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Review

Comparison between pollutants found in breast milk and infant formula in the last decade: A review

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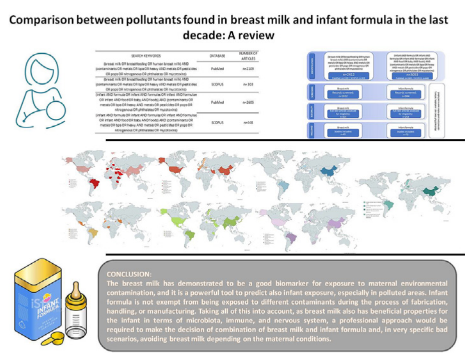
HIGHLIGHTS

- Description of emerging pollutants in breast milk and infant formula was made.
- In breast milk the most concerning contaminants found were metals and pesticides.
- In infant formula metals and mycotoxins were the most outstanding.
- Breast milk is a powerful tool to predict infant exposure to pollutants.

GRAPHICAL ABSTRACT



Abbreviations: 2-MCPD, 2-monochloropropane-1,2-diol; 3-MCPD, 3-monochloropropane-1,2-diol; 5-HMF, 5-(hydroxymethyl)-2-furancarboxaldehído; AAs, atomic absorption spectrometry; ADHD, attention-deficit/hyperactivity disorder; AFB1, aflatoxin B1; AFM1, aflatoxin M1; AFs, aflatoxins; Al, aluminum; AMA-AAs, gas chromatography (hydrocarbons analyzer)-atomic absorption spectrometry; As, arsenic; ASD, autism spectrum disorder; Au, gold; B, boron; b.w., body weight; Ba, barium; BBP, benzyl butyl phthalate; Be, beryllium; BFRs, brominated flame retardants; BHC, benzene hexachlorides; Bi, bismuth; BP, n-butylparaben; BP-3, benzophenone-3; BPA, bisphenol A; Ca, calcium; CALUX, chemically activated luciferase gene expression; CBCL, Child Behavior Checklist; Cd, cadmium; Cl, chlorine; Co, cobalt; CPF, chlorpyrifos; Cr, chrome; Cu, cooper; CV-AAs, cold vapour atomic absorption spectrometry; DBP, di-n-butyl phthalate; DEHP, di(2-ethylhexyl)phtalate; DIDP, di-isodecylphthalate; DINP, di-isononyl phthalate; DON, deoxynivalenol; DTT, 1,1,1-trichloro-2, 2-bis (4-chlorophenyl) ethane; ECNI, electron capture negative ion; ELISA, enzyme-linked immunosorbent assay; EP, ethylparaben; FAAs, flame atomic absorption spectroscopy; Fe, iron; FIMS, Flow-Injection Mercury System; Ga, gallium; GC-ECD, gas chromatography tandem electron capture detector; GC-EI, gas chromatography tandem electron ionization; GC-FID/MS, gas chromatography-flame-ionization detection tandem mass spectrometry; GC-HRMS, gas chromatography tandem high-resolution mass spectrometry; GC–MS, gas chromatography mass spectrometry; GC–MS/MS, gas chromatography tandem mass spectrometry; GC-QqQ-MS, ultra-sensitive gas chromatography method, coupled with tandem mass spectrometry; GE, glycidyl esters; Ge, germanium; GF-AAs, graphite furnace atomic absorption spectrometry; HBCDD, hexabromocyclododecane isomers; Hg, mercury; HMF, hydroxymethylfurfural; HPLC-AAs, high-performance liquid chromatography–atomic absorption spectrometry interface; HPLC-FLD-DAD, high performance liquid chromatography coupled with diode-array detector tandem fluorescence detector; HPLC-ICP-MS, high-performance liquid chromatography-inductively coupled plasma mass spectrometry; HR-CS-GFAAS, high-resolution continuum source-graphite furnace atomic absorption spectrometry; HRGC/MS, high-resolution gas chromatography coupled to mass spectrometry; HRMS, high-resolution mass spectrometry; HT-2, HT-2 toxin/trichothecene mycotoxin 2; I, iodine; IACC-HPLC with FD, IACC - high-performance liquid chromatography with field desorption; IARC, International Agency for Research on Cancer; ICP-MS, inductively coupled plasma mass spectrometry; ICP-MS/MS, inductively coupled plasma tandem mass spectrometry; ICP-OES, inductively coupled plasma optical emission spectrometer; In, indium; IQ, intelligent quotient; K, potassium; LCCPs, long-chain CPs; LC-MS/MS-APCI, liquid chromatography–tandem mass spectrometry with atmospheric pressure chemical ionization; Li, lithium; LRMS, low resolution mass spectrometry; MCCPs, medium-chain chlorinated paraffins; MeHg, methyl-mercury; Mg, magnesium; Mn, manganese; Mo, molybdenum; MOAH, aromatic hydrocarbons; MOH, mineral oil hydrocarbon; MOSH, hydrocarbons with saturated rings; MP, methylparaben; MP + EP, methyl parabens + ethyl parabens; MP-AES, microwave plasma-atomic emission spectrometer; Na, sodium; nAChRs, nicotinic acetylcholine receptors; Ni, nickel; OCPs, organochlorine pesticides; OPPs, organophosphorus pesticides; OTA, ochratoxin A; P, phosphorus; PAHs, polycyclic aromatic hydrocarbons; Pb, lead; PBDE, polybrominated diphenyl ethers; PBDE-135, 2,2′,3,3′,5,6′-hexabromodiphenyl ether; PBDE-209, 2,2′,3,3′,4,4′,5,5′,6,6′-decabromodiphenyl ether; PBDE-47, 2, 2′, 4, 4′-tetrabromodifenyl ether; PBDE-99, 2,2′,4,4,5-pentabromodiphenyl ether; PCBs, polychlorinated biphenyls; PCDDs, polychlorinated dibenzodioxins; PCDFs, polychlorinated dibenzofurans; PFAs, perfluorinated alkyl substances; PFOA, perfluorooctanoic acid; PFOs, perfluorooctanesulfonic acid; PHBA, p-hydroxybenzoic acid; Po, polonium; POPs, persistent organic pollutants; PP, N-propylparaben; PVC, polyvinyl chloride; PYR, pyrethroids; QuEChERS, Quick, Easy, Cheap, Effective, Rugged & Safe; RP-HPLC, reversed-phase high-performance liquid chromatography; S, sulfur; Sb, antimony; SCCPs, short-chain chlorinated parafins; Se, selenium; Si, silicon; Sn, tin; Sr, strontium; T2, T2 toxin; TBBPA, tetrabromobisphenol A; TCCD, 2,3,7,8-tetrachlorodibenzo-para-dioxin; TDI, tolerable daily intake; Te, tellurium; TSH, thyroid-stimulating hormone; UHPLC, ultra high-performance liquid chromatography; UNICEF, United Nations Children's Fund; UPLC-MS, ultra-performance liquid chromatography-tandem mass spectrometry; WHO, World Health Organization; ZEN, zearalenone; Zn, zinc.

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ABSTRACT

Since ancient times, breastfeeding has been the fundamental way of nurturing the newborn. The benefits of breast milk are widely known, as it is a source of essential nutrients and provides immunological protection, as well as developmental benefits, among others. However, when breastfeeding is not possible, infant formula is the most appropriate alternative. Its composition meets the nutritional requirements of the infant, and its quality is subject to strict control by the authorities. Nonetheless, the presence of different pollutants has been detected in both matrices. Thus, the aim of the present review is to make a comparison between the findings in both breast milk and infant formula in terms of contaminants in the last decade, in order to choose the most convenient option depending on the environmental conditions. For that, the emerging pollutants including metals, chemical compounds derived from heat treatment, pharmaceutical drugs, mycotoxins, pesticides, packaging materials, and other contaminants were described. While in breast milk the most concerning contaminants found were metals and pesticides, in infant formula pollutants such as metals, mycotoxins, and packaging materials were the most outstanding. In conclusion, the convenience of using a feeding diet based on breast milk or either infant formula depends on the maternal environmental circumstances. However, it is important to take into account the immunological benefits of the breast milk compared to the infant formula, and the possibility of using breast milk in combination with infant formula when the nutritional requirements are not fulfilled only with the intake of breast milk. Therefore, more attention should be paid in terms of analyzing these conditions in each case to be able to make a proper decision, as it will vary depending on the maternal and newborn environment.

Contents

1. Introduction

Mammals feed their infants with milk from the time they are born until they can acquire food by themselves (Gopalakrishna and Hand, 2020). This milk is also a mechanism for protection, as it can protect the mucosal surfaces of their immunologically inexperienced infants from infection. In this sense, the World Health Organization (WHO) recommends exclusive breastfeeding to infants for at least the first 6 months and breastfeeding with food supplementation up to 2 years of age, as it provides all the nutrients required for the healthy growth of the infant (Eidelman et al., 2012; Gopalakrishna and Hand, 2020). However, it is also important as a fertile ground for the establishment and growth of their gut microbiota, during this early and critical period of life (Andreas et al., 2015; Babakobi et al., 2020; Ballard and Morrow, 2013; Jeurink et al., 2013; Laursen et al., 2016).

