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Review

Reference ranges for select elements and metals in healthy biomatrices

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ABSTRACT

Introduction/Objective: This review aimed to consolidate and compare reference values (RVs) for various elements and metals in biological samples from healthy populations worldwide.
Methods: A Web of Science/PubMed/Scopus review was conducted. Original articles in the English language, from January 2012 to February 2022, with at least 120 participants and 3 evaluated elements, and biological samples of whole blood, serum, plasma, umbilical cord, and hair included in this review.
Results: Ninety-nine studies were screened and assessed, and eventually, 29 eligible studies from 15 countries and a total recruitment of 26,676 healthy subjects, ages ranging from zero to 80 years were included in this review. The results of evaluating 36 trace/micro/meso/macro/ toxic metals and elements in biological fluids and hair were extracted from eligible studies. Several indicators include reference range (lower, upper), arithmetic and geometric mean, median, percentile (lower, upper), and confidence interval (CI) 95 % of evaluated elements were reported. Due to geographical conditions, different demographic factors, and different analytical methodologies, the results of the analysis were various in different countries.
Conclusions: This review points out the necessity for localized RVs and standardized methodologies for accurate clinical evaluations and bio-monitoring. The findings call for extensive studies across diverse populations to develop comprehensive RVs for elements and metals, ensuring effective health assessments and environmental exposure controls.

1. Introduction

Trace elements (TEs) and macro elements (MEs) are crucial micronutrients for animals and plants that participate in many physiological processes and biochemical reactions [1–4]. Some of TEs/MEs are utilized as active centers of enzymes, trace bioactive substances, stabilizers, or cofactors of enzymes [4,5]. Their binding to receptors can regulate critical biological functions or inhibit the entry of specific molecules into cells, thereby stabilizing cellular structures. Key TEs in humans, comprising approximately 0.02 % of total body weight, include zinc (Zn), copper (Cu), selenium (Se), chromium (Cr), cobalt (Co), iodine (I), manganese (Mn), boron (B), fluoride (F), and molybdenum (Mo). Magnesium (Mg), sulfur (S), and calcium (Ca) are classified as meso elements (MeEs), while sodium (Na), potassium (K), chlorine (Cl), nitrogen (N), and phosphorus (P) fall under the MEs category [1,6,7]. Mg is integral to numerous enzymatic reactions, such as protein and fatty acid synthesis, and is vital for nerve impulse transmission and the structural integrity of muscles and the skeleton [8–10]. Zn is vital for immune system maturation, cell growth, and reproduction [11–15]. Se supports normal thyroid hormone metabolism and prevents lipid peroxidation and cellular damage [16,17]. While selenium deficiency is associated with increased lipid oxidation and cellular dysfunction,

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excess selenium can be toxic, particularly in individuals who already have adequate selenium levels [15,18–20]. This element also encompasses a protective biological role against toxicity exerted by toxic metals (TMs) such as arsenic (As), lead (Pb), mercury (Hg), and cadmium (Cd) [21–23]. While exposure to high levels of TEs can be toxic, TMs are inherently toxic even at trace concentrations [24–28].

TMs are non-biodegradable and persistent environmental contaminants naturally found in the earth's crust and released into the environment, particularly in industrial areas [25,29]. Cd, Pb, and Hg have been declared as dangerous elements by the United States Food and Drug Administration (FDA). Furthermore, according to the World Health Organization (WHO), these metals are among the top 10 chemicals of public health concern [30,31]. Due to bioaccumulation potential and toxicity in different organs and tissues, As, Pb, Hg, and Cd have been ranked as first, second, third, and fourth Priority List of Hazardous Substances by US Agency for Toxic Substances and Disease Registry (ATSDR), respectively [32–34].

Accurate analytical techniques are essential for assessing toxicant burden. Bio-monitoring of TEs, MeEs, MEs, and TMs offers insights into prolonged exposure and the impact of environmental elements/metals on living organisms. The analysis of non-invasive matrices, such as blood, hair, urine, and saliva, has proven to be an effective diagnostic tool for monitoring exposure to toxic elements and determining health and nutritional status [35–37]. Different surveys have established reference ranges using various methodological approaches.

RVs are commonly used to evaluate parameters like elemental content in human body fluids or tissues. The reference range, defined as the interval of values found in 95 % of healthy individuals, serves as a critical tool for interpreting laboratory results and determining the normality of an individual or group [38–41]. However, determining RVs is complex due to factors such as age, gender, genetic background, geographical location, physical activity, and environmental exposure. Consequently, RVs for elements/metals may vary across different populations. Methodological differences, including population selection, specimen sampling, sample preparation, analytical methods, storage conditions, and laboratory variations, further complicate the extraction of meaningful conclusions [42–45]. Due to the above-mentioned factors, some studies have been performed to establish element reference ranges in biological fluids and tissues from healthy people with different characteristics (i.e., age group and gender). RVs can be used for effective control of exposure to elements/metals. [38,43,46–52]. Recent human bio-monitoring programs across various countries have sought to control environmental toxicant exposures, necessitating a comprehensive review of elements/metals RVs based on different population characteristics. However, few reviews have been conducted to date. This study aimed to review current literature, compare metal concentrations in various sample types and populations worldwide, and provide a perspective on developing RVs for accurately interpreting elements/metals levels in healthy individuals.

2. Methods

2.1. Search strategy

Our search encompassed all available online resources in the following electronic databases: Web of Science, Scopus, and PubMed. The search was conducted in English using broad search terms: ("heavy metal*" OR "metal*" OR "element*" OR "trace element*" OR "toxic metal*" OR "mineral*" OR "bimetal*") AND ("reference value*" OR "reference range*" OR "normal value*" OR "reference interval*") AND ("biological sample*" OR "serum" OR "blood" OR "plasma" OR "hair"). In this review, the term 'bimetal' is defined to refer to studies investigating the interactions between two metals. This definition facilitated the identification of articles assessing the combined effects of metals on biological monitoring and reference levels. Additionally, the term 'mineral' was included to capture studies focusing on essential mineral elements, such as magnesium, zinc, and selenium.

2.2. Inclusion criteria

To evaluate data quality, stringent inclusion criteria, validated analytical methods, and internal quality control measures were employed. This review included only studies featuring healthy participants and those that assessed elements using precise methodologies. Publications needed to be in English and dated from June 2012 onwards. Exclusions were made for review articles, conference presentations, and book chapters. Initially, the titles and abstracts of identified papers were screened by two independent investigators to select relevant articles. The full texts of the selected studies (118 studies) were then reviewed, and irrelevant articles were omitted. Ultimately, 99 full texts were assessed for eligibility, resulting in the inclusion of 29 studies from 15 countries that reported RVs of at least three elements and metals in healthy subjects, focusing on biological sample types (whole blood, serum, plasma, scalp hair, umbilical cord blood) with no less than 120 healthy subjects (Fig. 1). Minimum 120 healthy participants are set based on biomonitoring principles and reference studies to ensure statistically valid and representative data from the general population. In biomonitoring studies, a sample size greater than 100 participants is typically recommended to create a reliable distribution of reference values [38].

Regarding method validation, the included studies primarily relied on established and widely accepted analytical methods used in human biomonitoring programs. Most studies utilized validated analytical techniques such as inductively coupled plasma mass spectrometry (ICP-MS(and atomic absorption spectroscopy (AAS) for element evaluation. Some studies also employed multiple methods, including colorimetric techniques, UV spectrophotometry, and other standardized approaches. AAS is known for its high specificity, cost-effectiveness, and relatively simple operation, making it suitable for routine metal analysis. However, it has limitations, including lower sensitivity compared to ICP-MS, the inability to analyze multiple elements simultaneously, and a narrow dynamic range [53–56]. In contrast, ICP-MS offers superior sensitivity, a broad dynamic range, and the ability to detect multiple elements in a single run, making it highly advantageous for trace and ultra-trace metal analysis. Additionally, ICP-MS can measure isotope ratios, which is beneficial in geochemical and biomedical research. However, its disadvantages include higher operational costs, complex instrumentation, and susceptibility to matrix interferences, requiring careful sample preparation [56]. High Resolution ICP-MS (HR-ICP-MS), has ultra-high precision and ability to differentiate cadmium species. This method has some limitations including very high cost and limited accessibility [56,57]. Between these methods, AAS is better suited for analyzing metallic elements with low cost and reasonable accuracy. ICP-MS is extremely sensitive and accurate but comes at a higher cost and requires skilled operators [53–57]. In our review, studies that did not implement internal quality control and regular calibration of instruments were excluded. In addition, geographical variations, demographic factors, and different analytical methodologies were considered as influential variables. To minimize errors from contamination or instrument drift, studies that did not adhere to regular calibration standards and contamination control measures were excluded. Overall, the findings indicate that data from recent studies are more reliable due to the higher sensitivity of analytical techniques and improved contamination control compared to older studies.

2.3. Data extraction

The extracted information from the included articles encompassed the type of elements/metals, first author, year, country, sample size (number, age, sex), and type of biological samples. Additionally, reference ranges (lower and upper), arithmetic mean (AM), standard deviation (SD), geometric mean (GM), median (Med), percentiles (lower and

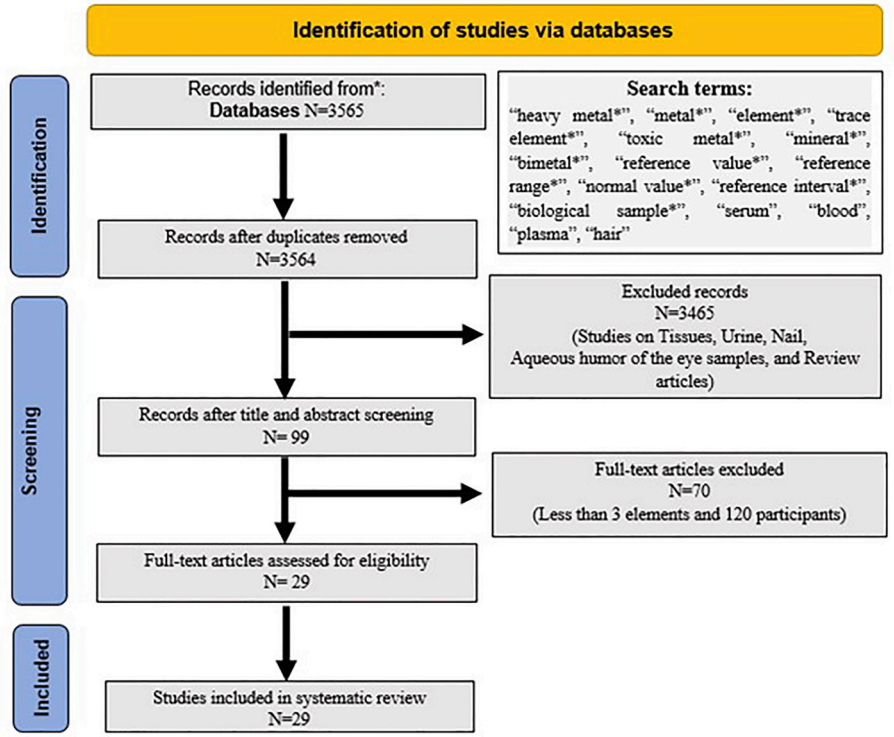

Fig. 1.

upper), and 95 % confidence intervals (CI) which had calculated in studies via statistical software's (e.g. SPSS, R and NCSS) were recorded. For studies lacking a total AM, a combined mean was calculated by R software using the formula: Combined mean = (mean of Group 1 × Number of values in Group 1) + (mean of Group 2 × Number of values in Group 2) + …]/(Number of values in Group 1 + Number of values in Group 2 +…). For non-normal distributions, logarithmic transformation and GM were applied for improved data analysis.

2.4. Study quality assessment

For quality control and reduction of potential biases in geographical diversity, data were collected from various countries, with a wide population spectrum, approximately twenty-seven thousand healthy participants. For control of confounding variables, differences due to gender, age, and geographical location were considered in the analysis of results.

The assessment of methodological quality was performed using the modified Newcastle-Ottawa Scale (NOS) for cross-sectional studies and case control studies [58]. For the cross-sectional studies, the score was calculated based on the three categories: sample selection (3 items, maximum 4 scores), comparability between groups (2 item, maximum 4 scores), analysis (one items, maximum 2 scores), and outcome (one items). Therefore, the maximum score was ten points and also indicated the highest methodological quality. Studies were considered high quality if they were scored above median, five points for cross-sectional studies. For the case-control studies, the score was calculated based on the three categories: selection (4 items), comparability (2 item), and exposure (3 items). Therefore, the maximum score was nine points and also indicated the highest methodological quality. Studies were considered high quality if they were scored above median, five points for case-control studies. This adaptation focused on assessing the validity of analytical methods rather than outcome measure validity, ensuring that only robust and reliable techniques were considered. Details of the modified NOS tool and the scoring criteria are provided in supplementary Table 1 and 2.

3. Results and Discussion

Table 1 presents the basic information of the included studies, organized by continent and year. Out of the 29 eligible studies, most were conducted in Asia (n = 15) and Europe (n = 11), followed by South America (n = 2) and Australia (n = 1). The participants were primarily adults (both male and female), with a few studies involving adolescents, children, neonates, and breastfeeding mothers. Eighteen studies were identified as cross-sectional, while eleven studies were categorized as case-control.

In total, 36 different elements were analyzed across four biological sample types: blood (n = 22), serum (n = 5), hair (n = 5), and plasma (n = 2). Four studies evaluated more than one type of biological sample. The most frequently studied metals were Zn (n = 21), Pb (n = 20), Cd (n = 19), Cu (n = 18), and As (n = 14). The majority of studies employed inductively coupled plasma mass spectrometry (ICP-MS) for element evaluation, followed by atomic absorption spectrometry (AAS) and high-resolution inductively coupled plasma mass spectrometry (HR-ICP-MS). One study used multiple methods, including colorimetric, arsenazo III, xylidyl blue, and ultraviolet spectrophotometry. Table 2 details the number of participants for each measured element in the included studies.

3.1. Cadmium (Cd)

Cd is classified as a carcinogen by the International Agency for Research on Cancer (IARC), with substantial evidence linking it to cancers of the lung, prostate, and kidney [59,60]. Cd primarily accumulates in erythrocytes, making whole blood a more appropriate medium for measuring Cd levels compared to serum and plasma, which reflect both recent exposure and body burden. Exposure to Cd varies across different regions [61,62]. Previous studies may have reported elevated Cd levels in body fluids, potentially due to low sensitivity in analytical methods or inadequate contamination controls [63,64]. Consequently, this review includes only studies that employed validated and precise analytical techniques, such as ICP-MS and AAS [64]. While

Table 1
Basic information of eligible studies.

