2] | $I^2$ (%)[3] |
|---|---|---|---|---|---|---|---|---|---|
| Pakistan | 1 | 9.193 | 8.363 | 10.023 | 38.96 | 385.16 | 22 | < 0.001 | 94.30% |
| Greece | 1 | 0.514 | 0.303 | 0.726 | 6.23 | 27.54 | 1 | < 0.001 | 96.40% |
| India | 1 | 0.525 | 0.426 | 0.625 | 32.94 | 420.91 | 11 | < 0.001 | 97.40% |
| Turkey | 1 | 14.589 | 7.951 | 21.227 | 0.88 | 5.80 | 2 | 0.055 | 65.50% |
| Sweden | 1 | 0.390 | 0.340 | 0.440 | 3.12 | 0.00 | 0 | . | .% |
| Egypt | 1 | 20.400 | 5.380 | 35.500 | 2.19 | 19.60 | 2 | < 0.001 | 89.80% |
| Poland | 1 | 0.892 | 0.785 | 1.000 | 6.19 | 2.57 | 1 | 0.109 | 61.00% |
| Brazil | 2 | 7.908 | 0.000 | 22.418 | 3.31 | 47.15 | 1 | < 0.001 | 97.90% |
| Romania | 1 | 2.114 | 1.487 | 2.741 | 4.13 | 1.33 | 1 | 0.249 | 24.80% |
| USA | 1 | 0.933 | 0.000 | 1.921 | 1.7 | 0.00 | 0 | . | .% |
| Jordan | 1 | 10.478 | 7.447 | 13.509 | 0.35 | 0.00 | 0 | . | .% |
| **Overall** | **12** | **4.304** | **4.113** | **4.495** | **100** | **10,386.81** | **51** | **< 0.001** | **99.50%** |

Degrees of freedom
P value of heterogeneity
Estimates of heterogeneity
* WHO "normal condition levels" in human breast milk (μg/l): 3–4 (1 g of human breast milk is equivalent to 0.970 mL) (Bansa et al., 2017; Parr et al., 1991)

(Waseem et al., 2014).

### 3.2.2. *The rank order of PTEs in the human milk*

The rank order of PTEs in the breast milk samples was Fe (258.44 μg/kg) > Zn (205.16 μg/kg) > Cu (32.29 μg/kg) > Mn (4.30 μg/kg) > Cr (2.62 μg/kg) > Hg (0.44 μg/kg) > As (0.21 μg/kg) > Cd (0.16 μg/kg) > Pb (0.03 μg/kg). Compare the WHO recommendation commonly known as "normal condition levels" in human breast milk (1 g of human breast milk is equivalent to 0.970 mL)(Bansa et al., 2017; Parr et al., 1991), concentrations of all PTEs are below the allowable level, except for Zn and Mn. These results are significant for neonatal intensive care units and high-risk neonates, especially preterm infants.

The primary sources of PTEs in the environment are natural, agricultural, industrial solid waste, inland effluent, and atmospheric sources. Human activities(mining, electroplating, metallurgical smelting actions, and using pesticides and fertilizers) also significantly aggravate environmental pollution (Medfu Tarekegn et al., 2020). The three main pathways of PTEs entering the body are ingestion, inhalation, and dermal contact absorption; some studies have reported that ingestion is the primary pathway for human health risks (Tong Sh et al., 2020).

Fe has the highest PTEs concentration in breast milk as Fe is the fourth most abundant element in the Earth's crust and the most abundant transition metal, and most commonly found in nature in its oxides (Bhateria and Singh, 2019; Faust, 2018; Hassanien and Ali, 2018). It can be absorbed into the human body from different environmental matrices, such as air, water, soil, and food (Abbaspour et al., 2014; Ezeonu et al., 2012; Kamble et al., 2013; Kenzhebayeva et al., 2019). Furthermore, Fe plays a crucial role in several biological reactions in the human body and has an important part in an array of enzymes, systems of energy transduction, and oxygen carriers. Its deficiency in infants is significant and can impair brain development and cause anemia (Peixoto et al., 2019; Sigel et al., 2013). In most cases, pregnant women cannot change their dietary habits. Therefore, human milk fortification with oral Fe is necessary (Idemili-Aronu et al., 2022; Mahundi, 2021; Mattila et al., 2021; Milman et al., 2016).