Human milk in the first few days after birth is called colostrum, is produced until the 5th day of lactation, and is essential for the health of the newborns, as demonstrated in different studies (Devillers et al., 2011; Gopalakrishna and Hand, 2020; Quesnel et al., 2012; Wen et al., 2019). This colostrum is characteristic for having lower levels of fat and carbohydrates, but high content on proteins, both antimicrobial/immune-stimulatory and nutritional proteins (Gopalakrishna and Hand, 2020). Later, colostrum leads to mature milk. The composition of breast milk provides the infant several properties as immunoprotection, antioxidant effects, reduction of chronic diseases risk (types 1 and 2 diabetes, celiac disease, etc.), as well as cognitive developmental benefits, and improvement of maternal health (positive hormonal effects, physical and psychosocial effects) (Anderson, 1986; Matos et al., 2015). This milk has a higher concentration of lipids than colostrum: 87 % of it corresponds to water and 13 % are macro and micronutrients (Pajewska-Szmyt et al., 2019). Thus, as the breast milk will adapt to the needs of the growing infant changing the lipid and protein content, the molecules secreted with affinity to them will vary (Ballard and Morrow, 2013; LaKind et al., 2001).

In this regard, the ability of some pollutants to be transferred from mother to the infant through breastfeeding is well-known (Dewan et al., 2013; Müller et al., 2019; Skaare et al., 1988). This is of relevance, as fetuses and infants may be vulnerable to the exposure to these pollutants, as they can disrupt developmental processes that may cause permanent physiological changes (Müller et al., 2019). In addition, developing infants may accumulate higher concentrations and prolong the excretion of these toxicants due to their immature metabolic capacity (Müller et al., 2019; FAO/WHO, 2010; World Health Organization (WHO), 2010).

Table 1
Regulatory limits for main chemical contaminants and residues found in breast milk and infant formula. Calculated values according to the age and weight (WHO).

Contaminant or residue	Threshold levels in formula	Tolerable daily intake (TDI)	Calculated values according to the age and weight			References
			3 months (6.5 kg)	6 months (8 kg)	12 months (9.5 kg)	
Metals						
Ni	2.8 μg/kg	1.1 μg/kg b.w.	7.15 μg	8.8 μg	10.45 μg	(Schrenk et al., 2020; EFSA, 2015a)
Cu	120 μg/100 kcal	200 μg/day				(EFSA, 2016; Otten et al., 2006)
As	2.1 μg/kg	0.3 μg/kg b.w.	1.95 μg	2.4 μg	2.85 μg	(FAO/WHO, 2010; Rome et al., 2011)
Pb	20 μg/kg	3.57 μg/kg b.w.	23.21 μg	28.56 μg	33.92 μg	(EFSA, 2006; FAO/WHO, 1988)
Hg	–	4 μg/kg b.w.[a]	26 μg	32 μg	38 μg	(FAO/WHO, 2010; Rome et al., 2011)
MeHg		1.6 μg/kg b.w.	10.4 μg	12.8 μg	15.2 μg	(EFSA, 2004a)
Al	286 μg/kg	1000 μg/kg b.w.	6500 μg	8000 μg	9500 μg	(FAO/WHO, 2010; Rome et al., 2011)
Cd	20 μg/kg	0.36 μg/kg b.w.	2.34 μg	2.88 μg	3.42 μg	(EFSA, 2006; EFSA 2009)
Cr	10 μg/100 kcal	2.8 μg/kg b.w.	18.2 μg	22.4 μg	26.6 μg	(EFSA, 2015b)
Co	–	0.0012 μg/day[a]				(EVM, 2003)
Fe	2500 μg/100 kcal	500 μg/day				(EFSA, 2015a)
Mn	100 μg/100 kcal	3 μg/day				(EFSA, 2016; Otten et al., 2006)
Sn	50,000 μg/kg	14,000 μg/kg b.w.	9100 μg	11,200 μg	13,300 μg	(EFSA, 2005a; EFSA, 2006)
Zn	2400 μg/100 kcal	1000 μg/day				(EFSA, 2016)
Se		Until 6 months: 15 μg/day From 7 to 12 months: 20 μg/day				(Agostoni et al., 2014)
Ba		200 μg/kg b.w.	1300 μg	1600 μg	1900 μg	(US EPA, 2005)
Mo		10 μg/day				(Agostoni et al., 2013)
Sr		130 μg/kg b.w.	845 μg	1440 μg	1710 μg	(FAO/WHO, 2010)
I		70-130 μg/day				(Agostoni et al., 2014)
Nitrogen compounds						
Melamine	–	200 μg/kg b.w.[a]	1300 μg	1600 μg	1900 μg	(Alexander et al., 2010)
Chemical compounds derived from heat treatment						
Acrylamide	50 μg/kg	2.6 μg/kg b.w.	16.9 μg	20.8 μg	24.7 μg	(EFSA, 2015b; Tardiff et al., 2010)
Glycidol	–	2.1 μg/kg b.w.[a]	13.65 μg	16.8 μg	19.95 μg	(EFSA, 2016)
3-MCPD	125 μg/kg	2 μg/kg b.w.	13 μg	16 μg	19 μg	(EFSA, 2020; EFSA, 2018)
2-MCPD	–	1.2 μg/kg b.w.[a]	7.8 μg	9.6 μg	11.4 μg	(EFSA, 2016)
Benzo[*a*]pyrene	1 μg/kg	7300 μg/kg b.w.				(EFSA, 2007b; EFSA, 2008)
PAH2	–	170 μg/kg b.w.[a]	1105 μg	1360 μg	1615 μg	(EFSA, 2008)
PAH4	1 μg/kg	340 μg/kg b.w.[a]	2210 μg	2720 μg	3230 μg	(EFSA, 2008; EFSA, 2007b
PAH8	–	490 μg/kg b.w.[a]	3185 μg	3920 μg	4655 μg	(EFSA, 2008)
Dioxins	0.003 μg/kg					(EFSA, 2006)
Furan		64 μg/kg b.w.[b]	416 μg	512 μg	608 μg	(Knutsen et al., 2017)
5-HMF		1600 μg/person/day				(Arribas-Lorenzo and Morales, 2010)
Mycotoxins						
AFB1	0.1 μg/kg	0.4 μg/kg b.w.	2.6 μg	3.2 μg	3.8 μg	(EFSA, 2006; Schrenk et al., 2020a)
OTA	0.5 μg/kg	14.5 μg/kg b.w.	94.25 μg	116 μg	137.75 μg	(EFSA, 2006; Schrenk et al., 2020a)
AFM1	0.025 μg/kg	0.0002 μg/kg b.w.	0.0013 μg	0.0016 μg	0.0019 μg	(EFSA, 2006; Kuiper-Goodman, 1990)
DON	200 μg/kg	1 μg/kg b.w.	6.5 μg	8 μg	9.5 μg	(EFSA, 2006; EFSA, 2014a)
ZEN	20 μg/kg	0.25 μg/kg b.w.	1.625 μg	2 μg	2.375 μg	(EFSA, 2006; EFSA, 2014a)
Fumonisins (B1 + B2)	200 μg/kg	2 μg/kg b.w.	13 μg	16 μg	19 μg	(EFSA, 2006; EFSA, 2014a)
T2 + HT-2		100 ng/kg b.w.	0.65 μg	0.8 μg	0.95 μg	(EFSA, 2011a)
Pesticides						
OCPs	10 μg/kg					(EFSA, 2018)
OPPs		0.3 μg/kg b.w.	1.95 μg	2.4 μg	2.85 μg	(EFSA, 2012a)
Carbamates		0.558 μg/kg b.w.	3.63 μg	4.46 μg	5.30 μg	(EFSA, 2007c)
Pesticides	10 μg/kg					(EFSA, 2018)
Haloxyfop		0.65 μg/kg b.w.	4.23 μg	5.2 μg	6.18 μg	(EFSA, 2014b)
Atrazine	50 μg/kg					(EFSA, 2015b)
Triazine	5000 μg/kg					(EFSA, 2011b)
Packaging materials						
Phthalates		7.9 μg/kg b.w.	51.35 μg	63.2 μg	75.05 μg	(EFSA, 2005b)
BPA		4 μg/kg b.w.	26 μg	32 μg	38 μg	(Bolognesi et al., 2015)
PFAs		0.0063 μg/kg b.w.	0.0041 μg	0.005 μg	0.006 μg	(Schrenk et al., 2020b)
DEHP		50 μg/kg b.w.	325 μg	400 μg	475 μg	(EFSA, 2005b)
DBP		10 μg/kg b.w.	65 μg	80 μg	95 μg	(Silano et al., 2019)
BBP		500 μg/kg b.w.	3250 μg	4000 μg	4750 μg	(Silano et al., 2019)
DIDP		150 μg/kg b.w.	975 μg	1200 μg	1425 μg	(Silano et al., 2019)
DINP		150 μg/kg b.w.	975 μg	1200 μg	1425 μg	(Silano et al., 2019)
Other environmental contaminants						
PBDE-47		309 μg/kg b.w.	2008.5 μg	2472 μg	2935.5 μg	(EFSA, 2011c)
PBDE-99		12 μg/kg b.w.	78 μg	96 μg	114 μg	(EFSA, 2011c)
PBDE-153		83 μg/kg b.w.	539.5 μg	664 μg	788.5 μg	(EFSA, 2011c)
PBDE-209		1.7 μg/kg b.w.	11.05 μg	13.6 μg	16.15 μg	(EFSA, 2011c)
MOH		480 μg/kg b.w.	3120 μg	3840 μg	4560 μg	(EFSA, 2012b)
SCCPs		30 μg/kg b.w.	195 μg	240 μg	285 μg	(Schrenk et al., 2020c)