Continent	Reference (Author, Year)	Country	Elements	Healthy Subjects			Sample Type	Analysis Method
				N	Age (Years)	Sex		
Asia	Haijuan Wang et al, 2012	China	Ca, Fe, Pb, Zn	4429	0–7	Male: 2628 Female: 1801	Blood	AAS
	Tasneem Gul Kazi 2012	Pakistan	As, Cd, Se, Zn	120	30–50	Male	Blood/ Serum	AAS
	Hassan Imran Afridi 2014	Pakistan	Cd, Hg, Zn, Se	166	30–60	Male:84 Female:82	Blood/ Hair	AAS
	Iman Al-Saleh, 2014	Saudi Arabia	Cd, Hg, Pb,	1566	16–50	Female	Cord Blood Maternal Blood	AAS
				1578	–	–	Placenta Blood	
	Long-Lian Zhang et al, 2015	China	Cd, Cu, Mn, Pb, Zn	556	12–60	Male: 318 Female: 330	Blood	ICP-MS
	Jingwen Chen et al, 2015	China	Ca, Cu, Mg, Fe, Pb, Zn	6741	0–6	Male: 4388 Female: 2353	Blood	AAS
	Cimi Ilmiawati, 2015	Japan	Cd, Hg, Pb	229	9.075	Boy:118 Girl: 111	Blood/ Hair	ICP-MS
	Roya Kelishadi, 2016	Iran	Cu, Cr, Mg, Zn	520	7–19	Boy and Girl	Serum	AAS
	K. Liu et al, 2016	China	Ca, Cu, Mg, Pb, Zn	677	21–35	Female	Blood	ICP-MS
	Muyan Li et al, 2017	China	Ca, Cu, Fe, Mg, Zn	559	30–37	Female	Blood	AAS
	Long Li et al, 2017	China	Ge, Pb, Zn	1302	6–60	Male: 318 Female: 330	Blood	ICP-MS
	Zhe Li et al, 2018	China	As, B, Ca, Cd, Cr, Cu, Fe, K, Mg, Mn, Pb, Se, Zn	669	46.73 ± 12.58	Male and Female	Blood	ICP-MS
	Xuefei Chen Et al, 2018	China	Ca, Cu, Fe, Mg, P, Zn	614	37.45 ± 12.12	Male: 518 Female: 96	Serum	Colorimetric method/ arsenazo III method/ xylidyl blue/ ultraviolet spectrophotometry
	Hao-Long Zeng et al, 2019	China	As, Ca, Cd, Cr, Cu, Fe, Hg, Mg, Mn, Pb, Tl, Zn	477	5–80	Male and Female	Blood	ICP-MS
	Lu Gong et al, 2021	China	As, Ca, Cd, Cr, Cu, Fe, Hg, Mg, Mn, Pb, Tl, Zn	209	20–43	Female	Blood	ICP-MS
Australian	Komarova et al. 2021	Australia	Ag, Al, As, Bi, Br, Cd, Co, Cr, Cu, Hg, I, Mn, Mo, Ni, Pb, Sb, Se, Tl, U, V, Zn	120	44.6	Male: 59 Female: 61	Blood	ICP-MS
Europe	Bjermo Et al. 2013	Sweden	Cd, Hg, Pb	273	F:48.2 M:52.5	Female:145 Male:128	Blood	ICP-MS
	Baeyens Et al. 2014	Belgium	As, Cd, Cr, Cu, Mn, Ni, Pb, Tl	207	14.8	Adolescents	Blood	HR-ICP-MS
				241	0	Neonates		
				235	30.3	Mothers		
	Vrijens et al. 2014	Belgium	Cd, Pb, Cr, Ni, Cu, Mn, Tl	200	14.8	Male and Female	Blood	HR-ICP-MS
	Catherine Nisse 2017	France	Al, As, Be, Cd, Co, Cr, Hg, Mn, Ni, Pb, Tl, V, Zn	991	20–59	Male/ Female	Blood	ICP-MS
	Margarita G. Skalnaya 2017	Russia	Cu, Fe, Zn	125	51–61	Female	Serum	ICP-MS
	Anatoly V. Skalny1 2018	Russia and China	Al, As, Be, Cd, Co, Cr, Cu, Fe, Hg, I, Li, Mn, Ni, Pb, Se, Si, Sn, V, Zn	393	51	Male/ Female	Hair	ICP-MS
	Anatoly V. Skalny 2018	Russia	Al, As, Ca, Cd, Co, Cr, Cu, Fe, Hg, I, K, Li, Mg, Mn, Mo, Na, Ni, P, Pb, Se, Si, Sn, Sr, V, Zn	158	31.7	Female	Hair	ICP-MS
	Aleksandar Stojsavljević, 2019	Serbia	As, Cd, Pb, Th, U	305	41 ± 2	Male:151 Female:154	Blood	ICP-MS
	Janja Snoj Tratnik 2019	Slovenia	As, Cd, Cu, Hg, Mn, Pb, Se, Zn	1084	18–49	Male: 548 Female: 536	Blood/ Hair	ICP-MS
	Heesterbeek Et al. 2020	Netherlands & UK	As, Ba, Ca, Cd, Co, Cr, Cu, Fe, Mg, Mn, Mo, Pb, Sb, Se, V, Zn	236	73.48	Male:104 Female: 132	Plasma	ICP-MS
	Hoet et al. 2021	Belgium	Al, As, Sb, Be, Bi, Cd, Co, Cu, Mn, Hg, Mo, Ni, Pb, Se, Tl, Sn, V, Zn	380	18–70	Male:178 Female: 202	Plasma/ Blood	ICP-MS

(*continued on next page*)

Table 1 (*continued*)

Continent	Reference (Author, Year)	Country	Elements	Healthy Subjects			Sample Type	Analysis Method
				N	Age (Years)	Sex		
South America	Carmen Freire, 2015	Brazil	As, Cd, Mn	1196	–	Male/ Female	Blood	ICP-MS
	Eliel Marcio Pedro, 2019	Brazil	Cd, Cu, Li, Mo, Pb, V, Zn	120	37.0 (30.0–47.0)	Male: 33 Female: 87	Serum	ICP-MS

Note: Atomic absorption spectrophotometry (AAS), High Resolution Inductively Coupled Plasma Mass Spectrometry (HR-ICP-MS), Inductively coupled plasma-mass spectrometry (ICP-MS).

recent studies generally offered more reliable data, variations in Cd concentrations among studies may arise from differences in environmental exposure and other factors, rather than analytical errors (48, 53). Due to significant heterogeneity in analytical techniques, population characteristics, and reporting standards across the included studies, we did not perform a formal subgroup *meta*-analysis by geographic region. However, we included relevant regional comparisons in our descriptive synthesis approach. Additionally, Cd can exist in both inorganic (Cd^{2+}) and organic forms. HR-ICP-MS is capable of differentiating between these Cd species, whereas AAS has lower precision in distinguishing various forms [65,66]. The observed discrepancies in Cd levels across studies may partially result from variations in Cd speciation, which have been taken into account in our interpretation of the results. In our review, 19 studies (Table 3) analyzed the concentration of Cd in blood, serum, and/or plasma [23,47,48,50,67–81]. Statistical methods used to calculate combined mean and GM for Cd levels. For studies that did not report the AM, the combined mean was calculated based on sample size. In cases where data distribution was skewed, the GM along with a 95 % confidence interval (95 % CI) was reported. The highest Cd was reported by Tasneem Gul Kazi et al. [67], which was 4.7 μg/L and 5.08 μg/L of Cd AM in blood and plasma, respectively, and then a study in Brazil [78] reported Cd AM of 3.18 μg/L. In a study in Serbia in 2019 for 305 participants, Cd GM was 0.32 μg/L, and in females and males, it was 0.38 μg/L and 0.28 μg/L, respectively [79]. For instance, the Serbian study reported that females had a significantly lower level of Cd than males, which may be associated with increased absorption of Cd in the digestive system in females compared to males. Also, elderly people had insignificantly more Cd than the young ones, which could be related to 2.5 months of Cd half-life in blood, less excretion in urine, and long-term accumulation, especially in the adrenal cortex [79]. On the other hand, a study conducted in South America in 2015 measured the blood Cd level in the blood of 1059 non-smoking men and reported that Cd was below the detection limit [47]. Furthermore, Cimi Ilmiawati et al. who examined the level of Cd in the blood of 229 children, found that Cd AM was 0.25 μg/L and the median level of Cd was higher in girls than boys and suggested secondhand smoking as an independent risk factor for blood Cd levels [69]. The authors concluded that it may not be possible to predict the level of Cd in the blood, but total consumption of seafood may be a good predictor for the blood levels of Cd [69]. Another study conducted by Bjermo et al. in 2013 on 477 male and female participants in Switzerland, which examined dietary habits, lifestyle factors, and meat consumption in individuals, reported that Cd levels are directly related to age and inversely related to plasma ferritin level and consumption of meat [71]. However, this study showed that Cd levels were not associated with seafood, offal, alcohol, vegetables, fruits, cereals, and drinking water type [71]. Other studies suggested smoking and iron deficiency as the main factors contributing to increasing blood levels of Cd. Further, Cd exposure can be due to occupation type (mining, industry, and vehicle) and outdoor activity [48,67]. Cd can be bound with particles in the soil or taken from the water by fish, plants, and animals, and eventually human beings can be contaminated by consuming them. In some areas, the consumption of Cd may reach 10 μg/L to 60 μg/L per day, which may be related to the intake of certain foods such as fish or rice (i.e. in countries where the consumption of fish and rice is high). Also, smoking can cause a significant increase in Cd in smokers compared to non-smokers, which is estimated to be three times higher in smokers than non-smokers and 2.5 times higher in former smokers compared to never-smokers [47,68,69]. In a study conducted by Tratnik J.S. et al. [80] vegetable consumption was associated with Cd blood levels in rural of Savinjsko-Posavska and industry-contaminated areas of Zasavje. However, it was not the same for the industry-contaminated areas of Celje, and the probable reason attributed to the consuming purchased rather than local home-grown vegetables. The authors also suggested consuming game meat as another potential source of Cd contamination in the studied female group. A study conducted in Saudi Arabia in 2014 [68] analyzed Cd levels in umbilical cord blood and maternal blood in 1578 pregnant women. The level of Cd in the blood of mothers was significantly higher than that of cord blood, and there was a correlation between the Cd level in cord blood and the age of the mother. Also, the level of Cd in mothers who lived in areas with heavy traffic was higher than in mothers who lived in other areas such as farms or deserts, and it was higher in those who refused to report their total family income.

The study by Baeyens et al. in Belgium [75], who studied on 235 mothers and 241 neonates, reported that Cd GM in cord blood were four to five times lower than in the maternal bloods. The blood level of Cd in mothers who smoked during pregnancy and those who were former smokers was higher than in non-smokers, although Cd concentrations in cord blood were only slightly increased. Also, a significant correlation between living in an urban area with increased Cd concentrations in the cord blood of mother/neonate pairs and maternal blood of the mothers was shown. Furthermore, a significant decrease in blood Cd concentrations with the increasing educational level of the mothers was observed. They conceded that more mothers with a higher educational degree did not smoke before and during pregnancy [75].

Three studies from Russia, China, and Pakistan studied Cd levels in hair [23,77]. The Cd AM (combined mean) was higher in Pakistan [23] (Cd AM: 1.76 μg/g) than in Russia [77] (Cd AM: 0.018 μg/g) and China [77] (Cd AM: 0.007 μg/g). In another study in Russia, the hair levels of Cd in pregnant women were reported as 0.009 μg/g and, in their newborns, as 0.043 μg/g [82]. The study conducted by Skalny A.V. et al. on 393 healthy participants (140 from China and 253 from Russia) showed that the hair content of Cd in Russian residents was about three times higher than Chinese participants, and the hair levels of Cd in Russian men were 93 % higher than in women. The suggested reason for the high levels of Cd in the Russian compared to Chinese subjects was the strong development of industry and the increase in metal emission in this area [77]. Another study in Pakistan attributed high hair levels of Cd to heavy traffic, population growth, industrial areas that burn plastic and manufacture various materials [23].

Cd, as a highly toxic heavy metal, has varied implications for human health across different age groups, sexes, and geographical regions. Additionally, the toxicokinetics of Cd demonstrate its prolonged biological half-life, contributing to bioaccumulation and long-term adverse effects [83,84]. Furthermore, Cd disrupts cellular processes by inducing oxidative stress, inflammation, and apoptosis, thereby exacerbating its toxicity [85–87]. Evidence indicates that sex-based differences influence Cd absorption and retention; for instance, a Serbian study found that although females had significantly lower blood Cd levels than males, this paradox may be due to increased gastrointestinal absorption in

Table 2
The number of participants in included studies for each evaluated element.

