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Review article

Arsenic, lead, mercury and cadmium: Toxicity, levels in breast milk and the risks for breastfed infants

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ABSTRACT

Metals are ubiquitous in nature, being found in all environmental compartments, and have a variety of applications in human activities. Metals are transferred by maternal blood to the fetus via the placenta, and exposure continues throughout life. For the general population, exposure comes mainly from water and food consumption, including breast milk. In this paper, we reviewed studies on the toxicity of arsenic, lead, mercury and cadmium, the toxic metals of most concern to human health, focusing on the potential risks to newborns and infants. A total of 75 studies published since 2000 reporting the levels of these metals in breast milk were reviewed. Lead was the metal most investigated in breast milk (43 studies), and for which the highest levels were reported (up to 1515 μg/L). Arsenic was the least investigated (18 studies), with higher levels reported for breast milk (up to 149 μg/L) collected in regions with high arsenic concentrations in water (>10 μg/L). Data from 34 studies on mercury showed that levels in breast milk were generally higher in populations with high fish consumption, where it may be present mainly as MeHg. Cadmium levels in breast milk were the lowest, with means <2 μg/L in most of the 29 studies reviewed. Results of risk assessments indicated that the intake of arsenic, lead and mercury by infants through breastfeeding can be considered a health concern in most regions of the world. Although the potential risks to infants are mostly outweighed by the benefits of breast milk consumption, it is essential that contaminants be continuously monitored, especially in the most critical regions, and that measures be implemented by health authorities to reduce exposure of newborns and infants to these metals, and thus avoid unnecessary health risks.

Contents

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1. Introduction

Metals are ubiquitous in nature, but some comprise a group of contaminants to which exposure, even at relatively low levels may represent a risk to human health. Arsenic ranks first on the National Priorities List of the Agency for Toxic Substances and Disease Registry (ATSDR), which prioritizes substances based on a combination of their frequency, toxicity, and human exposure potential. Lead, mercury and cadmium rank 2nd, 3rd and 7th on this list, respectively (ATSDR, 2015).

Human exposure to metals can occur during occupational activities, mainly through inhalation and dermal routes in mining and industry, and over a lifetime, from water and food consumption and exposure to soil, dust and air (ATSDR, 2007a, 2007b; WHO, 2004; EFSA, 2009a; Carlin et al., 2016). The presence of toxic metals in human milk has been reported worldwide (e.g., Gürbay et al., 2012; Chao et al., 2014; Ettinger et al., 2014), and breastfed babies are particularly vulnerable and sensitive to their toxic effects due to their rapid growth, organ immaturity, and susceptibility of their nervous system during the first year (Isaac et al., 2012). Furthermore, newborns absorb metals to a greater extent than adults and have a lower capacity to excrete compounds in the bile, decreasing body clearance (Oskarsson et al., 1998).

Lactation is a highly complex process that begins about 40 h after birth, and is triggered by the hormones progesterone, estrogen, prolactin and oxytocin (Gundacher and Zödl, 2005). Breast milk is a fundamental source of nutrients for newborns and babies, as it contains proteins, fats, carbohydrates, and elements essential to the proper functioning of the body. It is also a source of lactoferrin, α-lactalbumin and lisoenzymes, substances that create a protective barrier against environmental factors, increasing defense mechanisms and stimulating the development of immunological systems in children (Grzelak et al., 2014). Breast milk influences the intestinal microflora, ensures the structural and functional maturity of mucous membranes, reduces the risk of allergies and autoimmune disorders, and contributes to the proper development of the gastrointestinal, central nervous, endocrine and immune systems (Leon-Cava et al., 2002). The WHO recommends that babies be exclusively breastfed up to 6 months of age, and for an additional 2 years along with appropriate complementary foods (WHO, 2007).

The composition of human milk is not constant and depends on the nutritional status of the mother, her diet, stage of lactation, socio-demographic status, and lifestyle (Ballard and Morrow, 2013; Garcia-Esquinas et al., 2011; Vieira et al., 2013). The transport of xenobiotics into milk is supposed to follow the same pathways as those of other milk components, with toxic metals entering milk through ways similar to those of essential trace elements (Oskarsson et al., 1998). Trace element regulation mechanisms in milk involve the capturing of metals by specific transporters in the mammary epithelial cells and their subsequent discharge in the alveolar lumen of the mammary glands (Rossipal and Krachler, 1998; Kelleher and Lönnerdal, 2005; Bressler et al., 2007). Studies conducted with rats and mice indicated that lead was almost exclusively found in the casein fraction, the highest proportions of cadmium and methylmercury found in fat, and inorganic mercury in whey fractions (Oskarsson et al., 1998). In human milk, mercury possesses a greater ability to interact with milk protein, while cadmium and lead are equally distributed between light and low molecular weight components (see review by Gundacker and Zödl (2005)).

This paper briefly summarizes arsenic, lead, mercury and cadmium toxicology, focusing particularly on infants and children, and reviews the literature of studies reporting levels of these toxic metals in human breast milk worldwide. Exposure and risk assessment results of metal intake through breastfeeding are also reviewed, and the risks of exposure to breastfed infants discussed. For the incidence data, a query was conducted on the Pubmed, Science Direct and Google Scholar databases for studies published since 2000 (last search June 2016) using the keywords “human milk”, “breastmilk” and “breast milk”, associated with “metal”, “arsenic”, “lead”, “mercury” or “cadmium”. Additional papers were identified in published reviews related to contaminants in breast milk.

2. Human exposure and toxicity

2.1. Arsenic

Arsenic (As) occurs naturally in volcanic ashes, volcanic rock, clay, iron oxides, mineral sulfur and organic matter. Human exposure to arsenic occurs primarily through the consumption of water and seafood, particularly shellfish (EFSA, 2009a). Arsenic is found in the environment in organic forms, including monomethylarsenic (MMA), dimethylarsenic (DMA), arsenobetaine, and arsenocholine, as well as in inorganic (IAs) forms (As^{III} and As^{V}). A systematic review conducted by Lynch et al. (2014) evaluated over 6500 data on inorganic arsenic and its metabolites in food, including seafood and specific foods for children. Algae was the food with the highest concentration (mean of 1000 μg/kg, n=312, mostly as IAs), followed by rice and its byproducts (130 μg/kg, n =1126, mostly as IAs), and seafood (130 μg/kg, n=835; mostly as DMA).

Over 80% of inorganic arsenic is absorbed through the human gastrointestinal tract, and excretion occurs mainly via urine (ATSDR, 2007a). Certain characteristics of arsenic are summarized in Table 1. Studies conducted in Taiwan and other countries showed greater risk of lung, bladder, kidney or skin cancer from exposure to arsenic in drinking water, where it was predominantly present in inorganic form (WHO, 2001). Inorganic arsenic compounds, including arsenic trioxide, arsenite, and arsenate are classified as carcinogenic to humans by the International Agency for Research in Cancer (Group I), with extensive evidence of lung, bladder and skin cancer, and positive association with kidney, liver and prostate cancer (IARC, 2016). Although the mechanisms involved in the carcinogenicity of arsenic are not yet fully understood, it may nevertheless be considered genotoxic, since it induces micronuclei, DNA strand breaks, sister chromatid exchanges, aneuploidy and oxidative stress through the generation of reactive oxygen species during its biotransformation (see revision by Bustaffa et al. (2014)).

Inorganic arsenic and the methylated metabolites MMA and DMA cross the placentary barrier (Vahter, 2008), exert epigenetic effects by methylation of DNA (Reichard et al., 2007), and interact with multiple nuclear receptors (Bodwell et al., 2006). As a result, functional changes may occur leading to the development of other diseases later in life (Vahter, 2008). Vahter (2009) suggested that high

Table 1
Some characteristics of arsenic, lead, mercury and cadmium.

	IAs	Pb	IHg	MeHg	Cd
IARC classification[a]	Group 1	Group 2B	Group 3	Group 2B	Group 1
PTWI, μg/kg bw/week or PTMI, μg/kg bw/month	–	–	PTWI: 4[d]	PTWI: 1.6[e]	PTWI: 2.5[b] PTMI: 25[c]
BMDL, μg/kg bw/day	3.0[d]	0.5[f] (developmental toxicity in children)	–	–	–
Oral absorption	over 75%[g]	Adults: 3–15% Children: 30–50%[f,j]	Up to 20%; increases in a milk diet[i]	>90%[i]	5%[h]
Half-life (plasma)	3–4 hs[g]	20–40 days[j]	20–66 days[i]	44–88 days[i]	3–4 months[m] ~ 12 yrs (kidney)[h]
Cross the placenta	Yes[g]	Yes[f,j]	Poorly[i]	Yes[i]	Yes[h]
Neurotoxic	Yes[g]	Yes[f,j]	Inconclusive[i]	Yes[e,i]	Inconclusive[h]
Genotoxic	Yes[d,g]	weak, indirect[f]	Inconclusive[i]	Inconclusive[i]	Indirect[h,l]
Embryotoxic	Yes[g]	Inconclusive[k]	Inconclusive[i]	Yes[e,i]	No[h]

Group 1 – carcinogenic to humans; Group 2A- probably carcinogenic to humans; Group 2B: possibly carcinogenic to humans; Group 3- not classifiable as to its carcinogenicity to humans; PTWI: provisional tolerable weekly intake; PTMI: provisional tolerable monthly intake; BMDL – benchmark dose lower bound.

[a] IARC, 2016.
[b] EFSA, 2012a.
[c] JECFA, 2011b.
[d] JECFA, 2011a.
[e] JECFA, 2004.
[f] EFSA, 2010.
[g] ATSDR, 2007b.
[h] ATSDR, 2012.
[i] UNEP, 2008.
[j] ATSDR, 2007a.
[k] CDC, 2010.
[l] EFSA, 2009b.
[m] Järup and Akesson, 2009.

levels of methylated arsenic in pregnant women are the result of *de novo* synthesis of choline by phosphatidylethanolamine methyltransferase, which is upregulated during pregnancy to supply fetal needs of choline for cerebral development (Zeisel, 2006). Exposure to arsenic can also cause reproductive toxicity, including increases in fetus mortality, underweight newborns, spontaneous abortions, eclampsia, and birth defects (WHO, 2001). As^{III} is the single form of arsenic which is protonated at physiologic pH, and is transported by the aquaglyceroporins (Liu et al., 2004; Rosen, 2002) present in mammary glands during lactation (Matsuzaki et al., 2005).

Recent epidemiologic studies have found a long latency period for lung cancer and other chronic diseases related to arsenic, even when exposure was limited to a short period during childhood or in the uterus. Exposure during these two periods may also have adverse reproductive outcomes for mothers, and induce changes in cognitive development of children (McClintock et al., 2012).

A limit of 10 μg/L was established by the WHO for arsenic in drinking water (WHO, 2004). However, some regions of the world have naturally high arsenic levels in water compartments which exceed that limit, including Argentina, Bangladesh, Chile, China, Hungary, India, Taiwan, and certain regions of the United States (Hopenhayn-Rich et al., 2000; Nordstrom, 2002; Rahman et al., 2011; McClintock et al., 2012). It is well established that almost all arsenic in drinking water is in inorganic form (JECFA, 2011a; EFSA, 2009a).