(continued on next page)

Table 1 (*continued*)

Contaminant or residue	Threshold levels in formula	Tolerable daily intake (TDI)	Calculated values according to the age and weight			References
			3 months (6.5 kg)	6 months (8 kg)	12 months (9.5 kg)	
MCCPs		6 μg/kg b.w.	39 μg	48 μg	57 μg	(Schrenk et al., 2020c)
TBBPA		1000 μg/kg b.w.	6500 μg	8000 μg	9500 μg	(Alexander et al., 2011)
HBCDDs		2.35 μg/kg b.w.	15.27 μg	18.8 μg	22.32 μg	(Alexander et al., 2011)
Perchlorate	20 μg/kg					(EFSA, 2014c)
MP + EP		10,000 μg/kg b.w.	65,000 μg	80,000 μg	95,000 μg	(EFSA, 2004b)

Abbreviations: b.w.: body weight; Ni: nickel; Cu: cooper; As: arsenic; Pb: lead; Hg: mercury; Al: aluminum; Cd: cadmium; Cr: chrome; Co: cobalt; Fe: iron; Mn: manganese; Sn: tin; Zn: zinc; 3-MCPD: 3-monochloropropane-1,2-diol; 2-MCPD: 2-monochloropropane-1,2-diol; PAH: polycyclic aromatic hydrocarbons; AFB1: aflatoxin B1: OTA: ochratoxin A; AFM1: aflatoxin M1; DON: deoxynivalenol; ZEN: zearalenone; T2: T-2 toxin; H-T2: HT-2 toxin; OCPs: organochlorine pesticides; OPPs: organophosphorus pesticides; BPA: bisphenol A; PBDEs: polybrominated diphenyl ethers; PFAs: perfluorinated alkyl substances; MOH: mineral oil hydrocarbon; SCCPs: short-chain chlorinated parafins.

[a] Maximum recommended values, as no explicit toxic thresholds have yet been set.

[b] Selected $BMDL_{10}$ due to the absence of an established TDI.

On the other hand, although breast milk is the natural and ideal source of feeding for infants to provide both the energy and the nutrients that they need, this is not always possible, and a great alternative would be the use of infant formula. For this, the composition of infant formula needs to meet the nutritional requirements according to the WHO and the United Nations Children's Fund (UNICEF) (World Health Organization (WHO), 2021), in order to provide all infant nourishment needs from 3 to 36 months old in substitution of breastfeeding. It is made of bovine milk, milk from other sources, or a mixture with/without other ingredients to complement infantile nutritional requirements. In this way, infant formula can be found as skimmed, diluted with vegetable oils, complemented with vitamins, minerals, and iron, and with added soy or rice for medical requirements like formulae for special needs (Martin et al., 2016). This composition, at macro and micronutrient levels, should be similar to natural breast milk. The quality and safety of infant formulas are highly regulated by government agencies, and all manufacturers must ensure the accomplishment of national and international quality criteria (Martin et al., 2016).

The consumption of both breast milk and formula will depend on the infant and their age. Although the breast milk intake is difficult to calculate, the infant formula usually comes with guidelines according to the manufacturer. In this sense, the intake of milk/formula is usually around 1 L, depending on the infant, divided in different servings during the day (Nestlé, 2008). There are maximum limits for contaminants and toxins established for these products, like those described by Codex Alimentarius (CODEX ALIMENTARIUS, 2016, 2017). In Table 1 are described the regulatory limits for main chemical contaminants and residues found in breast milk and infant formula.

Pollutants such as heat-treatment chemicals, pesticides, toxins, residues of packaging materials, and metals/metalloids, among others, can appear in both breast milk and infant formula. In the case of natural breast milk, the infant can be exposed to maternal environment, diet, and medical treatments. In the case of the infant formula, the different processes involved in their production, packing, transport, or storage process may also interfere (de Mendonça Pereira et al., 2020). The potential risk of these contaminants through the diet will depend on the levels and time of exposure.

The main contaminants taking part in childhood nourishment consist of the following: metals and metalloids (including arsenic (As), aluminum (Al), cadmium (Cd), lead (Pb), or mercury (Hg), among others), nitrogenous compounds (such as melamine or dicyandiamine), chemical compounds resulting from heat treatments (as advanced glycation end products (AGEs), acrylamide, furan, chloropropanols or glycidil esters (GE)), pharmaceutical drugs (antibiotics, hormones, etc.), mycotoxins (such as aflatoxins, ochratoxin A or zearalenone), pesticides (persistent organic pollutants (POPs), organochlorines (OCPs), organophosphates (OPPs), carbamates, pyrethroids, glyphosate, triazines, etc.), packaging materials (polyvinyl chloride (PVC), phthalates, bisphenol A) and other environmental contaminants (de Mendonça Pereira et al., 2020).

Taking all of this into account, the aim of the present review is to make an exhaustive search into the literature to compare the types of pollutants that can be present in both types of nutrition. With this information and considering different factors such as the environment and life conditions, a more convenient choice can be made in terms of the nutrition of the infants.

2. Material and methods

2.1. Search methodology

The databases Scopus and Pubmed/Medline were used for searching the required information to achieve the objectives of this review. The access to these manuscripts was granted through the library of the University of Seville, which has an open access agreement with the main publishers.

Search was performed using the following terms: for breast milk articles, the descriptors used were (breast milk OR breastfeeding OR human breast milk) AND (contaminants OR metals OR bpa OR heavy AND metals OR pesticides OR pops OR nitrogenous OR phthalates OR mycotoxins) from 2012 to 2022; and for infant formula the descriptors used were (infant AND formula OR infant AND formulas OR infant AND formulae OR infant AND food OR baby AND foods) AND (contaminants OR metals OR bpa OR heavy AND metals OR pesticides OR pops OR nitrogenous OR phthalates OR mycotoxins) from 2012 to 2022. All terms were included in titles, keywords or abstracts. The different numbers of manuscripts found are gathered in Table 2.

2.2. Data treatment and analysis

A compilation of relevant information and data about the main contaminants present in breast milk and infant formula worldwide was made. The data screening was focused on those studies with a large number of samples, located in concrete areas, with a clear population, and where the methodology used was described, and the detection of the product itself was trust-worthy in terms of sensitivity, and coming from original research works, and available internationally (written in English).

The papers finally selected for inclusion in this review were based not only on the title, but also on the screening of the abstract and full text (Fig. 1). It is important to note that other relevant studies related to this topic were found by cross-referencing.

Once the data was obtained, two databases were built, one for the data related to breast milk and the other with the data related to infant formula. Both databases contained the following 6 sections: (1) location, (2) number of samples (N), (3) contaminants/residues found, (4) analytical methods, (5) main outcomes, (6) references.

3. Results and discussion

After applying the selection criteria, a total of 65 and 73 manuscripts were included for breast milk and infant formula, respectively, discovering the main health effects of each group of pollutants. Thus, the studies were divided according to the toxicants into different categories.

Table 2
Search in the two main databases for the terms used. Different number of articles found in the two main databases used for this purpose, which included information about breast milk or infant formula, and its main contaminants.

Search keywords	Database	Number of articles	Year of the search
(breast milk OR breastfeeding OR human breast milk) AND (contaminants OR metals OR bpa OR heavy AND metals OR pesticides OR pops OR nitrogenous OR phthalates OR mycotoxins)	PubMed	n = 2109	2022
(breast milk OR breastfeeding OR human breast milk) AND (contaminants OR metals OR bpa OR heavy AND metals OR pesticides OR pops OR nitrogenous OR phthalates OR mycotoxins)	SCOPUS	n = 303	2022
(infant AND formula OR infant AND formulas OR infant AND formulae OR infant AND food OR baby AND foods) AND (contaminants OR metals OR bpa OR heavy AND metals OR pesticides OR pops OR nitrogenous OR phthalates OR mycotoxins)	PubMed	n = 2605	2022
(infant AND formula OR infant AND formulas OR infant AND formulae OR infant AND food OR baby AND foods) AND (contaminants OR metals OR bpa OR heavy AND metals OR pesticides OR pops OR nitrogenous OR phthalates OR mycotoxins)	SCOPUS	n = 448	2022

3.1. Metals

Metal ions are required for the maintenance of many biological functions in the human body (Gupta, 2018). Therefore, it is important to have a good amount of them, while an excess, especially of those known as heavy metals, can exert toxicity on the organism (Gupta, 2018). Concerning this, while chromium (Cr) and copper (Cu) present a very narrow concentration range between beneficial and toxic effects in the organism, some others such as Al, As, barium (Ba), beryllium (Be), bismuth (Bi), Cd, gallium (Ga), germanium (Ge), gold (Au), indium (In), Pb, lithium (Li), Hg, or nickel (Ni), have no established biological function (Chang, 1996; Tchounwou et al., 2012).