Author, Year, Country	Elements																																		
	Ag	Al	As	B	Ba	Be	Bi	Br	Ca	Cd	Co	Cr	Cu	Fe	Ge	Hg	I	K	Li	Mg	Mn	Mo	Na	Ni	P	Pb	Sb	Se	Si	Sn	Sr	Th	Tl	U	V	Zn
Haijuan Wang et al, 2012, China									4429					4429												4429										4429
Tasneem Gul Kazi 2012, Pakistan			120							120																		120								120
Hassan Imran Afridi 2014, Pakistan										166						166												166								166
Iman Al-Saleh, 2014, Saudi Arabia										1566						1574										1577										
Long-Lian Zhang et al, 2015, China										556			556								556					556										556
Jingwen Chen et al, 2015, China									6741				6741	6741						6741						6741										6741
Cimi Ilmiawati, 2015, Japan										229						229										229										
Roya Kelishadi, 2016, Iran												516	486							520																520
K. Liu et al, 2016, China									677				677							677						677										677
Muyan Li et al, 2017, China									559				559	559						559																559
Long Li et al. 2017, China															1302											1302										1302
Zhe Li et al, 2018, China			669	669					669	669		669	669	669				669		669	669					669		669								669
Xuefei Chen Et al, 2018, China									614				614	614						614					614											614
Hao-Long Zeng et al, 2019, China			260						260	260		176	461	461		260				455	260					260							176			461
Lu Gong et al, 2020, China			209						209	209		209	209	209		209				209	209					209							209			209
Komarova et al. 2021, Australia	120	120	120				120	120		120	120	120	120			120	120				120	120		120		120	120	120					120	120	120	120
Bjermo et al. 2013, Sweden										273						273										273										
Baeyens et al. 2014, Belgium			683							683		200	683								683			199		683							683			
Vrijens et al. 2014, Belgium										200		200	200								200			200		200							200			
Catherine Nisse 2017, France		987	987			987				987	987	561				987					987			987		987							987		987	987
Margarita G. Skalnaya 2017, Russia													125	125																						125
Anatoly V. Skalny1 2018, Russia and China		393	393			393				393	393	393	393	393		393	393		393		393			393		393		393	393	393				393	393

(*continued on next page*)

Table 2 (*continued*)

Author, Year, Country	Elements																																		
	Ag	Al	As	B	Ba	Be	Bi	Br	Ca	Cd	Co	Cr	Cu	Fe	Ge	Hg	I	K	Li	Mg	Mn	Mo	Na	Ni	P	Pb	Sb	Se	Si	Sn	Sr	Th	Tl	U	V	Zn
Anatoly V. Skalny 2018, Russia		158	158						158	158	158	158	158	158		158	158	158	158	158	158	158	158	158	158	158		158	158	158	158				158	158
Aleksandar Stojsavljević, 2019, Serbia			305							305																305						305		305		
Janja Snoj Tratnik 2019, Slovenia			1084							1084			1084			1084					1084					1084		1084								1084
Heesterbeek et al. 2020, Netherlands & UK			236		236				236	236	236	236	236	236						236	236	236				236	236	236							236	236
Hoet et al. 2021, Belgium		380	380			380	380			380	380		380			380					380	380		380		380	380	380		380			380		380	380
Carmen Freire, 2015, Brazil			1059							1059											1059															
Eliel Marcio Pedro, 2019 Brazil										120			120						120			120				120									120	120
Total Participants for each Element	120	2038	6663	669	236	1760	500	120	14,552	9653	2274	3438	14,351	14,594	1302	5833	671	827	551	10,838	6994	894	158	2437	772	21,468	736	3326	551	931	158	305	2755	425	2274	20,506

Table 3
Reference values for toxic metals levels in human Blood, Serum, Plasma, Umbilical cord blood (μg/L) and hair (μg/g).

Authors	N	Sample Type							Percentile		CI 95 %	
			Min	Max	AM	SD	GM	Med	Min	Max	Min	Max
Lead (Pb)												
Komarova et al. 2021 Australia	Total: 120	Blood	3.8	49.6	13.6							
Lu Gong et al, 2020 China	Female:209	Blood			17		12.79		P5:7.42	P95:21.26		
Heesterbeek et al. 2020 Netherlands & UK	Total:236	Plasma						0.05				
Hoet et al. 2020 Belgium	Total:380	Blood		40					P2.5:4.28	P97.5:31.6	27.8	41
	Female: 202	Blood		35					P2.5:4.15	P97.5:27.8	26.2	35.5
	Male:178	Blood		45	10.6				P2.5:4.7	P97.5:35.4	28.2	45.6
Aleksandar Stojsavljević, 2019 Serbia	Total: 305	Blood					20.94		P2.5: 7.44	P97.5:45.11	20.29	27.49
	Female: 154	Blood					20.04		P2.5:7.13	P97.5:43.77	18.76	27.43
	Male:151	Blood					23.7		P2.5:9.871	P97.5:44.15	18.8	33.46
Eliel Marcio Pedro, 2019 Brazil	Total:120	Serum	20.3	44.5	36							
Janja Snoj Tratnik 2019 Slovenia	Total:1084	Blood	3.86	116			)95 % CI(: 18.0)17.5–18.5(		P5:9.13	P95:32.5		
	Male: 548	Blood	3.86	116			)95 % CI(: 19.3)18.5–20.1(		P5: 916	P95:37.4		
	Female:536	Blood	4.25	7.19			)95 % CI(: 16.7)16.2–17.3(		P5:8.82	P95:28.0		
Hao-Long Zeng et al, 2018 China	Total: 260	Blood			21.86		17.84		P5:8.69	P95:48.14		
	Male:153	Blood			24.22		20.32		P5:10.04	P95:51.82		
Anatoly V. Skalny 2018 Russia	Woman Spontaneous pregnancy:158	Hair	0.205	0.6	0.344							
	Children Spontaneous pregnancy: 158	Hair	0.677	2.161	1.284							
Zhe Li et al, 2018 China	Total:669	Serum			5.43	3.89						
Anatoly V. Skalny1 2017 Russia and China	Taipei Total:140	Hair			0.324*							
	Yuzhno-Sakhalinsk Total:253	Hair			0.445*							
	Yuzhno-Sakhalinsk Female:186	Hair	0.141	0.562	0.278							
Long-Li et al, 2017 China	Total: 1302	Blood					24.1		P5:3.00	P95:56.00	23.2	25.1
	Female:537	Blood					20.6		P5:2.05	P95:47.6	19.3	21.8
	Male:765	Blood					26.6		P5:4.48	P95:58.9	25.3	27.9
Catherine NISSE 2016 France	Nonsmoker:987	Blood	19.1	21.0	20.1		)95 % CI(: 16.7)16.1–17.3(		P10:7.96	P95:41.5	39.5	48.4
K. Liu et al, 2016 China	Female:677	Blood			42	14.61						
Long-Lian Zhang et al, 2015 China	Total:556	Blood					42.32		P25:31.31	P75:59.56	40.4	44.17
Cimi Ilmiawati, 2015 Japan	Children: 229	Blood	4.1	30	10	3.2	9.6	Median(IQR) 9.6 (4.1)				
Jingwen Chen et al, 2015 China	Total:6741	Blood			52.6	40.8						
	Girl:2353	Blood			49.9	31.6						

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Table 3 (*continued*)

Authors	N	Sample Type							Percentile		CI 95 %	
			Min	Max	AM	SD	GM	Med	Min	Max	Min	Max
	Boy:4388	Blood			54.1	44.9						
Baeyens et al. 2014 Belgium	Adolescents:207	Blood	14.8				95 % CI: 14.8 (14.0–15.6)		P90)95 % CI): 27.6 (23.1–32.1)	P95:32.9	18.4	47.4
	Neonates:241	Blood	8.6				95 % CI: 8.6 (8.1–9.2)		P90)95 % CI: (15.9 (13.9–17.9)	P95:20.1	13.6	26.5
	Mothers:235	Blood	11.1				95 % CI: 11.1 (10.6–11.7)		P90)95 % CI(: 18.9 (17.1–20.7)	P95:21.2	17.4	25.1
Iman Al-Saleh, 2014 Saudi Arabia	Female: 1572	Cord blood	1.54	565.5	25.51	25.92			P25:15.94	P75:26.89		
	Female: 1577	Maternal Blood	0.73	259.5	28.97	18.51			P25:19.34	P75:33.14		
Vrijens et al. 2014 Belgium	Total:200	Blood					95 % CI: 14.8 (13.9–15.7)		P90:25.1			
Bjermo et al. 2013 Sweden	Total:273	Blood						13	P5:5.8	P95:29		
	Female: 145	Blood						12	P5: 5.3	P95:25		
	Male:128	Blood						15	P5:7.0	P95:29		
Haijuan Wang et al, 2012 China	Total: 4429	Blood	10	260	61.7	22.92						
Cadmium (Cd)												
Komarova et al. 2021 Australia	Total:120	Blood	<0.8	0.99	0.8							
Lu Gong et al, 2020 China	Female:209	Blood			0.82		0.63		P5:0.26	P95:1.84		
Heesterbeek et al. 2020 Netherlands & UK	Total:236	Plasma						0.012				
Hoet et al. 2020 Belgium	Total:380	Blood		2.5					P2.5:0.18	P97.5:2.22	2.04	2.85
	Nnon smoker:72 % total	Blood		2.0					P2.5:0.21	P97.5:2.22	1.39	2.18
	Female: 202	Blood		2.5					P2.5:0.28	P97.5:2.21	2.12	2.54
	Male:178	Blood		2.2					P2.5:0.17	P97.5:2.19	1.99	2.22
Janja Snoj Tratnik 2019 Slovenia	Total:1084	Blood	< LOD	4.8			95 % CI: 0.28 (0.27–0.30)		P5: < LOD	P95:1.01		
	Male:548	Blood	< LOD	4.8			95 % CI: 0.23 (0.22–0.25)		P5: < LOD	P95:1.22		
	Female:536	Blood	< LOD	3.08			95 % CI: 0.35 (0.33–0.37)		P5: < LOD	P95:0.87)		
Aleksandar Stojsavljević, 2019 Serbia	Total: 305	Blood					0.32		P2.5:0.06	P97.5:1.70	0.35	0.56
	Female:154	Blood					0.35		P2.5:0.11	P97.5:1.78	0.43	0.61
	Male:151	Blood					0.28		P2.5:0.05	P97.5:0.85	0.27	0.48
Eliel Marcio Pedro, 2019 Brazil	Total:120	Serum	2	18.97	3.18							
Hao-Long Zeng et al, 2018 China	Total: 260	Blood			1.27		0.7		P5:0.22	P95:6.44		

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Table 3 (*continued*)

Authors	N	Sample Type							Percentile		CI 95 %	
			Min	Max	AM	SD	GM	Med	Min	Max	Min	Max
		Blood			1.58		0.76		P5:0.22	P95:6.92		
	Male:153											
	Woman Spontaneous	Hair	0.004	0.016	0.009							
Anatoly V. Skalny 2018	pregnancy:158											
Russia	Children Spontaneous	Hair	0.021	0.072	0.043							
	pregnancy: 158											
Zhe Li et al, 2018	Total:669	Serum			1.01	0.78						
China												
	Taipei Total:140	Hair			0.00699							
Anatoly V. Skalny 2017					*							
Russia and China	Yuzhno-Sakhalinsk	Hair			0.01871							
	Total:253				*							
	Yuzhno-Sakhalinsk	Hair	0.007	0.035	0.015							
	Female:186											
Catherine NISSE 2016	Total:987	Blood	0.31	0.34			95 % CI:		P10:0.14	P95:0.69	0.64	0.82
France					0.32		0.26 (0.25–0.28)					
Cimi Ilmiawati, 2015	Children: 229	Blood	<LOQ	0.87	0.36	0.12	0.34	Median (IQR)				
Japan								0.35 (0.20)				
Carmen Freire, 2015	Nonsmoker1059	Blood	<LOD	9.03	0.25	GSD:			P5:<LOD	P95:0.61	0.57	0.65
Brazil						8.46						
Long-Lian Zhang et al, 2015	Total:556	Blood					0.59		P25:0.39	P75:0.99	0.54	0.65
China												
Hassan Imran Afridi 2014	Total:166	Blood			4.09*							
Pakistan		Hair			1.76*							
Baeyens et al. 2014	Adolescents:207	Blood					95 % CI:		P90 95 % CI:	P95:0.74	0.38	1.11
Belgium							0.210 (0.192–0.230)		0.471			
									(0.333–0.609)			
	Neonates:241	Blood					95 % CI:		P90 95 % CI:	P95: 0.439	0.068	0.811
							0.073 (0.066–0.081)		0.160			
									(0.095–0.226)			
	Mothers:235	Blood					95 % CI:		P90 95 % CI:	P95:0.878	0.447	1.31
							0.312 (0.291–0.334)		0.728			
									(0.592–0.864)			
Iman Al-Saleh, 2014		Blood	0.245	15.325	0.78	0.623			P25:0.586	P75:0.853		
Saudi Arabia	Female:1566											
	cord blood											
	Female:1565	Blood	0.233	3.157	0.986	0.313			P25:0.766	P75:1.207		
	maternal blood											
Vrijens et al. 2014	Total:200	Blood					95 % CI:			P90:0.41		
Belgium							0.21 (0.19–0.23)					
Bjermo et al. 2013	Total:273	Blood						0.19	P5:0.09	P95:1.1		
Sweden												
	Female: 145	Blood						0.22	P5: 0.09	P95:1.2		
	Male:128	Blood						0.17	P5:0.08	P95:0.85		
Tasneem Gul Kazi 2012												
Pakistan (4		Blood			4.7	1.34						
	Male: 120	Serum			5.08	2.41						
Mercury (Hg)												
Komarova et al. 2021 Australia	Total:120	Blood	<0.8	9.3	2							
Lu Gong et al, 2020 China	Female:209	Blood			1.76		1.41		< LOQ	3.84		

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Table 3 (*continued*)

Authors	N	Sample Type							Percentile		CI 95 %	
			Min	Max	AM	SD	GM	Med	Min	Max	Min	Max
Hoet et al. 2020 Belgium	Total:380	Blood		7					P2.5:<LOD	P97.5:6.36	4.75	7.15
Janja Snoj Tratnik 2019 Slovenia	Total:1084	Blood	< LOD	31			95 % CI: 1.18 (1.12–1.24)		P5: 0.3	P95:4.78		
	Male:548	Blood	< LOD	31			95 % CI: 1.25 (1.15–1.34)		P5:0.26	P95:5.13		
	Female:536	Blood	< LOD	10.2			95 % CI: 1.11 (1.04–1.19)		P5:0.31	P95: 4.06		
Janja Snoj Tratnik 2019 Slovenia	Total:947	Hair	10×10^{-3}	7068×10^{-3}			95 % CI: 275×10^{-3} ($258–292$) $\times 10^{-3}$		$P5:48 \times 10^{-3}$	$P95:1203 \times 10^{-3}$		
	Male:444	Hair	11×10^{-3}	7068×10^{-3}			95 % CI: 282×10^{-3} ($256–311$) $\times 10^{-3}$		$P5:46 \times 10^{-3}$	$P95:1396 \times 10^{-3}$		
	Female:503	Hair	10×10^{-3}	1947×10^{-3}			95 % CI: 268×10^{-3} ($248–290$) $\times 10^{-3}$		$P5:52.3 \times 10^{-3}$	$P95:993 \times 10^{-3}$		
Hao-Long Zeng et al, 2018 China	Total: 260	Blood			2.57		1.9		P5:<LOQ	P95:5.97		
	Male:153	Blood		2.84			2.21		P5:0.77	P95:6.03		
Anatoly V. Skalny 2018 Russia	Woman Spontaneous pregnancy:158	Hair	0.177	0.487	0.306							
	Children Spontaneous pregnancy: 158	Hair	0.057	0.188	0.102							
Anatoly V. Skalny12017 Russia and China	Taipei Total:140	Hair			1.211*							
	Yuzhno-Sakhalinsk Total:253	Hair			0.864*							
	Yuzhno-Sakhalinsk Female:186	Hair	0.497	1.255	0.804							
Catherine NISSE 2016 France	Nonsmoker: 987	Blood	1.94	2.14	2.04		95 % CI: 1.40 (1.31–1.50)		P10:0.49	P95:5.10	4.51	5.66
Cimi Ilmiawati, 2015 Japan	Children:229	Blood	1.16	15.7	5.11	2.49	4.55	Median(IQR) 6.45 3.09)				
Iman Al-Saleh, 2014 Saudi Arabia	Female: 1561 cord blood	Blood	0	26.532	3.354	2.673			P25:1.497	P75:4.600		
	Female: 1574 maternal blood	Blood	0	206.41	3.005	6.319			P25:0.940	P75:3.507		
Hassan Imran Afridi 2014 Pakistan	Total:166	Blood			0.88*							
	Total:166	Hair			1.05*							
Bjermo et al. 2013 Sweden	Total:273	Blood						1.1	P5:0.31	P95:3.5		
	Female: 145	Blood						0.97	P5: 0.17	P95:2.9		
	Male:128	Blood						1.3	P5:0.39	P95:4.4		
Arsenic (As)												
Komarova et al. 2021 Australia	Total:120	Blood	0.2	41.64	2.2							
Hoet et al. 2020 Belgium	Total:380	Blood		9					P2.5:0.58	P97.5:8.7	6.82	9.21