Zn is part of more than three thousand proteins found in the human body, also playing regulatory functions in mammalian cells and plays an important role during embryogenesis and embryo development (Boskabadi et al., 2021; Dumrongwongsiri et al., 2022; Peixoto et al., 2019). Zn concentrations (205.16 μg/kg) was higher than WHO "normal condition levels" (0.7–2 μg/kg). For Zn, like Fe, the two ways of environmental exposure from different pathways and supplements can effectively increase its concentration. However, determining each scenario's effectiveness is impossible and requires Long-term interventions and cohort studies. Iqbal and Ali (Iqbal and Ali, 2021) reported that although Zn supplements reduce the risk of preterm birth, no substantial effect was found for other fetomaternal outcomes. They also emphasized that further studies need to decide the recommended Zn dose or intake during pregnancy. On the other hand, according to (Castillo–Castañeda et al., 2019), the presence of Zn ions can affect Cu absorption in breast milk.

Cu is the 25th most abundant element in the Earth's crust and the third most used metal globally (Shabbir et al., 2020). Cu is also essential for several enzymes (ceruloplasmin, cytochrome oxidase, catechol oxidase), which present electron transport, oxidation, and melanin synthesis (Khalid et al., 2020; Nighat et al., 2016; Rehman et al., 2021).

Based on the results of (de Oliveira Trinta et al., 2020), Cu correlates with immunological increases and antioxidant processes(activity versus reactive oxygen species, ROS) in infants.

Mn is an essential enzymatic cofactor for carbohydrate and lipid metabolism and a micronutrient for bone growth (Kumar et al., 2017). Although several studies reported that Fe and Mn content in mothers' milk is not enough for the nutritional requirements of preterm infants (Domellöf, 2021; Oliveira et al., 2020), the results of the present study showed that their concentration in the breast milk is higher than WHO "normal condition levels." This high concentration, similar to the above, is likely due to supplements during pregnancy. Therefore, it is suggested that in future studies, drugs used by mothers during pregnancy be recorded in order to be able to analyze their effect in this regard. In the environment, Mn is present in rocks, soil, water, and food, and its exposure can be started before birth from maternal exposure. According to (Conley et al., 2022), although blood Mn levels were strongly associated with its blood concentration, it may not be a suitable biomarker of cumulative long-term exposure (Milatovic et al., 2022).

Cr is an essential micronutrient present in supplements used during pregnancy and alters the antioxidant status in the brain. Although Cr(III) is an essential microelement for normal human metabolic activity, Excessive exposure can harm health (Wang et al., 2018). In contrast, Cr (VI) has high toxicity and carcinogenesis (Kaur et al., 2020; Yoshinaga et al., 2018). Some major Cr (VI) mechanisms that cause cellular damage are high levels of oxidative stress, chromosome breaks, and DNA adduct formation (DesMarias and Costa, 2019; Kariminejada et al., 2021). It is also classified as a Group' A' human carcinogen (Wise et al., 2022). Some studies report that Cr is secreted significantly in breast milk (Cardoso et al., 2014; Elaridi et al., 2020; Samiee et al., 2019). Although one of the most critical exposure pathways is anthropogenic sources and industrial activities (Ukhurebor et al., 2021); but (Motas et al., 2021) reported that the highest concentrations of Cr, Mn, and Fe in human milk were detected in women living in the agricultural zone.

