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Mind the gap regarding the knowledge of infant exposure to mycotoxins, acrylamide, bisphenols and heavy metals through human milk

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ABSTRACT

Breastfeeding offers infants nutritional, immunological, neurological and emotional benefits, although some toxic compounds can also be detected in human milk and transported along this food chain, such as mycotoxins, bisphenols, heavy metals, and acrylamide. This narrative review collects data from around the world regarding the occurrence of these contaminants in human milk with a view to evaluate infant exposure to these compounds and the potential associated health risks. The factors driving the presence of these toxins in human milk are explored, as are some strategies and measures to minimize their transfer to infants. The incidence and the levels of toxic compounds reported in bibliography vary, ranging from trace levels to considerably high concentrations. The data obtained suggest that breastfed infants better tolerate exposure to toxic compounds than infants fed with milk formulas, even though in some cases the estimated daily intake may exceed the established reference values. Certain measures should be adopted to minimize the exposure of mothers and breastfed infants to toxic compounds, such as monitoring of good practices throughout the food chain and dietary control, avoiding commodities more susceptible to contamination.

1. Introduction

Breastfeeding provides the lactating infant with nutritional, immunological, neurological and emotional benefits, which has led to worldwide recommendations to practice exclusive breastfeeding for 6 months, followed by safe complementary feeding along with breastfeeding for up to 2 years (Figueiredo de Mendonça Pereira et al., 2020). Human milk is a wealthy source of nutritive compounds, including carbohydrates, lipids, proteins, amino acids, vitamins and minerals, as well as non-nutritive elements that contribute to the infant's development and well-being like enzymes, immunoglobulins, nucleic acids, hormones, growth factors and cells (e.g., macrophages, lymphocytes and epithelial cells: LaKind et al., 2004). Indeed, human milk directly modulates the immunological development of the infant through the vertically transmission of immune factors and personalized microbiota from the mother to the child during lactation (Marchant et al., 2018). In this sense, human milk confers protection against gastrointestinal and respiratory infections, and it reduces the risk of inflammatory diseases like asthma, atopy, obesity, diabetes and inflammatory bowel disease, as well as enhancing the infants cognitive development (Alotiby, 2023).

Despite the numerous benefits of breastfeeding for both mothers and infants, in recent years there has been increased public concern about the accumulation of toxic compounds in breast milk and their transmission. For instance, some environmental contaminants enter the food chain, such as mycotoxins, bisphenols, heavy metals and chemical compounds resulting from heat treatment processing (e.g., acrylamide), and they may be detected in human milk and maternal urine or blood at the time of delivery (Fig. 1). Humans are exposed to many potential contaminants and maternal diet is thought to be a key source of contaminants to which the infant may be exposed through lactation, influencing their development (Cummings et al., 2010). Significantly, breastfed infants are particularly sensitive and vulnerable to the toxic effects of these compounds due to their rapid growth, organ immaturity and the susceptibility of their nervous system. Moreover, newborns are less capable of excreting these compounds in bile, diminishing body clearance (Hatzidaki et al., 2023; Singh et al., 2023).

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The presence of toxic compounds in human milk has been widely reported worldwide, highlighting the problem of infant exposure, although there is scare information involving the accumulation of some of these compounds, such as acrylamide. Consequently, there is a need for more and larger studies to more precisely estimate the risk of infant exposure, obtaining information to better understand the impact of toxic compounds on the mother's and infants' health. Identifying toxic compounds in human milk and understanding the factors driving their accumulation is important to implement strategies and measures that minimize their transfer to infants, and to draw up uniform regulations controlling them in different countries.

2. Mycotoxins

2.1. The characteristics of mycotoxins

Mycotoxins are produced by filamentous fungi before or after harvest, and during crop manipulation or storage, and although more than 300 mycotoxins have been identified, aflatoxins (AFs), ochratoxins (OTs), deoxynivalenol (DON) and zearalenone (ZEA) are those most often detected in food crops. The main producers of mycotoxins are the *Aspergillus*, *Penicillium*, *Alternaria*, *Fusarium* and *Claviceps* genuses (Ganesan et al., 2022; Marin et al., 2013) (Fig. 2). The principal substrates or crops capable of supporting the growth of mycotoxigenic fungi and mycotoxin accumulation, and of their by-products, are cereals, oilseeds, dried fruits, coffee, spices and medicinal plants (Kovač et al., 2022). Mycotoxins have diverse chemical groups, which are related to the wide range of toxic effects they have in humans and animals that include genotoxicity, teratogenicity, neurotoxicity, hepatotoxicity, immunotoxicity, gastrointestinal toxicity, and nephrotoxicity, sometimes even leading to the development of cancer (Arroyo-Manzanares et al., 2021; Gacem et al., 2020).

Human biomonitoring is recognized as an efficient way to assess human exposure to mycotoxins through any route, without the need to identify the main source of exposure. This approach is usually based on the accurate measurement of biomarkers in human fluids (urine, plasma, serum, breast milk, etc.), and therefore, validated biomarkers and analytical methods must be available, along with easy access to biological matrices. Moreover, these measurements are independent of the variability of mycotoxin levels in foods, and they are not affected by mycotoxin toxicokinetics and toxicodynamics, taking into consideration absorption, distribution, metabolism and excretion (Arce-López et al., 2020).

European Commission (EC) Regulation (1881/2006, 2006) establishes the maximum content for the following mycotoxins in several foods intended for human consumption: AFs, OTA, DON, ZEA, HT-2, T-2, patuline (PAT), fumonisins (FBs), citrinin and ergot sclerotia (The Commission of the European Communities, 2006). Tolerable daily intakes (TDIs) have been established for some mycotoxins (e.g. OTA, PAT, DON, T2 and HT2, and ZEA) by some regulatory agencies and authorities, such as: the European Food Safety Authority (EFSA) Panel on Contaminants (EFSA, 2002; 2006; 2015; EFSA CONTAM Panel, 2014); the Joint Food and Agriculture Organization/World Health Organization (FAO/WHO) Expert Committee on Food Additives (JECFA, 2001); and the EC Scientific Committee (European Commission Scientific Committee on Food, 2002; Arcella et al., 2017). In the case of AFs, considered as genotoxic and carcinogenic compounds responsible for hepatocellular carcinoma, risk assessment is based on the margin of exposure (MoE) approximation since no TDI value has been established for this compound (IARC, 1993; JECFA, 2001). Moreover, it was concluded that health-based guidance was no longer appropriate for OTA as a risk assessment based on a MoE approach is more acceptable (EFSA, 2020).

The exposure of nursing mothers to mycotoxins varies in function of

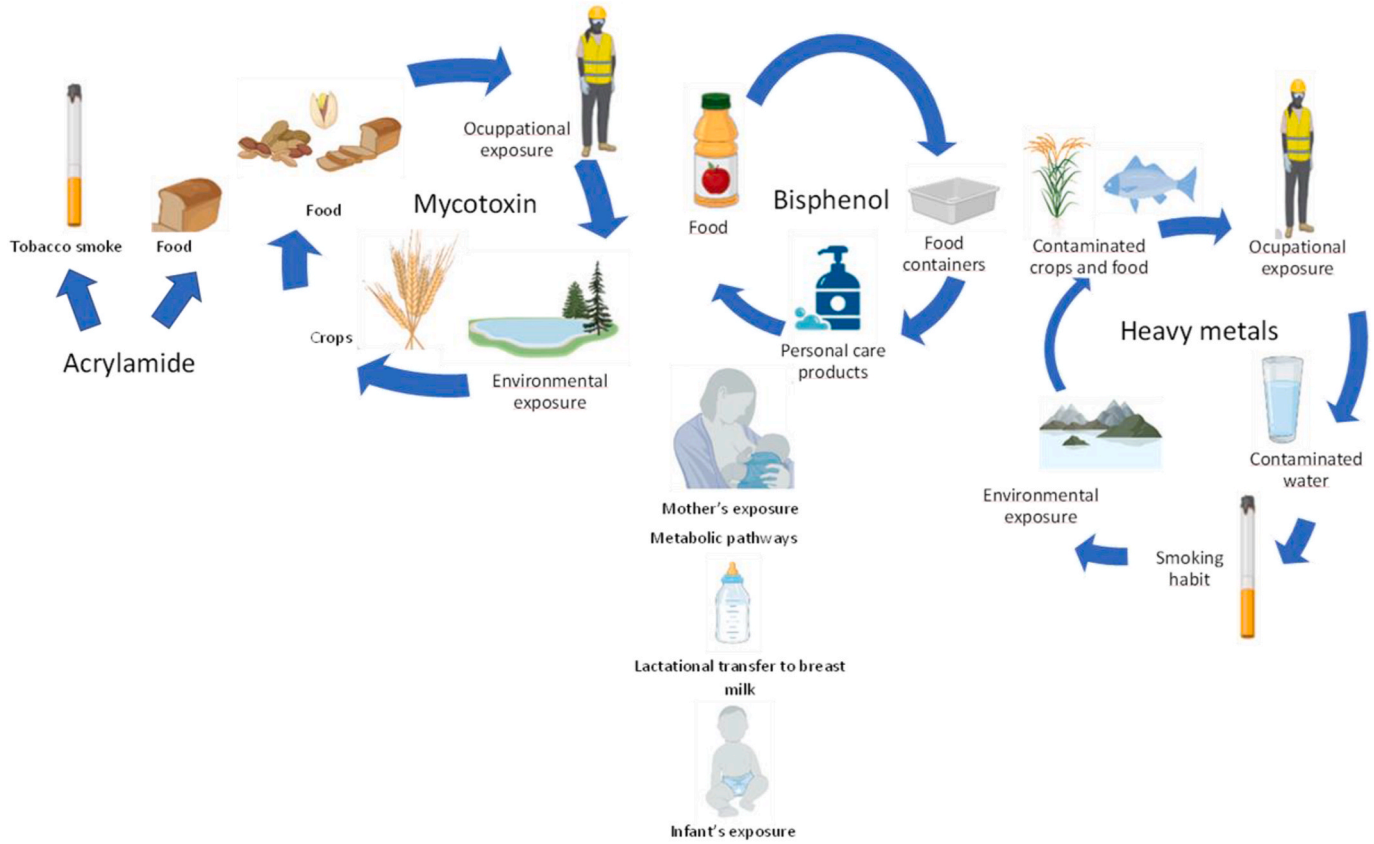

Fig. 1. Sources of contaminants exposure in breastfeeding Women's and breastfed Infants. Created with BioRender.com.