In Chile, data from 1950 to 1996 showed high late fetal mortality (OR = 1.7; CI: 1.5–1.9), neonatal mortality (OR = 1.53; CI: 1.4–1.7), and post neonatal mortality (OR = 1.26; CI: 1.2–1.3) in a region with a history of high arsenic levels in water, in comparison with a region with low levels (Hopenhayn-Rich et al., 2000). A epidemiologic study conducted in Bangladesh observed 1152 pregnant women and their babies for a period of 1 year, with urine samples collected after confirmation of pregnancy and in the 30th week of gestation for arsenic analysis (Rahman et al., 2011). Estimated risk of occurrence of lower respiratory tract diseases increased 69% for infants of mothers with higher arsenic concentrations in urine.

The mechanism and factors that may affect the excretion of arsenic in breast milk are not completely known, but fetuses and babies are probably protected by increased methylation of arsenic during pregnancy and breastfeeding (Fängström et al., 2008; Gürbay et al., 2012; Vahter, 2009). In a study conducted in Argentina in an area with high arsenic concentration in water (200 μg/L), the median concentration of arsenic was 34 μg/kg in the placenta, and 9 μg/L in cord blood, with a significant correlation with maternal blood levels (Concha et al., 1998). All arsenic in the blood plasma of newborns and their mothers, and about 90% of the arsenic in the urine of both, was present as DMA, a result also found by other authors (Fängström et al., 2008; Islam et al., 2014), indicating that methylation of arsenic occurred during pregnancy and the metal was transferred to the fetus as DMA. Fängström et al. (2008) indicated that the methylated arsenic metabolites in blood plasma do not pass easily through the mammary glands. The authors found that the arsenic concentrations in breast milk were negatively correlated with %DMA ($r_s = -0.19$), and positively correlated with %iAs ($r_s = 0.16$) in maternal urine. Thus, efficient maternal methylation of iAs leads to lower arsenic excretion in breast milk, which contains essentially inorganic arsenic, mainly as As^{III}.

In 2010, the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 2011a) concluded that the provisional tolerable weekly intake (PTWI) previously adopted for arsenic (15 μg/kg bw, or 2.1 μg/kg bw/day) was no longer safe for humans, and established a benchmark dose, and a lower confidence level ($BMDL_{0.5}$) of 3 μg/kg bw/day as the reference point for risk assessment (Table 1). This dose corresponds to a 0.5% increase in the incidence of lung cancer associated with dietary exposure to inorganic arsenic over background in northeastern Taiwan (JECFA, 2011a).

2.2. Lead

Lead is a toxic metal widely present in nature, primarily in inorganic form, and is produced in activities such as mining and smelting, and in battery manufacturing (WHO, 2010a). The general

population is exposed to lead mainly through food consumption, with about 5–15% of the oral intake being absorbed by the gastrointestinal tract, a rate that is higher in children under 6 years of age (WHO, 2010a). The higher gastrointestinal absorption of lead by children is related to the uptake pathways for essential minerals (e.g. calcium and iron), which are more active than in adults (HERAG, 2007). Inorganic lead compounds are classified by the IARC as potentially carcinogenic to humans (Group 2 A), and organic lead compounds are "not classifiable to its carcinogenicity to humans" (Group 3) (IARC, 2016). Organic lead compounds are metabolized to ionic lead both in humans and animals, when the toxicity associated with inorganic lead is expected to be exerted (IARC, 2016). Table 1 summarizes some characteristics of lead.

Erythrocytes have high affinity for lead, and over 90% of what is absorbed is bound in the blood stream just after exposure. With age, lead is deposited in bone tissue, with a half-life of 10–30 years (WHO, 2010a). For the adult population, the cardiovascular and renal systems are the most critically affected by lead exposure, while for infants and children the effects on the central nervous system are the most critical (Sanders et al., 2009; EFSA, 2010; JECFA, 2011b). Encephalopathy, decreased nerve conduction, and cognitive deficits may occur in children with blood lead concentrations lower than the level that would induce similar effects in adults (ATSDR, 2007b). The particular vulnerability of fetuses and infants to the neurotoxicity of lead may be due in part to the immaturity of the blood-brain barrier, and to the lack of the high-affinity lead-binding protein in astroglia, which trap divalent lead ions in adults (Lindahl et al., 1999; EFSA, 2010; Schnaas et al., 2006). The various molecular, intracellular and cellular mechanisms that cause lead neurotoxicity also include the induction of oxidative stress, and interference in enzyme calcium dependents (eg. nitric oxide reductase), which amplify apoptosis of neurons (Nemsadze et al., 2009).

Gulson et al. (1997), using lead isotopic ratios of immigrant women arriving in Australia and of the local population, showed that mobilization of lead from bone contributed significantly to blood lead levels during the last trimester of pregnancy, a critical time for the development of the central nervous system, exceeding the normal exchange of bone lead stores observed in the non-pregnant condition. These increases were detected among subjects with blood levels < 5 μg/dL, and were attributed to a low daily calcium intake, as calcium may reduce mobilization of skeletal mineral stores to supply calcium needs during pregnancy and lactation (Gulson et al., 1998, 2003). Lead skeleton mobilization was even higher during the post-pregnancy period, and was the major source of lead in breast milk, in addition to the diet and other exogenous factors (Gulson et al., 2003).

Various studies have shown the transfer of lead from the mother to the fetus via placenta prenatally, and via breast milk postnatally. In Mexico, Ettinger et al. (2004) found lead concentration in breast milk to be significantly correlated with the levels in umbilical cord and maternal blood lead at delivery, and with maternal blood lead and patella lead at 1 month postpartum. In another study with the same group (Ettinger et al., 2014), the mean mother milk:plasma ratio was 7.7; infant blood lead level (3.4 ± 2.2 μg/dL) increased by 1.8 μg/dL per 1 μg/L milk lead ($p < 0.0001$, $R^2 = 0.3$). Li et al. (2000) also found a significant correlation between lead levels in cord blood and breast milk with those in maternal blood in China.

In a cohort study with 175 children conducted in Mexico, Schnaas et al. (2006) found that lead exposure during the early third trimester of pregnancy can affect child intellectual development, with the strongest effects of lead being on the intelligence quotient (IQ) occurring within the first few micrograms of blood lead levels. IQ tests include a variety of tasks that probe cognitive abilities including memory, verbal and spatial reasoning, planning, learning, and comprehension and use of language (EFSA, 2010). The authors hypothesized that prenatal lead exposure would have a more powerful and lasting impact on child development than postnatal exposure.

Furthermore, a number of cross-sectional and prospective epidemiological studies have related lead blood levels to neurobehavioral effects on infants and children chronically exposed to lead (WHO, 2010a; Miranda et al., 2007; Counter et al., 2008; Roy et al., 2009). Most studies report a 2–4 point IQ deficit for each 10 μg/dL increase in blood lead within the range of 5–35 μg/dL (WHO, 2010a).

Lanphear et al. (2005) examined data collected from 1333 children who participated in seven international population-based longitudinal cohort studies initiated prior to 1995 and who were followed from birth or infancy until 5–10 years of age. There was an inverse correlation between blood lead concentration and IQ scores, and the authors concluded that environmental lead exposure in children who have maximal blood lead levels < 10 μg/dL was associated with intellectual deficits. No threshold for these effects was identified, and the dose-response relationship was steeper at low lead exposure than at higher exposure levels.

Based on the various available studies, the JECFA (2011b) and the EFSA (2010) concluded that the previous PTWI of 25 μg/kg bw/day for lead was associated with a decrease of at least 3 IQ points in children, with no evidence of a threshold for critical lead-induced effects. A $BMDL_1$ of 0.50 μg/kg bw/day was established for neurodevelopmental effects in children (Table 1).

2.3. Mercury

Mercury (Hg) is a metal naturally found in the environment in inorganic, organic and elemental (Hg°) forms. Elemental mercury is used in chlorine gas production and in caustic soda for industrial use, as well as electrical equipment, lamps, thermometers, pressure gauges, barometers, and dental amalgams. Inorganic mercury occurs as salts of its divalent and monovalent cationic forms, mainly chlorine and sulfur (Poulin and Gibb, 2008).

Amalgam fillings are the most important source of exposure to mercury vapor (Hg°) by the general population, and an association between meconium Hg and IHg in the placenta and the number of dental amalgam fillings has been reported (Ask et al., 2002; Gundacker et at., 2010). The major effect from chronic exposure to IHg is kidney damage, and may include morphological changes, renal tubular damage, regeneration of the tubular epithelium, and proximal tubular necrosis (WHO, 2003).

Methylmercury (MeHg) is formed in nature by methylation of inorganic mercury by reducing sulfate aquatic bacteria. The MeHg has a lipophilic property and can be absorbed by plankton, which is eaten by fish and shellfish with greater concentrations occurring at higher trophic levels of the food chain (Polak-Juszczak, 2012; Pouilly et al., 2013). While less than 15% of IHg is absorbed by the gastrointestinal tract, about 95% of MeHg ingested is absorbed, and diffuses to various tissues of the body, including kidney and brain (CDC, 2009). Various studies show that the consumption of fish and other foods of marine origin contributes significantly to mercury levels in human hair, including children and their mothers (Gundacker et al., 2010; Castano et al., 2015).

Ethylmercury (EtHg), an organic mercury compound, is the major component of Thimerosal, a preservative present in various vaccines administered to expecting women and babies, mainly in developing countries. Thimerosal is injected intramuscularly, with approximately 100% absorption (Dorea et al., 2013), and a half-life in blood of 20 days in adults and 7 days in infants, much lower than that for methylmercury (about 70 days; Clarkson et al., 2003). EtHg, as well as MeHg, have been detected in blood samples of babies and neonates immediately after vaccination (Pichichero et al., 2008). Animal

models demonstrate that EtHg is less neurotoxic than MeHg, but more studies are needed to demonstrate whether repeated doses of EtHg in combination with different MeHg background exposures have consequences in fetuses and infants, particularly due to possible additive and synergistic effects (Dorea et al., 2013).

While inorganic mercury is usually free in plasma, MeHg tends to bind to hemoglobin in red blood cells (RBCs), with about 1% bound to glutathione (GSH) (Oliveira et al., 2014). MeHg can enter mammalian cells using a molecular mimicry mechanism. After forming a stable bond with cysteine, the MeHg-Cys complex is transported by the L-type large neutral amino acid transporter (LAT-1), which is important for the high Hg levels found in the brain after exposure (Farina et al., 2011).

The mechanisms involved in the neurotoxicity of MeHg are not completely understood, but Farina et al. (2011) identified three interrelated events that are important for MeHg-induced neurotoxicity: $Ca2+$ dyshomeostasis, glutamate dyshomeostasis, and increased reactive oxygen species (ROS) generation (oxidative stress). *In vivo* studies show that MeHg can alter the expression of genes involved in small GTPase signaling pathways regulating cell growth and proliferation, and can induce mitotic arrest and caspase-dependent apoptosis in developing brains (see review by Antunes dos Santos et al. (2016)). In a cohort study with 138 mother-infant pairs, Cardenas et al. (2015) showed that in utero exposure to mercury can affect leukocyte composition and may disrupt the epigenome even at low levels. Furthermore, exposure to both arsenic and mercury in utero may interact jointly to affect the epigenome by hypermethylating relevant CpG regions (cytosine followed by guanine) having the potential to influence neurodevelopment and other childhood health outcomes.