Despite the mechanisms regulating the secretion of essential metals in milk to the newborn from the mammary glands, levels of these compounds have been found in breast milk (Cardoso et al., 2017; Tchounwou et al., 2012). These types of compounds usually have high lipid solubility, together with their accumulation in some specific body tissues (Cardoso et al., 2017). Due to the biological relevance of metal exposure in infants, several studies have been carried out regarding their presence in both breast milk and infant formula.

According to their position on the periodic table and their properties, these elements can be divided into metals (such as iron (Fe), Cr, cobalt (Co), Cu, Hg, etc.) and metalloids (boron (B), silicon (Si), Ge, As, antimony (Sb), tellurium (Te) and, polonium (Po)).

Among the most common ones, it is important to mention As, Hg, Pb, and Cd due to their toxic properties. As is one of five toxic metals (together with Hg, Pb, Cd, and Cr) of priority list published by the Agency for Toxic Substances and Disease Registry (Agency for Toxic Substances and Disease Registry, 2022). This metalloid is environmentally present in both organic and inorganic forms. Inorganic forms are soluble in water, and they are able to accumulate in soils and move up through the food chain, while organic forms are absorbed in the digestive tract as As(III) and As (V). This As(V) is reduced to As(III), and in this process are generated reactive intermediates that can lead to toxic effects such as lower body of newborn child, weakening of cognitive functions, or respiratory disease (Carignan et al., 2015). The exposure and accumulation of As can be due to drinking water contamination. On the other hand, Hg is present in the environment in organic (MeHg), inorganic (Hg^{2+}) or elemental (Hg^{0}) forms. These forms are present in the atmosphere or in water. The presence of Hg in breast milk is usually due to the consumption of fish, the use of

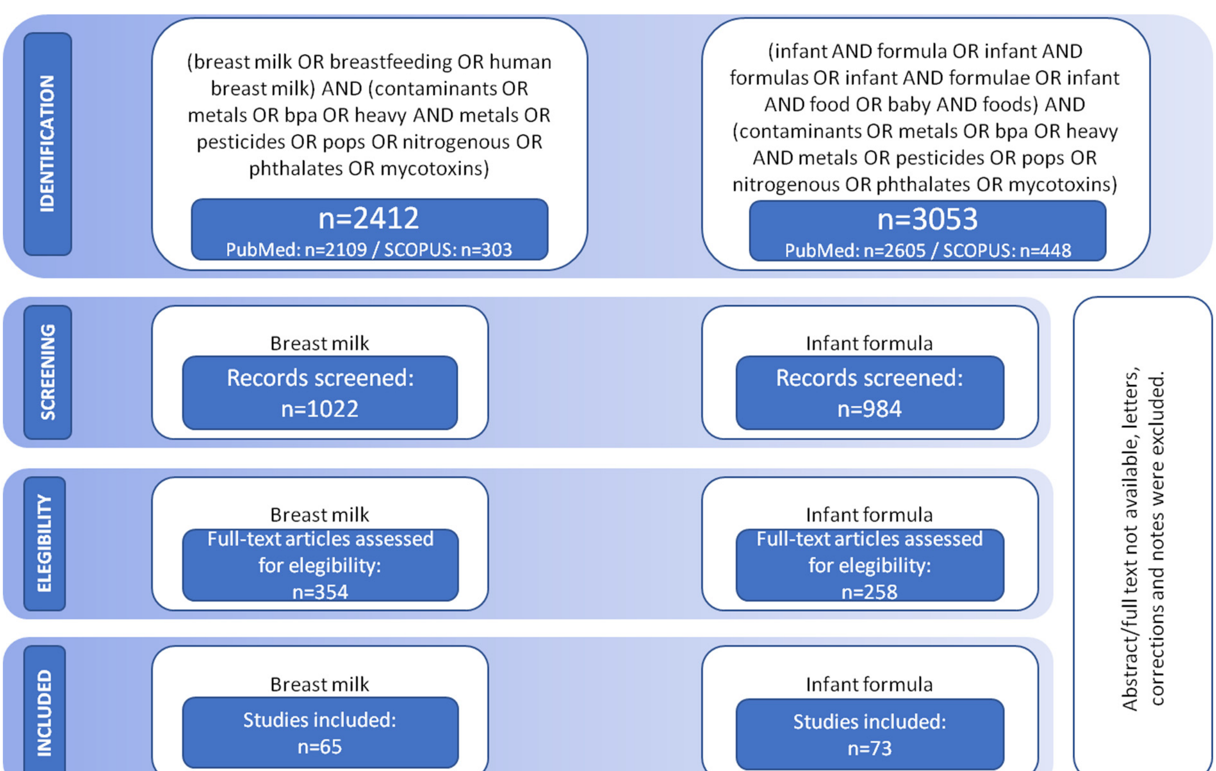

Fig. 1. Schematic representation of data treatment.

amalgam fillings, or the residence in mining areas (Maeda et al., 2019). The absorption pathways of different forms of Hg are respiratory, digestive, and transdermic. Once inside, it either accumulates in kidneys and tissues with high fat-density, or is excreted through urine, feces, or bile. Inorganic Hg can also cross the blood-brain barrier due to its high lipophilicity and be transported to the placenta due to this physicochemical property (Holmes et al., 2009). This lipophilicity leads to the finding of Hg levels in breast milk, and the exposure during lactation may be related with damage to neuronal development (Al-Saleh et al., 2013). Some other relevant compounds that can be found in milk are Pb and Cd. Lead can get into organisms by digestive, respiratory, and transdermic pathways, and is transported by red blood cells into the liver, kidneys, and nervous system, or accumulated in hair. It is excreted by urine, feces, sweat, and in nursing mothers by breast milk (Babayigit et al., 2016). This element has high affinity for thiol groups and contributes to the production of reactive oxygen species, which generates oxidation of enzymes, proteins, and even DNA (Flora et al., 2012). Lead is accumulated in bones, where it remains for life, but can be released into the body and milk as a result of bone resorption during pregnancy and lactation (Gulson et al., 2004). Concerning Cd, the exposure is depending on lifestyle such as smoking, diet and place of residence. Cadmium can get into the body through respiratory and digestive tracts, binds to proteins like albumins and metallothionein, and is transported by blood (Zalups and Ahmad, 2003). When it binds to chlorine (Cl), they form $CdCl_2$, which affects liver and kidneys through long-term accumulation by strong affinity to the complex Cd-metallothionein and is excreted by feces and urine. It is associated with asthma prevalence and preterm birth (Wang et al., 2016).

Besides those compounds, it is also important to consider the maternal environmental exposure to trace elements like Al, magnesium (Mg), Cu, Fe, molybdenum (Mo), selenium (Se), zinc (Zn), Ba, and strontium (Sr), which can occur through lifestyle, air, area of residence, food, or sometimes by artisanal aluminum cookware (Weidenhamer et al., 2017). Manganese, Cu, Fe, Mo, Se, and Zn are essential for several enzymatic reactions as arginine, glutamine synthetase, for synthesis of hemoglobin, integrity of central nervous system, antioxidant capacity, and cofactor as enzymes, whereas for Ba and Sr there is no current evidence of their essentiality. In this sense, Mn is important for development and for the antioxidant system as cofactor of certain enzymes (Prashanth et al., 2015), but can be accumulated in certain brain regions, which can lead to neurotoxic effects (Dobson et al., 2004). Furthermore, Cu is an essential component of enzymes present in electron transport, oxidation, and synthesis of melanin (Uauy et al., 1998). Moreover, Fe is important in an array of enzymes, oxygen transport and energy-transduction systems (Siegel et al., 2011), and its deficiency is related to anemia. Zinc participates in the structure of three thousand proteins in humans and has a regulatory function in mammalian cells. Chromium is a transition metal naturally present in the environment and some industrial processes release amounts of Cr via food, air, or water. This metalloid can easily cross the placenta, causing fetal damage as well (Barker et al., 2002). Lastly, Ni can be found in air, soil, water, biological material, and in anthropogenic activities (dental or orthopedic implants, metallurgical, tobacco, etc.) (Cempel and Nikel, 2006). This element is involved in iron metabolism and can stabilize the tertiary structure of nucleic acids and proteins (Nielsen, 1982). However, it is responsible of some allergic contact dermatitis (Nielsen, 1982) by dermal contact, and a potent carcinogen by inhalation (Haber et al., 2000).