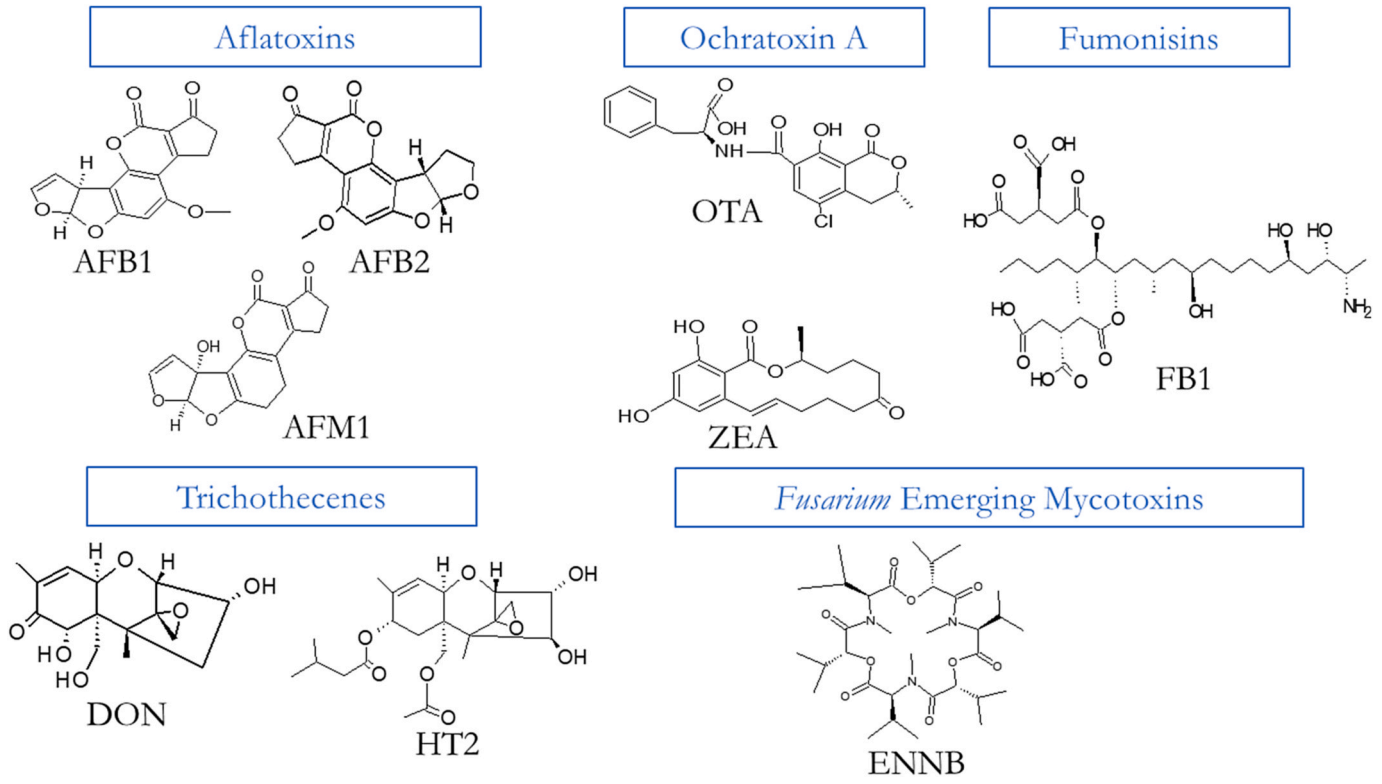

Fig. 2. Molecular structure of the most relevant mycotoxins.

several factors, such as seasonal changes, where they live and individual dietary habits, potentially making it a public health concern (Braun et al., 2018; Warth et al., 2016). Mycotoxin transfer rates vary at different stages of lactation, and they are influenced by maternal hydration, the frequency of infant feeding, as well as the physico-chemical properties of specific mycotoxins that affect their uptake and biodistribution. The diet of the breastfeeding mothers is crucial when determining presence of mycotoxins in human milk and their transfer. In

Table 1
Aflatoxins metabolites contents in human milk.

Mycotoxin	Country	Incidence (%)	Levels range (ng/L)	Analytical method	Reference
America					
AFM1	Brazil	5%	0.013–0.025 ng/g	HPLC coupled to fluorescence detection	Ishikawa et al. (2016)
AFM1	Colombia	90%	0.9–18.5	HPLC coupled to fluorescence detection	Diaz & Sánchez (2015)
AFM2		nd			
AFM1	Mexico	89%	3.01–34.24	ELISA	Cantú-Cornelio et al. (2016)
Africa					
AFM1	Egypt	36%	10.27–21.43	HPLC coupled to fluorescence detection	Polychronaki et al. (2006)
AFM1	Egypt	56%	January: 4.2–108 July: 6.3–497	HPLC with fluorescence detection	Polychronaki et al. (2007)
AFM1	Nigeria	100%	2.33–7.08	HPLC with fluorescence detection	Ekeanyanwu et al. (2020)
Asia					
AFM1	Bangladesh	51.6%	4.0–6.66	ELISA	Islam et al. (2021)
AFM1	Iran	98%	0.3–26.7 ng/kg	ELISA	Sadeghi et al. (2009)
AFM1	Iran	6%	7.1–10.8	ELISA	Ghiasian & Maghsood (2012)
AFM1	Iran	16%	11.1–39.3	ELISA Confirmed by HPLC with fluorescence detection	Jafari et al. (2017)
AFB1	Iran	93%	10–80	ELISA	Azarikia et al. (2018)
AFM1		100%	0.1–13.6		
AFM1	Jordan	100%	9.71–137.18 ng/kg	ELISA	Omar (2012)
AFM1	Lebanon	94%	0.2–7.9	ELISA	Elaridi et al. (2017)
AFM1	Malaysia	0%	nd	HPLC with fluorescence detection	Shuib et al. (2017)
AFM1	Nepal	94%	0.04–315.99	UHPLC with fluorescence detection	Pokharel et al. (2021)
Europe					
AFM1	Cyprus	80%	5.36–28.44	ELISA	Kunter et al. (2011)
AFM1	Portugal	33%	5.1–10.6.	ELISA	Bogalho et al. (2018)
AFM1	Serbia	Colostrum (35%) Mature milk (100%)	5.40–570.16	ELISA	Radonić et al. (2017)
AFM1	Turkey	66%	0.38–9.43	ELISA	Aksoy et al. (2009)
AFM1	Turkey	25%	1.3–6.0	ELISA	Atasever et al. (2014)

Nd:not detected; Incidence %: (number of positive samples/total number samples) x100.

infants, the level of maternal mycotoxin exposure affects the mycotoxins consumed by the infant and detected in each month of life. In particular, greater mycotoxin exposure was observed in the transition from complementary feeding to weaning (Ortiz et al., 2018). Demand feeding is recommended for newborns, although the interpretation of the needs by mothers may influence the number of breastfeeds per day and hence, mycotoxin transmission (Manz et al., 1999).

2.2. Mycotoxins in human milk

2.2.1. Aflatoxin metabolites - AFM1 and AFM2

Aflatoxin M1 (AFM1) is one of the principal hydroxylated metabolites of aflatoxin B1 (AFB1) and when detected in milk, it is considered a biomarker of AFB1. This metabolite originates through AFB1 detoxification and it displays about 10% of the mutagenicity attributed to its precursor (Marchese et al., 2018). AF accumulation in human milk has been studied in several countries, such as Iran, Turkey, Egypt, Nigeria, Bangladesh, Nepal, Portugal, Cyprus, Lebanon, Serbia, Mexico, Brazil and Jordan (Table 1). In most cases, AF and AFM1 levels were reported below the maximum tolerance limits established in European and United States legislation. The levels reported range from trace levels to concentrations of 500 ng/L, and the rate of positive samples oscillates from as little as 6%–100% in some studies (Table 1). Although a direct correlation of AFM1 levels with food consumption habits is not always seen and the variability in the data makes it difficult to relate the presence of AFM1 to a specific dietary pattern, cheese, cereal and bread consumption has been positively associated with AFM1 levels. A temporal variation was also observed over the year, with a higher frequency of AFM1 detected in the summer months.

In terms of incidence, a higher prevalence and levels of AFM1 were observed in some countries in Africa, Asia and Europe, such as Egypt, Nepal, Jordan, Tanzania and Serbia (Hernández et al., 2021). In Cyprus, AFM1 was detected in a high percentage (80%) of human milk samples at a mean concentration of 7.84 ng/L, although there was no direct correlation of socio-demographic status, food consumption or smoking habits with these AFM1 levels (Kunter et al., 2011). In Nigeria, a high prevalence of AFM1 was also observed in samples from 225 lactating mothers (Ekeanyanwu et al., 2020) and similarly, in Lebanon 93.8% of 111 human milk samples were positive for AFM1. Again the collecting period was significantly associated with the AFM1 concentration, which was lower in the fall and winter seasons than in spring and summer. Meat and cereal consumption was not correlated with AFM1 levels, whereas white cheese intake was positively associated with the presence of this metabolite. Furthermore, no significant association was evident between anthropometric sociodemographic factors and AFM1 concentrations (Elaridi et al., 2017). In central Mexico, 89% of 112 samples from nursing mothers were AFM1 positive and some factors, like diet (e.g., consumption of carbonated soft drinks, eggs and sunflower oil products) and the season of collection were positively correlated with the detection of AFM1, which accumulated more in winter (12.78 ng/L) and spring (12.09 ng/L) than in summer (7.91 ng/L: Cantú-Cornelio et al., 2016). Likewise, AFM1 was detected in 90% of breast milk samples provided by 50 nursing mothers in Colombia, while AFM2 was not. Higher AFM1 levels were observed in those women who ate at least three servings of corn arepa and at least three servings of pasta and rice in the previous 72 h (Diaz & Sánchez, 2015).

High AFM1 levels were observed in all samples in Jordan, with the average concentration (67.78 ng/kg) of human milk tested (n = 80) above the maximum limit tolerated in the U.S.A. and Europe. Concerning nutritional habits, a correlation between AFM1 levels and cereal consumption was observed, yet not with the consumption of vegetables, fruit or meat products (Omar, 2012). Along the same lines, 100% of mature milk and 36.4% of colostrum samples (total n = 60) in Serbia were contaminated (Radonić et al., 2017). A study on 1675 mother-infant dyads conducted in Nepal detected AFM1 in 94% of samples, and a positive correlation between seasonal period and AFM1 levels was observed, with more AFM1 detected in samples collected in the pre-winter and winter period relative to spring. Regarding habits of consumption, foods like milk, yogurt, ripe pumpkin and hydrogenated oil were positively associated with AFM1 levels, whereas legume intake was related with less AFM1 in breast milk (Pokharel et al., 2021).

Contrary to these results, AFM1 was not observed in any of 45 samples of human milk collected in Penang (Malaysia: Shuib et al., 2017) and in Brazil, AFM1 was found in 5 out of 94 breast milk samples (5.3%), highlighting a low exposure to AFB1 in lactating mothers (Ishikawa et al., 2016). In Egypt, only 36% of breast milk samples collected from 388 mothers were positive for AFM1 and some nutritional factors like body weight, corn oil consumption and an early stage of lactation contributed to the presence of AFM1 (Polychronaki et al., 2006). More recently, the temporal variation in AFM1 was assessed over a one year period in 50 of these AFM1 positive women, with a higher AFM1 frequency in summer months (>80%) than in winter months (<20%) and higher concentrations (6.3–497 ng/L milk) also detected in July relative to January (4.2–108 ng/L milk: Polychronaki et al., 2007).