MeHg crosses the blood brain barrier and the placenta, and may affect the neurological development of fetuses. Mercury concentrations in cord blood correlate well with fetal brain mercury concentrations during the third trimester, indicating methylmercury exposure during late pregnancy (Poulin and Gibb, 2008; WHO, 2010b). Mercury levels are higher in umbilical cord-blood than in the blood of mothers (Stern and Smith, 2003). Oskarsson et al. (1998) reported a higher plasma clearance and a larger distribution volume for methylmercury in lactating mice than in non-lactating mice, probably due to the increased biliary excretion, greater blood/plasma volume and lower plasma protein content during lactation. The milk mercury excretion in mice over 9 days was approximately 4% and 8% of the administered dose of methylmercury and inorganic mercury, respectively.

Sakamoto et al. (2002) showed a lower risk of MeHg exposure by infants during lactation among the high fish-consuming Japanese population. The geometric mean of red blood cells (RBC)-Hg in umbilical cords was about 1.4 times higher than in mothers, with a strong correlation between these two parameters. All the infants showed declines in RBC-Hg during a 3-month breast-feeding period, probably due to the low Hg transfer through breast milk, and the rapid growth of infants after birth. The authors concluded that the risk was especially high during gestation but may decrease during breast-feeding.

Studies to investigate the outcome of prenatal exposure to MeHg and adverse neurological effects on children have reached different conclusions. In a study conducted on Faroe Island (North Atlantic), whose population has a high consumption of pilot whale meat, mothers' exposure to mercury was assessed through mercury concentration in cord blood and hair (Grandjean et al., 1997). Tests applied to 917 children of about 7 years indicated neuropsychological dysfunctions mainly related to language attention and memory, with the association remaining even after the exclusion of children whose mothers' hair mercury concentrations were above 10 μg/g. In general, a delay in development at 6 months was observed in children with higher levels of mercury. On the other hand, a study conducted with 771 mother-child pairs in the Seychelles Islands (Indian Ocean) found no adverse neurodevelopmental outcomes at 66 months of age associated with prenatal or postnatal MeHg exposure and a high fish consumption diet (Davidson et al., 1998). A follow-up study was conducted with this Seychelles population (up to 19 years old) and no correlation was found with effects on the neurological (Myers et al., 2003; Davidson et al., 2011) and auditory functions (Orlando et al., 2014). A cohort study conducted with 492 Italian babies with low levels of mercury (1 μg/g in hair, 0.33 μg/L in breast milk) found that fish consumption and mothers' IQs were significantly associated with neurodevelopment performance of babies at 18 months, but not with mercury exposure (Valent et al., 2013).

In a study conducted in the Amazon region of Brazil, Marques et al. (2014) found higher levels of MeHg in the hair of fishing village children in comparison with those living in the vicinity of tin-ore kilns and smelters who had higher neurodevelopment delays due to high lead exposure, as discussed above. A deficit in neurodevelopment was found in children with higher levels of EtHg in hair. However, another study conducted by the same group evaluating 194 children living near a tin mine in the same region (Marques et al., 2015) found that hair EtHg and maternal consumption of fish were not associated with low neurodevelopment scores.

Based on the available epidemiological studies, including those conducted by Grandjean et al. (1997) and Davidson et al. (1998), the JECFA established a PTWI of 1.6 μg/kg bw for MeHg in child-bearing-aged women due to the possibility of pregnancy and to protect the fetus (JECFA, 2004). In 2010, the JECFA withdrew the previously established PTWI of 5 μg/kg bw for THg, and established a PTWI of 4 μg/kg bw for IHg (JECFA, 2011a).

2.4. Cadmium

The predominant commercial use of cadmium is in the production of batteries, dyes, coatings, plastic stabilizers, and ironless alloys (CDC, 2009). Cadmium in food may originate from contaminated soil which, in turn, may have been contaminated by irrigation water, with deposition originating from air pollution, or from phosphate or manure fertilizer. The highest mean concentrations can be found in edible offal, legumes, cereals and potatoes (0.02–0.13 mg/kg; EFSA, 2009b). Tobacco leaves accumulate high levels of cadmium from the soil, and cigarette smoke is the major source of exposure for smokers (CDC, 2009; ATSDR, 2012). Recent studies have also shown that jewelry and toys can be a source of exposure to cadmium (Guney and Zagury, 2012).

Cadmium is classified by IARC as carcinogenic to humans (Group 1), and causes lung cancer in exposed workers (Table 1), with some evidence of prostate cancer (IARC, 2016). The gastrointestinal tract absorbs 5–10% of ingested cadmium, but several factors may affect absorption, including vitamin D, calcium or iron deficiency, metal-metal interactions with iron, lead and chromium, and metal-protein interactions such as metallothionein and interaction with glutathione (ATSDR, 2012; CDC, 2009). Cadmium absorption may increase with iron deficiency, which may contribute to higher absorption of cadmium by women (CDC, 2009). The placenta may act as a partial barrier to fetal exposure to cadmium, as the concentration in cord blood is about half of that in maternal blood; cadmium levels in human milk are 5–10% of the levels in blood (ATSDR, 2012). Cadmium and lead absorption increases in early childhood and with iron deficiency, given the increase in the number of carriers shared by all 3 metals in the duodenum (Sreedharan and Mehta, 2004). Kippler et al. (2009) found a significant positive association between cadmium concentration in erythrocytes and in breast milk (BM), and a breast milk-plasma ratio of approximately 3–4, indicating no barrier against cadmium

transport from plasma to breast milk. BM-Cd was positively associated with manganese ($r(s)=0.56$; $p<0.01$) and iron ($r(s)=0.55$; $p<0.01$) in breast milk, but not with plasma ferritin. On the other hand, BM-Cd was negatively associated with BM-Ca ($r(s)=-0.17$; $p=0.05$), indicating that cadmium inhibits the transport of calcium to breast milk. The authors concluded that cadmium shares common transporters with iron and manganese for transfer to breast milk, but inhibits secretion of calcium to breast milk.

Absorbed cadmium accumulates mainly in the kidney and liver, with an estimated half-life of 6–38 years, and 4–19 years, respectively, and no direct metabolism is known (ATSDR, 2012). The kidney is the critical target and shows the earliest sign of cadmium toxicity. However, the accumulation of cadmium in the kidney with no apparent toxic effects occurs due to the formation of cadmium-thionein or metallothionein, which is considered non-toxic (ATSDR, 2012). Cadmium can disrupt signaling cascades and lead to a variety of toxic effects, mainly due to its physicochemical similarity with calcium ion (Ca^{2+}), which may disrupt Ca-mediated signaling pathways, possibly through significant changes in the activation of calmodulin and calmodulin-dependent protein kinase II in cell death pathways, such as apoptosis, necrosis or autophagy (Choong et al., 2014).

In 2010, the JECFA withdrew the PTWI for cadmium of 7 μg/kg bw/week set by the Committee in 1988, and established a monthly intake (PTMI) of 25 μg/kg bw due to its long half-life in the body (JECFA, 2011b), corresponding to a weekly intake of 5.8 μg/kg body weight. In 2009, the EFSA recommended a tolerable weekly intake (TWI) of 2.5 μg/kg body weight in order to ensure a high level of protection for all consumers, including exposed and vulnerable subgroups of the population (EFSA, 2009b). This decision was confirmed in 2011 (EFSA, 2012a).

3. Presence of arsenic, lead mercury and cadmium in breast milk

Monitoring breast milk is a non-invasive form of detecting environmental contaminants, having the advantage of allowing the exposure of both the mother and the lactating baby to be assessed at the same time (Hooper and McDonald, 2000; Abballe et al., 2008; CDC, 2010). Two metal analysis techniques are mainly used for different matrices, including milk: atomic absorption spectrometry (AAS) using either flame, cold vapor hydride generator (CVAAS) or electrothermal AAS in graphite furnace (ETAAS), and inductively coupled plasma with mass spectrometry detection (ICP-MS). In most methods, the milk is submitted to microwave acid digestion under controlled temperature and pressure (Kosanovic et al., 2008; Sardans et al., 2010; Amarasiriwardena et al., 2013).

Table 2 summarizes the data for arsenic, lead, mercury and cadmium in breast milk reported by the 75 studies reviewed by this study. Fig. 1 shows the distribution of the studies according to region and metal analyzed. A larger number of studies were conducted in Europe (23), and a lower number in North America (3 studies), with lead the most analyzed metal. In the majority of studies, more than one metal was analyzed in the samples.

The analytical variability and validity of the reported results were not assessed, with the exception of one study conducted in Nigeria (Adesiyan et al., 2011), where the results reported in μg/dL were too high, probably due to a typing or unit error. It is important to be aware that inaccuracies involved in the analytical methods affect the results, particularly at low concentrations (CDC, 2010). Furthermore, positive sample percentages (Table 2) are highly dependent on the limit of detection (LOD) or limit of quantification (LOQ) of the method used, mainly when incidences are low, and may not be comparable. Also, it was not clear in most studies how the samples reported as non-detected or below the LOD/LOQ were treated in estimations of the means. In addition to uncertainty regarding the analytical method, extremely high values found in certain studies may be due to contamination during sample collection and storage, mainly for lead, which is the most abundant toxic metal in the environment.

3.1. Arsenic

For this review, 18 studies published since 2000 that measured levels of arsenic in breast milk were retrieved, six conducted in Asia, six in Europe, and none in Latin America (Table 2). The techniques used to analyze arsenic in milk included CVAAS, ETAAS and ICP-MS, which has the lowest LOD (0.007–0.3 μg/L) (Felip et al., 2014; Miklavcic et al., 2013; Björklund et al., 2012; Fängström et al., 2008; Almeida et al., 2008). Separation of the different arsenic metabolites [As(III), As(V), MA, and DMA] was performed by high performance liquid chromatography coupled to hydride generation and ICP-MS (Fängström et al., 2008).

The highest levels of arsenic in breast milk were found for a district in West Bengal, India (up to 149 μg/L; Samanta et al., 2007), a region with levels of arsenic in water higher than 50 μg/L. Higher levels were found in samples from women who had higher levels of arsenic in urine, hair, and nails. In this population, when breast milk was not sufficient or available, infants drank tube well water as early as the first month after birth, as well as cow/goat milk diluted with water, which increased exposure to arsenic from an early age. The authors found the levels of arsenic in breast milk much lower than in urine (mean of 438 μg/L), which is a much more efficient arsenic excretion route than lactation. Indeed, Fängström et al. (2008) considered the excretion of arsenic through breast milk to be low and concluded that exclusive breastfeeding protects the infant from exposure to arsenic. A similar conclusion was reached by Carignan et al. (2015) in the United States, an area with low levels of arsenic in the water (<1 μg/L). Fängström et al. (2008) also found that arsenic levels in urine were significantly lower in exclusively breastfed children than in those consuming other foods.

Higher mean levels of arsenic were found in colostrum (3.6–14 μg/L; Almeida et al., 2008), decreasing considerably in intermediate and mature milk (Almeida et al., 2008; Islam et al., 2014). Islam et al. (2014) found that arsenic in human milk was weakly correlated with maternal urine levels at 1 and 6 months postpartum ($r=0.13$ and 0.21, respectively; $n=29$ and 25) and did not correlate with infants' urine levels. Fängström et al. (2008) however, found a significant association between the TAs in milk and the levels in the urine of 2–3 month-old babies ($rs=0.64$, $p<0.001$), as well as with arsenic in maternal blood and saliva. Arsenic was essentially present in breast milk as As^{III}, in addition to As^{V}, DMA and MMA, and was the only form present at total arsenic levels ≤ 1 μg/L. The Fängström et al. study was the only one to identify the forms of arsenic present in breast milk, an important piece of information as inorganic arsenic is the only toxicological relevant form of arsenic for humans (IARC, 2016).