Focusing on the development, exposure to toxic metals and metalloids in prenatal and postnatal stages can cause a negative impact on the offspring health from birth by leading to cancer, allergy, or neurodevelopmental disorders and cognitive impairments (Weyde et al., 2021). For instance, the exposure to Pb during development can lead to several adverse effects on the hematologic, gastrointestinal, and renal systems (Tatsuta et al., 2020). In addition, Cd, As, Pb, and Mn have also been linked to anthropometric changes such as lower birth weight, shorter gestational age, or smaller head circumference (Rahman et al., 2021). Furthermore, Ni has also been related to different types of cancer and, additionally, to dermatitis or epigenetic changes and apoptosis induction (Yüksel et al., 2021).

From the early stages of life, ranging from prenatal to the first years of life of the newborn, neurodevelopment might be one of the most important functions to be developed. Emerging evidence relates Pb-, Cd-, and Hg-exposure to reduced intelligence score and neuropsychological test scores, both abnormalities in neurodevelopment, while Mn has also been associated with poor neurobehavioral performance (Lee et al., 2021). Cadmium has also been linked to lowered cognition and neurodegenerative disorders such as Parkinson's and Alzheimer's diseases (Sulaiman et al., 2020). In addition, Al is also one of the metals that might play an important role in the development of these disorders. Aluminum-induced neurotoxicity is yet to be completely elucidated, although it is known that this chemical plays important roles such as acceleration and promotion of some characteristics of brain aging, and Al salts can lead to glial activation and cytoskeletal changes in neural cells (Sulaiman et al., 2020). Moreover, Hg has a very strong capacity to permanently damage the nervous system, including personality, sensory, cognitive, and memory deficits (Sulaiman et al., 2020). These developmental stages are so sensitive to changes because it is during this time that different processes such as synaptic pruning, myelination, and neuronal transmission, among others, take place, and the exposure to metals can cause disturbances on a correct development (Bauer et al., 2020).

Among the most important neurodevelopmental disorders, in the recent years, autism spectrum disorder (ASD) has drawn an increased attention since it refers to a wide range of disorders characterized by a varied array of behavioral aberrations, communication difficulties, and even challenges in social interaction (Sulaiman et al., 2020; Wang et al., 2019). The symptoms of ASD become noticeable in the early years of childhood, between the second and fifth year of life, and they persist on adulthood, being associated with other coexisting conditions that range from epilepsy to attention-deficit/hyperactivity disorder (ADHD) (Wang et al., 2019). The pathogenesis of ASD remains still not understood and appears to be multifactorial, with a combination of genetic and biological factors with environmental influences during a certain window on the development where increasing metal exposure due to a rise of industrialization plays and important role (Sulaiman et al., 2020).

Taking all the above into account, the detection of these compounds in breast milk and infant formula is essential in terms of children's safety. Concerning the metals and metalloids found in breast milk, the most common found were Pb, Mn, Zn, Cd, Hg, and Ni. In this sense, in Africa, a study performed in Morocco measuring the levels of Pb in breast milk led to a mean value lower than the TDI established by the EFSA, although the levels were higher than this value in some of the samples tested (Cherkani-Hassani et al., 2021a). This element was also measured in Nigeria, where a study of some other metals such as Cd, Cr, Cu, Fe, and Zn, was also performed, dividing the findings by age range. In this sense, also dangerous levels of Pb were detected in all the cohorts measured, together with high levels of Cd, and levels close to the TDI value were observed in 18-25 years old mothers for Cr (Ekeanyanwu et al., 2020). Similar elements were found in Asia, as a study performed in Turkey in 34 mothers led to excessive values of Pb, Cd, and Ni (Nazlıcan et al., 2022). These pollutants were also found in America, as 4 different studies performed in Brazil led to higher values of Mn, As, Pb, Cd, Cu, Se, Zn, Fe, and I than the recommended, while elements such as Al, Hg, and Mo gave a safe mean between all the subject, although some of them presented also higher values than the ones considered safe (Alves Peixoto et al., 2019; Bastos et al., 2018; Mello-Neto et al., 2010; Trinta et al., 2020). In addition, in Europe, high levels of Zn, Mn, Fe, Ni, Se, and Cu were detected in Spain, while levels lower than the TDI of As, Cd, Pb, Hg, and Cr were found. However, in the last case, although the mean was considered safe, some of the samples gave values very above the concentration recommended (Motas et al., 2021). All these findings are gathered in Table 3.

Regarding the metals found in formula, exceeding values of these pollutants have been found in Africa, America, Asia, and Europe as well,

Table 3
Levels of metals found in breast milk expressed by mean ± SD, or as median: range.

Location	Samples (n)	Contaminants	Methods	Main outcomes	Ref.
Africa					
Morocco	n = 70	Pb	ICP-MS	Pb: 23.08 ± 62.75 μg/L	(Cherkani-Hassani et al., 2021b)
Nigeria	n = 225 divided by age:	Cd, Cr, Cu, Fe, Pb, Zn	HPLC, AAS	18-25 years old:	(Ekeanyanwu et al., 2020)
	18-25: n = 34 26-30: n = 118 31-35: n = 45 36-40: n = 28			Cd: 25 ± 13 μg/L Cr: 20 ± 13 μg/L Cu: 34 ± 11 μg/L Fe: 51 ± 59 μg/L Pb: 44 ± 13 μg/L Zn: 7 ± 51 μg/L 26-30 years old:	
				Cd: 31 ± 14 μg/L Cr: 18 ± 12 μg/L Cu: 37 ± 14 μg/L Fe: 47 ± 24 μg/L Pb: 39 ± 12 μg/L Zn: 8 ± 6 μg/L 31-35 years old:	
				Cd: 28 ± 13 μg/L Cr: 26 ± 11 μg/L Cu: 45 ± 6 μg/L Fe: 67 ± 57 μg/L Pb: 39 ± 15 μg/L Zn: 18 ± 13 μg/L 31-35 years old:	
				Cd: 27 ± 16 μg/L Cr: 14 ± 42 μg/L Cu: 29 ± 14 μg/L Fe: 31 ± 16 μg/L Pb: 31 ± 12 μg/L Zn: 6 ± 21 μg/L	
Zimbabwe	n = 120 (control vs medium exposed vs occupational exposure)	Hg	CV-AAS	Control group: 0.5 μg/L Medium exposure group: 1.10 μg/L High exposure group: 1.20 μg/L (No limits or deviation was given)	(Bose-O'Reilly et al., 2020)
America					
Brazil	n = 106	Cd, Pb, Al, As, Hg, Mn, Pb	FIMS, ICP-OES	Al: 2307 ± 2300 μg/L Mn: 119 ± 170 μg/L As: 63 ± 100 μg/L Hg: 10 ± 10 μg/L Pb: 531 ± 400 μg/L Cd: 74 ± 10 μg/L	(Bastos et al., 2018)
Brazil	n = 156	Ba, Cu, Fe, Mn, Mo, Se, Sr, Zn	ICP-MS	Ba: 11.6: 0.6–88.2 μg/L Cu: 618.3: 95.4–954.5 μg/L Fe: 380: 110.5–3594 μg/L Mn: 4.5: 1.6–22.2 μg/L Mo: 9.3: 0.1–39.1 μg/L Se: 12.6: 3.0–70.6 μg/L Sr: 43.5: 14.9–71.1 μg/L Zn: 2614.4: 422.8–17,727.2 μg/L	(Alves Peixoto et al., 2019)
Brazil	n = 25 Pre-term: n = 12 Full-term: n = 13	Fe, Cu, Zn, I	HPLC-ICP-MS	Pre-term:	(Trinta et al., 2020)
				Fe: 997 ± 1240 μg/L Cu: 506 ± 241 μg/L Zn: 4150 ± 3090 μg/L I = 458 ± 324 μg/L Full-term:	
				Fe: 733 ± 1120 μg/L Cu: 234 ± 136 μg/L Zn: 2910 ± 3090 μg/L I: 2550 ± 1300 μg/L	
Brazil	n = 161	Fe	ICP-OES	16-19 years old: 400 ± 210 μg/L 20-29 years old: 320 ± 200 μg/L 30-41 years old: 390 ± 540 μg/L	(Mello-Neto et al., 2010)
	16-19 years old: n = 18 20-29 years old: n = 74 30-41 years old: n = 44				

(continued on next page)

Table 3 (*continued*)