In Turkey, the occurrence of AFM1 in breast milk samples from 73 lactating women was correlated with the dietetic habit of moldy cheese consumption, with approximately 25% of samples positive. (Atasever et al., 2014). A higher incidence of AFM1 and higher concentrations were evident in an earlier study of breast milk samples from 50 mothers (Aksoy et al., 2009). In Portugal, 32.8% of 67 human milk samples contained AFM1, the presence of which was positively correlated with a summer collection, some socio-demographic factors (e.g., a lower educational level of the mother), an early phase of lactation and the consumption of certain food categories like rice and chocolate (Bogalho et al., 2018). More recently, 51.6% of 62 breast milk samples studied in Bangladesh were positive for trace levels of AFM1. Moreover, no significant correlations were obtained between maternal food consumption and AFM1 levels (Islam et al., 2021). In Iran, a slightly lower incidence of AFM1 (16%) was observed in 250 human milk samples, with the sample collection area (urban or rural regions) significantly influencing these results, as did the dietary pattern, which could in turn be related to the area of collection. Indeed, bread and cereal consumption (such as rice, non-alcoholic beer) may increase the risk of AFM1 exposure (Jafari et al., 2017). Another study of AFM1 in breast milk collected from lactating mothers (n = 132) in Iran detected a prevalence of 6% of samples (Ghiasian & Maghsood, 2012), although almost 100% of samples collected from 160 lactating women were positive for AFM1 in another study performed in Iran. However, in that case no significant correlation between AFM1 presence and some socio-economic factors like education, nationality or the clinical condition. Along similar lines, daily consumption of fruit and vegetables, and meat products was not positively correlation with the presence of AFM1. The opposite was observed with the daily consumption of cereals, a food group that is widely associated with mycotoxin contamination (Sadeghi et al., 2009). Similarly, AFB1 and AFM1 were reported in 93 and 100% of 88 breast milk samples collected from different regions of Iran, with no significant differences between the samples collected from urban and rural areas (Azarikia et al., 2018). Moreover, the detection of AFB1 was positively correlated with the diet exposure to eggs and bread, and the presence of AFM1 with wheat flour and traditional dough.

2.2.2. Ochratoxin A

Ochratoxin A (OTA) is a nephrotoxic and carcinogenic compound commonly found in human biological fluids and as such, when ingested by lactating mothers it may well appear in breast milk. An association between OTA and the onset of renal disease has been proposed, such that its presence in human milk could be associated with future renal dysfunction in infants. The appearance of OTA in milk has been reported in different countries (Egypt, Turkey, Iran, Morocco, India, Brazil, Chile, Germany, and Italy), with incidences varying from 2 to 100% and ranging from trace levels to 13,111 ng/L (Table 2). Ochratoxin B (OTB) is a dechloro-analogue of OTA that was detected in 42% of breast milk

Table 2
Ochratoxin A and Aflatoxins contents in human milk.

Mycotoxin	Country	Incidence (%)	Levels range (ng/L)	Analytical method	Reference
America					
OTA	Brazil	66%	0.3–21	HPLC with fluorescence detector	Iha et al. (2014)
AFM1		2%	0.3–0.8		
AFB2	Brazil	1%	LOQ level (5)	HPLC with fluorescence detector	Andrade et al. (2013)
AFB1			nd		
AFG1			nd		
AFG2			nd		
AFM1			nd		
OTA			nd		
OTA	Chile	79%	LOD (10) −186	HPLC with fluorescence detector	Muñoz et al. (2014)
Asia					
OTA	Iran	97%	1.6–60	ELISA	Dehghan et al. (2014)
OTA	Iran	2%	45	ELISA confirmed by HPLC with fluorescence detector	Taghizadeh et al. (2017)
OTA	Iran	1%	90/140	ELISA confirmed by HPLC with fluorescence detector	Afshar et al. (2013)
AFM1		<1%	20		
Africa					
OTA	Egypt	72%	1890 (mean)	(HPLC) and microfluorometric detection	Hassan et al. (2006)
OTA	Morocco	55%	80–10.040	ELISA	Cherkani-Hassani et al. (2020)
Europe					
OTA	Germany	50%	10–100	HPLC-MS/MS	Muñoz et al. (2013)
OTA	Italy	79%	1.1–75.1	HPLC with fluorescence detector	Biasucci et al. (2011)
OTA	Italy	74%	<5 -405	HPLC with fluorescence detector	Galvano et al. (2008)
AFM1		5%	<7 -140		
OTA	Italy	86%	0.5–57	HPLC with fluorescence detector	Turconi et al. (2004)
AFB1		1 sample	11.4		
AFM1		1 sample	194		
OTA	Slovakia	30%	<2.3–60.3	HPLC	Dostal et al. (2008)
OTA	Turkey	100%	620.87–13111.30	HPLC with fluorescence detector	Gürbay et al. (2010)
OTA	Turkey	23%	10–100	ELISA	Altun et al. (2019)
OTA	Turkey	100%	100–2390	ELISA	Yalçin et al. (2020)
AFM1		98.7%	<LOD (2) −6.94		

Incidence %: (number of positive samples/total number samples) x100.

samples collected in India at up to 62.2 ng/L (Mehta et al., 2021). Some of the dietary products consumed by the lactating mothers that were positively associated with OTA accumulation included bread, breakfast cereals, legumes, dried fruits, processed meat and cheese. However, conflicting results were obtained regarding the correlation between the lactating stage and OTA levels.

In Egypt, OTA was found in 72% of samples collected from 50 lactating mothers at a mean concentration of 1.89 ng/mL. The high dietary intake of liver paste, cakes, breakfast cereals, cheese products and processed meat was positively associated with OTA contamination, as was the intake of juices (Hassan et al., 2006). In Morocco, 55% of 82 colostrum samples contained OTA, which was significantly affected by dietary habits like the consumption of industrial dairy products and frequent consumption of dried fruits, legumes and canned foods. The period of breast milk collection was also related to the OTA levels (Cherkani-Hassani et al., 2020). In Turkey, OTA was detected in 22.8% of breast milk samples of 92 lactating mothers (Altun et al., 2019). Elsewhere, a higher incidence and concentrations of OTA was reported, with OTA detected in all breast milk samples collected from 75 mothers in the range 621–13111 ng/L (Gürbay et al., 2010). Also in Turkey, changes in OTA and AFM1 content were evaluated in breast milk samples from 78 lactating mothers at different stages of lactation (5–14 days post-partum, 6th week post-partum and 18th week post-partum), detecting OTA and AFM1 in almost all the samples. The mean AFM1 was significantly higher at 6 weeks post-partum than after 5–14 days, while no marked effect was observed for OTA. In terms of sampling season, AFM1 and OTA levels were higher in spring and winter than in summer and autumn (Yalçin et al., 2020). OTA was also investigated at various stages of breastfeeding in samples provided by 21 Chilean mothers, with a mean concentration in breast milk collected during the first 6 days (colostrum, 86 ng/L) 2.5-fold higher than that observed in mature milk (Muñoz et al., 2014). Human milk mycotoxin contamination in Iran varies considerably, with 96.6% of the samples from 87 mothers positive for OTA in a ranges of 1.6–60 ng/L in one study (Dehghan et al., 2014), while only one breast milk sample of those collected from 41 lactating Iranian women was positive for OTA (45 ng/L) elsewhere (Taghizadeh et al., 2017). Similarly, a further study only detected OTA in 2 of 136 human milk samples, in a range of 90 and 140 ng/L, and AFM1 in one sample at 20 ng/L (Afshar et al., 2013).

In Germany, OTA was detected in more than 50% of 90 human milk samples, with significant differences in content between the two regions of collection: Dortmund and Hannover (Muñoz et al., 2013). In Slovakia, 23 of 76 human milk samples were positive for OTA, with the levels detected in 9 of these samples in the range of 2.3–60.3 ng/L (Dostal et al., 2008). Similarly, in Italy OTA was determined in 78.9% of 57 maternal milk samples collected from Italian and immigrant women living in Italia. No significant difference in OTA content was observed between Italian and non-Italian women, and regarding dietary patterns, soft drink consumption was correlated with OTA levels in milk in non-Italian mothers (Biasucci et al., 2011). Also in Italy, when AFM1 and OTA were evaluated in 82 mature breast milk samples collected at Italian hospitals, the presence of OTA was related with maternal dietary habits and positively correlated with the consumption of bread, bakery and cured pork meat products (Galvano et al., 2008). In a previous study in Italy, bread consumption was also significantly correlated with OTA levels (Turconi et al., 2004). In Brazil, a study into both AFM1 and OTA in 100 human milk samples observed a much higher incidence of OTA (66%) than AFM1 (2%), as seen in Italy (Iha et al., 2014). Also in Brazil, a study of AFs and OTA in 224 human breast milk, milk bank samples highlighted their lower incidence and content (Andrade et al., 2013).

2.2.3. *Multimycotoxins*

There are only a few studies in the literature into the appearance of multimycotoxins in human milk samples. Some studies focusing on AFM1 and OTA, the most widely studied mycotoxins in human milk, also explored the presence of ZEA and DON, as well as other mycotoxins like emerging mycotoxins (Table 3). These mycotoxins have been detected in varying amounts up to 15,000 ng/L and detected in all the

Table 3
Multimycotoxin contents in human milk.

Mycotoxin	Country	Incidence (%)	Levels range (ng/L)	Analytical method	Reference
America					
AFM1	Brazil	nd		HPLC-MS/MS	Coppa et al. (2021)
FB1		3%	2200–3400		
OTA		5%	180–2600		
DON		nd			
ZEA		nd			
Asia					
AFM1	India	41%	<LOD (3.9)–1200	HPLC-MS/MS	Mehta et al. (2021)
AFM2		18%	<LOD (3.9)-33.9		
AFB1		8%	<LOD (7.8)-27.1		
AFB2		43%	<LOD (7.8)-265.0		
AFG1		5%	<LOD (7.8)-45.3		
AFG2		19%	39.0–241.0		
OTA		13%	<LOD (7.8)-39.8		
OTB		42%	<LOD (3.9)-62.2		
AFM1	Iran	52.2%	5.16–13.5	ELISA/HPLC	Samiee et al. (2020)
OTA		nd			
ZEA		nd			
Africa					
AFM1	Nigeria	1%	87 max conc	LC-MS/MS	Braun et al. (2018)
BEA		56%	19		
ENNB		9%	9		
OTA		15%	96		
Europe					
ZEA	Italy	100%	260–1780	ELISA	Massart et al. (2016)
ZEA	Spain	37%	2100–14130	UHPLC-HRMS	Rubert et al. (2014)
αZEA		3%	16700		
βZEA		3%	39800		
ENA		6%	20100–25200		
ENA1		6%	42200–51100		
ENB		6%	99800–110300		
ENB1		6%	90700–101100		
HT-2		29%	12200–62500		
NEO		20%	10300–36900		
NIV		9%	53100–69700		
ZEA	Turkey	100%	35.7–682	Direct solid-phase enzyme	Dinleyici et al. (2018)
DON			400–14997	Immunoassay	
AFM1	Turkey	np	2.59–3.82	ELISA	Memiş et al. (2021)
OTA			1.05–1.58		
ZEA			0.23–0.51		
DON			5.28–12.52		

Nd:not detected; Np: not provided; Incidence %: (number of positive samples/total number samples) x100.

samples examined in some cases.