Hg is a potentially toxic element that has received much attention due to its toxicity, even in low concentrations (Raj and Maiti, 2019). WHO "normal condition levels" in human breast milk for Hg were 1.4–1.7 (μg/l) (1 g of human breast milk is equivalent to 0.970 mL) (Bansa et al., 2017; Parr et al., 1991). Exposure of pregnant women, lactating mothers, and weaning offspring to Hg is a tremendous public health concern, especially in the high consumption of carnivorous fish or sea mammals (Sakamoto et al., 2022). Cherkani-Hassani et al. (2021) reported a significant relationship between Hg concentration in breast milk and the occurrence of previous miscarriage, anemia before pregnancy, taking supplements during pregnancy, consumption of cereals, and the use of lipstick (Örün et al., 2021) stated there is a relationship between high Hg concentration and maternal vitamin use. It may have been related to the Hg contamination of vitamin supplements, or these mothers are prone to take medicine for various complaints due to subtle Hg exposure.

As is a metalloid that occurs in many minerals. Exposure to As is usually due to the consumption of water and seafood, especially shellfish. Exposure to Pb and Hg can cause neurotoxic problems. The organic forms of As are relatively nontoxic compared to the inorganic forms (Bassil et al., 2018). Although (Samiee et al., 2019) reported that the transfer of As to the mammary glands is limited, and this issue protects infants from exposure to As, there is an information gap in the discrimination between intrauterine postnatal effects (Rebelo and Caldas, 2016).

Cd is reported among the top 10 toxic metals on the Agency for Toxic Substances and Disease Registry (Huang et al., 2019). During pregnancy, Cd can be transferred to the fetus from placental transfer. This process continues after birth in the lactation period through the transport from the maternal blood to the mammary glands (Cherkani-Hassani et al., 2017). According to (Cherkani-Hassani et al., 2020) study, Cd concentration in human milk has a significant association with the area of residence(low in mothers living in urban areas), gestational duration (high in mothers who delivered preterm), mode of delivery(high in mothers who delivered by cesarean), level of maternal education(high in mothers by low level of education), use of cosmetic powders(high when high frequency using), dietary habits(high when the frequency of consumption of milk, dairy products and dry fruits and low in *a* high frequency of consumption of wheat bread).

Pb is a PTEs naturally occurring in the earth's crust without known biological activity (Yurdakök, 2015). Pb can cause central nervous system disorders, encephalitis, anemia, hepatitis, kidney, liver, heart, and blood vessel failure, damage to the immune system, the genital system, the digestive tract, and the development of cancer. Letinil; et al. (2016) reported that Pb concentrations were almost 2-fold higher in the colostrum of non-smokers and about 2.5 times higher who continued smoking during pregnancy. According to (Dursun et al., 2016) study, There was a negative correlation between the level of Pb and Hg and a positive correlation between the level of Pb and Cd in breast milk. However, As, Cd, Cr, Hg, and Pb, even in small amounts, are hazardous and can accumulate in the mother's skeleton and release during the lactation period (Lorenzetti et al., 2021). Due to the competitive effect between calcium absorption and Cd, Hg, and Pb, adequate calcium intake during pregnancy and lactation reduces their mobilization in bones and releases Pb during lactation (Lorenzetti et al., 2021; Rădulescu and Lundgren, 2019; Shiyu et al., 2020). Also, exposure of infants to toxic metals during pregnancy was more than through breastfeeding (Bansa et al., 2017).

Ultimately, it is necessary to compare our results with a similar systematic review study (Ghane et al., 2022). Based on the results obtained, PTE concentrations in the breast milk were Cu (1.84 mg/kg) > Zn (1.80 mg/kg) > Fe (1.03 mg/kg) > Ni (0.60 mg/kg) > Pb (0.10 mg/kg) > As (0.15 mg/kg) ≈ Cd (0.15 mg/kg) and the non-carcinogenic risk assessment of the PTEs in breast milk indicated different patterns in various countries, and the calculated TTHQ level of metals in infants was < 1 value. As it is known, the results of the two studies are different from each other. One of the most important reasons for this difference in the results of the two studies can be related to the literature search strategy. In the present study, collected literature studies were published between 2000 and 2021, and in Ghane et al., articles were published between 1982 and 2020. Given the current policy momentum on universal health coverage and primary health care reform globally, there is an urgent need for high-quality and new studies to evaluate the data available from existing studies. The selection of more recent studies makes meta-analysis results more real and valuable. The next difference is in the calculation of health risk assessment. In Ghane et al., standard deviation, the main input variable for calculating health risk assessment, was considered for the ingestion rate of human breast milk, EF, Ed, and BW, and the average life expectancy. However, in the present study, the standard deviation was considered for per capita consumption and body weight. In addition, based on studies conducted by (Fakhri et al., 2022; Mahdavi et al., 2022), BW does not have log-normal distribution, but in Ghane et al., BW has log-normal distribution.