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Table 3 (*continued*)

Authors	N	Sample Type							Percentile		CI 95 %	
			Min	Max	AM	SD	GM	Med	Min	Max	Min	Max
Lu Gong et al, 2020 China	Female:209	Blood			3.72		2.05		P5:0.75	P95:9.31		
Heesterbeek et al. 2020 Netherlands & UK	Total:236	Plasma						0.435				
Aleksandar Stojsavljević, 2019 Serbia	Total: 305	Blood					0.5		P2.5: 0.04	P97.5:1.89	0.56	0.81
	Female: 154	Blood					0.53		P2.5: 0.04	P97.5:1.70	0.55	0.83
	Male:151	Blood					0.45		P2.5:0.04	P97.5:2.11	0.43	0.94
Janja Snoj Tratnik 2019 Slovenia	Total: 1084	Blood	< LOD	28.9			95 % CI: 0.89 (0.85–0.94)		P5: 0.35	P95:3.74		
	Male:548	Blood	< LOD	22.4			95 % CI: 0.83 (0.79–0.88)		P5: 0.36	P95:3.4		
	Female:536	Blood	0.2	28.9			95 % CI: 0.96 (0.89–1.03)		P5: 0.32	P95:5.16		
Hao-Long Zeng et al 2018 China	Total: 260	Blood			3.03		2.25		P5:0.93	P95:8.14		
	Male:153	Blood			2.98		2.36		P5:1.02	P95:7.46		
Anatoly V. Skalny, 2018 Russia	Woman Spontaneous pregnancy:158	Hair	0.006	0.016	0.01							
	Children Spontaneous pregnancy: 158	Hair	0.023	0.062	0.037							
Anatoly V. Skalny1 2017 Russia and China	Taipei Total:140	Hair			0.0492*							
	Yuzhno-Sakhalinsk Total:253	Hair			0.0353*							
	Yuzhno-Sakhalinsk Female:186	Hair	0.021	0.057	0.021							
				2.88	2.69		95 % CI: 1.70 (1.58–1.83)		P10:0.52	P95:6.91		
Catherine NISSE 2016 France	Nonsmoker:987	Blood	2.51								6.19	7.62
Zhe Li et al 2018 China	Total:669	Serum			4.71	3.74						
	Female:											
	Male:											
Carmen Freire 2015 Brazil	Nonsmoker:1059	Blood	<LOD	30.75	4.92	GSD: 1.93	4.22		P5:2.31	P95:9.61	9.35	9.87
Baeyens et al. 2014 Belgium	Adolescents: 207	Blood					95 % CI: 0.62 (0.55–0.69)		P90 95 % CI: 2.12 (1.52–2.71)	P95:2.89	1.75	4.04
	Neonates:241	Blood					95 % CI: 0.54 (0.47–0.62)		P90 95 % CI: 2.18 (1.53–2.83)	P95:3.89	1.07	6.72
	Mothers:235	Blood					95 % CI: 0.64 (0.57–0.72)		P90 95 % CI: 2.04 (1.38–2.69)	P95: 2.99	0.15	5.83
Tasneem Gul Kazi 2012 Pakistan	Male: 120	Blood			2.16	0.38						
		Serum			1.98	0.28						

* Combined mean, Arithmetic mean (AM), Confidence interval (CI), Geometric mean (GM), Geometric standard deviation (GSD), Interquartile range (IQR), Limit of detection (LOD), Maximum (Max), Minimum (Min), Median (Med), Standard deviation (SD), Percentile (P).

women [79]. Age is another important determinant—elderly individuals tend to have slightly higher Cd levels, potentially attributable to reduced urinary excretion and the metal's long biological half-life and accumulation in organs such as the adrenal cortex [83,84,88]. Children are particularly susceptible to Cd exposure due to their developmental vulnerability [89]. One study reported higher Cd levels in girls compared to boys, identifying secondhand smoke exposure as a significant independent risk factor [69]. Furthermore, dietary habits, smoking, and iron status significantly affect Cd burden [90,91]. Research from Switzerland reported a direct relationship between Cd levels and age and an inverse relationship with meat consumption and plasma ferritin levels, while seafood and plant intake were not consistently associated with blood Cd concentrations [71]. Regional factors also modulate Cd exposure; urban and industrial areas, especially those with high traffic, show higher maternal and neonatal Cd levels, as seen in studies from Saudi Arabia and Belgium. Additionally, lower maternal education levels and smoking during pregnancy were linked with elevated Cd in cord blood [68,75]. The cumulative evidence highlights the complex interplay between biological, behavioral, and environmental factors in determining Cd exposure and its health outcomes, emphasizing the need for targeted public health strategies in vulnerable subpopulations.

3.2. Lead (Pb)

20 studies (Table 3) examined the level of Pb in biological sample types, of which 9 studies were conducted in Europe [48,50,71,75–77,79–81], one in South America [78], and one in Australia [74], and the rest of the studies were conducted in Asian countries (China, Saudi Arabia, and Japan) [68–70,72,73,92–95]. Most of the selected studies in our review, used blood as a biological sample type. It has been suggested that during the preparation of serum for Pb analyses, care should be taken because the concentration of Pb in serum and packed cells of whole blood is 10 % and 90 %, respectively, so even small hemolysis serum collection and separation may cause a high increase (double or more) of serum Pb [79].

In Chinese studies, the lowest Pb AM in the blood samples was reported in Zhe Li et al. [72] study (Pb AM: 5.43 μg/L), and the highest was reported by Haijuan Wang et al. (Pb AM: 61.7 μg/L) [95]. Differences study populations, different geographical locations, variations in sampling and Pb measurement methods may be attributed to significant variation of Pb levels between the theses two Chinese studies. Study by Zhe li et al. [72] (5.43 μg/l) was conducted on a population with low environmental pollutant exposure, possibly including individuals from urban areas with stricter pollution control. Study by Haijuan wang et al. [95] (61.7 μg/l) included a population with higher exposure to industrial and environmental lead sources. This study likely involved individuals from industrial areas or children with high levels of environmental exposure. Urban and industrial areas in China, particularly regions with heavy industrial activities, battery manufacturing, or past use of leaded gasoline, typically exhibit higher lead pollution levels. Conversely, regions enforcing stricter pollution regulations (e.g., restrictions on pollutant emissions and replacement of lead-based water pipes) show lower lead exposure levels. Some studies used whole blood, which generally yields higher lead concentrations. Others used serum or plasma, which tends to show lower lead levels. Studies using ICP-MS typically report higher accuracy and sensitivity. Older techniques such as AAS may report slightly different values due to lower sensitivity [56,57]. The findings from Haijuan wang's study highlight that lead exposure remains a serious public health concern in certain regions, necessitating enhanced monitoring [95].

In a study conducted in Brazil [78], Pb AM was 36 μg/L and in a study in Australia [74] it was 13.6 μg/L. However, in studies conducted in Europe, Pb GM was variable from 16.7 μg/L in France [76] and 18 in Slovenia [80], to 20.94 μg/L in Serbia [79]. The suggested source of Pb reported in the Serbian study [79] was the drinking water, food, and polluted air. They also reported that the level of Pb in men was not significantly higher than in women, and it attributed to the difference in lifestyle.

In a study conducted by Cimi Ilmiawati, et al. [69] in 2015 in Japan, Pb levels were measured in 229 children and found that Pb AM was 10 μg/L, which was 2 to 4 times higher than the median Pb reported in Europe and America. The researchers suggested that secondhand smoking may be related to increased blood Pb levels in this study. Children exposed to cigarette smoke face a risk of Pb ingestion through contact with contaminated surfaces, such as dirty hands and toys. Cigarette smoke contributes to environmental pollution by releasing airborne particles and heavy metals, including Pb, which settle on surfaces like carpets, furniture, and walls [96]. Due to their hand-to-mouth behaviors, children are especially vulnerable to Pb exposure after touching these contaminated surfaces. Additionally, outdoor cigarette smoke releases Pb and other heavy metals into the environment, posing significant risks to children in urban areas or near heavily trafficked roads [96]. Elevated blood lead levels in children can result in severe health issues, including impaired brain development, learning disabilities, and heightened susceptibility to neurological and behavioral disorders [97,98]. Implementing stricter smoking regulations in homes and public areas could reduce children's exposure to cigarette smoke and consequently minimize Pb contamination and other toxic pollutants. Besides, epidemiologists claimed that there are no safe levels for childhood Pb exposure, and limits of 0.1–1.0 lg/dL for Pb may Pb to a loss of 1 IQ point.

In a study conducted in Slovenia [80] on 1084 participants in 2019, the individuals were selected from twelve study regions, including rural and urban areas, as well as areas known or potentially contaminated. They found that Pb-contaminated soil from previous contact was the main source of Pb among the population. The highest levels of blood Pb were among military recruits living in some studied areas. They suggested that age (19 % higher for older than 25 than for those under 25 years old), water supply (24 % higher in public versus private), alcohol consumption (18 % higher for those who drink monthly), smoking (15 % higher for smokers than non-smokers), and game consumption (11 % higher for consumers than non-consumers) were additional significant determinants of blood Pb levels of participants. The risk factors reported in this study were similar to the findings of the other study conducted in 2013 by Bjermo et al. [71] in Sweden which confirmed that alcohol and game consumption may play an important role in the elevation of blood Pb levels.

Similar risk factors were reported by Long Li et al. [92] in China who found that among the 1302 participants, alcohol intake elevated the Pb GM (28.3 μg/L) compared to those who did not drink alcohol (23.4 μg/L; $p = 0.002$). There was a higher concentration of Pb between smokers (29.1 μg/L) and non-smokers (23.1 μg/L, $p < 0.001$). Moreover, they showed that among the 537 Chinese women, Pb concentration in blood was significantly higher in women who used cosmetics (24.4 μg/L) and hair dye (24.5 μg/L) than those who did not use cosmetics (20.0 μg/L, $p < 0.05$) and hair dye (19.6 μg/L, $p < 0.05$). Haijuan Wang et al. [95] studied Pb levels in 4436 children and suggested that blood Pb levels in children age 0 to 7 had a negative correlation with blood Fe and Ca levels and another study in China found that the blood Pb levels were stable across different stages of pregnancy.

On the other hand, two studies (conducted in Taipei, Taiwan, China, and Yuzhno-Sakhalinsk, Sakhalin, Russia) [77,99] evaluated pb content in hair, the pb AM in the Chinese study was 0.32 μg/g, and in Russia it was 0.44 μg/g. However, in a study conducted in Russia on pregnant women, the amount of Pb was 0.34 μg/g, and 1.28 μg/g in their 9-month-old children [99]. Also, the level of hair pb in men of Taipei and Yuzhno-Sakhalinsk was three times higher than that of women, and it was concluded that the level of heavy metals can be affected by gender and geography. The higher level of heavy metals in Yuzhno-Sakhalinsk men compared to women was attributed to the high level of men's outdoor activity, the higher level of metal emission, and gender-

Table 4
Reference values for trace elements levels in human Blood, Serum, Plasma, Umbilical cord blood (μg/L) and hair (μg/g).