In this sense, the presence of aflatoxins, OTA and OTB was studied in 100 human milk samples in India. AFM1 was that found at the highest levels, up to 1200 ng/L, and in some cases exceeding the limits established by the EC. Moreover, the consumption of bread was positively associated with the appearance of AFM1 (Mehta et al., 2021). In Iran, AFM1, OTA and ZEA was assessed in milk samples from 90 nursing mother and in contrast to the previous study, none of the contaminated samples exceeded the established limit for AFM1. In addition, AFM1 levels were significantly correlated to infant age and milk consumption from lactating mothers (Samiee et al., 2020). In Brazil, FB1 and OTA were detected in only 3 and 5% of samples from 74 lactating women, but at levels ranging from 2200 to 3400 ng/L and 180–2600 ng/L, respectively (Coppa et al., 2021). In Spain, a multi-class mycotoxin study into various mycotoxins revealed mycotoxins to be present in 35 human milk samples, with incidences from 6 to 37% and at concentrations between 2.1 and 110.3 ng/mL. ZEA, HT-2 and NEO were the mycotoxins detected with higher prevalence, while DOM was only detected in one sample (Rubert et al., 2014). In Nigeria, a study based on different mycotoxin groups (28 mycotoxins including AFs, OTA, DON, ZEA, ENNs and BEA) and their key metabolites was carried out on 75 samples collected from 22 lactating women. BEA was the most frequently detected mycotoxin as it was found in 56% of the samples, although it was only quantified in six samples reaching concentrations up to 0.019 ng/mL. The rest of the mycotoxins were detected at trace levels (Braun et al., 2018).

In a study performed in Turkey, the maternal intake of fish, meat, dried fig or apricot, flaked red spice and spices was correlated with ZEA levels, while the consumption of meat was positive correlated with DON levels (Dinleyici et al., 2018). Also in Turkey, the relationship between AFM1, OTA, ZEA and DON in human milk and infant growth was investigated. ZEA potentially influenced infant growth in a manner that depended on maternal smoking (Memiş et al., 2021). By contrast, in a study performed in Italy ZEA values were significant correlated with weight and the mother's BMI before pregnancy and after birth (Massart et al., 2016).

3. Acrylamide

3.1. Characteristics and general considerations of acrylamide

Acrylamide (AA) is a toxic food contaminant that is mainly produced via the asparagine route of the Maillard reaction when food rich in carbohydrates is heated >120 °C. It is detected in baked products, breakfast cereals, fried nuts, cocoa-based products, coffee and potatoes. The main factors influencing AA formation in heat-processed foods are the composition of the raw food (free asparagine and reducing sugar content), high temperature (>120 °C), type of cooking and low moisture conditions (Bachir et al., 2022; Rifai & Saleh, 2020). AA has neurotoxic effects in both animals and human, and the IARC has classified it as a probable carcinogen in humans (group 2A: IARC, 1994). Moreover, this compound is related to immunotoxicity, genotoxicity and reproductive toxicity, and attempts to combat its toxicity include the inhibition of

mutagen formation, induction of acrolein detoxifying enzymes, reactive oxygen species (ROS) scavenging, enhanced DNA repair, and alterations to signaling pathways implicated in apoptosis and proliferation (Zhao et al., 2017). The nervous system is an important target for AA as it induces degeneration of peripheral nerves and of nerve terminals in areas like the cerebral cortex, hypothalamus and hippocampus (Kopá Nska et al., 2022; Matoso et al., 2019).

Regarding AA toxicokinetics, it is absorbed through the skin, and through the respiratory and digestive tract, and it is rapidly distributed across different tissues due its good solubility in water, with significant accumulation in the skin, muscle, blood and liver. Moreover, AA can cross the placenta in humans and it can also accumulate in human milk (Lindeman et al., 2021; Matoso et al., 2019), being transferred to the developing fetus and newborns, respectively. AA is mainly transformed to glycidamide via epoxidation and to mercapturic acids via glutathione conjugation (Mojska et al., 2021).

International organizations have warned against the presence of AA in foods and its consumption to prevent any prejudicial health effects. Although no maximum residue levels (MRLS) have been set, the EU Regulation 2017/2158 established mitigation measures and benchmark levels for AA (Commission Regulation, 2017). As such, a wide range of benchmark levels (40–4000 μg/kg) have been established for different foodstuffs like coffee, chips, bread, cereals and biscuits, with lower levels established for those foodstuffs intended for infants and young children. Nevertheless, no benchmark levels were indicated for milk or breast milk in the EU regulation. Moreover, as AA is a carcinogenic, genotoxic and neurotoxic compound, the MoE criterion is recommended for its risk assessment. In this sense, the EFSA Panel on Contaminants selected BMDL10 values of 0.17 mg/kg bw/day for neoplastic effects and 0.43 mg/kg bw/day for neurotoxicity in order to estimate the health risk of dietary exposure (EFSA, 2015).

3.2. Acrylamide in human milk

In general, few studies in the literature have assessed AA levels in human milk. In Poland AA levels in human milk were assessed at different lactation stages, analyzing 47 colostrum and 26 mature milk samples by LC-MS/MS. As a result, 23% of colostrum samples had AA above the LOD (limit of detection, 0.1 μg/L), in the 0.11–1 μg/L range, while 58% of mature milk samples contained levels ranging between 0.11 and 0.86 μg/L. The median of AA in mature milk (0.14 μg/L) was significantly higher than in colostrum (0.05 μg/L). Regarding dietary intake, the main source of AA was soft bread and moreover, the estimated intake of AA from a hospital diet was significantly lower than that in a home diet (Mojska et al., 2021). In Sweden, AA was determined in 15 samples collected from individual mothers and in 4 pooled samples, only recording AA levels above the LOD (0.5 μg/kg) in one sample (0.51 μ/kg). By contrast, three out of eight breast milk substitute samples had quantifiable AA (0.6–0.7 μ/kg) (Fohgelberg et al.,

2005). In Germany, AA was quantified at 3.17 and 18.8 μg/L in breast milk samples collected from two lactating mothers 3–10 h after consumption of products rich in AA (Sörgel et al., 2002). Thus, factors like variable intrasubject bioavailability and metabolism, as well as dietary intake, seem to affect the AA levels observed. Regarding the risk to infants of AA, a MoE >10,000 was reported for most infants (Mojska et al., 2021), indicating a low risk. However, due to the scare information available in literature, further studies will be needed to obtain a more comprehensive picture of infant exposure to AA via breast milk.

4. Bisphenols

4.1. The characteristics of bisphenols

Bisphenols are reported in plastics and epoxy-resins. Among the most common bisphenols is BPA (bisphenol A), which has been widely studied due to its potential endocrine-disrupting properties, specifically through its binding to estrogen receptors. These polymers are used as food contact materials, for instance as polycarbonate plastics in food containers and beverages cans. BPA degradation is related to the surroundings contamination, and its prejudicial effects on the environment and health make it necessary to replace BPA with other bisphenols. BPA analogues have the basic bisphenol structure based on benzene rings. (Fig. 3). For instance, bisphenol S (BPS) with two functional phenol groups linked by sulfonyl group is more persisting in the environment than BPA, which phenols are linked by methylene group. Moreover, the similarities in the structure of BPA with its analogues may lead to comparable toxicity profiles (Lee et al., 2021). Human exposure to bisphenols essentially occurs through canned food and beverage consumption, but also through dust inhalation and skin absorption. BPA constitutes the bisphenol most often detected in foodstuffs but its analogue (BPP) is also found at similar levels.

Bisphenol pollutants are related to reproductive toxicity, neurotoxicity, immunotoxicity, altered metabolism and alterations to the gut microbiome (Fig. 3: McDonough et al., 2021). The toxic and teratogenic effects of BPA and its derivatives have been analyzed in zebrafish embryo/larvae and their estrogenic mechanisms evaluated (Moreman et al., 2017). A toxicity ranking of BPAF > BPA > BPF > BPS was established, with larval deformities including cardiac edema, spinal malformations and craniofacial deformities. Differences in the effects and potency of the different bisphenols were observed, and the estrogenic effects followed the order BPAF > BPA = BPF > BPS. Thus, it was concluded that BPA derivatives induce similar toxic and estrogenic effects as BPA.

Exposure of human to bisphenols has become a serious public concern basically for the high sensitivity of the developing organs as these endocrine disruptive chemicals can cross the placenta, and neonates or infants may be exposed through breastfeeding with human milk. In this sense, evaluating exposure by analyzing biological fluids from mothers (urine, blood, breast milk, colostrum) and newborn infants (umbilical cord blood, neonatal urine, meconium), and from placental tissues or amniotic fluid, may constitute a useful tool to better understand fetal or newborn exposure to bisphenols (Caballero-Casero et al., 2016). In order to reduce the risk to public health associated with BPA in foodstuffs, the EFSA established a temporary TDI (t-TDI) of 4 μg/kg bw/day based on data available in literature (EFSA CEF Panel, 2015). This t-TDI was recently replaced by a TDI of 0.2 ng BPA/kg bw/day (EFSA CEP Panel, 2023).

4.2. Bisphenols in human milk

Most bisphenols, bisphenol A (BPA) and its analogues (bisphenol B (BPB), bisphenol S (BPS), bisphenol F (BPF) and bisphenol AF (BPAF)) have been detected in biological samples at trace levels (Ocaña-Rios et al., 2022), and as free bisphenols in blood can pass into the mammary gland and be excreted in breast milk, they are a good indicator of exposure. There appears to be little data available regarding the presence of bisphenols in human milk but in general, BPA is more frequently detected than its analogues (Table 4). Moreover, it is necessary to accurately assess the bisphenol exposure of lactating mothers and infants through biomonitoring studies.