### 3.3. Analytical methods and instruments for measuring PTEs in human milk

Choosing suitable analysis methods and instruments for PTEs is a severe challenge due to the complexity of the human milk matrix (Draghici et al., 2011; Zeiner et al., 2007). Accordingly, many analytical techniques have been used for measuring PTEs, such as Thin layer chromatography(TLC)(Jumde and Gumule, 2015; Kholghi et al., 2020), UV–VIS spectrometry(Hasankola et al., 2020; Zhou et al., 2019), Atomic absorption spectrometry (AAS) by Flame Atomic Absorption(FAA) (Muhib et al., 2016; Wang et al., 2015), Graphite Furnace Absorption (GFA)(Forero-Mendieta et al., 2022; Zhong et al., 2016) and Vapor Generation Absorption(VGA)(Mostafavi and Ebrahimi, 2019; Perelonia et al., 2021), X-ray fluorescence (XRF)(Byers et al., 2019; Zhou et al.,

**Table 10**
Non-carcinogenic (THQ) risk in the infants due to ingestion of human milk.

| Country | AS | Cd | Total Cr | Cu | Fe | Methyl Hg | Mn | Pb | Zn |
|---|---|---|---|---|---|---|---|---|---|
| Austria | NC | NC | NC | NC | NC | 2.61E-[illegible] | NC | 6.80E-03 | NC |
| Brazil | 1.65E+ 00 | 5.95E-01 | NC | NC | 1.54E-02 | 8.24E-01 | 7.00E-03 | 1.20E+ 00 | NC |
| Cyprus | 3.90E-02 | 7.10E-03 | NC | NC | | NC | | 5.30E-03 | NC |
| Egypt | 9.37E+ 00 | 2.02E-01 | NC | 9.73E-02 | 7.02E-[illegible] | NC | 1.80E-02 | 1.33E+ 00 | 5.42E-02 |
| Greece | NC | 2.70E-03 | NC | 1.56E-01 | 1.15E-02 | NC | 5.00E-04 | 1.40E-03 | 2.11E-01 |
| Hungary | 2.20E-02 | 3.10E-03 | NC | NC | NC | NC | NC | 8.70E-03 | NC |
| India | 7.40E-02 | 1.39E-02 | NC | NC | NC | 3.01E-01 | 5.00E-04 | 1.12E-02 | NC |
| Iran | 4.70E-02 | 3.68E-02 | NC | NC | NC | [illegible]8E-01 | NC | 1.79E-01 | NC |
| Iraq | NC | 1.23E-01 | NC | 4.09E-02 | | NC | NC | 5.16E-02 | NC |
| Jordan | 1.68E+ 00 | 1.01E-01 | NC | 3.76E-01 | 7.41E-02 | NC | 9.20E-03 | 3.44E-01 | 1.99E-01 |
| Nigeria | | 3.64E-01 | NC | 1.46E-02 | 1.10E-03 | NC | | 1.62E-01 | 5.20E-03 |
| Pakistan | 1.07E-01 | 8.48E-01 | NC | NC | 6.93E-02 | 1.24E+ 00 | 8.[illegible]-03 | 3.90E-01 | 2.99E+ 00 |
| Poland | 9.30E-02 | 1.30E-03 | NC | 1.69E-01 | 1.25E-01 | NC | 8.00E-04 | 3.70E-03 | 3.16E-01 |
| Romania | 2.44E-01 | 6.40E-03 | NC | 2.35E-01 | NC | NC | 1.90E-03 | 9.00E-04 | 3.96E-01 |
| Saudi Arabia | NC | 2.66E-02 | NC | NC | NC | 5.03E-01 | NC | 1.38E-01 | NC |
| Sweden | 3.00E-02 | 1.40E-03 | NC | 1.89E-01 | 7.80E-03 | NC | 3.00E-04 | 6.70E-03 | 1.85E-01 |
| Taiwan | 3.20E-02 | 1.02E-02 | NC | NC | NC | NC | | 4.21E-02 | |
| Turkey | 5.30E-02 | 4.29E-01 | NC | 1.87E-01 | 2.72E-02 | 2.92E-01 | 1.28E-02 | 1.05E-02 | 1.69E-01 |
| USA | NC | 4.90E-03 | NC | 4.00E-03 | NC | NC | 8.00E-04 | 3.84E-02 | 9.00E-04 |