Location	Samples (n)	Contaminants	Methods	Main outcomes	Ref.
Asia					
South Korea	n = 207	Hg	AMA, AAS	15 days: Hg: 1.19 ± 1.24 μg/L 30 days: Hg: 0.79 ± 0.73 μg/L	(Park et al., 2018)
Saudi Arabia	n = 155	Hg	AAS, GC–MS, AMA	1.191 ± 0.764 μg/L	(Al-Saleh et al., 2013)
Turkey	n = 34	Cr, As, Cd, Hg, Pb	ICP-MS	Cr: 8.249 ± 11.69 μg/L As: 1.64 ± 1.85 μg/L Cd: 0.37 ± 0.47 μg/L Hg: 2.59 ± 3.47 μg/L Pb: 12.12 ± 9.08 μg/L	(Nazlıcan et al., 2022)
Turkey	n = 64	Pb, Cd, Ni, As	AAS	Pb: 391.45 ± 269.01 μg/L Cd: 4.62 μg/L (1 sample) Ni: 43.94 ± 33.82 μg/L As: Not detected	(Gürbay et al., 2012)
Europe					
Cyprus	n = 50	Pb, Cd, As, Hg	ELISA, ICP-MS	Pb: 1.19 ± 1.53 μg/L Cd: 0.45 ± 0.23 μg/L As: 0.73 ± 0.58 μg/L Hg: 0 ± 0.20 μg/L	(Kunter et al., 2017)
Norway	n = 300	Cd, Pb, Hg	ICP-MS/MS	Hg: 0.2 ± 0.17 μg/kg Cd: 0.08 ± 0.10 μg/kg Pb: not detected	(Vollset et al., 2019)
Poland	n = 320	Cd, Pb, Cu, Zn	GF AAS	Cd: 2.114 ± 2.112 μg/L Pb: 6.331 ± 4.614 μg/L Cu: 0.137 ± 0.092 μg/L Zn: 1.623 ± 1.763 μg/L	(Winiarska-Mieczan, 2014)
Spain	n = 50	Al, Zn, As, Cd, Pb, Hg, Cr, Mn, Fe, Ni, Cu, Se	ICP-MS	Al: 34.3 ± 133.0 μg/L Zn: 1402.6 ± 1742.7 μg/L As: 0.9 ± 2.71 μg/L Cd: 0.4 ± 1.6 μg/L Pb: 5.2 ± 16.7 μg/L Hg: 5.6 ± 12.4 μg/L Cr: 16.1 ± 63.6 μg/L Mn: 10.7 ± 63.6 μg/L Fe: 679.1 ± 1387.3 μg/L Ni: 25.3 ± 33.8 μg/L Cu: 368.5 ± 301.0 μg/L Se: 44.5 ± 49.5 μg/L	(Motas et al., 2021)
Spain	n = 242	Pb, Hg, Cd, As	ICP-MS	As: 1.49: 0.56-3.50 μg/L Hg: 0.26: 0.05-1.17 μg/L Pb: 0.14: 0.10-6.31 μg/L Cd: not detected	(Freire et al., 2022)

being Fe, Zn, Mn, and Ni the most common ones. In the case of Africa, high values of Zn have been found in Egypt, Ethiopia, and Tanzania (Eticha et al., 2018; Ghuniem et al., 2020b; Sager et al., 2018). In addition, high levels of Fe, Cu, Mn, and As were found in Egypt (Ghuniem et al., 2020b; Ghuniem et al., 2020a; Ibrahim et al., 2020), while in Nigeria, high levels of Mn, Cr, Co, As, Pb, and Cd were reported as well (Igweze et al., 2020a,b; Igweze et al., 2019). Additionally, although the results together led to a value higher than the one established by EFSA, higher levels were detected for Al and Hg in some of the cases as well (Igweze et al., 2020a,b). Furthermore, in Tanzania, high levels of calcium (Ca), Co, I, potassium (K), Mg, Mn, Mo, sodium (Na), phosphorus (P), sulfur (S) and Ba, among others, were also detected (Sager et al., 2018). Concerning America, a study performed using only 3 samples led to high levels of Zn in Brazil, while also in a Brazilian study, high levels of As, Cr and Ni were detected (de Mendonça Pereira et al., 2020; de Paiva et al., 2019). In Asia, exceeding levels of Fe, Zn, Mn, Ni, and Co were found in Jordan (Tahboub et al., 2021), while in Pakistan, the exceeding values were found for Fe and Zn, while high levels of Cd were found only for some of the samples (Saeed et al., 2021). In Europe, the metal exceeding the TDI value in most countries was Fe, according to studies performed in Italy (Astolfi et al., 2021), Malta (Vella and Attard, 2019), and Spain (Gómez-Nieto et al., 2020; Paz, 2017). In addition, high levels of Mn and Zn were also found in Malta and Spain (Motas et al., 2021; Vella and Attard, 2019), while exceeding levels of Co were found in Italy (Astolfi et al., 2021) and of Ni in Malta (Vella and Attard, 2019). These studies are collected in Table 4.

As a conclusion, more metals were found in infant formula in Africa, Asia, and Europe, while it seemed to be safer metal-wise in America, as can be seen represented in Supplementary Fig. 1.

3.2. Chemical compounds derived from heat treatment

Among the pollutants that can be found in both breast milk and infant formula, it is also worth to mention the presence of chemical compounds derived from heat treatment. In this category, different types of contaminants such as polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), dioxins, acrylamide, etc. can be found (Acharya et al., 2019). In this regard, PAHs are a large group of chemicals containing 2 to 7 fused aromatic rings (Kim et al., 2013). These pollutants are released into the environment, and thus reach humans through both natural and anthropogenic sources, such as incomplete burning of fuels, garbage, or tobacco and plant material (Kim et al., 2013; Polynuclear aromatic hydrocarbons in Drinking-water Background document for development of WHO Guidelines for Drinking-water Quality, 2003; Zhang and Tao, 2009). These compounds are well-known for being carcinogenic, mutagenic, and teratogenic (Kim et al., 2013) and, although the organism is able to metabolize them after acute exposure, long-term exposure can lead to their accumulation in adipose tissues and visceral organs (Acharya et al., 2019). Among these compounds, the ones found in breast milk and/or infant formula according to the classification of the international agency for research on cancer (IARC) were benzo[*a*]pyrene as a carcinogenic to humans (1A); naphthalene, benzo[*a*]

Table 4
Levels of metals found in infant formula expressed by mean ± SD, or as median: range.

Location	Samples (n)	Contaminants	Methods	Main outcomes	Ref.
Africa					
Egypt	n = 83	Cd, Cr, Co, Cu, Fe, Pb, Mn, Ni, Sn, Zn	ICP-OES and GFAAS	Cd: 5–17 μg/kg Fe: 32,000–86,870 μg/kg Cu: 0-8760 μg/kg Mn: 0-7110 μg/kg Zn: 22,460-87,300 μg/kg Cr, Co, Ni, and Pb: not detected	(Ghuniem et al., 2020b)
Egypt	n = 28	Pb, Cd, Sb, Cu, Zn, Fe, Cr, Sn, Co, Mn, Ni	ICP OES + UN	Mn: 3300 μg/kg Fe: 47,400 μg/kg Cd: 20 μg/kg Cu: 1000 μg/kg Zn: 11,400 μg/kg Cr, Pb, Sb: Not detected	(Ghuniem et al., 2020a)
Egypt	n = 60	Pb, As, Cd, Hg, Al	ICP-MS	Milk based: Pb: 424 ± 6 μg/kg As: 205 ± 3 μg/kg Cd: 14 ± 0.1 μg/kg Hg: 298 ± 7 μg/kg Al: 464 ± 29 μg/kg Milk-cereal based: Pb: 145 ± 4 μg/kg As: 214 ± 8 μg/kg Cd: 14 ± 0.1 μg/kg Hg: 296 ± 14 μg/kg Al: 352 ± 9 μg/kg	(Ibrahim et al., 2020)
Ethiopia	n = 5	Cd, Pb, Zn	AAS	Cd: Not detected Pb: 0-103 μg/kg Zn: 27,888-71,553 μg/kg	(Eticha et al., 2018)
Nigeria	n = 26	Fe, Z, Mn, Cr, Co	AAS	Milk based: Fe: 4080 ± 1950 μg/kg Zn: 6710 ± 2100 μg/kg Mn: 150 ± 90 μg/kg Cr: 610 ± 700 μg/kg Co: 120 ± 320 μg/kg Cereal based: Fe: 3710 ± 1090 μg/kg Zn: 6110 ± 1450 μg/kg Mn: 90 ± 60 μg/kg Cr: 360 ± 620 μg/kg Co: 10 ± 20 μg/kg Cereal mix based: Fe: 4490 ± 1560 μg/kg Zn: 7140 ± 2560 μg/kg Mn: 100 ± 80 μg/kg Cr: 400 ± 360 μg/kg Co: 10 ± 10 μg/kg	(Igweze et al., 2019)
Nigeria	n = 26	Al, As and Hg	AAS	Al: 410-2470 μg/kg As: 20-1560 μg/kg Hg: 0-50 μg/kg	(Igweze et al., 2020a)
Nigeria	n = 26	Pb and Cd	AAS	Milk based: Pb: 610-3500 μg/kg Cd: 10-550 μg/kg Cereal based: Pb: 290-1950 μg/kg Cd: 20-370 μg/kg Cereal mix based: Pb: 470-2340 μg/kg Cd: 1-460 μg/kg	(Igweze et al., 2020b)
Tanzania	n = 8	Ca, Co, Cr, Cu, Fe, J, K, Mg, Mn, Mo, Na, P, S, Zn, Ba, Cd, Ni, Pb, Al, B, Be, Bi,	ICP-MS	Ca: 8477000: 7,205,000–8,867,000 μg/kg Co: 41: 33-63 μg/kg	(Sager et al., 2018)