In China, BPA was detected in 57% of breast milk samples collected from 149 lactating mothers and the dietary contribution of BPA was estimated in 63.7% of cases, suggesting non-dietary BPA exposure. Moreover, BPA levels in human milk (0-3-month, 0.187 μg/L) were significantly higher than those obtained in 4-12-month human milk (0.088 μg/L, Gao et al., 2021). A similar trend was observed in an earlier study (Nakao et al., 2015), where the levels of tetrabromobisphenol A (TeBBPA, a halogenated derivative of BPA) were higher in breast milk one week after birth, decreasing thereafter at one and three months, although the changes in BPA differed significantly from that of TeBBPA. As no clear trend was observed, further studies into the variation of BPA and its analogues over the period of lactation appear to be needed. Also

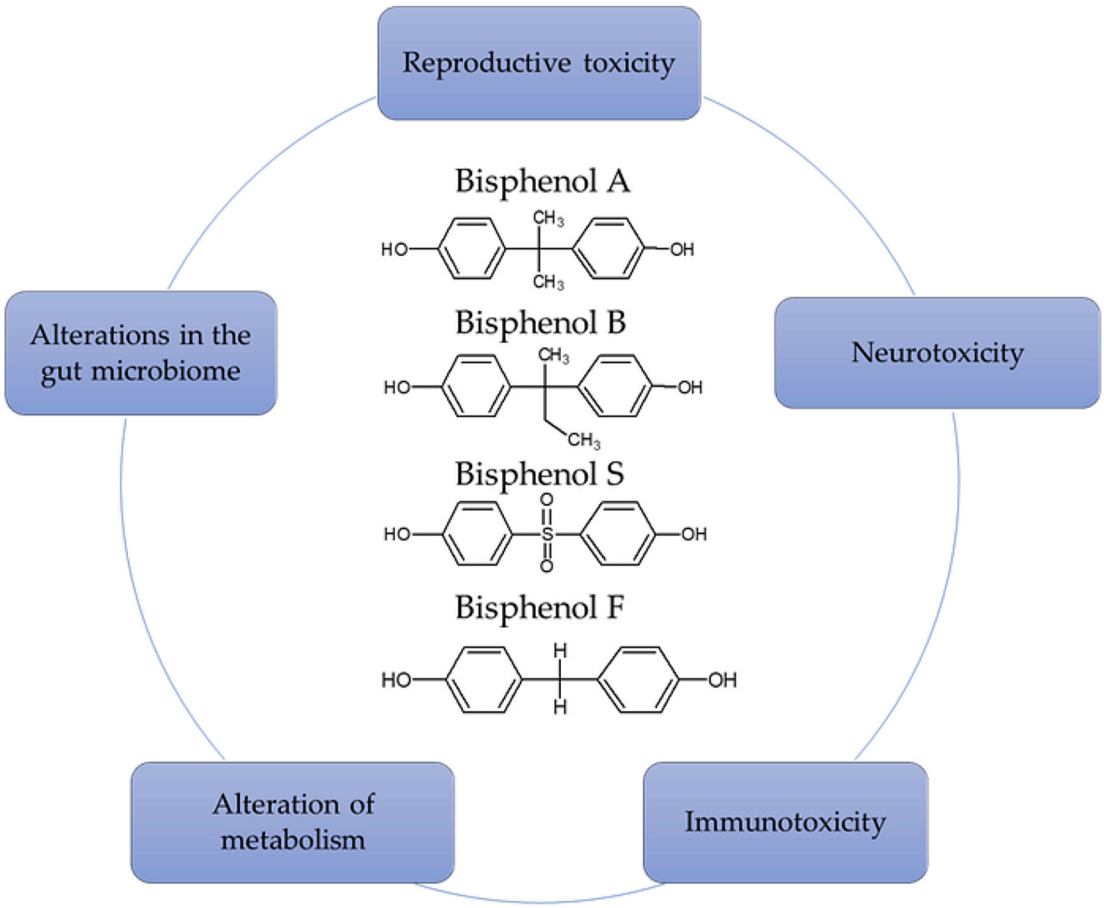

Fig. 3. Toxic effects of Bisphenol A and its analogues.

in China, the presence of BPA and its analogues BPF, BPS and BPAF, was reported in 20 human milk samples with different incidences ranging from 5% to 85%. BPA was the dominant bisphenol, detected in 85% of the samples, followed by BPF, while BPS was only detected in one sample (0.683 μg/L: Niu et al., 2017).

In Poland, the BPA, BPS, BPF and BPAF was analyzed in breast milk samples collected from 21 lactating mothers at two points, 3–6 weeks after delivery and >3 months. Of all the bisphenols studied, BPA was the most abundant bisphenol, detected at levels up to 4.86 ng/mL in the 3–6 week samples and up to 3.34 ng/mL in the >3 month breast milk samples. BPF was not detected in the samples. BPA was also the bisphenol that contributes most importantly to the hazard quotients in risk assessment (Czarczyńska-Goślińska et al., 2021). Also in Poland, BPA, BPS, BPF and BPB were detected at an incidence of 7, 100, 7 and 100%, respectively. All bisphenols were detected at levels below the LOD, excepting BPB (2.12–116.22 ng/mL), observed at slightly higher levels than previously (Tuzimski et al., 2020). These authors also reported BPA (0.42–11.56 ng/mL) and BPS (0.06–0.33 ng/mL) in 100% of 20 human milk samples. Similarly, they investigated the presence of BPA, BPS, BPF and BPB in human milk samples from urban and rural residents, and while BPA was more often detected than BPS, BPF and BPB remained < LOD (Tuzimski & Szubartowski, 2019).

In Spain, the occurrence of BPA, and its analogues BPF and BPS, was studied in human milk samples collected from 120 mothers living in Valencia (Spain). BPA was detected in 83% of samples, while its analogues were detected in fewer, BPF in 22% and BPS in 1% of samples. Moreover, factors like the location and the use of personal care products were significantly associated with BPA levels (Dualde et al., 2019). Previously, and also in Spain, BPA was found in 60% of 20 human milk samples, at levels ranging from 0.6 to 13.8 ng/mL, while its chlorinated derivative (Cl_2-BPA) was only observed in two samples at 0.2 and 0.4 ng/mL (Rodríguez-Gómez et al., 2014).

5. Heavy metals

5.1. Heavy metals generalities and characteristics

Heavy metals are widely distributed in the environment, found in water, soil and the atmosphere as a result of industrial and/or agricultural activities. Due to their persistence in the environment and toxicity, heavy metals constitute one of the most dangerous environmental contaminants. Exposure to these compounds can occur in several ways, such as the consumption of contaminated food or drinking water, or through the air. Common heavy metals as mercury (Hg), cadmium (Cd), lead (Pb) and arsenic (As: Liu et al., 2022) are associated with deleterious effects for human health as their concentration may increase over time in some vital body organs, such as the kidney, liver, heart and brain, disturbing their normal biological functions. The chemical species in which heavy metals occur is related to their biological activity, toxicokinetic, and their effects in biological systems and the environment.

Heavy metals can modulate a range of responses and metabolic pathways in the organism, including those associated with their bioactivation or detoxification. The specific pathways contributing to heavy metal toxicokinetics and metabolism are mainly carried out by phase I and II enzymes, mitogen-activated protein kinase and antioxidant defense enzymes (Wu et al., 2016). In mammals, the biological transformation of toxic compounds takes place in the liver and muscles. The toxicity of heavy metals depends on the chemical species, the route of exposure but also on the genetics and epigenetics factors (Tchounwou et al., 2012). The main mechanism driving heavy metal toxicity is the

Table 4
Bisphenols contents in human milk.

Bisphenol	Country	Incidence (%)	Levels range (ng/mL)	Analytical method	Reference
Asia					
BPA	China	57%	0.001–2.535	UHPLC-MS/MS	(Gao et al., 2021)
BPA	China	85%	0.050–0.548	LC-MS after EMR-Lipid purification and (PS–Cl derivatization	(Niu et al., 2017)
BPF		60%	0.010–0.166		
BPS		5%	0.683		
BPAF		15%	0.021–0.056		
Europe					
	Poland	Urban area		LC-QqQ-MS after QuEChERS	(Tuzimski & Szubartowski, 2019)
BPA		84%	0.23–0.69		
BPS		40%	0.29–0.68		
BPF		12%	0.22–0.29		
BPB		20%	<LOQ		
		Rural area			
BPA		68%	0.21–0.52		
BPS		28%	0.32–0.62		
BPF		8%	0.34–0.55		
BPB		8%	<LOQ		
	Poland			LC-QqQ-MS after QuEChERS	(Tuzimski et al., 2019)
BPA		100%	0.42–11.56		
BPS		100%	0.06–0.33		
	Poland			LC-QqQ-MS after QuEChERS/d-SPE Procedure	(Tuzimski et al., 2020)
BPA		7%	<LOQ		
BPS		100%	<LOQ		
BPF		7%	<LOQ		
BPB		100%	2.12–116.22		
	Poland	3–6 weeks		LC-MS/MS	(Czarczyńska-Goślińska et al., 2021)
BPA		76%	<LOD (0.19)-4.86		
BPS		100%	0.04–0.84		
BPF		0%	<LOD (0.2)		
BPAF		100%	<LOQ (0.1)-0.14		
		+3 months			
BPA		76%	<LOD (0.19)- 3.34		
BPS		100%	<LOQ (0.03)- 1.27		
BPF		0%	<LOD (0.2)		
BPAF		100%	<LOQ (0.1)-0.15		
	Spain			UHPLC-MS/MS	(Rodríguez-Gómez et al., 2014)
BPA		60%	0.6–13.8		
Cl_2BPA		20%	0.2–0.4		
	Spain			HPLC-MS/MS	(Dualde et al., 2019)
BPA		83%	<LOQ-42		
BPF		22%	<(0.13) −0.46		
BPS		1%	0.37		

Incidence (%): (number of positive samples/total number samples) x100.

production of ROS, which may induce protein modifications, lipid peroxidation and DNA damage, leading toward adverse health effects such as cancer, neurological and cardiovascular disorders, kidney damage and other endocrine abnormalities (Fig. 4: Rehman et al., 2017).

Heavy metals can reach human milk through the ingestion of contaminated foods or water by lactating mothers, and excessive exposure to these chemicals can irreversibly affect infant development (de Mendonça Pereira et al., 2020). The transport of heavy metals into milk is suspected to follow the same pathways of other milk components, such as essential trace elements. Thus, the mechanisms regulating trace elements in milk may be implicated in the capture of heavy metals by specific transporters in the cells of the mammary epithelial and their successive discharge in the alveolar lumen of the mammary glands (Rebelo & Caldas, 2016). The WHO has proposed safe limits for heavy metal contamination of human milk, establishing a Maximum Tolerable Limit (MTL) of 5 μg/L for Pb, 0.6 μg/L for As, 1.5 μg/L for Cr, 1.7 μg/L for Hg and 1 μg/L for Cd (Motas et al., 2021; WHO, 1989).