References: Bansa et al. (2017); Parr et al. (1991)

2018), Electrochemical Methods(Cui et al., 2015; Ding et al., 2021), Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-OES) (Fathabad et al., 2018; Yamini and Safari, 2018) and Inductively coupled plasma mass spectrometry (*ICP-MS*)(Ashrit et al., 2018; Zhang et al., 2020). In some studies, combining at least two analytical methods helps achieve the best results in different matri(Kwon et al., 2018; Li et al., 2021). Among them, AAS and ICP-MS/AES, due to high sensitivity, low levels of detail(LOD), and simultaneous determination of multiple elements, are suitable for measuring PTEs in many samples(Jin et al., 2020).

Among the studies reviewed in the present study (32 articles), analytical selected methods for measuring PTEs in human milk in 58.97%(n = 23) of the studies were AAS(10.26%(n = 4)FAA, 15.38% (n = 6)VGA, 20.51%(n = 8)GFA and 12.82%(n = 5) Blind), 30.77% (n = 12) of the studies was ICP/MS, 2.56%(n = 1) of the studies was Gamma Spectrometry and 7.69%(n = 3) of the studies was ICP/OES. It should be noted that in some studies (n = 8), a combination of two methods was used. Additional information is also presented in Table 3S. These methods have strengths and limitations, which are reviewed in previous studies (Arjomandi and Shirkhanloo, 2019; Llaver et al., 2021; Tyler and Jobin Yvon, 1995; Yuan et al., 2011). Among them, AAS and ICP-MS/AES, due to high sensitivity, low levels of detail(LOD), and simultaneous determination of multiple elements, are more often used for analyzing and detecting many samples (Jin et al., 2020). Significantly, the ICP-MS, also known as a green analytical method, have preferences such as high sensitivity, wide linear range, and strong anti-interference (Chojnacka and Mikulewicz, 2019; He et al., 2013).

However, different parameters should be considered for selecting the best method, such as the costs of the analyses, the time required, the required amount of samples, the limit of detection, sensitivity, and selectivity (Hung et al., 2010; Zeiner et al., 2007). In the first step, the PTEs concentration ranges should be estimated qualitatively. Then, the method for an exact quantification may be chosen depending on the analytical task (Zeiner et al., 2007).

### 3.4. Health risk assessment

Human health risk assessment integrates exposure and exposure-response data to predict the hazard potential for infants from PTEs exposures. Health risks caused by PTEs that enter the infant's body from different exposure pathways are divided into carcinogenic and non-carcinogenic risks (Shams et al., 2022). For this purpose, both non-carcinogenic risks (Eq. 4 and 5) and carcinogenic risks (Eq. 6) were estimated.