3.2. Lead

There are a large number of published studies that have investigated the levels of lead in human breast milk. The first studies date from the early 1980´s and had the objective of collecting data from different countries to establish an environmental background level for metals in human fluids (Iyengar, 1984). A WHO-sponsored multicenter study conducted in several countries on four continents found average concentrations of lead in human milk ranging from 2.0 to 16.8 μg/L, and values between 2 and 5 μg/L were considered a reference for populations not occupationally exposed to lead (WHO, 1989).

Table 2
Levels of arsenic, lead, mercury and cadmium in breast milk reported in studies published since 2000.

Country; Reference	Metal	N	% positive	Mean, median* or geometric mean** (range); μg/L or ng/g	Observation
Asia					
Bangladesh; Fängström et al., 2008	As	79	–	1.8 (0.25–19.0)	Mature milk
Bangladesh; Kippler et al., 2009	Cd	123	–	0.14* (< 0.05–1)	2 months pp
Bangladesh; Islam et al., 2014	As	29	–	1.12 (0.5–8.9)	30 days pp
		25	–	0.78 (0.5–2.32)	180 days pp
		19	–	0.7 (0.5–1.68)	270 days pp
China; Li et al., 2000	Pb	165	–	4.7	Colostrum, non occupational
		12	–	52.7	Colostrum, occupational
China; Li et al., 2014	THg	195	–	0.97 (0.42–8.40)	Colostrum
India; Sharma and Pervez, 2005	As	120	82.5	0.6 ± 0.1 to 5.2 ± 3.8	Mean range of various groups
	Pb		87.5	0.1 ± 0.0 to 22.3 ± 18.5	
	THg		87.5	0.1 ± 0.0 to 16.7 ± 11.1	
	Cd		82.5	0.1 ± 0.1 to 3.8 ± 12.9	
India; Samanta et al., 2007	As	226	17.3	17 (< LOD – 49)	Area with high levels of arsenic in water
		10	50	3.5 (< LOD–5)	Area with levels of arsenic within WHO limits
India; Isaac et al., 2012	Pb	25	84	13.21 ± 5.2 (9.0–21.0)	Non-industrial area
			88	21.5 ± 4.5 (15–25.5)	Industrial area
Japan; Honda et al., 2003	Cd	68		0.28 ± 1.82** (0.28–1.22)	5 – 8 days pp
Japan; Sakamoto et al., 2012	As	9	–	1.4 (0.4–1.8)	3 months pp
	Pb			0.29 (0.18–0.20)	
	THg			0.47 (0.28–0.77)	
	Cd			0.14 (0.06–0.22)	
Japan; Iwai-Shimada et al., 2015	THg	27	–	0.81 (0.14–1.87)	30 days pp
	MeHg		–	0.45 (0.06–1.2)	
Korea; Lit et al., 2014	THg	195	–	0.97* (0.42–8.40)	
Thailand; Chao et al., 2014	As	45	–	1.50 ± 1.50	1–4 days pp
				0.68 ± 1.09	5–10 days pp
				0.27 ± 1.26	30–35 days pp
				0.16 ± 0.24	60–65 days pp
	Pb	45	–	13.2 ± 3.6 (6.7–22.4)	1–4 days pp
			–	8.92 ± 2.60 (3.52–14.7)	5 to10 days pp
			–	11.7 ± 2.58 (0.76–11.7)	30–35 days pp
			–	2.93 ± 1.70 (0.45–7.8)	60–65 days pp
	Cd	45	–	1.37 ± 0.94	1–4 days pp
			–	0.65 ± 0.36	5–10 days pp
			–	0.49 ± 0.25	30–35 days pp
			–	0.34 ± 0.19	60–65 days pp
Taiwan; Chien et al., 2006a	Pb	35	–	8.59 ± 10.9	Chinese herb mothers (9)
				9.94/2.34	Colostrum/mature
		37	–	6.84 ± 2.68	Non consumers (7)
Taiwan; Chien et al., 2006b	THg	56	100	2.02 (0.24–9.45)	Colostrum – urban population
		12	100	2.04 (0.26–8.62)	Colostrum – fishing villages
Europe					
Finland; Kantola and Vartiainen, 2001	Cd	165	–	0.095 ± 0.12	Samples collected in 1987
		74	–	0.040 ± 0.06	1993–1995 samples
Austria; Gundacker et al., 2002	Pb	116		1.63 ± 1.66	6.6 ± 6 days pp
	THg	116		1.59 ± 1.2	
Austria; Gundacker et al., 2010	THg	21	62	0.2 (0.1–2)	2–8 weeks pp
				100% inorganic	
Croatia, Slovenia, Greece, Italy; Miklavcic et al., 2013	As	123	–	0.2 (0.4–11.9)	Croatian
		287	–	0.04 (0.04–2.9)	Slovenes
		30	–	0.8 (0.3–4.8)	Greek
		602	–	0.3 (0.04–12)	Italians
	THg	125	–	0.2	Croatian
		284	–	0.2	Slovenes
		44	–	0.6	Greek
		605	–	0.2	Italians
	MeHg	26	100	56% of the mean THg	Croatian
		7	100	47% of the mean THg	Slovenes
		21	100	7% of the mean THg	Greek
		224	100	60% of the mean THg	Italians
Cyprus; Kunter et al., 2016	As	50	–	0.73 ± 0.58 (0.03–1.97)	
	Pb		–	1.19 ± 1.53 (0–4.9)	
	THg			0–0.01	
	Cd			0.45 ± 0.23 (0.12–0.08)	
Germany; Sternowsky et al., 2002	As	187	17.6	0.15* (< 0.3–2.8)	2–90 days pp
					From 36 mothers
Greece; Leotsinidis et al., 2005	Pb	180	58,5	0.48 ± 0.60 (< 0.2–2.36)	Colostrum
		95	63.6	0.15 ± 0.25 (< 0.2–0.94)	Intermediate milk
	Cd	180	89	0.19 ± 0.15 (< 0.01–0.70)	Colostrum
		95	91.9	0.14 ± 0.12 (< 0.01–0.49)	Intermediate milk
Italy; Abballe et al., 2008	THg	29	–	2.6–3.0	Venice

Table 2 (*continued*)

Country; Reference	Metal	N	% positive	Mean, median* or geometric mean** (range); μg/L or ng/g	Observation
		10	–	3.53	Rome
	Pb	29	–	0.97–1.1	Venice
		10	–	0.85	Rome
	Cd	39		< 0.5	Venice and Rome
Italy; Valent et al., 2013	THg	492	–	0.33 (0–28.3)	Mature milk
	MeHg	182	–	0.17 (0.01–1.09)	
Italy; Felip et al., 2014	As	63	0	< 3	Samples were mixed in 7 pools, according to the region
	Pb		100	2.59–5.99	
	THg		0	< 0.3	
	Cd		0	< 0.1	
Poland; Winiarska-Mieczan, 2014	Pb	320	–	6.33 ± 4.61 (0.49–12.0)	All milk types
	Cd	320	–	2.1 (0.21–7.4)	
Poland; Olszowski et al., 2016	Cd	51	–	0.11 ± 0.07 (0.01–0.33)	
Portugal; Almeida et al., 2008	As	34	–	7.8 ± 2.2 (3.6–14.0)	Colostrum
	Pb	34	–	1.55 ± 1.38 (0.06–5.43)	Colostrum
	As	19	–	5.8 ± 1.1 (4.2–7.8)	Intermediate milk
	Pb	19	–	0.94 ± 1.05 (0.07–4.03)	Intermediate milk
Spain; Garcia-Esquinas et al., 2011	Pb	100	93	15.56 (12.92–18.72)	Mature milk
	THg	100	98	0.53 (0.45–0.62)	Mature milk
	Cd	100	96	1.31 (1.15–1.48)	Mature milk
Sweden; Bjornberg et al., 2005	THg	19	–	0.29* (0.06–2.1)	Colostrum
		20	–	0.14* (0.07–0.37)	6 weeks
		19	–	0.2* (0.06–0.4)	13 weeks
Sweden; Björklund et al., 2012	As	60	–	0.55 ± 0.70 (0.04–4.6)	Mature milk
	Pb	60	–	1.5 ± 0.9 (0.74–6.40)	Mature milk
	Cd	60	–	0.09 ± 0.04 (0.02–0.27)	Mature milk
Turkey; Turan et al., 2001	Pb	30	100	14.6 ± 5.5 (8.8–35.4)	Colostrum
	Cd		100	1.7 ± 1.7 (1.2–9)	
Turkey; Yalçin et al., 2010	THg	44	–	3.42 ± 1.66 (0.35–6.9)	All milk types
Turkey; Örün et al., 2011	Pb	144	95	20.6 (< LOQ–1515.0)	2 months pp
	Cd	144	60	0.67 (< LOQ–43.0)	
Turkey; Örün et al., 2012	THg	144	18	25.8 ± 44.6 (1.7–236) positive samples	Mature milk
Turkey; Gürbay et al., 2012	As	64	0	< 7.6	2–5 days pp
	Pb	64	93.8	391 ± 269 (4.35–1020)	
	Cd	64	1.6	4.62 (< 0.34–4.62)	
Slovakia; Ursinyova and Masanova, 2005	Pb	158	–	4.7 (nd – 24.4)	4 days pp
	Cd		–	0.43 (nd – 1.7)	
	THg		–	0.94 (nd – 4.74)	
Latin American					
Brazil; Boishio and Henshel, 2000	THg	44		5.7 ± 5.9 (nd – 24.8)	Amazonian riverines
Brazil; Anastácio et al., 2004	Pb	38	–	2.8 ± 2.5	Mature milk
Brazil; Costa et al., 2005	THg	23	86.9	5.73 ± 5.43	Federal District
Brazil; Koyashiki et al., 2010	Pb	92	–	2.9 ± 1.1 (1.0–8.0)	Mature milk
Brazil; Gonçalves et al., 2010	Cd	80	100	2.3 (0.02–28.1)	Colostrum
Brazil; Andrade et al., 2013	Pb	70	–	1.46 ± 1.28 (0.01–4.82)	Up to 6 months pp
Brazil; Cunha et al., 2013	THg	142	93.7	6.7 ± 6.45 (< 0.76–22.7)	Federal District, 15–90 days pp; 18 mothers
Brazil; Marques et al., 2013	Pb	37	–	12.6 ± 8.16 (0.9–29.4)	Close to a tin mine; 15 days up to 12 pp
		45	–	4.30 ± 4.01 (0–16.2)	Fishing village; 1–24 pp
Brazil; Vieira et al., 2013	THg	82	–	0.36 (0.09–3.74)	Amazonian urbans
	MeHg	45	–	0.12 (0.01–0.47)	
	THg	75	–	2.3 (0.12–6.48)	Amazonian riverines
	MeHg	46	–	0.87 (0.11–3.40)	
Brazil; Cardoso et al., 2014	Pb	58	–	0.260 (< 0.05–0.69)	Minas Gerais
	THg		–	< 0.200 (< 0.20–6.11)	
	Cd		–	0.770 (< 0.05–6.57)	
Brazil; Marques et al., 2014	Pb	51	–	8.2 (0.9–29.4)	Amazonian tin ore smelters and kilns
		45	–	2.5 (0.7–16.2)	Amazonian fishing village
Brazil; Santos et al., 2015	THg	15	100	59.41 (4.56–104.1)	Amazonian riverine
Ecuador; Counter et al., 2004	Pb	90	–	4.6 (0.4–20.5)	Women occupationally exposed
Ecuador; Counter et al., 2014	Pb	22	–	3.73 ± 7.3 (0.049–28.4)	Women occupationally exposed
México; Amarasiriwardena et al., 2013	Pb	200	–	(0.2–6.7)	Mature milk
Mexico; Ettinger et al., 2004, 2006	Pb	310		1.4 ± 1.1 (0.2–8.0)	1 month pp
		224		1.2 ± 1.0 (0.2–6.8)	4 month pp
		195		0.9 ± 0.8 (0.2–4.8)	7 month pp
Mexico; Gaxiola-Robles et al., 2013, 2014	THg	108	80.6	2.52 (0.03–24.9)	
		36	80.6	1.96 ± 2.01	1st gestation
		36	88.9	2.61 ± 4.32	2nd gestation
		36	88.9	3.00 ± 3.23	3rd gestation
Mexico; Gaxiola-Robles et al., 2014	As	108	24	0.01*(0.01–13.8)	7 days pp
Mexico; Ettinger et al., 2014	Pb	81	–	0.8 ± 0.7 (0.6–39.8)	Mature milk
Middle east					
Iran; Rahimi et al., 2009	Pb	44		10.4 ± 9.7 (3.2 – 24.7)	Industrial area