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Table 4 (*continued*)

Location	Samples (n)	Contaminants	Methods	Main outcomes	Ref.
		Ce, Cs, Er, Eu, Gd, Ho, La, Li, Lu, Nd, Pr, Rb, Sc, Si, Sm, Sr, Tb, Ti, Tl, V, Y		Cr: 76: 60-91 μg/kg Cu: 405: 218-664 μg/kg Fe: 2450: 1910-3380 μg/kg J: 2.08: 1130-6380 μg/kg K: 10452: 8,988,000-11,386,000 μg/kg Mg: 776000: 701,000-806,000 μg/kg Mn: 184: 157-265 μg/kg Mo: 308: 296-383 μg/kg Na: 2777000: 2,603,000-3,419,000 μg/kg P: 6843000: 5,923,000-7,411,000 μg/kg S: 2331000: 2,021,000-2759 μg/kg Zn: 31400: 26,800-33,800 μg/kg Ba: 594: 459-751 μg/kg Cd: 4: 2-8 μg/kg B: 740: 21-1550 μg/kg Ce: 2: 2-6 μg/kg Cs: 19: 13-29 μg/kg Li: 32: 7-57 μg/kg Rb: 6550: 5880-13,670 μg/kg Si: 2980: 2310-5600 μg/kg Sr: 2690: 2280-3030 μg/kg Ti: 110: 100-150 μg/kg Ni, Pb, Al, Be, Bi, Er, Eu, Gd, Ho, La, Li, Lu, Nd, Pr, Sc, Sm, Tb, Tl, V, Y: not detected	
America					
Brazil	n = 3	Cd, Pb, Al, Cu, Zn, Ni	GFAAS	Cd: 2 μg/kg Al: 1000 μg/kg Cu: 410 μg/kg Zn: 39,600 μg/kg Ni: 50 μg/kg Pb: not detected	(de Paiva et al., 2019)
Brazil	n = 140	As, Cd, Pb, Al, Cr, Ni	ICP-MS	As: 0.007-0.01 μg/kg Cd: 0.23 μg/kg Pb: 0.90 μg/kg Al: 50 μg/kg Cr: 37.75 μg/kg Ni: 25.47 μg/kg	(de Mendonça Pereira et al., 2020)
United States	n = 91	Pb, Cd	ICP-MS	Pb: 9.72 μg/kg Cd: 5.60 μg/kg	(Gardener et al., 2019)
Asia					
China	n = 93	Cr, As, Cd, Pb	ICP-MS	Cr: 2.51–83.80 μg/kg As: 0.89–7.87 μg/kg Cd: 0.13–3.58 μg/kg Pb: 0.36–5.57 μg/kg	(Su et al., 2020)
India	n = 10	As, Cd, Hg, Pb	ICP-MS	As: 0.018 μg/kg Cd: 0.014 μg/kg Hg: 0.013 μg/kg Pb: 0.016 μg/kg	(Pacquette and Anumula, 2016)
Iran	n = 80	Pb, Cd	GFAAS and ELISA	Pb: 12.57 μg/kg Cd: 4.97 μg/kg	(Dehcheshmeh et al., 2021)
Iran	n = 30	Zn, Cu	AAS	Zn: 3980 ± 250 μg/kg Cu: 530 ± 170 μg/kg	(Khaghani et al., 2010)
Jordan	n = 22	24 trace elements: Essential (Mg, Fe, Zn, Cu, Mn, Ni, Cr, Mo, Co, and Se), non-essential (Al, Ag, Ba, Bi, Cs, Ga, Li, Rb, Sr, U, and V), and potentially toxic elements (As, Cd, and Pb)	ICP-MS	Mg: 445,000 ± 256,000 μg/kg Fe: 65,002 ± 33,400 μg/kg Zn: 32,009 ± 19,000 μg/kg Cu: 2420 ± 1040 μg/kg Mn: 984 ± 959 μg/kg Ni: 344 ± 192 μg/kg Cr: 588 ± 381 μg/kg Mo: 135 ± 75 μg/kg Co: 55.4 ± 48.8 μg/kg Se: 120 ± 72 μg/kg Al: 4600 ± 3800 μg/kg Ag: 2.8 ± 1.6 μg/kg Ba: 434 ± 250 μg/kg Bi: 7.0 ± 2.8 μg/kg Cs: 10.4 ± 11.6 μg/kg Ga: 2.09 ± 1.73 μg/kg Li: 19.8 ± 13.9 μg/kg Rb: 2672 ± 1731 μg/kg Sr: 1597 ± 73 μg/kg U: 3.02 ± 2.05 μg/kg V: 21.9 ± 14.4 μg/kg As: 4.7 ± 3.9 μg/kg	(Tahboub et al., 2021)

Table 4 (*continued*)

Location	Samples (n)	Contaminants	Methods	Main outcomes	Ref.
				Cd: 8.0 ± 16.3 μg/kg Pb: 64.9 ± 39.9 μg/kg	
Lebanon	n = 78	Pb, Cd, As	ICP-MS	Pb: 371 ± 581 μg/kg Cd: 255 ± 179 μg/kg As: 88.7 ± 71.0 μg/kg	(Elaridi et al., 2021)
Pakistan	n = 10	Fe, Zn, Cu, Pb, Cd, Al	FAAS	Fe: 5230-7530 μg/kg Zn: 3200-5370 μg/kg Cu: 304.67-487.0 μg/kg Pb: 290-1050 μg/kg Cd: 280-980 μg/kg Al: 1480-2050 μg/kg	(Saeed et al., 2021)
Pakistan	n = 46	Ca, Mg, Cu, Zn, Fe, Mn	AAS	Ca: 3081 ± 277 μg/kg Mg: 540 ± 206 μg/kg Cu: 1 ± 0.76 μg/kg Zn: 8.97 ± 2.35 μg/kg Fe: 4.33 ± 2.22 μg/kg Mn: 0.0318 ± 0.02 μg/kg Pb: 0.0091 ± 0.01 μg/kg Cd: 0.1507 ± 0.28 μg/kg Cr: 0.0007 ± 0.00 μg/kg Ni: 0.0146 ± 0.01 μg/kg	(Lutfullah et al., 2014)
Turkey	n = 29	As, Pb, Cd	ICP-MS, GC–MS/MS	As: 0-30.67 μg/kg (detected in 16 samples) Pb and Cd: not detected	(Kilic et al., 2018)
Europe					
Italy	n = 19	Li, Na, K, Cl, Ca, P, Mg, Fe, Zn, Cu, I, Se, Mn, F, As, Cd, Pb, Hg, Sn, Cd, Cr, Mn, Ni, Pb, Zn, etc.	ICP-MS	Li: 7 ± 0.1 μg/kg Na: 571,720 ± 19,540 μg/kg Mg: 184,540 ± 6727 mg/kg Si: 19,520 ± 600 μg/kg P: 714,910 ± 19,727 μg/kg K: 2,292,360 ± 63,818 μg/kg Ca: 2,409,270 ± 22,000 μg/kg Ti: 98 ± 4 μg/kg Co: 11 ± 1 μg/kg Cu: 1246 ± 37 μg/kg Ga: 4 ± 1 μg/kg Rb: 2870 ± 53 μg/kg Sr: 1219 ± 73 μg/kg Mo: 154 ± 7.3 μg/kg Sn: 25 ± 2 μg/kg Cs: 8 ± 0.2 μg/kg Ba: 175 ± 4 μg/kg La: 4 ± 0.15 μg/kg Fe: 27,960 ± 600 μg/kg	(Astolfi et al., 2021)
Malta	n = 6	Toxic metals (Cr, Cu, Hg, Ni, Zn, Mn and Fe)	MP-AES	0-6 months formula: Cr: 290 ± 50 μg/kg Cu: 3330 ± 240 μg/kg Ni: 760 ± 0.00 μg/kg Fe: 18,340 ± 2510 μg/kg Mn: 2130 ± 410 μg/kg Zn: 27,240 ± 2770 μg/kg Hg: not detected 6-12 months formula: Cr: 240 ± 30 μg/kg Cu: 3370 ± 210 μg/kg Ni: 820 ± 60 μg/kg Fe: 18,870 ± 3060 μg/kg Mn: 2050 ± 210 μg/kg Zn: 33,000 ± 950 μg/kg Hg: not detected	(Vella and Attard, 2019)
Portugal	n = 26	Ni	GFAAS	Ni: 40.2 μg/kg	(Pereira et al., 2020)
Spain	n = 2	Cd, Cu	HR-CS-GFAAS	Cu: 3850 μg/kg Cd: not detected	(Gómez-Nieto et al., 2020)
Spain	n = 30	Na, K, Ca, Mg, Fe, Cu, Zn, Cr, B, Ba, Ni, Li, V, Sr, Mo, Mn, Al, Cd, Pb	ICP-OES	K: 4,107,000 ± 264,000 μg/kg Mg: 441,000 ± 16,500 μg/kg Na: 1,668,000 ± 88,700 μg/kg Ca: 4,544,000 ± 318,000 μg/kg Cr: 130 ± 20 μg/kg Cu: 3750 ± 400 μg/kg Fe: 55,900 ± 7550 μg/kg Zn: 34,200 ± 1090 μg/kg	(Paz, 2017)