Authors	N	Sample Type							Percentile		CI 95 %	
			Min	Max	AM	SD	GM	Med	Min	Max	Min	Max
Zinc (Zn)												
Komarova et al. 2021 Australia	Total: 120	Blood	4620	9250	6750							
	Total: 120	Plasma	820	1660	1150							
Hoet et al. 2020 Belgium	Total: 380	Blood	3700	7250					P2.5(90 %CI): 4005(43669–4112)	P97.5:7029	(90 % CI) 6919	(90 % CI) 7266
		Plasma	480	1150					P2.5(90 %CI): 500(462–556)	P97.5:1130	(90 % CI) 1066	(90 % CI) 1163
	Female: 202	Blood	3400	6850					P2.5(90 %CI): 3709(3350–4010)	P97.5:6678	(90 % CI) 6412	(90 % CI) 6866
		Plasma	430	1150					P2.5(90 %CI): 473(421–503)	P97.5:1105	(90 % CI) 996	(90 % CI) 1151
	Male:178	Blood	4000	7350					P2.5(90 %CI): 4388(64005–4806)	P97.5:7258	(90 % CI) 7012	(90 % CI) 7361
		Plasma	570	1150					P2.5(90 %CI): M:619(562–654)	P97.5:M:1125	(90 % CI) M:1066	(90 % CI) M:1162
Lu Gong et al, 2020 China	Female:209	Blood			5520	5460			P5:4310	P95:6870		
Heesterbeek et al. 2020 Netherlands & UK	Total:236	Plasma			754.5	106.0						
Eliel Marcio Pedro, 2019 Brazil	Total:120	Serum	2460.1	4119.1	2907.0							
Janja Snoj Tratnik 2019 Slovenia	Total: 1084	Blood	3010	11,733			(95 % CI) 6606 (6549–6663)		P5:5150	P95:8285		
	Female: 536	Blood	3010	11,733			(95 % CI) 6721 (6636–6807)		P5:5274	P95:8494		
	Male: 548	Blood	3400	10,301			(95 % CI) 6494 (6419–6571)		P5:5082	P95:8050		
Hao-Long Zeng et al, 2018 China	Total: 461	Blood			5950		5850		P5:4320	P95:5260		
	Female: 206	Blood			5690		5600		P5:4040	P95:5040		
	Male: 255	Blood			6160		6060		P5:4410	P95:5520		
Xuefei Chen et al, 2018 China	Total: 614	Serum	500.157	1667.19	778.022	122.91						
Anatoly V. Skalny 2018 Russia	Woman Spontaneous pregnancy:158	Hair	192.3	303.6	229.3							

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Table 4 (*continued*)

Authors	N	Sample Type							Percentile		CI 95 %	
			Min	Max	AM	SD	GM	Med	Min	Max	Min	Max
	Children Spontaneous pregnancy: 158	Hair	46.53	119.88	75.34							
Zhe Li et al, 2018 China	Total:669	Serum			1430	660						
Anatoly V. Skalny12017 Russia and China	Taipei Total:140	Hair			178.391 *							
	Yuzhno-Sakhalinsk Total:253	Hair			178.166 *							
	Yuzhno-Sakhalinsk Female:186	Hair	153	218.1	181.9							
Long-Li et al, 2017 China	Total: 1302	Blood					3140		P5:1410	P95:5020	3080	3200
	Female:537	Blood					3280		P5:1550	P95:5130	3180	3370
	Male:765	Blood					3040		P5:1320	P95:4860	2970	3120
Margarita G. Skalnaya 2016 Russia	Female: 125	Serum	840	1120	970							
K. Liu et al, 2016 China	Female: 677	Blood			5660	1680						
Muyan Li et al, 2016 China	Female: 559	Blood	5450	7600	6500							
Catherine NISSE 2016 France	Nonsmoker 987	Blood	5772	5888	5830	(95 % CI) 5752 (5691–5814)			P10:4707	P95:7257	7185	7455
Roya Kelishadi, 2016 Iran	Boy:260 Girl:260	Serum	807.2*	1825.3*					P 2.5: 885.5 (820, 980)	P 97.5: 1767.8 (1691.5, 1840.6)		
Long-Lian Zhang et al, 2015 China	Total:556	Blood					4607		P25:3696	P75:5536	4470	4737
Jingwen Chen et al, 2015	Total: 6741	Blood			5350	1400						
	Girl:2353	Blood			5410	1390						
	Boy:4388	Blood			5320	1400						
Hassan Imran Afridi 2014 Pakistan	Total:166	Blood			11090*							
		Hair			233.89*							
Tasneem Gul Kazi 2012 Pakistan (4	Male:120	Blood			11,900	1580						
		Serum			1020	220						
Haijuan Wang et al, 2012 China	Total:4429 Female:1801 Male:2628	Blood	2120	9020	4980	9870						
Copper (Cu)												
Komarova et al. 2021 Australia	Total:120	Blood	650	1420	840							
	Total:120	Plasma	670	2490	1100							
Lu Gong et al, 2020 China	Female:209	Blood			815.44		806.16		P5: 629.54	P95: 1041.1		

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Table 4 (*continued*)

Authors	N	Sample Type							Percentile		CI 95 %	
			Min	Max	AM	SD	GM	Med	Min	Max	Min	Max
Heesterbeek et al. 2020 Netherlands & UK	Total:236	Plasma			927.4	169.5						
Hoet et al. 2020 Belgium	Total:380	Blood	580	1590					P2.5(90 %CI): 610(571–622)	P97.5:1433	(90 % CI) 1343	(90 % CI) 1595
		Plasma	520	2100					P2.5(90 %CI): 598(512–631)	P97.5:1998	(90 % CI) 1791	(90 % CI) 2122
	Male:178	Blood	550	950					P2.5(90 %CI): 582(543–659)	P97.5:890	(90 % CI) 847	(90 % CI) 965
		Plasma	520	1300					P2.5(90 %CI): 581(510–643)	P97.5:1095	(90 % CI) 1047	(90 % CI) 1302
	Female: 202	Blood	600	1600					P2.5(90 %CI): 649(592–659)	P97.5: 1462	(90 % CI) 1612	(90 % CI) 2233
		Plasma	520	2200					P2.5(90 %CI): 610(502–663)	P97.5: 1095	(90 % CI) 1950	(90 % CI) 2233
Eliel Marcio Pedro, 2019 Brazil	Total:120	Serum	857.0	1277.1	1028.4							
Janja Snoj Tratnik 2019 Slovenia	Total:1084	Blood	532	2004			(95 % CI) 951 (941–961)		P5:737	P95:1262		
	Male: 548	Blood	532	1401			(95 % CI) 847 (839–856)		P5:708	P95:1041		
	Female:536	Blood	657	2004			(95 % CI) 1070 (1057–1083)		P5:857	P95: 1364		
Xuefei Chen et al, 2018 China	Total:614	Serum	698.5	1397	400.05	279.4						
Hao-Long Zeng et al, 2018 China	Total: 461	Blood			791.39		783.76		P5:634.11	P95:999.40		
	Female:206	Blood			810.8		802.65		P5:634.58	P95:1044.61		
	Male:255	Blood			775.72		768.83		P5:633.90	P95:960.07		
Anatoly V. Skalny 2018 Russia	Woman Spontaneous pregnancy:158	Hair	10.89	26.54	15.6							
	Children Spontaneous pregnancy: 158	Hair	8.51	13.67	10.79							
Zhe Li et al, 2018 China	Total:669	Serum			1300	480						
Anatoly V. Skalny12017 Russia and China	Taipei Total:140	Hair			10.908*							
	Yuzhno-Sakhalinsk Total:253	Hair			12.037*							
	Yuzhno-Sakhalinsk Female:186	Hair	10.09	15.02	11.95							
Margarita G. Skalnaya 2016 Russia	Female:125	Serum	620	1250	1090							

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Table 4 (*continued*)

Authors	N	Sample Type							Percentile		CI 95 %	
			Min	Max	AM	SD	GM	Med	Min	Max	Min	Max
K. Liu et al, 2016 China	Female:677	Blood			906.16	203.98						
Muyan Li et al, 2016 China	Female:559	Blood	992	1400	1150							
Roya Kelishadi, 2016 Iran	Boy:243 Girl:243	Serum	1506*	2291.3*					P 2.5: 1520 (1506, 1598)*	P 97.5:2218.8 (2145, 2251)*		
Long-Lian Zhang et al, 2015 China	Total:556	Blood					793.5		P25:674.6	P75:875.1	776.5	811.7
Jingwen Chen et al, 2015 China	Total: 6741 Girl:2353 Boy:4388	Blood Blood Blood			1570 1600 11,580	400 420 400						
Baeyens et al. 2014 Belgium	Adolescents:207	Blood					(95 % CI) 790(774–807)		P90 (95 % CI): 938(908–967)	P95:991	884	1098
	Neonates:241	Blood					(95 % CI) 600(585–615)		P90 (95 % CI): 754(711–797)	P95:826	754	898
	Mothers:235	Blood					(95 % CI) 1312 (1279–1347)		P90 (95 % CI): 1715(1631–1799)	P95: 1801	1613	1989
Vrijens et al. 2014 Belgium	Total:200	Blood				(95 % CI) 790(774–807)		P90 913				
Manganese (Mn)												
Komarova et al. 2021 Australia	Total:120	Blood	4.54	19.5	9.7							
	Total:120	Plasma	<1 0.0	3.1	1							
Heesterbeek et al. 2020 Netherlands & UK	Total:236	Plasma			0.936	0.681						
Lu Gong et al, 2020 China	Female:209	Blood			13.7		13.31		P5:9.02	P95:19.04		
Hoet et al. 2020 Belgium	Total:380	Blood	5.3	18					P2.5(90 %CI): 5.43(5.27–5.95)	P97.5:17.6	(90 % CI) 16.1	(90 % CI) 18.7
		Plasma		0.9 RL below LOQ should be taken with great caution					P2.5(90 %CI): <LOD	P97.5:0.9	(90 % CI) 0.82	(90 % CI) 0.98
	Female: 202	Blood	5.5	19					P2.5(90 %CI): 6.21(5.38–6.51)	P97.5:18.7	(90 % CI) 16.8	(90 % CI) 19.1
	Male:178	Blood	5.0	15					P2.5(90 %CI): 5.39 (4.94–5.69)	P97.5: 14.1	(90 % CI) 12.9	(90 % CI) 16.1
Hao-Long Zeng et al, 2018 China	Total: 260 Male:153	Blood Blood			12.93 12.73		12.4 12.17		P5:8.09 P5:7.81	P95:18.49 P95:18.49		
Anatoly V. Skalny 2018 Russia	Woman Spontaneous pregnancy:158	Hair	0.579	1.84	0.984							

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Table 4 (*continued*)

Authors	N	Sample Type							Percentile		CI 95 %	
			Min	Max	AM	SD	GM	Med	Min	Max	Min	Max
	Children Spontaneous pregnancy: 158	Hair	0.23	530	0.351							
Zhe Li et al, 2018 China	Total:669	Serum			5.93	5.54						
Anatoly V. Skalny12017 Russia and China	Taipei Total:140	Hair			0.2067*							
	Yuzhno-Sakhalinsk Total:253	Hair			1.478*							
	Yuzhno-Sakhalinsk Female:186	Hair	0.876	3.524	1.729							
Catherine NISSE 2016 France	Nonsmoker:987	Blood	8.21	8.55	8.38		(95 % CI) 7.98 (7.83–8.14)		P10:5.49	P95:13.0	12.7	13.7
Carmen Freire, 2015 Brazil	Nonsmoker:1059	Blood	1.96	119.12	14.61	GSD: 1.64	12.84		P5:5.98	P95:28.60	27.8	29.4
Long-Lian Zhang et al, 2015 China	Total:556	Blood					(95 % CI) 11.51		P25:8.81	P75:15.01	11.16	11.88
Baeyens et al. 2014 Belgium	Adolescents: 207	Blood					(95 % CI) 9.7 (9.3–10.1)		P90 (95 % CI): 3.6 (12.8–14.4) 1	P95:15.4	10	20.8
	Neonates:241	Blood					(95 % CI) 31.2 (29.8–32.8)		P90 (95 % CI): 52.2 (47.6–56.8)	P95: 57.7	47.5	68
	Mothers:235	Blood					(95 % CI) 12.1 (11.6–12.7)		P90 (95 % CI): 18.6 (16.8–20.5)	P95:21.6	18.1	25.1
Vrijens et al. 2014 Belgium	Total:200	Blood					(95 % CI) 9.66 (9.28–10.1)		P90: 13.8			
Selenium (Se)												
Komarova et al. 2021 Australia	Total: 120	Blood	118	224	141							
	Total: 120	Plasma	82	180	130							
Heesterbeek et al. 2020 Netherlands & UK	Total:236	Plasma			92.97	16.56						
Hoet et al. 2020 Belgium	Total: 380	Blood	80	155	110				P2.5(90 %CI): 83.2(77.3–86.4)	P97.5:148	(90 % CI) 143	(90 % CI) 158
		Plasma	65	125					P2.5(90 %CI): 66.7(60.0–70.3)	P97.5:122	(90 % CI) 116	(90 % CI) 132
	Female: 202	Plasma	55.5	130					P2.5(90 %CI):61.6 (50.2–69.1)	P97.5:122	(90 % CI) 116	(90 % CI) 133
	Male:178	Plasma	65	140					P2.5(90 %CI): 73.1(63.0–76.5)	P97.5:125	(90 % CI) 119	(90 % CI) 142

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Table 4 (*continued*)

Authors	N	Sample Type							Percentile		CI 95 %	
			Min	Max	AM	SD	GM	Med	Min	Max	Min	Max
Janja Snoj Tratnik 2019 Slovenia	Total: 1084	Blood	53.9	226			(95 % CI) 105 (103–106)		P5:74.2	P95:80.5		
	Male: 548	Blood	60.3	226			(95 % CI) 115 (114–117)		P5:87.3	P95:91.7		
	Female: 536	Blood	53.9	176			(95 % CI) 94.6 (93.1–96.1)		P5:70.7	P95:751		
Anatoly V. Skalny 2018 Russia	Woman Spontaneous pregnancy:158	Hair	0.313	0.499	0.404							
	Children Spontaneous pregnancy: 158	Hair	0.379	0.527	0.451							
Zhe Li et al, 2018 China	Total:669	Serum			126.09	32.11						
Anatoly V. Skalny12017 Russia and China	Taipei Total:140	Hair			0.511*							
	Yuzhno-Sakhalinsk Total:253	Hair			0.4097*							
	Yuzhno-Sakhalinsk Female:186	Hair	0.201	0.57	0.37							
Hassan Imran Afridi 2014 Pakistan	Total:166	Blood			226.51*							
	Total:166	Hair			1.66*							
Tasneem Gul Kazi 2012 Pakistan	Male: 120	Blood			180	6.83						
		Serum			77	13.5						
Chromium (Cr)												
Komarova et al. 2021 Australia	Total:120	Blood			<5							
	Total:120	Plasma			<1.7							
Lu Gong et al, 2020 China	Female:209	Blood			< LOQ		< LOQ		P5:< LOQ	P95:0.63		
Heesterbeek et al. 2020 Netherlands & UK	Total:236	Plasma			0.459	0.337						
Hao-Long Zeng et al, 2018 China	Total: 176	Blood			0.41		0.36		P5:<LOQ	P95:0.76		
Anatoly V. Skalny 2018 Russia	Woman Spontaneous pregnancy:158	Hair	0.044	0.162	0.083							
	Children Spontaneous pregnancy: 158	Hair	0.134	0.333	0.199							
Zhe Li et al, 2018 China	Total:669 Female: Male:	Serum			1.8	0.57						
Anatoly V. Skalny12017 Russia and China	Taipei Total:140	Hair			0.257*							
	Yuzhno-Sakhalinsk Total:253	Hair			0.344*							
	Yuzhno-Sakhalinsk Female:186	Hair	0.21	0.46	0.31							

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Table 4 (*continued*)

Authors	N	Sample Type							Percentile		CI 95 %	
			Min	Max	AM	SD	GM	Med	Min	Max	Min	Max
Catherine NISSE 2016 France	Nonsmoker:561	Blood	0.58	0.65	0.62		(95 % CI) 0.42 (0.39–0.47)		P10:0.11	P95:1.27	1.2	1.4
Roya Kelishadi, 2016 Iran	Boy:258 Girl:25	Serum	10.57*	17.72*					P2.5: 14.125 (13.15, 14.89)*	P97.5: 18.12 (13.6, 31.19)*		
Baeyens et al. 2014 Belgium	Adolescents: 200	Blood					(95 % CI) 0.253 (0.234–0.273)		P90 (95 % CI): 0.489 (0.376–0.601)	P95:0.608	0.45	0.767
Vrijens et al. 2014 Belgium	Total:200	Blood					(95 % CI) 0.26 (0.24–0.28)		P90:0.5			
Aluminum (AL)												
Komarova et al. 2021 Australia	Total:120	Plasma	4	82	6.9							
Hoet et al. 2020 Belgium	Total:380	Blood		<15 RL below LOD					P2.5:<LOD	P97.5:<LOD		
		Plasma		<3 RL below LOD					P2.5:<LOD	P97.5:<LOD		
Anatoly V. Skalny12017 Russia and China	Taipei Total:140	Hair			5.248*							
	Yuzhno-Sakhalinsk Total:253	Hair			5.436*							
	Yuzhno-Sakhalinsk Female:186	Hair	2.85	9.651	4.784							
Catherine NISSE 2016 France	Nonsmoker:987	Blood	3.96	4.45	4.21		(95 % CI) 2.26 (2.08–2.46)		P10:< LOD	P95:10.9 6.91	10.3	11.3

* Combined mean, Arithmetic mean (AM), Confidence interval (CI), Geometric mean (GM), Geometric standard deviation (GSD), Interquartile range (IQR), Limit of detection (LOD), Maximum (Max), Minimum (Min), Median (Med), Standard deviation (SD), Percentile (P).

dependent metabolic pathways [77].