Table 2 (*continued*)

Country; Reference	Metal	N	% positive	Mean, median* or geometric mean** (range); μg/L or ng/g	Observation
	Cd	44		2.4 ± 1.5 (0.62 – 6.3)	
Iran Behrooz et al., 2012	THg	34		0.12 ± 0.06 (nd–1.73)	Industrial area
		18		0.15 ± 0.22 (nd–1.21)	Coast area
		28		0.86 ± 0.26 (0.02–5.86)	Industrial and agricultural area
Iran; Goudarzi et al., 2013	Pb	37	–	7.11 ± 3.96 (3.06–19.5)	First 6 weeks pp
	THg	37	–	0.92 ± 0.54 (0.0–2.7)	
	Cd	37	–	1.92 ± 1.04 (0.45–5.87)	
Iran; Okati et al., 2013	THg	82	–	0.43 (0.0–2,45)	Under 6 months of lactation
Saudi Arabia; Al-Saleh et al., 2003	Pb	168	94,8	25.1 ± 38.8 (< 1.2–355)	Urban area
		194		37.3 ± 50.3 (< 1.2–490)	Agricultural area
	THg	168	87	4.15 ± 5.05 (< 0,2–47.2)	Urban area
		194		2.19 ± 2.61 (< 0.2–25.62)	Agricultural area
	Cd	150	95.1	1.18 ± 1.14 (< 0.123–11.7)	Urban area
		194		2.16 ± 19 (< 0.123–9.2)	Agricultural area
Saudi Arabia; Al-Saleh et al., 2013; 2015	THg	331	97.3	0.97 ± 0.665 (0.18–6.44)	3 – 12 months pp
United Arab Emirates; Abdulrazzaq et al., 2008	As	205	–	0.89 ± 0.078 (0.001–0.283)	From 38 mothers.
	Pb	205	–	0.019 ± 0.055 (0–0.55)	3 months pp
	THg	205	–	0.008 ± 0.025 (0–0.023)	
	Cd	205	–	0.003 ± 0.008 (0–0.115)	
United Arab Emirates; Kosanovic et al., 2008	As	120	–	0.196+0.032 (0.02–0.65)	–
	Pb	120	–	1.51+0.32 (0.025–2.41)	
	THg	120	–	0.115+0.05 (0.04–0.18)	
	Cd	120	–	0.27+0.04 (0.023–1.19)	
Palestine; Shawahna et al., 2016	Pb	89	100	4.0* (2–12)	15–210 days pp
North America					
Canada; Hanning et al., 2003	Pb	25	–	2.1 ± 1.7	Mature milk
United States; Sowers et al., 2002	Pb	15	–	6.1 ± 1.0	45 days pp
		15	–	5.6 ± 1.1	3 months pp
		15	–	5.9 ± 1.0	6 months pp
		15	–	4.3 ± 1.6	12 months pp
United States; Carignan et al., 2015	As	9	55.6	0.31* (< 0.22–0.62)	1.7–7 months pp
Other regions					
Indonesia, Tanzania and Zimbabwe; Bose-O'Reilly et al., 2008	THg	46	71.7	1.87 (< 1–149)	Mining area (occupational and non-occupational)
Ghana; Bentum et al., 2010	As	20	60	1.54 ± 1.94 (nd–6.22)	–
	Pb	20	40	4.8 ± 9.0 (nd–32.0)	–
	Cd	20	40	1.3 ± 2.9 (nd–12.3)	–
Nigeria; Adesiyan et al., 2011	Pb	180	–	83.1–87.1	Values reported as μg/dL[a]
	Cd	180	–	94.8–97.8	
Egypt; Moussa, 2011	Pb	30	–	1.7 ± .085 (0.26–3.33)	Nasr city
			–	5.92 ± .296 (4.2–7.74)	Helwan
			–	5.11 ± .25 (3.41–6.88)	El Khanka
	Cd	30	–	0.638 ± 0.032 (0.485–0.865)	Nasr city
			–	1.84 ± 0.092 (1.02–2.54)	Helwan
			–	2.56 ± 0.12 (1.25–3.86)	El Khanka
Australia; Gulson et al., 2001	Pb	72		0.55** 0.09–3.1)	First 6 months pp; samples from 9 mothers
Faroe Island; Needham et al., 2011	Pb	15	–	8.5*	–
	THg	15	–	2.31*	
	Cd	15	–	0.25*	

pp: postpartum; nd: non detected.

[a] Most likely the unit is not correct.
* is either mean or median
** is geometric mean

In the present review, we were able to retrieve 43 studies that analyzed lead in breast milk samples collected in different regions of the world, most of which also included analyses of the other metals (Table 2). The number of samples analyzed in these studies varied from less than 50 in Italy (Abballe et al., 2008) to over 300 in Mexico (Ettinger et al., 2006) and Saudi Arabia (Al-Saleh et al., 2003, 2015). In most studies, lead was analyzed by ETAAS, with a wide range of reported LODs (0.04–3.4 μg/L) (Marques et al., 2014', 2013; Winiarska-Meiczan, 2014; Goudarzi et al., 2013; Chao et al., 2014; Gürbay et al., 2012; Garcia-Esquinas et al., 2011; Abballe et al., 2008; Chien et al., 2006a; Leotsinidis et al., 2005; Ursinyova and Masanova, 2005; Al-Saleh et al., 2003). The study with the lowest LOD (0.01 μg/L) used isotopic dilution ICP-MS (Ettinger et al., 2014), while the other ICP-MS LODs ranged from 0.03 to 3 μg/L (Cardoso et al., 2014; Felip et al., 2014; Amarasiriwardena et al., 2013; Björklund et al., 2012; Örün et al., 2011; Almeida et al., 2008; Koyashiki et al., 2010; Sowers et al., 2002). The highest mean lead levels were found in Turkish milk colostrum samples (391 μg/L from Gürbay et al. (2012); Table 2).

Lead levels in colostrum are usually higher than in mature milk due to their greater protein content (Rothenberg et al., 2000). Chien et al. (2006b) found a significant decline in lead levels during lactation among Taiwanese mothers, with the mean of 9.9 μg/L in colostrum dropping to 2.3 μg/L in mature milk at 2 months postpartum (Table 2), with an estimated lead half-life of 33–35 days. Another study from the same research group found that milk from mothers who consumed traditional Chinese herbs, which can contain over 300 μg/g of lead, had significantly higher

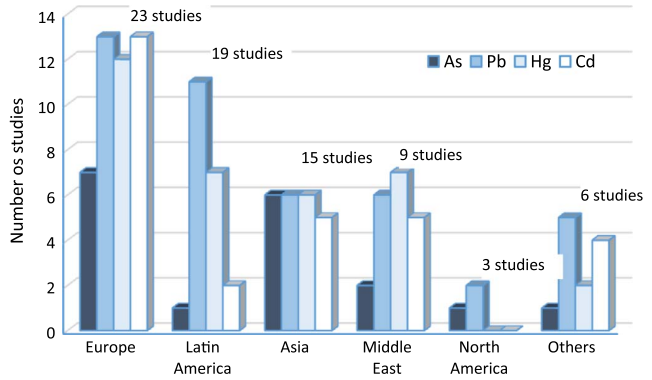

Fig. 1. Summary of the number of studies that analyzed arsenic, lead, mercury and cadmium published since the year 2000, according to the region. Others include Indonesia, Tanzania and African countries, Australia and Faroe Island. Most of the studies analyzed more than one metal. Literature search on Pubmed, Science Direct and Google Scholar databases (last on June 2016) using the keywords "human milk", "breast milk" and "breast milk", associated with "metal", "arsenic", "lead", "mercury" or "cadmium". Additional papers were identified in published reviews related to contaminants in breast milk.

levels of lead than milk from non-consumers (Chien et al., 2006a). Ettinger et al. (2006) also found a significant decrease in breast milk lead levels 1–7 months postpartum in Mexico (Table 2).

Örün et al. (2011) reported a 2-month postpartum sample in Ankara that contained 1515 μg/L, but no individual or environmental factor was identified that could justify such a high level (mean level was 20.6 μg/L). A significant correlation was found between mothers with a history of anemia, and the higher level of lead in breast milk. Another study, conducted ten years earlier in the same city, found a much lower level in colostrum (14.6 μg/L; Turan et al., 2001), but higher than that found in Greece (0.48 μg/L; Leotsinidis et al., 2005 (Table 2)). In a study conducted in Saudi Arabia, Al-Saleh et al. (2003) found a significant correlation between lead levels in breast milk (n=362) with average duration of lactation for all births and fish consumption (lower consumers had higher levels). The milk of mothers living in agricultural areas had higher lead levels than those in urban regions, although the difference was not significant.

In nature, lead occurs mostly in ore deposits along with other minerals, particularly zinc, accounting for about 20% of total primary lead supplies. Mining, smelting and refining of lead are known to cause contamination of the surrounding environment (ATSDR, 2007a), and to impact levels of the metal in the human body. In fact, two studies conducted in the north of Brazil showed significantly higher lead levels in milk from women living near a tin smelter compared with those living in a fishing village (Marques et al., 2013, 2014; Table 2). Marques et al. (2014) also found higher Pb levels in breast milk associated with longer residence periods in a contaminated region, and a significant association of higher levels with neurodevelopmental delays in 24-month old children living near tin ore smelters. Isaac et al. (2012) found higher lead mean levels in breast milk of women living in industrial areas of Southern India (21.5 μg/L) compared with those in non-industrial areas (13.2 μg/L), showing the impact of environmental contamination of lead by industrial activity. In China, mean level of lead in colostrum from occupationally exposed women were about 15 times higher than the mean for non-exposed women (4.7 and 52.7 μg/L, respectively; Li et al., 2000; Table 2).

