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Review article

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

Fernanda Maciel Rebelo [a], Eloisa Dutra Caldas [b,*]

[a] Brazilian Health Surveillance Agency, University of Brasilia, 70910-900 Brasilia, DF, Brazil
[b] Laboratory of Toxicology, Department of Pharmacy, University of Brasilia, 70910-900 Brasilia, DF, Brazil

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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.

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* Corresponding author.
E-mail address: eloisa@unb.br (E.D. Caldas).

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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