Lead toxicity exerts detrimental effects on multiple organ systems, primarily through its ability to disrupt cellular and enzymatic processes. Chronic exposure to lead has been associated with a wide spectrum of health disorders, including neurotoxicity, nephrotoxicity, hematological abnormalities, and reproductive dysfunction [98,100]. The metal interferes with heme biosynthesis, leading to anemia, and it accumulates in bones, where it can be mobilized during physiological stress or aging. In the nervous system, lead exposure, particularly during developmental stages, impairs cognitive function and behavior by disrupting synaptic transmission and neuronal differentiation [97,98]. Moreover, lead-induced oxidative stress and the disruption of calcium homeostasis play central roles in its pathogenic mechanisms [101,102]. These multifaceted toxic effects highlight the critical need for preventive strategies and strict regulation of lead exposure in both occupational and environmental settings.

3.3. Zinc (Zn)

Twenty-one studies (Table 4) evaluated Zn in biological fluids. Twelve studies are from Asia [2,23,67,70,73,92–95,103–105], 7 of Europe [48,76,77,80–82,106], and one from each of Australia [74] and Brazil [78]. Zn AM was reported at 6750 μg/L in the Australian study [74], and Zn AM in Brazil and Pakistan were 2907 μg/L and 1100 μg/L, respectively [78]. In Chinese studies, Zn GM was from 3.14 to 1.43 μg/L. Among the studies evaluated Zn content of hair, Zn AM was the highest in men and women in a study of Pakistan (234.14 μg/g, combined mean), while in China and Russia it was 178.4 4 μg/g and 178.17 4 μg/g, respectively [23,77].

Zn were measured mostly in blood and to a lesser extent in other biological specimens such as serum or plasma. Because the concentration of Zn in packed cells is about 10 times higher than in serum or plasma, it is necessary to ensure that no hemolysis has occurred in blood samples. The serum or plasma concentration of Zn is about 100 and it is higher in packed cells [48,67].

Xuefei Chen et al. reported that age had a negative correlation with Zn [103]. Some studies have reported that the level of Zn was higher in men than in women [48,104], but the study conducted in Slovenly, it has revealed that Zn levels in women were 11 % more than in men [80]. Moreover, according to a study conducted by Klishadi et al. on 520 boys and girls aged 7–19 years, serum Zn concentration was not different between the two sexes and different age groups [105]. Gender differences in zinc status may result from variations in dietary patterns, hormonal influences, and physiological differences in absorption and metabolism [107,108]. For instance, men typically consume more zinc-rich foods like meat and seafood, while women often consume plant-based foods with lower zinc bioavailability. Klishadi et al. reported that the level of Zn in Iran is comparable to the populations whose foods are enriched with Zn, and the intake of foods containing high Zn in Iran such as sheep and chicken as well as the consumption of free milk in schools have been suggested as the reasons of these similarities [105]. Several studies have suggested that Zn levels were directly associated with the consumption of seafood and inversely related to the intake of food supplements and fruit [80,109,110]. Women who consumed seafood at least once a week had an average of 5 % more blood Zn than those who consumed it less than once a week. It has also been found that the Zn blood levels in men who consumed fruit daily were 4 % lower than those who consumed fruit weekly or less and the reason attributed to the inhibition of Zn absorption by pyruvate content of fruits and vegetables. Seafood, particularly shellfish and fish, is a well-established source of highly bioavailable zinc, and its regular consumption is associated with higher Zn levels in biological samples [111]. Fruits, while low in Zn, contribute vitamins such as vitamin C, which may enhance zinc absorption and provide antioxidant support [112]. Furthermore, we highlight the role of nutrient-nutrient interactions, including competition with iron and copper for absorption, and potential interference from high calcium intake—all of which can significantly influence Zn bioavailability [113]. Consuming a nutritionally balanced diet rich in seafood, fruits, and synergistic micronutrients can help to optimal zinc utilization and overall physiological well-being. Hormones such as testosterone enhance zinc absorption in men, whereas estrogen fluctuations in women can affect zinc absorption, storage, and metabolism. Additionally, men may absorb zinc more efficiently due to differences in gut health and enzyme activity [114]. Women's zinc metabolism may fluctuate during life stages like pregnancy and lactation, where zinc demand increases [115,116]. In addition to predicting factors related to diet and hormones, we also reported an increase in blood Zn levels in polluted and urban areas compared to rural areas. There was no inverse relationship between Zn and any of the elements that may inhibit Zn absorption, such as Cu, Cd, and Hg. It has been suggested that rising Zn levels in polluted areas can indicate an increase in the uptake of Zn in cellular antioxidant defense through antioxidant enzymes such as Cu-Zn superoxide dismutase [80,109,110,117,118]. Zinc is a crucial cofactor for several antioxidant enzymes, including superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase, which protect cells from oxidative damage by neutralizing reactive oxygen species (ROS). Zinc plays a key role in modulating oxidative stress by activating Nrf2, a transcription factor that induces the expression of antioxidant response genes [119,120]. This enhances cellular defense against environmental pollutants, such as particulate matter and toxic gases. Zinc also inhibits the production of pro-inflammatory cytokines triggered by oxidative stress, reducing further tissue damage [121]. Moreover, it competes with toxic metals like cadmium and lead, minimizing their bioavailability and harmful effects, particularly in polluted areas. Thus, zinc supports respiratory health and mitigates damage from pollutants, offering a protective role in regions with high environmental contamination [122]. Zinc is an essential nutrient necessary for cellular growth, immune function, cognitive development, and skin health. Deficiency in zinc, particularly among children, can result in stunted growth, weakened immunity, increased susceptibility to infections, cognitive impairments, learning difficulties, and poor wound healing. Conversely, excessive zinc intake can cause toxicity, presenting symptoms such as nausea, vomiting, and abdominal cramps, while also interfering with the absorption of essential minerals like copper and iron [13,109,115,123,124]. Maintaining an appropriate zinc intake is critical for children's growth, immune function, neurological development, and overall health.

3.4. Copper (Cu)

Copper acts as a cofactor for enzymes involved in energy production, antioxidant defense, and connective tissue formation. Copper metabolism in the body is well controlled from a homeostatic point of view through feedback mechanisms to maintain proper copper balance in blood and tissues by proteins such as Menke's (ATP7A) and Wilson's (ATP7B), while metallothionein aids in copper storage. Cu content changes under physiological conditions such as pregnancy or pathological conditions (i.e. liver disease) [125,126]. In this study, 18 articles (Table 4) measured Cu concentration in blood, plasma, and/or serum, 7 studies from Europe [48,50,75,77,80,81,106], 9 studies from Asia [2,70,72,73,93,94,103–105], and the rest were from Australia [74], and South America [78]. In the studies conducted in China, Cu ranged from 400.34 μg/L to 1.57*103 μg/L [2,70,72,73,93,94,103,104]. In the studies conducted in Europe, the reference range of Cu GM varied from 873 μg/L to 951 μg/L [48,50,75,77,80,81,106]. Cu AM reported by Komarova et. of Australia was 840 μg/L [74] and in Brazil was 1028.4 μg/L [78]. Analytical methods, sample preparation, population demographics, health conditions, and sample collection timing can effect on Cu levels. Different analytical techniques are differential in sensitivity, precision, and detection limits [53–57]. Sample preparation factors, such as storage conditions, exposure to light, and preparation methods for blood or serum samples, were not the same in selected

studies. Demographic factors (like age, sex, and health status, along with dietary habits, geographic location, and lifestyle choices), health conditions, (such as copper metabolism disorders or inflammation) and can also contribute to variability in copper levels [127,128].

The reported level of Cu in healthy subjects in earlier studies ranged from 800 μg/L to 1400 μg/L [80,129]. Janja Snoj Tratnik et al. in a study with large sample population of 1,084 healthy participants aged 18 to 49 from Slovenia found a gender difference in the blood level of Cu, with a higher level in women (1070 μg/L) compared to men (847 μg/L) [80]. This study employed ICP-MS method, for measuring low copper concentrations in blood and hair and suggested gender, study area, age, and alcohol consumption were the most important predictors of Cu. Dual-sample approach provided a more comprehensive assessment of copper's metabolic and environmental variations. However, Janja Snoj Tratnik et al. did not control for confounding factors such as diet, supplement intake, hormonal status, or lifestyle variables, all of which may influence copper levels. Additionally, although the study identified gender differences, it did not examine the impact of estrogen, menstrual cycles, or menopausal status in women, thereby limiting the understanding of physiological differences.

A study conducted in Iran on both sexes and different age groups (7–19 years) did not indicate Cu deficiency in any age and sex groups [105]. In terms of the study area, polluted areas showed a higher level of Cu compared to rural and urban areas. The suggested reasons were the use of Cu-containing soils and Cu-containing fungicides in these regions. Because of an inverse association between Cu levels in blood and alcohol consumption, the authors suggested that alcohol intake may alter Cu metabolism [80]. Consistent with this study, another study of Wuhan in China in 2019 revealed that men had lower blood concentrations of Cu than women ($p < 0.05$) [104].

Xuefei Chen et al. in their study on 614 healthy individuals showed that age had a positive correlation with Cu. A whole blood analysis on 196 pregnant and 209 non-pregnant women in China showed that Cu (1649.56 μg/L) was higher in pregnant women (1649.56 μg/L) than non-pregnants (1041.10 μg/L). They justified that these differences may be the result of physiologic changes such as an increase in plasma volume, DNA and RNA demand, enzyme synthesis, and a decrease in concentrations of micronutrients and circulating element binding proteins [103].

Maintaining a precise balance between copper uptake and efflux is essential for cellular health. Copper is absorbed mainly in the small intestine, particularly the duodenum and jejunum, with absorption rates adjusting based on copper availability [126,130]. The copper transporter protein Ctr1 facilitates copper uptake into enterocytes. Once absorbed, copper binds to albumin and ceruloplasmin, which transport it to various tissues [131]. The liver plays a key role in regulating copper levels by producing ceruloplasmin, storing copper, and facilitating its excretion. Excess copper is excreted through the liver into bile, with a minor amount excreted in urine [132]. Elevated copper levels can trigger oxidative stress, damage DNA, and impair cell proliferation. Copper toxicosis is classified as primary when caused by a genetic metabolic defect, and secondary when due to excessive intake, increased absorption, or decreased excretion linked to underlying health conditions. Copper toxicity, may result from exposure to high levels of copper in drinking water or environmental sources or from consumption acidic foods prepared in uncoated copper cookware [133,134].

3.5. Arsenic (As)

Arsenic exists in both inorganic and organic forms, each exhibiting distinct toxicological profiles and pathways of exposure. Inorganic arsenic species, primarily arsenite (Asm) and arsenate (Asr), are more readily absorbed and significantly more toxic than their organic counterparts. Long-term exposure to inorganic arsenic has been classified as group 1 carcinogenic by the IARC [135,136]. Of the 14 studies (Table 3) evaluated As in body fluids, four studies were from Asia [67,72,73,104], one study was from Australia [74] and South America [47], and the rest were from Europe [48,75–77,79–82]. Among studies conducted in the Asia region, in 2 studies of China, As AM ranged from 3.72 μg/L to 4.71 μg/L, and in a study conducted in Pakistan, the As AM of 2.16 μg/L was reported [67,72,73]. In an Australian study consisting of 120 male and female participants, blood As levels were 2.2 μg/L [74], and in Carmen Freire et al. study of Brazil, it was 4.92 [47]. μg/L. However, in studies conducted in Europe, As GM was varied from 0.5*10–3 μg/L in Serbia to 1.7 μg/L in France [48,50,75–77,79–82]. As serum level in healthy individual has been reported between 1 μg/L and 5 μg/L [79]. In the study from Slovenia, As GM of 0.89 μg/L was reported. The authors concluded that there was no significant contact with environmental inorganic As, and it was mainly through foods containing organic As, and seafood consumption was suggested as the main predictor of overall exposure to As. The researcher of this study also noticed that based on geography, drinking water was the most important exposure route to inorganic As. They also described that the water supply in Slovenia usually contains small concentrations of As (below 10 μg/L), although some mineral springs may have high concentrations of minerals, and inorganic As levels may reach as high as 60 μg/L [80].

Another study conducted by Heesterbeek et al. in the Netherlands and UK reported a direct relationship between the plasma levels of As and fish consumption [81]. On the other hand, a study in Belgium analyzed the level of As in 235 mothers and 241 neonates and reported that an increase in the educational level led to an enhancement in As concentrations in the mother's blood as well as cord blood. They justified that an increase in the educational level was associated with an increase in the mother's age. However, the difference in educational level was not significantly correlated with fish consumption ($p = 0.7$) [75].