3.3. Mercury

A total of 34 studies published since 2000 that analyzed mercury in breast milk (THg) were retrieved for this review, five of which also analyzed MeHg and/or IHg (Table 2). The most widely used technique to analyze THg was CVAAS, with limit of detection ranging from 0.06 to 5 μg/L (Boishio and Henschel, 2000; Al-Saleh et al., 2003; Costa et al., 2005; Bose O'Reilly et al., 2008; Abballe et al., 2008; Gundacker et al., 2010; Vieira et al., 2013; Valent et al., 2013; Iwai-Shimada et al., 2015). MeHg was analyzed by gas chromatography coupled with electron capture detector (Miklavcic et al., 2013; Valent et al., 2013; Iwai-Shimada et al., 2015) or MERX™, which uses atomic fluorescence spectrophotometry (Vieira et al., 2013).

Seven studies were conducted in Latin America, six of which in Brazil, mostly in the Amazon region, where THg in breast milk reached 104 μg/L (mean of 59.4 μg/L; Santos et al., 2015). Overall, breast milk samples from high fish consumers in the Amazon (riverine community) had higher mercury levels compared to an urban population in the same region. Vieira et al. (2013) found this difference significant for both THg (2.3 and 0.36 μg/L, respectively) and MeHg (0.87 and 0.12 μg/L). Among urban mothers with low fish consumption (and with relatively higher dental amalgam fillings), the proportion of IHg in milk was higher (85%) than for riverine communities (62%). In another study conducted earlier in the same region, these levels were about 6 μg/L (Boishio and Henshel, 2000), similar to those found in two studies conducted in the Federal District (DF) of Brazil (Costa et al., 2005; Cunha et al., 2013), located in the Midwest region of the country and with a low fish consuming population. Cunha et al. (2013) found no significant correlation between fish consumption and THg levels, although a significant increase was found after the mothers had eaten a meal with salmon (day 75 postpartum). Although the levels of THg found in one Amazonian study and those found in the DF study were similar, most of the mercury present in the DF milk was most likely present as IHg, while in the Amazon the MeHg found was the predominant form, reflecting the high fish consumption in this region. Much lower THg levels were found by Cardoso et al. (2014) among mothers living in the Brazilian state of Minas Gerais (mean <0.2 μg/L), also a low fish consuming region. Costa et al. (2005) also found that THg levels in breast milk in the Federal District correlated well with the number of amalgam fillings of the mothers.

In a study also conducted with a Mediterranean population (Miklavcic et al., 2013), the levels of THg in breast milk were similar in Croatia, Slovenia and Italy (0.2 ng/g; Table 2). Although Slovenian women consumed the least amount of fish (mean consumption of 25 g/day), they had the highest number of amalgam fillings, which may have contributed to the total excreted mercury. The levels in Greece (39 g fish/day) were 3 times higher than in the other countries (0.6 ng/g), but only 7% was present as MeHg, although this percentage ranged from 47 to 60% in the other countries (Table 2). These results were unexpected as fish consumption is the main external source of MeHg.

An extensive study conducted by Valent et al. (2013) confirmed that in Italy (2.3 servings of fish/week) most of the mercury in breast milk was present as MeHg (mean of 58%). This percentage was similar to the one found in Japan (Iwai-Shimada et al., 2015), a high fish-consuming population (about 71 g/day, in average), with higher mercury concentrations detected in breast milk (mean of 0.81 μg/L). These authors found a correlation between THg or MeHg in breast milk and fish consumption only when the levels were adjusted for the milk lipid content.

Cunha et al. (2013) found no significant changes in the THg levels 15–90 days postpartum, all mature milk samples. In Sweden, Bjornberg et al. (2005) found a significant decrease in THg between day 4 (colostrum) and 6 weeks after delivery (median of 0.29 and 0.14 μg/L, respectively), remaining unchanged thereafter (Table 2). At 13 weeks, THg in breast milk was significantly associated with IHg in maternal blood ($r_S=0.61$; $p=0.006$) and MeHg in infant blood ($r_S=0.55$; $p=0.01$). The authors concluded that exposure to mercury was higher before birth than during

breastfeeding, and that MeHg seems to contribute more than IHg to postnatal infant exposure via breast milk.

Gundacker et al. (2002) found greater THg levels in the breast milk of Austrian mothers under 60 kg and in those who had premature infants. Similar to what was reported by Cunha et al. (2013), frequent consumption of cereals correlated well with higher mercury levels. In a later study, Gundacker et al. (2010) found that all mercury detected in breast milk from Austrian mothers was in inorganic form (Table 2).

In Mexico, Gaxiola-Robles et al. (2013) found a significant correlation between breast milk THg (80.8% of positive samples; mean levels of 2–3 μg/L), fish consumption and exposure to tobacco (active and passive smokers). These correlations were not confirmed in studies conducted in Turkey with a population with lower incidence of positive sample (18–44%) but higher levels of THg (mean of 3.4 and 20.6 μg/L; Yalçin et al., 2010; Örün et al., 2012).

3.4. Cadmium

Twenty nine studies published since 2000 that analyzed cadmium in breast milk were found in the databases, ten conducted in Europe and none in North America (Table 2). Cadmium was predominantly analyzed by ETAAS, with LODs ranging from 0.01 to 0.5 μg/L (Winiarska-Mieczan, 2014; Goudarzi et al., 2013; Chao et al., 2013; Gürbay et al., 2012; Garcia-Esquinas et al., 2011; Aballe et al., 2008; Leotsinidis et al., 2005; Ursinyova and Masanova, 2005; Al-Saleh et al., 2003) or by ICP-MS, with LODs in the range of 0.0027–0.3 μg/L (Cardoso et al., 2014; Felip et al., 2014; Björklund et al., 2012; Örün et al., 2011).

In most studies, mean levels were below 2 μg/L, with the maximum mean and highest levels found for Turkey (4.6 and 43 μg/L; Gürbay et al. (2012), Örün et al. (2011) and Table 2). In Brazil, Gonçalves et al. (2010) found a significant correlation between cadmium levels in colostrum and the consumption of rice, carrots and chayote, while Cardoso et al. (2014) found correlations between cadmium concentration profiles in mature breast milk (0.77 μg/L), soil (4.50 mg/kg) and water (12.5 μg/L).

Cadmium levels in breast milk decreased over the postpartum period (Chao et al., 2013; Leotsinidis et al., 2005), being higher among smoking women (Rahimi et al., 2009), as expected, and housewives, probably due to exposure to dust particles during housekeeping activities (Örün et al., 2011). Honda et al. (2003) found that cadmium in breast milk was significantly correlated with urinary concentration, reflecting mothers' body burden, and inversely correlated with calcium concentration in breast milk, an indication that it affects calcium secretion in this body fluid.

4. Risk assessment of infants to arsenic, lead, mercury and cadmium through breast milk

The process of assessing risk to a chemical may be divided into four steps: 1. hazard identification; 2. hazard characterization; 3. exposure assessment and; 4. risk characterization. The outcome of the first two steps indicates the most critical adverse effects and establishes the health-based guidance values, respectively. They are mostly based on laboratory animal data, but may also include human epidemiological studies, especially for metals. For mercury and cadmium, which have a threshold dose (no-observed-adverse-effect level, NOAEL), values may be expressed as PTWI (JECFA, 2011a, 2011b), tolerable weekly intake (TWI; EFSA, 2009a), reference dose (RfD; Rice, 2004) or minimal risk level (MRL; ATSDR, 2016). As discussed above, the previous PTWI for arsenic and lead were found not to be protective of human health (no-threshold dose), and BMDLs were established for different toxicological endpoints for these metals (Table 1).

In the exposure assessment step, the concentration of a substance (mean, median or other value) is multiplied by the consumption of the food in question (generally the mean consumption), and the product is then divided by the body weight of a given population (IPCS, 2009). When the chronic exposure involves more than one food, the total intake is the summation of the intakes of each food.

$$\text{Intake} = \frac{\text{consumption } X \text{ concentration}}{\text{body weight}}$$

In the risk characterization step for cadmium and mercury, a conclusion regarding a potential risk to human health may be reached by comparing the estimated intake with the health-based guidance value, and expressing it as either a percentage or a hazard index (HI). Risk may exist when the percentage is higher than 100 or if the HI is greater than 1. For arsenic and lead, risk characterization may be performed by estimating the margin of exposure (MOE), which is defined as a reference point derived from the dose response relationship, such as a BMDL, divided by the estimated human intake. A MOE should be as high as possible so as not to represent a public health concern (EFSA, 2005). It is important to emphasize, however, that the MOE is not a quantification of risk for a chemical, but gives an indication of the level of concern (Benford, 2016).

The uncertainties of the risk assessment depend on the quality of the data used in each step of the process (IPCS, 2009). Uncertainties regarding the PTWI, RfD or BMDL arise from the toxicological database and the dose-response models used in the estimations (Rice, 2004). Uncertainties in exposure assessments normally regard food consumption, body weight, and the concentration data used (whether the sample is representative of the population, the number of samples analyzed, the analytical method used, and how the non-detected samples are considered in the estimation of the mean).

Some of the studies shown in Table 2 also estimated exposure and assessed the risk of infants to arsenic, lead, mercury and/or cadmium through breastfeeding. In order to investigate a wider exposure scenario, when this information was not available, intakes were also estimated using the incidence data provided in some studies, with a milk consumption of 750 mL and a body weight of 5.5 kg, as given by da Costa et al. (2010) for a 2–3 month infant. The objective was to estimate a range of exposure levels for each metal in the various regions (low to highest exposure levels). Fig. 2 summarizes the mean/median intakes of arsenic, cadmium, lead and mercury by one- to six-month infants from different regions estimated from the studies. Details of the studies are discussed below. All intakes were expressed in μg/kg/week to facilitate comparison between metals. Additionally, exposure assessments for arsenic, lead and/or mercury conducted by the EFSA for the European population and by the Committee on Toxicity of the UK Food Standards Agency (COT) are also discussed.

In the context of this review, risk characterization was conducted when not available in the studies. Fig. 2 also indicates the toxicological parameters used in the risk characterization process – PTWI for MeHg and cadmium and BMDL for arsenic and lead.

4.1. Arsenic

In breast milk, arsenic is present essentially as IAs (Fängström et al., 2008), and the levels shown in Table 2 for total arsenic were assumed to correspond to IAs levels for risk assessment purposes. Only two of the studies estimated arsenic exposure from breastfeeding.