5.2. Heavy metals in human milk

Maternal exposure of heavy metals through breastfeeding represents a risk to infants during postnatal as toxic heavy metals can accumulate in the mother's body. Heavy metal contamination of human milk has been studied worldwide reporting a wide range of concentrations (Table 5). The considerable variations observed from one country to another may be related to the analytical techniques and sampling methods employed, the stages of lactation examined, as well as the environment and the socioeconomic status of the lactating mothers including in the studies. In some cases, the maximum levels set by the WHO or other agencies were exceeded and interestingly, most studies reported positive correlations between Cd and Pb levels in human milk and active or passive smoking. The consumption of fish was also correlated with Hg levels, and environmental and industrial pollution was positively related with heavy metal levels in human milk.

In Brazil, the presence of Cd, Cr and Pb was determined in 79 colostrum and 16 mature milk samples. Pb levels in colostrum (0.209 mg/L) and mature milk (0.136 mg/L) were high relative to the MTLs of 0.05 mg/kg established by ANVISA (a Brazilian regulatory agency: Filho et al., 2014). More recently, As, Cd, Pb and Hg were measured in samples from 106 donors of a human milk bank with median levels relative to dry weight of 13.8 ng/g (As), 7.1 ng/g (Hg) and 0.43 μg/g (Pb: Bastos et al., 2018).

In Spain, Hg, Pb and Cd was analyzed in breast milk samples collected from 100 lactating mothers, revealing geometric mean of 0.53 μg/L (Hg), 15.56 μg/L (Pb) and 1.31 μg/L (Cd). Interestingly, the Pb levels increased with greater exposure to motor vehicle traffic and the

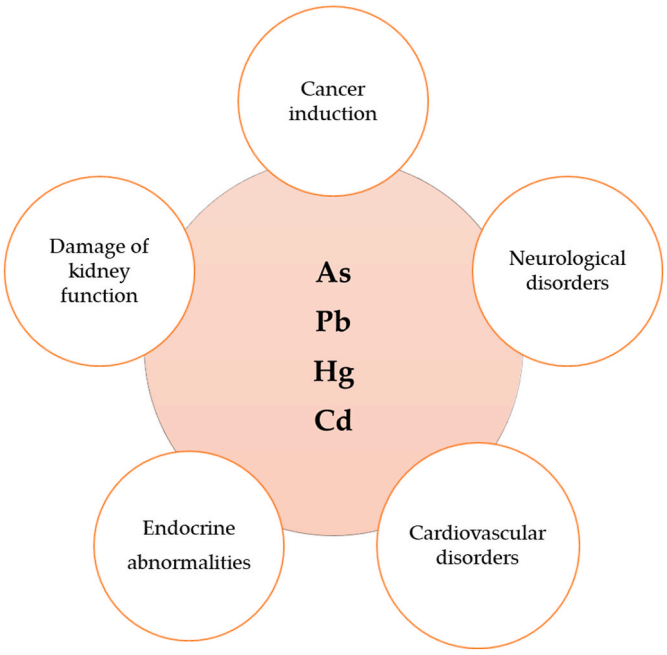

Fig. 4. Major adverse health effects associated with heavy metals in human milk.

consumption of potatoes, while Cd concentrations tended to increase in smoking mothers (García-Esquinas et al., 2011). More recently, several heavy metals were determined in human milk samples collected from 50 mothers in Spain, with high incidences of Cr and Hg detected (up to 454.7 μg/L of Cr). Breast milk collected from women living in industrial zones had maximal levels of As, Hg and Pb, while the highest concentrations of Cr were observed in mothers living in agricultural zones. In addition, the mean concentration of heavy metals exceeded the WHO recommendations and those of other international organizations. Diet significantly influences the accumulation of some heavy metals and for instance, the amount of water consumed was related to Pb levels, while vegetarian diets were associated with Pb, As and Cd accumulation (Motas et al., 2021).

In Italy, the occurrence of Hg, As, Cd and Pb was studied in 7 milk pools prepared from milk provided by 52 mothers. Of all the heavy metals, only Pb was detected at levels above the LOD (2.59–5.99 μg/L: de Felip et al., 2014). In another study performed in Italy, Cd, Hg and Pb was studied in milk pools obtained from 29 mothers in the Venice area, grouping samples in function of fish consumption, and in a milk pool obtained from 10 lactating mothers living in the Rome area. No correlations were found between fish consumption and heavy metal concentrations in milk (Abballe et al., 2008).

Regarding other European countries, a study based on heavy metals in colostrum milk provided by mothers living in areas with different levels of pollution was carried out in Romania: Bucharest (identified as the highly contaminated area, n = 12) and a small town (identified as less contaminated area, n = 7). Comparing the mean concentrations in both Bucharest and the small town suggested an influence of environmental pollution on heavy metal content (Bucharest vs small town: Prioteasa et al., 2018): Cd (0.6 μg/L vs 0.3 μg/L), Pb (<LOD vs 0.2 μg/L), As (5.5 μg/L vs 3.8 μg/L) and Cr (5.4 μg/L vs. 5.5 μg/L). In Slovenia, Cd, Pb, Hg and As were reported in milk samples at similar levels (<LOD -5.42 μg/L), with lifestyle and nutritional habits related to the accumulation of some heavy metals. Thus, Cd and Pb exposure were related to smoking habits, and game meat while Hg and As were associated with seafood consumption. Geochemical data for top soil constitutes a good environmental predictor of Pb and Hg exposure (Snoj Tratnik et al., 2019).

In Croatia, the Cd, Pb and Hg in breast milk samples from 107 lactating mothers was determined and as reported elsewhere, correlations were observed between smoking and the Cd/Pb levels in milk, as well as between weekly fish consumption and Hg concentrations (Grzunov Letinić et al., 2016). In Cyprus, Hg, Cd, As and Pb were analyzed in 50 human milk samples, with mean contents of 1.19 μg/L (Pb), 0.73 μg/L (As) and 0.45 μg/L (Cd), below the maximum WHO limits. Contrary to previous observations, no significant correlation was observed between heavy metal content and the geographical area (Kunter et al., 2011).

In Turkey, the levels of heavy metals were similar to those in other European countries with some exceptions. For instance, in 107 human milk samples, Pb was the heavy metal with the highest prevalence, detected in 83% of samples levels up to 46.14 μg/L but generally below the limits of safety in all cases (Dursun et al., 2016). More recently, the average Cr, As, Cd, Hg and Pb levels in 34 milk samples collected from breast-feeding mothers were 8.25, 1.64, 0.37, 2.60 and 12.12 μg/L, respectively. The highest exposure was observed for Cr and As, although factors like educational level, age and fish consumption were not significantly correlated with the heavy metal concentrations (Nazlıcan et al., 2022). Another study in Turkey, detected Pb, Hg and Cd in 74 human milk samples, with levels up to 279 μg/L and Pb levels above the recommended limits in 81% of samples (Örün et al., 2021). By contrast, As and Pb were detected in 42 breast milk samples collected from mothers living in urban and suburban areas of Turkey at <1 μg/L (Kiliç Altun et al., 2018).

In Asia, slightly higher levels of heavy metals were reported. For instance, the Pb, Cd and As in 180 milk samples collected from 45 mothers at different lactation stages in Taiwan indicated higher concentrations in colostrum (13.22 ng/mL Pb, 1.37 ng/mL Cd and 1.50 ng/mL As), with a trend towards a decrease in toxic metals as lactation advanced. The smoking behavior of the mothers was positively associated with Cd levels in breast milk, yet no significant correlation was seen between Cd content in colostrum and canned food consumption (Chao et al., 2014). Assessing the influence of working in industrial areas on Cd, Cr and Pb levels in 44 human milk samples in Thailand demonstrated an association between Cr and Pb in human milk with occupational exposure, while Cr accumulation was correlated with leafy green vegetable consumption (Wongsasuluk et al., 2020).

In Korea, Pb and Hg were analyzed in 207 samples collected from 157 lactating mothers 15 and 30 days after delivery. Hg was observed in all samples with a median concentration of 0.59 μg/L, while Pb was detected in 77% of samples with a median concentration of 4.71 μg/L. In addition, up to 45% of the breast milk samples exceeded the Pb limits established by the WHO (Park et al., 2018). Similarly, Pb was found at an average concentration of 2.13 μ/L in 60 human milk samples in China, while As and Cd were not detected (Deng et al., 2009). In another study conducted in China, Hg was detected between 0.42 and 8.40 μg/L in 195 human milk samples, with prenatal Hg exposure associated with the consumption of fresh fish during pregnancy (Li et al., 2014).

The heavy metals in human milk have been studied widely in Iran, with levels sometimes exceeded those recommended by different authorities. In one study, Pb, Hg, Ba and Cd were determined in 100 human milk samples at median concentrations of 41.9 μg/L (Pb), 2.8 μg/L (Hg) and 1.95 μg/L (Ba), with Cd levels <1 μg/L in all samples. The Pb and Hg levels exceeded the recommended WHO limits in 94% and 54% of samples, respectively. In addition, sociodemographic factors were not significantly correlated with the toxic heavy metal content of human milk (Vahidinia et al., 2019). Likewise, the Pb, As and Cr in breast milk from 100 lactating mothers collected at 2, 6, 8 and 12 months post-partum led to mean Pb, As and Cr contents of 41.90, 0.50 and 3.95 μg/L, respectively. The highest Pb levels were reported in breast milk collected 2 months after delivery and up to 94% of samples exceeded the recommended WHO limits for Pb (Samiee et al., 2019a). Also in Iran, similar levels of Pb and Cd were reported, with mean concentrations of 53.6 and 8.01 μg/L in 77% and 100% of samples, respectively. In

Table 5
Heavy metals contents in human milk.