Arsenic has a short biological half-life in fluids such as blood and serum, making its concentration a reflection of recent exposure rather than chronic accumulation. It is primarily absorbed through the gastrointestinal tract following the ingestion of contaminated food or water and is systemically distributed, particularly accumulating in the liver, kidneys, and lungs [137,138]. Prolonged exposure can lead to organ-specific toxicity. Within the liver, arsenic undergoes methylation to produce fewer toxic metabolites (MMA and DMA), although genetic polymorphisms in the arsenic methyltransferase (AS3MT) enzyme may impair this detoxification process, thereby increasing susceptibility to toxicity [139,140]. The primary route of arsenic excretion is via urine, making urinary arsenic a useful biomarker of recent exposure. However, variations in hydration status and other physiological factors may affect urinary concentrations [141]. In cases of chronic exposure, arsenic may accumulate in keratin-rich tissues such as hair and nails, serving as long-term indicators of exposure [142–144]. As is associated to various cancers—including those of the skin, lung, bladder, liver, and kidney—as well as cardiovascular diseases, neurodevelopmental impairments in children, cognitive decline, diabetes, peripheral neuropathy, and hepatic toxicity [145–148]. Organic arsenic compounds, such as arsenobetaine and arsenocholine, commonly present in seafood, are considerably less toxic due to their rapid excretion and limited bioaccumulation [149]. Nevertheless, certain metabolites of organic arsenic, such as monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA), may exhibit moderate toxicity under certain conditions. The differentiation between inorganic and organic arsenic forms is crucial for assessing health risks, with regulatory bodies such as the U.S. Environmental Protection Agency (EPA) enforcing stricter limits on inorganic arsenic levels in drinking water due to its higher toxicity [150,151].

3.6. Manganese (Mn)

Manganese is an essential trace element that acts as a cofactor for enzymes involved in crucial metabolic processes, including antioxidant defense and bone formation [152–154]. A total of 13 eligible studies

(Table 4) (seven studies from Europe [48,50,75–77,80,81], four of Asia [70,72,73,105], one from Australia [74], and South America [47]) have been analyzed Mn in biological fluids and hair. In a study from China, Mn (5.93 ± 5.54 μg/L) was reported in 669 healthy subjects [72]. Another study of Wuhan in China in 2019 revealed an age-related difference in the Mn concentrations in the whole blood [104]. Long-Lian Zhang et al. reported, GM Mn of 11.42 μg/L (11.07–11.75 μg/L) in the 648 Chinas population [70]. Whole blood analysis on 196 pregnant and 209 non-pregnant women in China showed that Mn (25.54 μg/L) ($p < 0.001$) was higher in pregnant women than in non-pregnant (Mn (19.04 μg/L) women. They attributed these differences to the physiological changes in blood volume and other blood elements in pregnancy [73]. This study identified a significant increase in Mn levels among older individuals, implying a potential link to physiological changes. However, it did not account for lifestyle factors such as diet, occupational exposure, and smoking, which can also influence Mn levels. Consequently, these findings may be challenging to generalize to other regions with distinct environmental exposures or dietary habits. In Brazil, in 2015, Carmen Freire et al. investigated the blood levels of Mn in a sample of blood donors (18 to 65 years, 75 % males, non-white (63 %)) and reported Mn AM and Mn GM of 14.61 μg/L and 12.84 μg/L, respectively. Mn concentrations in the north of Brazil were significantly higher than in other states. The authors suggested that the consumption of açai and other Amazonian fruits with a high content of Mn might be responsible for the high levels of Mn found in the Rio Branco population [47]. A study in Queensland reported the reference levels of Mn in blood and plasma 9.7 (4.54—19.5) μg/L and 1.0 (<1–3.1) μg/L, respectively [74].

Baeyens et al. investigated a large number of pollutants in the general Flemish population (adolescents (n = 210), mothers-newborns (n = 255), and adults (n = 204)) and found that the Mn GM in cord blood were nearly three times more than in mother blood (31.2 μg/L versus 12.1 μg/L) and the blood-Mn increased with increasing age groups. Furthermore, with increasing parity, a considerable rise was found in maternal blood-Mn concentrations (11.1 μg/L with parity = 1 child; 12.7 μg/L with parity = 2 children and 13.1 μg/L with parity = 3 or more children, p = 0.004) [75]. Metal and metalloid blood levels of 982 men and 1018 women were compared according to gender, age, and tobacco smoking in northern France, in a formerly heavily industrialized area. The mean blood levels of Mn were significantly higher in women than in men [Mn (GM = 8.12 vs 7.30 μg/L). Current smokers had lower mean levels of Mn with respect to non-smokers [76].

Deficiency in manganese can lead to developmental, neurological, and bone health issues, while excessive exposure, especially in occupational settings, can result in neurodegenerative disorders like manganism [155,156]. Establishing reference values for manganese intake, considering factors like age, gender, and environmental exposure, is vital to prevent both deficiency and toxicity, with ongoing research needed to refine these guidelines. Manganese concentrations in biological samples can be influenced by various factors, including analytical methods, sample preparation, and demographic characteristics The accuracy of manganese measurements depends on the sensitivity, detection limits, and calibration of techniques. Sample collection, storage, and processing also contribute to variability, with potential contamination of hair samples or differences in handling biological fluids like blood or urine [53–56,157]. Manganese levels may vary by age, with children showing different concentrations due to developmental and dietary factors, and gender differences are often observed, with men typically having higher levels. Geographic location plays a significant role, as populations in areas with higher industrial activity or elevated Mn levels in drinking water may have higher concentrations [157]. Diet is another critical factor, as manganese intake from food can influence its levels. Also, health conditions and medications, such as liver diseases or neurological disorders like Parkinson's disease, can affect manganese metabolism [158,159].

3.7. Mercury (Hg)

Mercury, particularly in its organic form methylmercury, is highly toxic and can cause severe health issues, including neurodevelopmental disorders in children and cognitive decline in adults. Inorganic mercury exposure, such as mercury vapor, is linked to kidney damage, cardiovascular problems, and reproductive health issues, especially in pregnant women [160,161]. 11 included studies (Table 3), 6 from Europe [48,71,76,77,80–82], 4 of Asia [23,68,69,73], and one of Australia [74] evaluated Hg in human body fluid samples. Hg AM in Asian countries ranged from 0.9 μg/L in Pakistan to 5.11 μg/L in Japan [23,68,69,73]. In Australia, the AM for Hg was 2 μg/L [74], and in European countries it was between 1.18 μg/L and 1.4 μg/L [48,71,76,77,80–82].

Cimi Ilmiawati, in 2015, measured Hg by cold vapor atomic absorption spectrometry in the blood and hair of 229 Japanese children from 9 to 10 years old. The blood Hg GM was 4.55 μg/L (1.16–15.79 lg/L). Hg levels in the blood of boys and girls had no significant differences. Participants in the upper quartile of Hg (n = 57) generally had a higher intake of tuna, alfonsino, monkfish, kelp, and total fish intake than subjects in the lower quartile (n = 57). They suggested that large tuna intake could predict Hg levels in the blood and hair. Approximately 95 % and 80 % of Hg in blood and hair are in the methylated form. A linear relationship between blood and hair Hg in Cimi Ilmiawati et al. study supported methylated Hg as the main form of Hg in samples [69]. This study demonstrates a strong correlation between Hg levels in blood and hair, supporting the use of hair as a reflective biomarker for recent methylmercury exposure. However, this cross-sectional study did not consider confounding factors such as dietary intake, genetic factors, and environmental exposure, which could affect Hg absorption and metabolism and had not ability to establish causality or track long-term exposure trends. In this study, hair could serve as a non-invasive biomarker for methylmercury exposure, especially in children, but emphasize the need for age-specific and diet-adjusted Hg reference values, as fish consumption strongly influenced Hg levels.

The blood level of mercury does not reflect Hg body burden, but it shows recent exposure to methylmercury and inorganic Hg. The most important sources of mercury are absorbed through the respiratory and digestive systems. The amount of toxin depends on its chemical form. Hg metal vapors have a high retention power in the body. In contrast, the gastrointestinal absorption of metallic mercury is negligible. Absorption of methylmercury from food may cause serious health complications [48].

Five included studies measured Hg content of hair including Japan, China and Pakistan from Asia and Russia and Slovenia from Europe [23,69,77,80,82]. The GM of Hg was reported in the Slovenian study while the other studies reported Hg AM. The highest Hg AM was reported in Taipei, which was 1.21 μg/g (combined mean) in 140 participants [77], followed 1.05 μg/g in 166 men and women in Pakistan [23]. In Japan, Hg AM was 0.77 μg/g in 229 children [69], while in the study of Russia, it was 0.3 and 0.1 in pregnant women and their children, respectively [82]. In a Slovenian study, the Hg GM (0.95 CI) in 947 participants was 0.275 μg/g, and according to gender, it was 0.282 μg/g and 0.268 μg/g in men and women, respectively [80]. The suggested reason for the high level of mercury in the residents of China was the higher consumption of seafood compared to Russia [77]. In a study of Japan, high level of mercury in the residents of this region was attributed to the high consumption of tuna fish, 80 % of which was in the form of methylmercury [69]. Likewise, a study in Slovenia reported that hair and blood levels of Hg clearly showed exposure primarily with fish consumption, especially along the coast. It also found that participants who ate seafood at least once a week had an average blood mercury level of 89 % and a hair mercury level of 2.3 times higher than those who ate seafood less frequently [80]. In contrast, compared with 3 amalgam fillings, 9 or more fillings increased blood mercury levels by 35 % [69].

Similar to other mentioned toxic heavy metals, the accuracy of Hg measurements depends on the sensitivity, detection limits, and

calibration of techniques. For instance, techniques like atomic absorption, atomic fluorescence, and spectrophotometry might yield different results. Sample preparation methods, such as the choice of sample type (blood, urine, different tissues), mercury extraction methods, and storage conditions, can significantly influence the results. Factors such as age, gender, health status, geographic location, and environmental behaviors (e.g., seafood consumption or occupational exposure to mercury) can lead to meaningful differences in mercury concentrations among individuals. Environmental conditions, such as air, water, and soil pollution, can also impact mercury levels in biological samples [56,57,160–163].

3.8. Selenium (Se)

Se is a crucial trace element with significant antioxidant properties, primarily through its role in the regulation of glutathione peroxidase enzymes. These enzymes are essential for the catalytic breakdown of hydrogen peroxide and organic hydroperoxides, thereby protecting cells from oxidative damage [164,165]. Se is predominantly incorporated into selenoproteins, which are involved in various physiological functions, including immune response, thyroid hormone metabolism, and redox homeostasis [166]. The biological activity of selenium is highly dose-dependent, with a narrow margin between its beneficial and toxic levels. Consequently, both Se deficiency and excess pose potential health risks. Se deficiency has been linked to several pathological conditions, and its status has been widely investigated in numerous countries to better understand its role in public health [167,168]. In this study, a total of 9 eligible studies (Table 4), (Five studies of Europe, three of Asia, one of Australia) have been analyzed Se in biological fluids and hair [23,48,67,72,74,77,80–82]. In the study carried out in Australia, Se levels in biological fluids were reported 141 μg/L [74], and in different studies in Europe, it ranged from 92 μg/L to 110 μg/L [48,77,80–82].

In studies where Se was analyzed simultaneously in blood and serum/plasma, it had a higher concentration in blood [48,67]. Hoet P. et al. performed a study on 380 voluntary subjects (18–70 years old) recruited by an occupational health service during annual medical check-ups and by the Louvain Center for Toxicology and Applied Pharmacology (LTAP) between 2016–2017, in the 10 provinces of Belgium, covering urban, suburban, and rural areas [48]. They reported reference value of Se as 93.7 μg/L (65 to 125 μg/L), in the plasma and 110 μg/L (80 to 155 μg/L) in the blood [48]. Heesterbeek et al. found a significant difference between the plasma levels of Se 124 μg/L (82—179) μg/L in females compared to that in males 130 (101–161) μg/L. The possible reason was not reported [81]. Also, Komarova et al. showed age-dependent changes in blood Se 137 (119–156) μg/L in under 40 years versus Se 144 (118–224) μg/L in over 40 years [74].

Hair Se was measured in 3 studies from Pakistan, Russia and China [23,77,82]. AM Se (combined mean) in Pakistan was 1.75 μg/g in men and women, respectively, while it was 0.51 μg/g in the Chinese and 0.41 μg/g in Russia studies [23,82]. In another study of Russia, it was 0.4 μg/g in pregnant women and 0.45 μg/g in their children. Se was the only essential element that was higher in a study of Taiwan Pacific Islands compared to the Sakhalin, Russian, which was attributed to high fish consumption in Taiwan [77].

Both deficiency and excess of Se can lead to significant pathophysiological conditions. Se deficiency is associated with several severe diseases, including Keshan disease, a cardiomyopathy predominantly affecting children and women of childbearing age, and Kashin-Beck disease, an osteoarthropathy prevalent in selenium-deficient regions. These disorders arise due to impaired function of selenoproteins, which are critical for antioxidant defense and thyroid hormone metabolism [169,170]. Conversely, excessive Se intake can lead to selenosis, characterized by symptoms such as gastrointestinal disturbances, hair and nail brittleness, neurological abnormalities, and in extreme cases, acute toxicity. Chronic high Se exposure has also been implicated in an increased risk of type 2 diabetes and possible neurotoxic effects [168]. Thus, maintaining optimal Se status is essential, as both deficiency and toxicity can disrupt redox balance, immune function, and metabolic homeostasis, contributing to the onset or progression of various human diseases.

3.9. Chromium (Cr)

Chromium, poses significant health risks due to its high oxidative potential and cellular permeability [171]. In this review, nine eligible studies (Table 4), (Five studies of Europe [50,75–77,81], three from Asia [72,73,105], and one of Australia [74]) have been analyzed Cr in biological fluids and hair. In a study from China, Cr (1.80 ± 0.57 μg/L) was reported in 669 healthy subjects [72]. Another study of Wuhan in China showed that Cr levels were not different among all the 477 samples [104]. Whole blood analysis on pregnant and non-pregnant women showed that Cr (2.73 μg/L) ($p < 0.001$) was higher in pregnant women than in non-pregnant [Cr (0.63 μg/L)] women. Lu Gong et al. attributed these dissimilarities to the variations in blood volume and elements in pregnancy [73]. Komarova et al. reported the reference levels of Cr < 5 μg/L and < 1.7 μg/L in blood and plasma, respectively [74]. In Baeyens et al. study, Cr was significantly higher in women than in men Cr (GM = 0.47 vs 0.37 μg/L), and it increased according to the age categories [75].