Carignan et al. (2015) estimated a median exposure of 0.04 μg/kg/day (5.6 kg bw; 810 mL of milk/day) for 1- to 3- month American infants (0.28 μg/kg/week), much lower than that estimated for

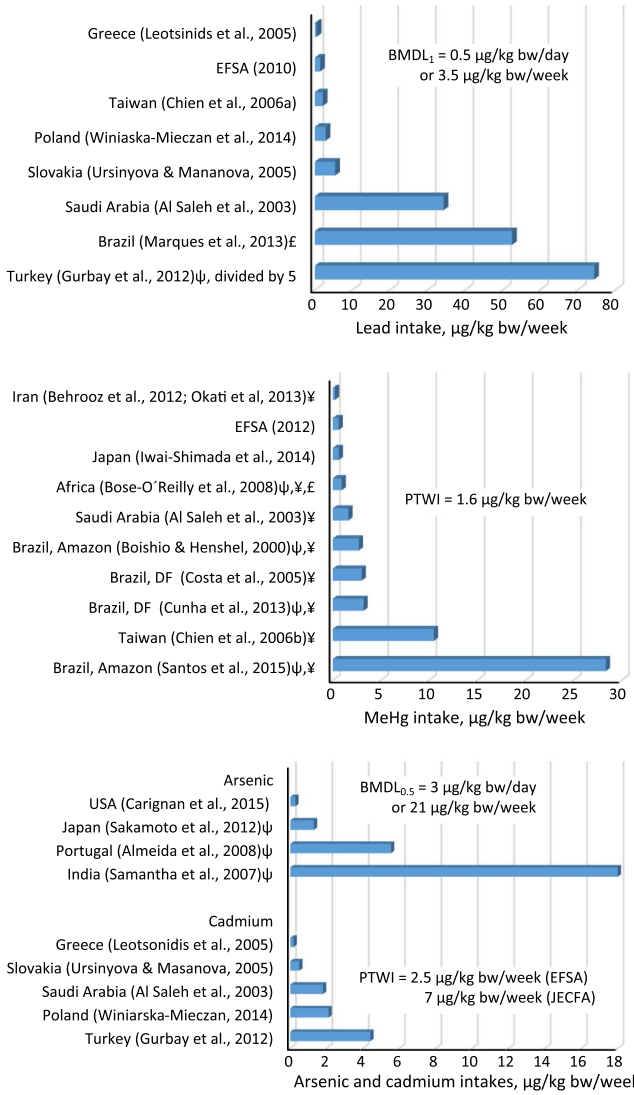

Fig. 2. Mean intakes of lead, mercury, arsenic and cadmium by 1–6 months infants through breast milk; ψ estimated from the concentration data provided (Table 2), assuming 750 mL daily consumption and 5.5 kg bw baby; ¥. calculated assuming that 50% of THg is present as MeHg; £. population living near mining areas. EFSA: European Food Safety Authority; JECFA: FAO/WHO Joint Expert Committee on Food Additives.

infants fed with formula (0.22 µg/kg/day), even when the water used to prepare the formula contained arsenic below 1 µg/L. The EFSA estimated a mean IAs intake of 0.04 µg/kg bw/day for 3-month European infants (6.1 kg, 800 mL milk; EFSA, 2014). Exposure reached 2 µg/kg bw/day for toddlers, the most critically exposed population to arsenic through the diet in Europe, mainly from the consumption of milk and dairy products. A lower median arsenic intake (0.02 µg/kg bw/day, or 0.14 µg/kg bw/week) was estimated by Sternowsky et al. (2002) for 3-month German infants (6 kg; 790 mL/day). The authors considered the exposure to be safe, as it was much lower than the PTWI of 15 µg/kg bw/week. Our estimation of arsenic mean intake from the consumption of intermediate milk of Portuguese mothers (Almeida et al., 2008; Table 2) yielded a much higher value (5.5 µg/kg bw/week). Using the approach currently employed to characterize the risk of exposure to arsenic and a $BMDL_{0.5}$ of 3 µg/kg bw/day (or 21 µg/kg bw/week), a median MOE of 75 was calculated for the American breastfed infants, and could reach 3.8 for Portuguese babies (mean).

The COT reported that arsenic was above the limit of quantitation in 7% of 91 breast milk samples from the UK analyzed in the SUREmilk pilot studies, with a maximum concentration of 4.0 µg/kg (COT, 2004). The maximum estimated intakes ranged from 0.64 µg/kg bw/day for infants under 2 months to 0.15 µg/kg bw/day at 8–10 months. Mean intakes were not reported. The Committee acknowledged that there were no appropriate safety guidelines for arsenic, and concluded that exposure to inorganic arsenic should be As Low As Reasonably Practicable (Achievable), which is known as the ALARP (ALARA) principle, applicable to compounds with no identified threshold of effect. A maximum MOE of 4.7 could be estimated for UK infants under 2 months.

The highest mean level of arsenic reported in the studies in Table 2 was found in India (19 µg/L; Samanta et al., 2007). Using this level, and a milk consumption of 750 mL for a 5.5 kg 2–3 month baby, we estimated an arsenic intake of 2.6 µg/kg bw/day (or 18.2 µg/kg/week), much higher than that reported in Europe and the USA, and a MOE of 1.2. As pointed out before, this high exposure level reflects the high arsenic levels found in the water sources in the region, although the estimated intake based on concentration levels found in Bangladesh (Table 1), also a region with high arsenic levels in water, was much lower (up to 1.7 µg/kg bw/week). The estimated mean intake from limited data in Japan (9 milk samples; Table 1) was 1.3 µg/kg/week.

The EFSA (2005) considered that a MOE of 10,000 or higher for genotoxic compounds, if based on the $BMDL_{10}$ from an animal study, would be of low concern from a public health point of view and might be considered as a low priority for risk management actions. This level allows for 100-fold for specie differences (10-fold) and human variability (10-fold), and an additional 100-fold for additional uncertainties (inter-individual human variability in cell cycle control and DNA repair, and effects that can occur below the reference point). In its evaluation of arsenic, the EFSA (2014) did not estimate a MOE nor did it discuss a level above which the exposure would be considered of low health concern. In this review, an attempt was made to estimate this level taking two points into consideration: 1) the additional carcinogenic risk in the $BMDL_{10}$ related to a MOE of 10,000 (10%) is 20 times higher than the extra risk in the $BMDL_{0.5}$ established for arsenic (0.5%), and 2) the $BMDL_{0.5}$ was based on human studies, so uncertainty due to specie differences (10-fold) can be disregarded. A MOE value that may be used in the risk characterization of arsenic exposure would be 10,000 ÷ 20 ÷ 10, or 50. Therefore, a MOE of 50 or higher for arsenic, based on the $BMDL_{0.5}$ from a human study, would be of low concern from a public health point of view.

In this paper, the estimated MOEs, based on mean or median intakes of breast milk by 2-3 months infants, were above 50 for American infants, as well was for exposures lower than 0.06 µg/kg bw/day, which correspond to a consumption of 750 mL breast milk (5.5 kg infant) containing less than 0.44 µg/L of arsenic (Table 2). Higher arsenic levels, which would lead to MOE lower than 50, were found in breast milk samples from all Asian countries, in some European countries (Greece, Portugal and Sweden), in the United Arab Emirates, and in Ghana (Table 2). Fig. 2 shows the arsenic intakes for 1–6 month infants through breast milk estimated for USA, Japan, Portugal and India (from 0.28 to 18.2 in µg/kg bw/week).

4.2. Lead

Nine studies shown in Table 2 included exposure assessments of breastfed infants to lead. None of the studies used the MOE to characterize risk which, in the context of this paper, was done using a $BMDL_1$ of 0.5 µg/kg bw/day (EFSA, 2010; 3.5 µg/kg bw/week). Al Saleh et al. (2003) estimated a mean intake of 34.3 µg/kg bw/week by infants in Saudi Arabia (850 mL, 5–6 kg bw), and reported that 46.7% of the infants had weekly lead intake levels

exceeding the PTWI of 25 μg/kg bw/week. Chien et al. (2006a) found higher daily intakes of lead in breastfed Taiwanese infants at birth (median of ~1.8 μg/kg bw/day; 400 mL milk), which decreased to below 0.3 μg/kg bw/day (2.1 μg/kg bw/week) after 3 months (760 mL milk). Two of the 72 infants (2.6%) had a HI greater than 1. The estimated MOEs were 0.1 and 1.7 for the Saudi Arabian and Taiwanese infants, respectively.

Three studies were conducted in Europe. Leotsinids et al. (2005) estimated lead intake of Greek infants assuming a consumption of 100–150 mL/kg bw/day of colostrum and intermediate milk, respectively. The 90th percentile of the intakes were 1.0 and 1.1 μg/kg bw/day, respectively, much lower than the PTWI, which corresponded to 3.6 μg/kg bw/day. The authors estimated a median intake for intermediate milk of 0.49 μg/kg bw/week. Ursinyova and Masanova (2005) estimated mean lead intake of 5.4 μg/kg bw/week for Slovakian breastfed infants using a daily milk consumption equivalent to 1/6 of the infants' body weight. The intake from the consumption of milk for two of the 158 mothers exceeded the PTWI. The estimated mean MOEs for Greek and Slovakian breastfed infants were 7 and 0.64, respectively.

Using lead levels found in the 2-5 d breast milk samples, Gürbay et al. (2012) estimated the intake of 3-month Turkish breastfed infants (750 mL/day) ranging from 22.9 to 5356 μg/week (mean of 2052 μg/week). Considering a body weight of 5.5 kg, a mean intake of 373 μg/kg bw/week can be estimated. This intake, however, is probably overestimated since metal levels, including lead, decrease in mature milk (Chao et al., 2014; Chien et al., 2006a, 2006b). Winiarska-Mieczan (2014) estimated that the weekly intake of lead by Polish infants decreased from 2.9 to 2.8 μg/kg bw at 1-3 months to 0.84 μg/kg bw at 12 months using the recommended volume of powdered milk for infants as a parameter for breast milk consumption. The authors expressed these values as % of the BMDL of 3.5 μg/kg bw/week (84–24%), and concluded that although the intakes did not exceed the "admissible levels", they were nevertheless high. It is important to emphasize however that this BMDL is not an admissible level of lead exposure, but is a level that corresponds to a 1 IQ point decrease in cognitive ability in children (EFSA, 2010). A MOE of 1.2 may be estimated for 1–3 month Polish infants.

In the UK, the COT (2004) reported that lead was above the LOQ in 7% of 114 breast milk samples analyzed, with a maximum concentration of 2.6 μg/kg, and a maximum intake ranging from 0.42 μg/kg bw/day for infants below 2 months of age to 0.1 μg/kg bw/day at 8–10 months, lower than the JECFA PTWI in effect at that time. The Committee concluded that this exposure does not raise toxicological concerns.

In a study conducted in Brazil (State of Rondônia, Amazonian region), Marques et al. (2013) estimated a median exposure to lead in the first 6 months of breastfeeding (140 mL milk/kg bw/day) of 3 μg/kg bw/day for rural infants, and of 7.5 μg/kg bw/day (52.5 μg/kg bw/week) for infants living in the vicinity of tin smelters. Our calculations indicate MOEs of 0.16 and 0.07 for rural and smelter neighboring infants, respectively. In another study conducted in the country however, mean lead levels were much lower (0.26 μg/L; Table 2), and we estimated a MOE of 14.

In its dietary risk assessment of lead for 3-month breastfed infants, the EFSA (2010) calculated MOEs of 2.4 for average consumers, which decreased (higher risk) in infants fed with formula and in children up to 7 years (MOE < 1). In its evaluation, the EFSA concluded that the risk from lead exposure for infants can be significant when the MOE is lower than 1; risk is likely to be low when the MOE is between 1 and 10; and a MOE of 10 or greater indicates no appreciable risk of a clinically significant effect on IQ. Most of the calculated MOEs in the present study were either below 1 or between 1 and 10, indicating a potential risk to breastfed infants. Fig. 2 shows the mean lead intakes by 1- to 6-month infants through breast milk discussed above.