The Target Hazard Quotient (THQ) assessed non-carcinogenic health risks. When THQ> 1, infants are threatened (Atamaleki et al., 2021). In present study, The Lowest and highest THQ in infants due to AS was Hungary (2.20E-02) and Egypt (9.37E+00); Cd, Poland (0.13E-02) and Pakistan (0.84E-2); Cu, USA (40E-4) and Jordan(0.37E-2); Fe, Nigeria (11.00E-4) and Egypt(0.70E-2); Methyl Hg, Iran(0.14E-2) and Pakistan(1.23E00); Mn, Sweden(3.00E-4) and Egypt(0.01E-2); Pb, Greece (14.00E-4) and Egypt (1.33E0.00); and Zn, USA(9.00E-4) and Pakistan(2.96E0.00), respectively (Table 10). The high value of THQ for As, Hg, Pb, and Zn can be associated with a high concentration of PTEs, and continuous and effective monitoring is required to reduce the amount of PTEs contaminants.

Also, Total Target Health Quotient (TTHQ) values of PTEs in the human milk were computed. TTHQ shows the sum of each THQ for the whole PTEs. If TTHQ > 1, infants are considered carcinogenic health risks (Atamaleki et al., 2021). Accordingly, in the present study the rank order of country based on TTHQ was Egypt (11.778) > Pakistan (5.643) > Brazil (4.293) > Jordan (2.780) > Turkey (1.179) > Romania (0.883) > Poland (0.707) > Saudi Arabia (0.667) > Nigeria (0.546) > Sweden (0.419) > Iran (0.410) > India (0.400) > Greece (0.382) > Austria (0.268) > Iraq (0.215) > Taiwan (0.084) > Cyprus (0.051) > USA (0.049) > Hungary (0.033) (Fig. 1). TTHQ in Egypt, Pakistan, Brazil, Jordan, and Turkey was higher than 1; infants are not at safe, non-carcinogenic risk (Fig. 1).

In the following, Carcinogenic Risk (CR) was used as the cumulative probability of individual developing cancer. Following US-EPA guidance, a CR < 1E-06 represents negligible levels, values CR < 1E-4–1E-6 are acceptable levels, while CR > 1E-4 signifies a high cancer risk to humans (Atamaleki et al., 2021). The rank order of country based on CR of inorganic As was Egypt (4.22E-03) > Jordan (7.54E-04) > Brazil (7.42E-04) > Romania (1.10E-04) > Pakistan (4.82E-05) > Poland (4.19E-05) > India (3.34E-05) > Turkey (2.40E-05) > Iran (2.11E-05) > Cyprus (1.76E-05) > Taiwan (1.46E-05) > Sweden (1.33E-05) > Hungary (9.98E-06). CR in Egypt, Jordan, Brazil, and Romania was an unsafe cancer risk (CR>1E-4), and CR in other countries was in threshold cancer risk (CR <1E-4–1E-6) (Fig. 2).

## 4. Conclusion

After a systematic search among Scopus, PubMed, and Web of Science databases, 32 studies measured the concentration of PTEs in human milk included in this work. The extracted data were meta-analyzed, and their health effects were assessed via the health risk models (carcinogenic and non-carcinogenic). According to the meta-analysis results, Fe