In human body, Cr^{6+} readily crosses cell membranes via sulfate and phosphate anion transporters and undergoes intracellular reduction to trivalent chromium, generating ROS as byproducts. These ROS cause oxidative stress, DNA damage, and disruption of mitochondrial function, contributing to carcinogenesis, particularly in the lungs. Epidemiological and experimental studies have linked prolonged exposure to Cr^{6+} with increased incidences of respiratory diseases, dermal irritation, liver and kidney damage, and various cancers, especially among occupationally exposed populations. The genotoxic and cytotoxic properties of Cr are primarily attributed to its capacity to induce DNA strand breaks, chromosomal aberrations, and mutations through oxidative mechanisms, highlighting its classification as a Group 1 human carcinogen by the IARC [171–173].

3.10. Aluminum (Al)

Aluminum is a ubiquitous environmental metal with no known physiological role in the human body, yet its accumulation is increasingly associated with a range of pathological conditions [174,175]. Therefore, we evaluated five studies (Table 4), 4 from Europe [48,76,77,81] and one of Australia [74] evaluated Al in human body fluid samples. Of three studies that evaluated Al in blood and plasma, Al levels were below the limit of detection (LOD < 15 in blood and LOD < 3 in plasm) in 380 participants in Hoet et al. study in Belgium [48], while Al AM in studies of France [76] and Australia [74] were 4.21 μg/L in blood and 6.9 μg/L in plasma, respectively.

Chronic exposure to Al has been implicated in neurodegenerative diseases such as Alzheimer's, where it contributes to oxidative stress, mitochondrial dysfunction, and the aggregation of β-amyloid plaques. Mechanistically, Al disrupts iron homeostasis and promotes the generation of reactive oxygen species (ROS), leading to lipid peroxidation, protein denaturation, and DNA damage. It can also interfere with enzyme systems and cellular signaling pathways, exacerbating inflammatory responses and cell death. The toxicokinetics of Al reveal poor gastrointestinal absorption, but once absorbed, it accumulates preferentially in the brain, liver, and bones, with slow excretion, thereby increasing the risk of long-term toxicity. These findings emphasize the need for heightened public health awareness and regulation of Al exposure sources such as food additives, cookware, and industrial emissions [174–178].

3.11. Other Elements/Metals

Other TEs/TMs (supplementary Table.3) beyond those described

above are illustrated in Appendices A. Blood levels of antimony (Sb), beryllium (Be), thallium (Tl), nickel (Ni), and vanadium (V) in the general population aged 20–59 years of Northern France, in a formerly heavily industrialized area, were compared according to sex, age, and tobacco smoking. Be and V was detected in 57 % and 19 % of participants, respectively. Also, the vanadium level was not reported. The mean levels of Be, Ni, Sb, and Tl did not significantly differ between groups in terms of sex and smoking status. According to the type of tube, the mean levels of Be, Ni, Tl, and Sb collected in the B&D tubes were markedly higher than those detected in the SARSTEDT tubes. The authors argued that the type of the tubes was one possible explanation for the difference in TE/TM levels among studies and suggested that the same tubes for sampling and comparing levels of blood pollutants in a particular population group with reference values would be needed.

3.12. Toxicity and metals interactions

Environmental exposure to TMs, has emerged as a growing global health concern due to its complex role in the etiology of numerous chronic diseases. The burden of exposure arises not only from industrial emissions and urban pollution but also through dietary intake and climatic conditions that influence metal bioavailability [179,180]. Individuals consuming seafood rich in mercury, rice grown in cadmium-contaminated soils, or meat with high lead content are particularly vulnerable. Furthermore, regional environmental factors—such as mineral composition of soil and air pollution—significantly affect metal distribution in food chains and human tissues, thereby affecting nutritional status and increasing toxic burden [129,160,181–185].

Toxic metals are consistently associated with a range of adverse outcomes such as neurotoxicity, nephrotoxicity, immunotoxicity, carcinogenesis, and cardiovascular disease. The severity of these health risks is modulated by the chemical form of the metal, route and duration of exposure, and host-specific variables like age, sex, nutritional state, and genetic susceptibility [186–189]. Vulnerable populations—particularly children, pregnant women, and the elderly—exhibit heightened sensitivity due to immature or declining detoxification systems [190,191]. Essential trace elements play a vital role in supporting metabolic processes, enzymatic activity, and antioxidant defense mechanisms [192]. However, both deficiency and excess of these elements can lead to significant pathological outcomes. For instance, zinc deficiency impairs immune function and cognitive development, whereas excessive zinc intake can disrupt copper metabolism, leading to secondary deficiencies [111,134,193,194]. Selenium is crucial for maintaining redox homeostasis, yet elevated levels may result in selenosis and thyroid dysfunction [195]. Similarly, chronic overexposure to manganese has been associated with neurotoxic effects resembling Parkinsonian syndromes, and iron overload can cause damage to hepatic, cardiac, and endocrine systems [196,197]. These findings underscore the importance of maintaining optimal trace element levels to preserve physiological function and prevent disease.

The interaction between toxic and essential metals introduces significant complexity in their absorption, metabolism, and toxicity profiles. These interactions can manifest as competitive, synergistic, or antagonistic effects. For example, Zn and Cu compete for intestinal absorption, while excess Se may provide protection against mercury toxicity. Concurrent exposure to Pb and Cd, however, can exacerbate cumulative toxicity. Additionally, metal interactions influence tissue distribution, cellular uptake, and excretion kinetics, which are crucial for understanding toxicodynamic responses [23,34,71,136,148,198,199].

Variability in reference values (RVs) for both essential and toxic metals across different populations and studies reflects differences in environmental exposure, dietary habits, socioeconomic conditions, and genetic backgrounds. Disparities in analytical techniques—such as the use of ICP-MS, AAS, or HR-ICP-MS—further complicate efforts to standardize measurements. Consequently, establishing universal toxicity thresholds remains a significant challenge. To address these complexities, there is an urgent need for region-specific risk assessment frameworks that consider local exposure sources, age- and sex-specific vulnerabilities, and the interactive behavior of metals.

Toxicity thresholds for heavy metals depend on various factors, including exposure routes, duration, and individual characteristics such as age, gender, and nutritional status [190]. Regulatory bodies, such as the WHO, ATSDR, and FDA, have established permissible limits for metals like lead, cadmium, mercury, and arsenic due to their serious health risks, particularly for vulnerable groups such as children, pregnant women, and the elderly. Children are especially susceptible to heavy metal toxicity due to higher absorption rates and underdeveloped metabolic systems. Prenatal exposure to metals can disrupt fetal development and cause neurological impairments [105,200,201]. Similarly, diminished kidney and liver function in older adults impairs metal excretion, increasing the risk of chronic diseases associated with metal accumulation. Prolonged exposure to metals such as cadmium, lead, and arsenic can result in chronic toxicity and occupational health issues. The severity of these effects is influenced by factors such as the chemical form of the metal, exposure duration, and individual sensitivity; for instance, inorganic arsenic is more toxic than its organic counterparts. Elevated lead levels in children are associated with intellectual disabilities, neurocognitive and behavioral disorders, respiratory issues, cardiovascular diseases, and cancer. Blood metal concentrations also vary across populations due to environmental and demographic factors, as demonstrated in studies of Inuit populations in Nunavik. Given these variations, defining universal toxicity thresholds is complex, and risk assessments must account for age-related vulnerabilities, population-specific factors, and regional environmental exposures [24,27,29,34,59–61,84,86,91,99,100,111,124,136,137,146–149,168,178,199,202,203].

3.13. Challenges, limitations and Recommendations

3.13.1. Challenges

The development and certification of RVs for elemental and metal analysis continue to face significant challenges. These include the intrinsic complexity and heterogeneity of RV matrices, risks of contamination, temporal variability, and inconsistencies across certification standards. Additional obstacles such as high implementation costs, limited resources, and poor alignment between existing RVs and the specific matrices of target samples further complicate their application. Environmental and geographical factors also contribute to variability, underscoring the necessity for context-specific approaches. These challenges highlight an urgent need for ongoing research and stronger interdisciplinary and intersectoral collaboration among academia, industry, and regulatory bodies to enhance RV development and harmonization. A multidisciplinary framework that incorporates insights from toxicology, epidemiology, biochemistry, and environmental sciences is vital to establish more accurate and representative RVs for toxic and trace elements. Structured collaboration through joint research initiatives, scientific symposia, and the strategic use of digital platforms can promote data sharing, improve methodological consistency, and support more effective responses to complex environmental and public health concerns.

Moreover, the studies included in this review revealed several sources of bias and confounding, such as demographic variability (e.g., age, sex, lifestyle), dietary influences (notably seafood intake impacting arsenic and mercury levels), and differential environmental or occupational exposures. Methodological limitations—such as the absence of standardized reference values, risk of contamination during sample handling, and inconsistent reporting of statistical measures including confidence intervals—were also prevalent. Addressing these methodological gaps is critical to improving the reliability, validity, and comparability of future research in this domain.

4. Limitations

The language limitation may have led to the exclusion of some valuable studies, published in other languages (e.g., chinese, spanish, russian, japanese, and persian), but also helped reduce data heterogeneity. The minimum three-element criterion helped improve data comparison, but may have excluded useful single-element data. Differences in analytical methods and lack of raw data from some studies are other limitations of our study. It is recommended that future studies utilize a broader range of articles, languages, and analytical methods to improve the accuracy of reference values. In this review, we aimed to address potential confounding factors, including dietary habits (e.g., seafood consumption, rice, contaminated vegetables), lifestyle (e.g., smoking, alcohol consumption, physical activity), occupation (e.g., workers in industries, mines, polluted urban areas), age and gender and also geographical factors and environmental exposure, however, some studies did not provide complete data on these factors, which is a limitation of our study.

5. Recommendations

Advancing toxic metal exposure assessment requires a globally inclusive, multidisciplinary approach focused on improving the accuracy and clinical relevance of reference values (RVs). Standardizing analytical methods—including sampling, instrumentation (e.g., ICP-MS, AAS), and quality control—is critical for ensuring cross-study comparability. Harmonized biological monitoring protocols will further strengthen RV development. Research must prioritize high-risk groups such as children, pregnant women, the elderly, smokers, and populations near industrial or mining zones. Diverse participant inclusion enhances generalizability and helps uncover population-specific vulnerabilities. Future studies should incorporate demographic, environmental, nutritional, and genetic variables, as factors like diet, pollution, soil composition, and genetic polymorphisms affect metal bioavailability and toxicity. Longitudinal cohorts are essential to investigate chronic exposure effects and metal accumulation in key organs, linking them to diseases such as cancer, cardiovascular conditions, and neurodegeneration. Spatial and geostatistical mapping of exposure and disease trends can highlight environmental health disparities.

Metal monitoring efforts should be guided by risk assessment models that use pollution trends, epidemiological data, and toxicity simulations, helping to prioritize high-risk metals and support the creation of certified reference materials. Finally, translating research into policy requires evidence-based regulation of metal levels in the environment, consumer products, and food. Integrated biomonitoring programs and early-warning systems can facilitate timely interventions. Public education, professional training, and cross-sector collaboration are essential for effective risk communication, regulatory compliance, and long-term mitigation of toxic metal exposure.

6. Conclusions

This systematic review synthesizes data from 29 studies involving 26,676 healthy individuals across 15 countries, providing RVs for trace elements TEs and toxic metals TMs across diverse biological matrices. The findings highlight the urgent need for region-specific RVs and standardized methodologies to improve clinical interpretation and environmental health assessments. Variability in reported RVs reflects differences in geography, demographics, environmental exposures, dietary habits, and analytical platforms (e.g., ICP-MS, AAS), as well as inconsistencies in statistical reporting formats. These discrepancies highlight the necessity for harmonized protocols in sampling, analysis, and data reporting.

Adoption of internationally recognized biomonitoring guidelines (e.g., WHO, CDC, FDA) and investment in advanced instrumentation will improve data quality and comparability. Establishing globally and regionally stratified RVs based on diverse populations will strengthen exposure assessments and support *meta*-analyses. Integrating biomonitoring data with epidemiological evidence can help prioritize high-risk metals—particularly Pb and Cd—and elucidate their links to disease. National surveillance programs are essential for tracking trends, protecting vulnerable groups (e.g., children, pregnant women, elderly), and informing policy. Future directions include harmonization of methods, expanded monitoring in underrepresented regions, and deeper investigation into inter-element interactions. Strengthened international collaboration will be key to building a unified global framework for metal biomonitoring and advancing public health protection worldwide.

Author Contributions

Fatemeh Maghool: contributed to designing the project, data collection, data analysis and results interpretation, implementation, writing, reviewing and editing of the manuscript and designing the figures. Mohammad Hassan Emami: contributed to designing the project, implementation, writing, reviewing and editing of the manuscript. Samane Mohammadzadeh: contributed to designing the project, data collection, data analysis and results interpretation, implementation, writing, reviewing and editing of the manuscript and designing the figures. Safoora Mohammadzadeh: contributed to data collection, data analysis and results interpretation, implementation, writing, reviewing and editing of the manuscript. Nasrin Zare: contributed to data collection, data analysis and results interpretation, implementation, writing, reviewing and editing of the manuscript. Farideh Saberi: contributed to data collection, data analysis and results interpretation, implementation, writing, reviewing and editing of the manuscript. Alireza Fahim: contributed to implementation, writing, reviewing and editing of the manuscript. Owais Yousuf: contributed to implementation, writing, reviewing and editing of the manuscript. Zakieh Keshavarzi: writing, reviewing and editing of the manuscript. Pouria Samadi: contributed to implementation, writing, reviewing and editing of the manuscript.

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CRediT authorship contribution statement

Mohammad Hassan Emami: Writing – review & editing, Project administration, Methodology, Conceptualization. **Safoora Mohammadzadeh:** Writing – original draft, Resources, Investigation, Data curation. **Nasrin Zare:** Writing – original draft, Validation, Investigation, Data curation. **Farideh Saberi:** Writing – original draft, Investigation, Data curation. **Alireza Fahim:** Writing – original draft, Methodology, Formal analysis. **Owais Yousuf:** Writing – original draft, Validation, Formal analysis, Data curation. **Zakieh Keshavarzi:** Writing – original draft, Validation, Investigation. **Pouria Samadi:** Writing – review & editing, Writing – original draft, Validation, Investigation. **Samane Mohammadzadeh:** Writing – review & editing, Visualization, Investigation, Formal analysis, Conceptualization. **Fatemeh Maghool:** Writing – review & editing, Validation, Project administration, Data curation, Conceptualization.

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.

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Appendix A. Supplementary material

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Data availability

Data will be made available on request.

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