4.3. Mercury

In most of the studies shown in Table 2, only THg was analyzed in the breast milk samples. Currently, the PTWIs for mercury are for IHg (4 μg/kg bw) and for MeHg (1.6 μg/kg bw), which is relevant for pregnant women and infants (JECFA, 2011b). The mean ratio of MeHg to THg in breast milk varies widely (from 0 to 0.6, mostly around 0.5; Table 2), and is considered to be greater in populations with higher fish consumption, reaching over 0.8 in some countries (Valent et al., 2013; Miklavcic et al., 2013). For the purpose of this review, when MeHg was not measured, it was considered to represent 50% of the THg present.

Two Brazilian studies conducted risk assessments of breastfed infants to mercury, both in the Federal District. Costa et al. (2005) estimated a THg mean and maximum intake (150 g milk/bw/day) of 0.86 and 3.46 μg/kg bw/day, respectively. The authors stated that 56.3% of the samples would indicate intakes higher than the reference value set by the WHO in 1991 for THg (0.5 μg/kg bw/day). Based on our previous assumption, MeHg mean intake in this study corresponded to 0.43 μg/kg bw/day, or 3 μg/kg bw/week, representing 188% of the PTWI.

In the assessment conducted by Cunha et al. (2013), 18 nursing mothers provided samples 15–90 days postpartum (142 samples) during 2003 and 2004, the same period as in the study by Costa et al., yielding similar THg mercury concentrations (Table 2). Infant weights were measured at 30, 60, and 90 days, and consumption volumes were estimated from the time the infant spent breastfeeding at each sampling point, assuming a milk flow of 13.5 mL/min. The intakes exceeded the THg PTWI (5 μg/kg bw/week) at least once during the period for 77.8% of the samples, with one sample reaching over 800% of the PTWI. Only four mothers did not provide samples that would lead to an exceedance of the PTWI at any sampling time. The estimated mean intake of THg was 6.4 μg/kg bw/week, or 3.2 μg/kg bw/week of MeHg (200% of the PTWI).

The study by Santos et al. (2015) in the Brazilian Amazon provided the highest mean levels of THg among all the studies in Table 2 (59.4 μg/L). Based on this level and a daily milk consumption of 750 mL for a 5.5 kg baby, we estimated a mean THg intake of 56.7 μg/kg bw/week, or 28.4 μg/kg bw/week for MeHg. Another study conducted in the same region found a much lower mean THg level (5.7 μg/L; Boischio and Henshel, 2000), and we estimated an intake of 5.4 μg/kg bw/week, and 2.7 μg/kg bw/week of MeHg, which corresponds to 170% PTWI.

The EFSA (2012b) conducted an assessment for MeHg in European infants under six months of age (6.1 kg bw) using contamination data from Miklavcic et al. (2013) and Valent et al. (2013) (Table 2). The mean intakes ranged from 0.09 to 0.62 μg/kg bw/week (800 mL milk consumption), and from 0.14 to 0.94 μg/kg bw/week for high consumers (1200 mL milk), and did not exceed the TWI of 1.3 μg/kg bw/week.

Iwai-Shimada et al. (2015) estimated intakes for Japanese one-month-old infants (4 kg bw and 800 mL milk) ranging from 0.08 to 1.68 μg/kg bw/week for MeHg (median of 0.63 μg/kg bw/week). The authors compared the intakes of MeHg with the Japanese and EFSA TWI (2 and 1.3 μg/kg bw/week, respectively), the JECFA (1.6 μg/kg bw/week), and a reference dose (RfD) from USEPA of 0.1 μg/kg bw/day. For the more restricted situation (USEPA), exposure exceeded the RfD in 12 of the 27 cases, with the median intake corresponding to 40% of the JECFA PTWI.

Chien et al. (2006b) estimated a mean THg intake of 3 μg/kg bw/day for newborn Taiwanese babies. Assuming that 50% of mercury is present as MeHg, the Monte Carlo simulation showed that HI for mercury was greater than one for 12.9% of urban babies, and for 18.8% of fishing village babies (MRL of 0.3 μg/kg bw/day). The mean MeHg intake represented 660% of the PTWI.

Behrooz et al. (2012) estimated a mean THg intake of 0.065 μg/kg bw/day for Iranian infants based on the actual infant birth weights and a daily milk intake of one-sixth of the infants' weight. Okati et al. (2013) found a similar result for 7 kg Iranian infants (1050 mL milk/day), with a mean of 0.064 μg/kg bw/day. These THg intakes corresponded to 0.22 μg/kg bw/week of MeHg (14% of the PTWI). In Saudi Arabia, Al-Saleh et al. (2003) estimated a much higher mercury intake for 5–6 kg infants (3.25 μg/kg bw/week), with 17.1% of the infants exceeding the THg PTWI. The calculated mean MeHg intake represented 100% of the PTWI.

A study conducted by Bose-O'Reilly et al. (2008) involved women with a very high mercury burden in four different gold mining areas in Indonesia, Tanzania and Zimbabwe. The authors estimated that the THg intake by a 3-month infant (6 kg, 850 mL milk/day) exceeded the RfD of 0.3 μg/kg bw/day in 47.8% of the cases, with the highest intake being 21.2 μg/kg bw/day (7100% RfD). The authors stated that no conclusion regarding a possible health risk of environmental mercury could be reached given the clear benefits of breastfeeding in developing countries. Based on the mean THg level (1.7 μg/L; Table 2) the estimated mean intake of MeHg was 0.93 μg/kg bw/week, representing 58% of the PTWI. Fig. 2 summarizes the intakes of MeHg by 1–6-month infants through breast milk discussed in this review. It is important to emphasize that the intakes may be overestimated for low fish consumption populations.

4.4. Cadmium

Four of the studies reported in Table 2 conducted exposure assessments for cadmium (and for lead, as discussed above) through breastfeeding. In Greece, the estimated 90th percentile of cadmium intakes from the consumption of colostrum and intermediate milk were 0.32 and 0.52 μg/kg bw/week, respectively; median values were 0.10 and 0.18 μg/kg bw/week (Leotsinidis et al., 2005). Ursinyova and Masanova (2005) estimated (milk consumption equal to 1/6 the body weight) a mean cadmium intake of 0.5 μg/kg bw/week for Slovakian newborn infants (0.02-1.99 μg/kg bw/week). In Poland, the mean exposures at 1, 6 and 12 months were 1.8, 2.1 and 0.82 μg/kg bw/week, respectively (Winiarska-Mieczan, 2014). In both studies, the authors compared the exposure with the TWI of 2.5 μg/kg bw/week set by the EFSA, which was not exceeded in any of the cases. Mean intake of cadmium by Saudi infants through breastfeeding (850 mL, 5.5 kg) estimated by Al Saleh et al. (2003) was 1.8 μg/kg bw/week, with 2.6% of the infants (n=344, 5 months old, on average) having intakes higher than the PTWI of 7 μg/kg bw/week.

The highest mean level of cadmium in breast milk of the studies in Table 2 was found in a study conducted in Turkey (4.6 μg/L; Gürbay et al., 2012. Using this level and a daily milk consumption of 750 mL for a 2-3 month baby (5.5 kg), we estimated a mean cadmium intake of 4.4 μg/kg bw/week for Turkish breastfed infants. This level is higher than the EFSA TWI (176%), but lower than the PTMI set by the JECFA, which corresponds to 5.8 μg/kg bw/week. These two contradictory risk conclusions demonstrate that risk assessment results need to be seen in light of the conservativeness of the parameters used and the uncertainties involved in the estimations. Fig. 2 summarizes the intakes of cadmium by 1- to 6-month infants through breast milk discussed in this review.

5. Summary and conclusions

Arsenic, lead, mercury, and cadmium are toxic metals ubiquitous in nature, to which exposure can be a public health concern. These metals cross the placenta and the blood brain barrier, and are excreted through breast milk. Exposure to lead and mercury has been related to neurotoxic problems later in life, although studies to discriminate intrauterine and postnatal effects are still needed. Currently, there is no safe dose of exposure established for lead or arsenic.

Monitoring breast milk is a non-invasive way of determining human exposure to metals and other contaminants. This review covers 75 studies that assessed arsenic, lead, mercury and/or cadmium levels in breast milk samples collected worldwide, with about one-third of the studies conducted in Europe. Mean or median levels of arsenic in intermediate and mature breast milk from non-occupational mothers were higher in India, reflecting high levels of this metal in the water sources of the region, and for methyl mercury in the Brazilian Amazon. Cadmium levels in breast milk were the lowest among the metals, mostly below the LOQ of the method. Lead was the metal most investigated and most detected in the studies.

Risk assessments conducted using current methods and toxicological parameters indicate that the risks for breastfed babies in most regions cannot be excluded, mostly due to arsenic, lead and mercury. Arsenic intakes led to MOEs below 10 in most studies. However, bottle-fed infants, who consume milk powder diluted in water, had higher arsenic intakes. Therefore, breastfeeding is protective for the babies, mainly in areas with high levels of arsenic in water. All the Brazilian studies indicated MeHg intakes exceeding the safety exposure parameter, reaching 1700% PTWI in a Brazilian Amazon riverine community, most likely due to high fish consumption, including piscivorous fish, which may contain high MeHg levels due to the bioconcentration in the aquatic food chain. Although the benefits of a high fish consumption diet are widely recognized due to its high-quality protein, fatty acids and other essential nutrients (IOM, 2005), women of child-bearing age and nursing mothers should avoid consuming piscivorous fish (USFDA, 2014).

The highest mean levels of lead in breast milk were found in Turkey, with an intake that led to a MOE of 0.01, with a potential for neurotoxic effects. The same conclusion may also be reached for infants from other regions, including Saudi Arabia, Brazil and Slovakia (MOE <1). Cadmium intakes were also higher in Turkey, representing 173% of the TWI established by the EFSA, but were below the PTWI established by the JECFA.

It is clear from most studies that breastfeeding exposes infants to more than one metal simultaneously, and most likely reflects the intrauterine exposure. Although the risk assessments discussed in this review were for each metal separately, it is important to point out that co-exposure to metals, in addition to other environmental contaminants, acting through the same mechanism and/or targeting the same organ, may lead to combined adverse effects with greater health impact on infants and children (Cardenas et al., 2015; Govarts et al., 2016).

The presence of environmental contaminants in human milk and the potential risks to the infants have been long recognized by researchers and health authorities worldwide. However, the World Health Organization and national governments strongly recommend breastfeeding, as it is accepted that the risks are outweighed by the benefits of breast milk consumption (WHO, 2007; Mead, 2008; VKM, 2013). This conclusion, however, does not preclude the responsibility of health authorities and researchers from continuing to monitor the levels of these metals in breast milk, particularly in regions with high levels of contamination, either by natural sources (as for arsenic in areas with high levels in water) or anthropogenic sources (as for lead in mining areas). Risk communication initiatives to reduce exposure among women of childbearing age by health authorities include:

- Women should be advised to avoid the consumption of predatory fish during pregnancy and when breastfeeding to decrease MeHg exposure.

- Women should be aware that arsenic exposure is much lower for breastfeeding babies than for babies fed with bottles;
- Women should be removed from polluted and mining areas and should avoid smoking to decrease exposure of the fetus and infants to lead and cadmium, among other contaminants.

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