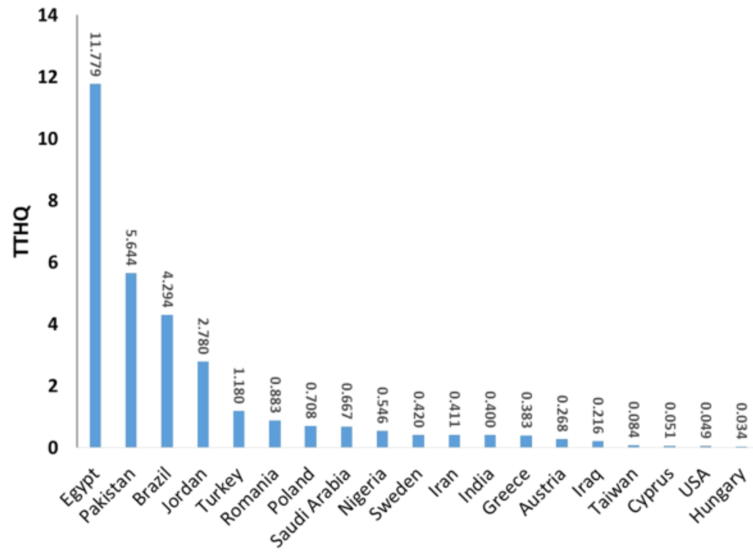


**Fig. 3.** TTHQ in infant due to consumption of mother milk content of heavy metals.

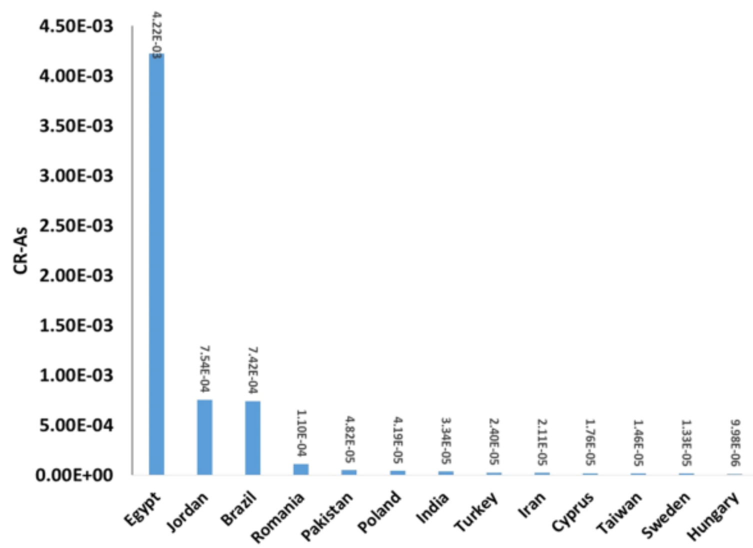


**Fig. 4.** CR in infant due to consumption of mother milk content of inorganic As.

had the most concentration in human milk, followed by Zn, Cu, Mn, Cr, Hg, As, Cd, and Pb, respectively. The total non-carcinogenic risk showed a considerable effect (TTHQ > 1) for Egypt, Pakistan, Brazil, Jordan, and Turkey. The counties, including Egypt, Jordan, Brazil, and Romania, also were at an unsafe carcinogenic risk (CR > 1E-4). As discussed above, lactating mothers can intake PTEs from different sources. However, their diet can be the main reason directly affecting the milk's content. Therefore, monitoring their environment, feeding behavior (especially supplements taken during pregnancy), and the quality of food consumption is necessary to reduce the exposure. Periodic biomonitoring surveys in each country can also help estimate the level of exposure of lactating women and newborns. The reason remains unclear without developing our knowledge about the screened mothers' diet. (Figs. 3 and 4).

**Ethical approval**

Not applicable.

**Consent to participate**

The authors declare their Consent to Participate in this article.

**Consent to publish**

The authors declare their Consent to Publish this article.

## CRediT authorship contribution statement

**Aliasghar Neshat:** Investigation, Data curation, Resources, Conceptualization, Methodology, Writing – original draft. **Ali Oghazyan:** Investigation, Data curation, Resources, Conceptualization, Methodology, Writing – original draft. **Fatemeh Kariminejad**, Investigation, Data curation, Resources, Conceptualization, Methodology, Writing – original draft. **Trias Mahmudiono:** Literature searching, Writing – review & editing. **Yadolah Fakhri:** Literature searching, Writing – review & editing. **Amir Mohammad Sheikh Asadi:** Literature searching, Writing – review & editing. **Amir Mohammad Sheikh Asadi:** Supervision, Writing – review & editing. **Ali Atamaleki:** Supervision, Writing – review & editing. **Amin Mousavi Khaneghah:** Supervision, Writing – review & editing.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data Availability

No data was used for the research described in the article.

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jfca.2022.104933.

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