Heavy metals	Country	Incidence (%)	Levels range (μg/L)	Analytical method	Reference
America					
	Brazil	np		FAAS/GFAAS	(Filho et al., 2014)
Colostrum					
Cd			0.13–152		
Cr			0.14–305		
Pb			0. 41-2031		
Mature milk					
Cd			0.13–65.4		
Cr			17.6–2339.9		
Pb			0.41–659		
Hg	Brazil	28%	<0.007–0.061 mg/Kg (dw)	FIMS	(Bastos et al., 2018)
As		53%	<0.005–0.575 mg/Kg	ICP-OES	
Pb		16%	<0.431–3.509 mg/Kg		
Cd		1%	<0.074–0.115 mg/Kg		
Asia					
Pb	China	np	2.13 (mean)	ICP-MS	(Deng et al., 2009)
As			nd		
Cd			nd		
Hg	China	np	0.42–8.40	AAS	(Li et al., 2014)
Pb	Egypt	np	11–5339	ICP-OES	(Mansour et al., 2015)
Cd			1–61		
Cd	Iran	np	0.62–6.3	GFAAS	(Rahimi et al., 2009)
Pb			3.18–24.7		
Cd	Iran	np	0.0–4800	FAAS	(Nazarpour et al., 2013)
Hg	Iran	np	0.0–2070	AAS	(Goudarzi et al., 2013)
Cd			450–5870		
Pb			3060–19470		
Pb	Iran	77%	382	GF-AAS	(Khanjani et al., 2018)
Cd		100%	151		
Pb	Iran	96%	<LOQ (1)- 1950	ICP-MS	(Vahidinia et al., 2019)
Hg		54%	<LOQ (1)- 28.7		
Ba		48%	<LOQ (1)- 166		
As	Iran			ICP-MS	(Samiee et al., 2019b)
Contaminated areas		100%	3–30.10		
Non-contaminated areas		100%	3.2–15.4		
Pb	Iran	88%	1.5–1950.01	ICP-MS	(Samiee et al., 2019a)
As		20%	0.5–5.8		
Cr		78%	0.5–29.5		
Hg	Korea	100%	0.08–5.66	GF-AAS	(Park et al., 2018)
Pb		77%	< LOD (0.3) −94.2		
	Taiwan	np		AAS	(Chao et al., 2014)
Colostrum					
Pb			13.22 (mean)		
Cd			1.37		
As			1.5		
Transitional milk					
Pb			8.92		
Cd			0.65		
As			0.68		
Early mature milk					
Pb			11.72		
Cd			0.49		
As			0.27		
Mature milk					
Pb			2.93		
Cd			0.34		
As			0.16		
Cd	Thailand	np	0.31 (mean)	ICP-MS	(Wongsasuluk P et al., 2020)
Cr			14.06		
Pb			8.64		
Africa					
As	Ghana	np	7–120.4 ng/g	ICP-MS	(Bansa et al., 2017)
Pb			5.3–117.2 ng/g		
Hg			1.36–63.52 ng/g		
Cd			0.6–6.3 ng/g		
Cr	Morocco	62.83%	1.5–199.36	GF-AAS	(Ait lhaj et al., 2021)
Pb		27%	5.5–8.5		
Cd		8%	1–24.5		
Cd	Nigeria	np	11–51	GF-AAS	(Ekeanyanwu et al., 2020)
Cr			6–48		
Cu			13–59		

(*continued on next page*)

Table 5 (*continued*)

Heavy metals	Country	Incidence (%)	Levels range (μg/L)	Analytical method	Reference
Pb			12–59		
Europe					
Hg	Austria	62%	0.1–2	GFAAS	(Gundacker et al., 2010)
	Croatia	np	0.58–1.3 μg/Kg (dry matter)	ICP-MS	(Grzunov Letinić et al., 2016)
Smokers			1.7–10 μg/Kg (dry matter)		
Cd			0.59–1.6 μg/Kg (dry matter)		
Pb			2–12 μg/Kg (dry matter)		
			0.24–7.8 μg/Kg (dry matter)		
Non-Smokers					
Cd					
Pb					
Hg					
Pb	Cyprus	np	0–4.91	ICP-MS	(Kunter et al., 2011)
As			0.03–1.97		
Hg			0–0.01		
Cd			0.12–0.80		
Cd	Italy	np	<0.5	CVAA/AAS	(Abballe et al., 2008)
Pb			0.85–1.07		
Hg			2.63–3.53		
As	Italy		<LOD (3)	DRC-ICP-M	(de Felip et al., 2014)
Cd			<LOD (0.1)		
Hg			<LOD (0.3)		
Pb		100%	2.59–5.99		
Bucharest area	Romania	np		ICP-MS	(Prioteasa et al., 2018)
Cd			<LOD (0.002)-2.1		
Pb			<LOD (0.001)		
As			2.9–8.9		
Cr			0.53–8.87		
Small town area					
Cd			<LOD (0.002)-1		
Pb			<LOD (0.001)-1.42		
As			2.5–4.9		
Cr			0.56–8.87		
Cd	Slovenia	42%	<LOD (0.1)-3.65	ICP-MS	(Snoj Tratnik et al., 2019)
Pb		54%	<LOD (0.2)-5.42		
Hg		96%	<LOD (0.5)-3.39		
As		98%	<LOD (0.05)-3.70		
Hg	Spain	97%	0.03–2.63	GFAAS	(García-Esquinas et al., 2011)
Pb		93%	1.7->20		
Cd		96%	0.25–2.8		
As	Spain	12%	0–15.3	ICP-MS	(Motas et al., 2021)
Cd		6%	0–7.8		
Pb		30%	0–89.2		
Hg		58%	0–83.6		
Cr		99%	0–454.7		
Pb	Turkey	83%	<LOQ (0.03)- 46.14	ICP-MS	(Dursun et al., 2016)
Hg		53%	<LOQ (0.02)- 11.52		
Cd		9%	<LOQ (0.02)-1.62		
As	Turkey	np	<1	ICP-MS	(Kiliç Altun et al., 2018)
Pb			<1		
Pb	Turkey	91%	<LOD (0.2)-297	ICP-MS	(Örün et al., 2021)
Hg		87%	0.01–18.7		
Cd		99%	0.04–9.25		
Cr	Turkey	100%	0.55–67.7	ICP-MS	(Nazlıcan et al., 2022)
As		100%	0.03–7.97		
Cd			0.02–1.80		
Hg		35%	0–11.7		
Pb			0.55–35.4		

Np: not provided; Incidence (%): (number of positive samples/total number samples) x100.

addition, Cd was reported to be higher in breast milk from mothers who took fat off their meat before eating it and those who had a vaginal delivery (Khanjani et al., 2018). Another study in Iran, detected slightly lower mean concentrations of Cd (2.44 μg/L) and Pb (10.39 μg/L), moreover, the Cd content of breast milk increased significantly in mothers who were exposed to smoking (Rahimi et al., 2009). Elsewhere in Iran, the As content in 20 breast milk samples collected from lactating mothers living in As contaminated areas (mean 10.75 μg/L) and 20 samples of women from non-contaminated areas (mean 7.73 μg/L) were both high, and not-significantly different. It was also suggested that products like seafood and rice constituted potential sources of As contamination (Samiee et al., 2019b). The mean Hg, Cd and Pb concentrations detected in 37 milk samples collected from lactating women were 0.92, 1.92 and 7.11 mg/L (Goudarzi et al., 2013), and likewise, the Cd in breast milk provided by 100 mothers in Iran was slightly higher (mean 5 mg/mL), with higher Cd levels in breast milk collected from mothers living nearer to an industrial area (Nazarpour et al., 2013).

Heavy metal biomonitoring studies have also been performed in African countries and in Morocco, with the frequency of Cr (63%), Pb (27%) and Cd (8%) in 95 human milk samples associated with mean concentrations of 8.84, 3.20 and 0.60 μg/L, respectively. Moreover, the mean value of Cr was above the recommended WHO limits (Ait lhaj et al., 2021). The As, Pb, Hg and Cd in breast milk collected form 114

mothers in Ghana gave median values of 27.8 ng/g (As), 11.0 ng/g (Pb), 8.4 ng/g (Hg) and 1.20 ng/g (Cd). Thus, a considerable proportion of babies were exposed to Hg, As and Pb, perhaps more than should be (Bansa et al., 2017). In breast milk samples collected from 225 mothers in Nigeria, several heavy metals were detected but with Pb and Cd the most prevalent. In general, no significant correlations were observed between heavy metal levels and the diet of lactating mothers, except for the relationship of bean consumption to Cr and Cu levels (Ekeanyanwu et al., 2020). Higher levels were reported for Cd and Pb in breast milk samples collected from 32 lactating women in different regions of Egypt. Due to industrial pollution, Cd and Pb levels differed significantly between regions and a significant increase in heavy metal concentrations was evident in those mother's passively or actively exposed to smoking (Mansour et al., 2015).

6. Impact of toxic compounds on infant health and microbiota

As indicated above, chemical contaminants can be transferred to the fetus via maternal and/or placental cord blood, or to lactating infants via breastfeeding. Thus, many environmental and dietary contaminants transferred to human milk are associated with adverse health effects, such as limited and retarded fetal growth, neurobehavioral and developmental problems, and cognitive dysfunction, as well as subtle developmental effects in the immune system (Fig. 5) (Palmieri et al., 2019; Schreiber, 2001).

Infants and young children are more susceptible to toxic compounds than adults, and the adverse effects may exceed three times the adults effects due to the characteristics of their weight ratio, and metabolism (Mehta et al., 2021). Deficiencies in endocrine-regulated pathways or low vitamin levels have been linked to the effects of chemical contaminants during the perinatal and lactational periods, such as bisphenols. BPA may act on hormone-mediated pathways to alter normal growth and development in infants, and prenatal or childhood exposure to BPA has been linked to neurodevelopmental problems, metabolic disorders, obesity and early puberty (Braun and Hauser, 2011). In the case of AA, gestational exposure has adverse effects on fetal growth (Hogervorst et al., 2022).

Regarding the damaging effects of mycotoxins in infants, experimental models have shown these contaminants can induce several intestinal alterations, affecting digestion, absorption, permeability and the composition of the intestinal microbiota. They are also associated with a decrease in mucin secretion and the activation of cytokine production. Mycotoxins have also been implicated in neurodevelopmental disorders, bone marrow failure, altered defense functions, pulmonary hemorrhage, and recurrent pneumonia in infants and children (Adaku Chilaka and Mally, 2020). Specifically, associations have been seen between maternal dietary AF exposure and fetal growth retardation, and with immune dysfunction and poor micronutrient absorption in infants. Moreover, FB exposure is associated with neural tube defects (Alvito & Pereira-da-Silva, 2022), while ZEA and its metabolites disrupt the estrogenic system, resulting in premature breast and sexual development.

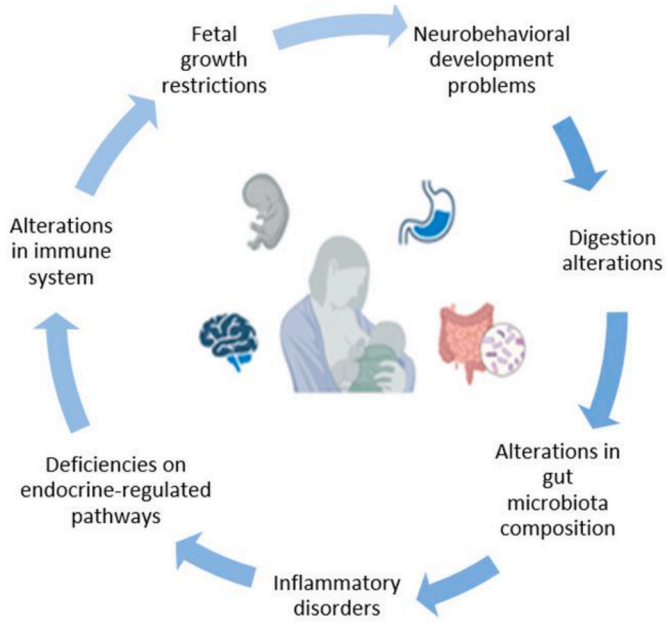

Fig. 5. Potential effects of toxic compounds on breastfed infant's health. Created with BioRender.com.

Heavy metals provoke a variety of adverse effects in infants, including hyperactivity, intellectual and behavioral alterations, deficits in fine motor function, cancer, skin lesions, and reduced fertility (Palmieri et al., 2019). For instance, exposure to As can cause reproductive toxicity, increased fetal mortality, spontaneous abortions, underweight newborns, eclampsia and birth defects. Regarding Pb, the effects on the central nervous system (CNS) are most critical in infants and children, and in fetuses and infants this neurotoxicity may be due to the immaturity of the blood brain barrier (BBB). Regarding Hg, methylmercury (MeHg) affects the fetus's neurological development because it crosses the BBB and the placenta. Moreover, Hg levels in cord blood are well correlated with Hg levels in the fetal brain during the third trimester of pregnancy (Rebelo & Caldas, 2016). Due to its ability to cross the placenta and the BBB, Cd reaches the fetus and the brain in the early stages of fetal or infant development, resulting in its effects on CNS development, provoking cognitive and behavioral dysfunctions that include poor learning memory (Chandravanshi et al., 2021).

Furthermore, infant exposure to chemical contaminants disrupts gut development, and the communication between the brain and the gut, which may hinder the capacity to establish correct neuro-immuno-endocrine functions, and increase the risk of developing neurological and inflammatory disorders (Roca-Saavedra et al., 2018; Sarron et al., 2020). The gut microbiota has a metabolic role in decontaminating some of the chemical compounds ingested and hence, the gut microbiota can prevent health complications by transforming contaminants into less hazardous compounds. The human microbiota is acquired from maternal-infant transmission at birth and during breastfeeding, followed by environmental acquisition at later stages. Maternal exposure to toxic compounds can modify the infant's microbiota, with as yet unknown health consequences. As such, chemical contaminants could induce changes in intestinal microbial profiles, decreasing the number of bacterial species. Evaluating the impact of contaminants and chemicals on the neonatal microbiota is complicated as the neonatal microbiota differs from that of adults, and the bacterial detoxification capacity may well be less well-developed in infants than in adults (Calatayud Arroyo et al., 2021).

7. Food contaminant risk assessment in breastfed infants

7.1. Assessment of dietary mycotoxin exposure

In Nigeria, infant exposure to AFs, DON, OTA and emerging mycotoxins was evaluated through the mycotoxin concentrations in human milk, constituting their sole food intake. The intake estimates (EDIs) revealed exposures below TDI values, yet the mycotoxin transfer into milk and urine, and the resulting chronic low-dose exposure, makes further monitoring studies necessary (Braun et al., 2022). In northern India a deterministic risk assessment of AFB1, AFB2, AFG1, AFG2, AFM1, AFM2, OTA, OTB in infants 2–4 months was performed, revealing estimated intakes in 41% of infants above the provisional maximum TDI (PMTDI) limits established for AFM1. AFs are classified as carcinogens and they have also been linked to stunted growth in children, such that further research will be necessary to better understand the implications of this exposure on maternal and child health (Mehta

et al., 2021).

In Austria a longitudinal study of mycotoxins in human milk was carried out and the estimated exposure of infants to specific mycotoxins (AME, BEA, ENNA, ENNA1, ENNB, ENNB1, OTA) was on average below 1 ng/kg bw/day, which did not exceed the recommended maximum daily intake. However, exposure is expected to be higher in populations with lower food safety standards, highlighting the need to study the factors influencing contamination through large-scale studies that assess intra- and inter-individual, as well as geographical aspects (Braun et al., 2020). In Italy, the estimated exposure of infants with celiac disease and control mothers to AFM1 was 1.6 ng/kg bw/day and 1.2 ng/kg bw/day, respectively, approximately 15 and 11 times higher than the threshold established by the JECFA, respectively. Exposure to ZEA was below the TDI of 1 μg/kg bw/day, yet prompt regulatory and food-control policies will be necessary to protect babies from the risk of mycotoxins (Valitutti et al., 2018). In Germany, the exposure of nursed infants to several mycotoxins was studied to evaluate whether maternal exposure to a dose equal to the TDIs is also safe for infants. As such, single dose and continuous daily intake scenarios were considered. In the single dose scenario, the exposure of infants through breast milk was lower than the corrected TDI (TDI/3) for six of the eight mycotoxins studied, DON and PAT exceeding this by a factor of 2. In terms of the continuous daily intake, the exposure of nursed infants to OTA exceeded the child adjusted TDI by 29.2-fold (Degen et al., 2017). Also in Germany, infant exposure to OTA via human milk intake was evaluated in Dortmund and Hannover. In 29% of samples the TDI of 3 ng/kg bw/day was exceeded, although in general infant exposure to OTA in Germany is usually low than in other countries (Muñoz et al., 2013).

By contrast, infants <6 months of age who had been introduced to maize foods in combination to breastfeeding could be at a high risk of mycotoxin exposure. In Northern Tanzania, infants <6 months of age were exposed to AFs in the range 0.14–120 ng/kg bw/day, above the limits of health concern recommended by the EFSA (0.017 ng/kg bw/day), while FB exposure ranged from 0.005 to 0.88 μg/kg bw/day (Magoha et al., 2016). Thus, mycotoxin exposure via complementary infant food was estimated to be higher, even in European countries.

7.2. Acrylamide dietary exposure

In Poland, infant exposure to AA through colostrum consumption was estimated to be 4.5–6 times lower than in infants breastfed in the second month of life. In general, the MoE calculated by these authors was higher than 10,000, although MoE values were below 10,000 in 5% of infants in the second month of life and 5% of infants on the third day of life, revealing a possible risk to infants (Mojska et al., 2021). Furthermore, the risk of AA exposure was lower in infants fed with breast milk than in those feed with formulas. Similarly, AA intake in Sweden was estimated to be 0.04 μg/kg bw/day during the first six months for exclusively breastfed children, while it was 0.5 μg/kg bw/day in the period between 7 and 12 months of age, when other manufactured products were introduced into the diet of infants (Fohgelberg et al., 2005). Little information is available in the literature about AA in human milk and hence, more studies are necessary to better estimate infant risk.

7.3. Bisphenols dietary exposure

In Spain, mainly in Valencia, breastfed infants were exposed to very low levels of total bisphenols, with an EDI for breastfed infants reaching a geometric mean of 0.04 μg/kg bw/day and a 95th percentile of 1.0 μg/kg bw/day, both below the TDI of 4 μg/kg bw/day fixed by the EFSA. However more studies are necessary to further extend this information (Dualde et al., 2019). Likewise, in a study of human milk in Poland BPA constituted the main source of potential risk for infants, although the hazard index (HQ) calculated for the cumulative impact indicated that the milk was safe for them even at the highest concentrations found, with values for the cumulated risk from parabens and BPA no higher than 0.128 (Czarczyńska-Goślińska et al., 2021).

7.4. Heavy metal dietary exposure

In Turkey, the potential risk of neonatal exposure to heavy metals through human milk consumption was evaluated, revealing estimated daily intakes of 1.72 μg/kg bw/day (Cr), 0.34 μg/kg bw/day (As), 0.08 μg/kg bw/day (Cd), 0.54 μg/kg bw/day (Hg) and 2.53 μg/kg bw/day (Pb). In the case of As, 32.3% of samples exceeded the reference value such that the potential risks of neonatal exposure should be borne in mind (Nazlıcan et al., 2022). In Saudi Arabia, a risk assessment revealed HQ values below 1 for Cd, inorganic Hg and Mg, but the HQ exceeded 1 for methylmercury in 68.5% of samples, indicating a potential health risk for infants through human milk consumption (Al-Saleh, 2021). In Iran, a study revealed a potential risk of infants to toxic metals through breastfeeding, especially Pb. In this regard, HQ values for Pb and As were >1 in 61% and 10% of the samples, respectively, while in the case of Cr the HQ was <1.0 for all samples (Samiee et al., 2019a). Also in Iran, a potential risk of As toxicity in infants via the consumption of human milk was reported, with an unacceptable HQ of 55% in infants breastfed in areas contaminated with As and of 41% in infants breastfed in non-contaminated areas (Samiee et al., 2019b). In Finland, exposure to Cd, Pb and inorganic As was determined in children aged 12 months, grouped as children who were still breastfeeding or not. The BMDL01 for neurological damage related to Pb exposure was exceeded in 60% of the non-breastfed and by 50% of the breastfed children and the BMDL01 for cancer risk related to As exposure was also exceeded by 77% of the non-breastfed and by 61% of the breastfed children. In the same line, these results showed that nearly 90% of the non-breastfed and more than the 50% of the breastfed children exceeded the tolerable weekly intake of Cd (Suomi et al., 2019).

8. Practical recommendations and future perspectives

Although the potential risk of mycotoxin, bisphenol, acrylamide and heavy metal exposure in infants through human milk consumption have been reported, the benefits of human breastfeeding are recognized and outweigh the potential risks. Moreover, the risks observed appear to be higher in non-breastfed children. Nevertheless, more studies should be conducted to evaluate the continuous daily intake of these compounds in order to more accurately assess their risk.

Some measures can be implemented to reduce infant and mother exposure to these chemicals. For instance, the presence of heavy metals should be routinely monitored, particularly in the most contaminated regions, exploring the factors that potentially contribute to their accumulation in mothers and infants. Moreover, it will also be important to establish and standardize reference values. Regarding mycotoxins, ensuring good agricultural and manufacturing practices throughout the food chain may prevent infants and adult exposure to mycotoxins, with exposure to mycotoxins potentially prevented by the application of adequate regulations.

Other strategies to minimize chemical exposure in infants consist of specific consumption recommendations for mothers, varying their diet and food sources, or limiting the commodities that are more susceptible to accumulate toxic compounds. For instance, to reducing the exposure of breastfeeding mothers to acrylamide could be achieved by limiting their consumption of thermally processed products rich in carbohydrates. Moreover, educating lactating mothers to exercise care when selecting the food they consume should yield benefits, with mothers aiming to maintain a healthy diet before and throughout the reproductive period, including the stages of lactation.

In conclusion, the data presented in this review highlights the need to 'biomonitor' the levels of toxic compounds in human milk. It is important to understand the factors that drive the accumulation of these compounds in human milk in order to implement correct prevention

measures and good practices, the first tools that will help avoid exposure of the population to these toxic compounds. Finally, it is important to establish harmonized guidelines and regulatory processes worldwide in order to guarantee standardized and correct measures of control.

CRediT authorship contribution statement

Noelia Pallarés: Writing – original draft, Data curation. **Emilia Ferrer:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Houda Berrada:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Francisco J. Barba:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Manuel Salgado-Ramos:** Writing – review & editing, Data curation. **María Carmen Collado:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

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

Data availability

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

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