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Table 4 (*continued*)

Location	Samples (n)	Contaminants	Methods	Main outcomes	Ref.
				Mn: 1000 ± 230 μg/kg Mo: 140 ± 10 μg/kg V: 280 ± 160 μg/kg Ni: 70 ± 40 μg/kg Li: 960 ± 440 μg/kg Sr: 2470 ± 950 μg/kg Ba: 1200 ± 420 μg/kg B: 1590 ± 210 μg/kg Al: 4020 ± 2010 μg/kg Cd: 10 ± 0.00 μg/kg Pb: 70 ± 20 μg/kg	

anthracene, chrysene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, and indenol[1,2,3-c,d]pyrene as possibly carcinogenic to human (2B); and acenaphthene, fluorene, phenanthrene, fluoranthene, pyrene, and benzo [*g*,*h*,*i*]perylene as not classifiable to human (3) (Acharya et al., 2019). Concerning dioxins, these are pollutants produced by combustion and various industrial productions such as industrial waste incineration, metal smelting, pesticides, etc. (Luo et al., 2021; WHO, 2016). These compounds are a compilation of polychlorinated dibenzofurans (PCDFs), polychlorinated dibenzodioxins (PCDDs), and PCBs (Tavakoly Sany et al., 2015). Among them, TCDD (2,3,7,8-tetrachlorodibenzo-para-dioxin) is especially harmful, by causing modulation of the immune system, teratogenesis and tumor promotion (Tavakoly Sany et al., 2015). Regarding edible oils, due to their industrial processing to improve the organoleptic and quality of the refined product, the high-temperature deodorization step leads to the formation of fatty acid esters of 3-monochloropropanediol (3-MCPD), which is classified as possible carcinogenic for human (group 2B) (IARC, 2018); 2-monochloropropanediol (2-MCPD), which seems to affect striated muscle tissues and heart (Food Safety Authority, 2016); and glycidol, which has been labeled as probably carcinogenic to humans by IARC (2A) (Beekman et al., 2020; IARC, 2018; Hrncirik and van Duijn, 2011; Pudel et al., 2011). Regarding acrylamide, its main sources are fried, baked, and roasted high carbohydrate foods containing asparagine and reduced sugars, which are widely consumed worldwide (Lindeman et al., 2021). Acrylamide is considered to show an endocrine-disrupting potential, due to the existence of studies that relate the acrylamide exposition to detrimental effects on reproduction, hypothalamus-pituitary-thyroid (HPT) axis alterations and neurotoxic effects (Matoso et al., 2019).

Concerning the effects on development, the exposure to these compounds has been mainly related to changes on anthropometric indices, also closely related to thyroid-stimulating hormone (TSH) values, and neurodevelopmental impairments in newborns. Being the development of the fetus and the neonate a critical stage, the exposure to these pollutants can impact on growth rate and metabolic capabilities, which would lead to the lowered anthropometric indices and neurodevelopmental issues referred (Dehghani et al., 2022).

Focusing on the effects on anthropometric parameters, PHAs has been reported to exert an adverse correlation between exposure to these compounds and height and chest circumference in children (Xu et al., 2015). However, these compounds have the ability to reach the neonate way before birth, through the placenta, the same way they can reach the neonate through breast milk, causing decreased levels of TSH, and the consequences of hypothyroidisms and abnormal growth (Dehghani et al., 2022; Xu et al., 2015). For PHAs, a correlation between these compounds and evidence of higher risks of neurodevelopmental delay and close relation to developmental disability such as ADHD and ASD, and intellectual disabilities (Wallace et al., 2022).

Quite similar problems have been linked to PBDEs, even though information about the consequences of the exposure to these pollutants is scarce, it is known that they are likely able to cause changes on thyroid hormone levels, leading to an impact on the endocrine system, and thus, to effects on the neurodevelopment of the children (Jagić et al., 2021).

The exposure to PCBs also has an impact on behavior and cognitive development after both pre- and postnatal exposure. For the postnatal exposure, authors reported association of PCBs to sleeping problems, and both anxiousness and depression on the Child Behavior Checklist (CBCL), together with possible cognitive deficits being transient and decreasing as the children matures (Yim et al., 2022). Not only postnatal exposure has been related to anxiety and depression symptoms, but also prenatal exposure has been observed to have an impact that could transcend to adolescence, resulting in anxiety symptoms at these stages of life. When dioxin is also added, the mixture of both PCBs and dioxin can enhance the impact on mental development but also lead to psychomotor problems (Yim et al., 2022).

Concerning acrylamide, although it is known to reach the fetus and has been detected in breast milk, potential adverse neurodevelopment after early life exposure has so far not been studied in humans (Lindeman et al., 2021). However, acrylamide intake during pregnancy has been reported to be negatively associated with fetal growth (Duarte-Salles et al., 2013).

Provided all the above, in breast milk, there is only one study carried out in Africa, detecting high levels of the dioxins PCBs in samples from Ghana (Asamoah et al., 2018). In this study, the authors measured levels of these toxics on primiparae and multiparae, finding no significant difference between the values detected in both cohorts (Asamoah et al., 2018). However, they also did a comparison of the levels detected on habitants living on an electronic-waste site and compared to subjects living on a reference site, detecting higher levels of most of the PCB studied in the e-waste site (Asamoah et al., 2018). However, neither of those values was higher than the TDI recommended. Regarding America, a study performed in the USA led to the detection of different PAHs, including benzo(*a*)pyrene, which is carcinogenic (Acharya et al., 2019). Furthermore, another study performed in the same country led to high levels of PCBs, being higher in mothers coming from an urban area compared to those coming from an agricultural area, although the levels detected in both areas are considered safe when compared to the TDI (Weldon et al., 2011). Regarding the reports of dioxin levels in Asia, there are four studies performed in China, India, and Malaysia (Bao et al., 2020; Bawa et al., 2018; Leong et al., 2021; Luo et al., 2021). Among them, one study performed a comparison between the levels of dioxins in a Chinese electronic-waste place compared to a reference place was performed in one of them, leading to higher concentrations of these toxicants in the electronic-waste site, although some dioxins were detected at even higher levels than the TDI recommended for both types of areas (Luo et al., 2021). However, the rest of the studies led to the detection of non-toxic levels of these compounds. The studies performed on breast milk concerning heat-treatment products in Europe led to the detection of levels of different dioxins, although neither of them was dangerous according to the TDI established by EFSA in Croatia, Sweden, and Spain (Gyllenhammar et al., 2021; Schuhmacher et al., 2019; Šimić et al., 2020). All this information is compiled in Table 5.

As can be seen in Table 6, dioxins were not measured in infant formula, however, the presence of different types of PAHs, furans, acrylamide, 3-MCPD, 2-MCPD, and glycerol was detected. In this regard, in the USA,

Table 5
Levels of heat treatment-products found in breast milk expressed by mean ± SD, or as median: range.

Location	Samples (n)	Contaminants	Methods	Main outcomes	Refs.
Africa					
Ghana	n = 128 (n = 47 primiparae, and n = 58 multiparae)	Dioxins	GC–MS/MS	Electronic-waste site:	(Asamoah et al., 2018)
				PCB-18: 1.06 ± 0.98 μg/L PCB-28: 1.30 ± 1.25 μg/L PCB-52: 0.19 ± 0.20 μg/L PCB-101: 0.08 ± 0.11 μg/L PCB-138: 0.86 ± 0.92 μg/L PCB-153: 0.42 ± 0.92 μg/L PCB-180: 0.53 ± 0.78 μg/L Primiparae:	
				PCB-18: 1.07 ± 0.81 μg/L PCB-28: 1.33 ± 0.87 μg/L PCB-52: 0.16 ± 0.10 μg/L PCB-101: 0.07 ± 0.43 μg/L PCB-138: 0.85 ± 0.68 μg/L PCB-153: 0.31 ± 0.09 μg/L PCB-180: 0.47 ± 0.39 μg/L Multiparae:	
				PCB-18: 1.05 ± 0.88 μg/L PCB-28: 1.28 ± 0.70 μg/L PCB-52: 0.20 ± 0.12 μg/L PCB-101: 0.08 ± 0.04 μg/L PCB-138: 0.87 ± 0.53 μg/L PCB-153: 0.50 ± 0.11 μg/L PCB-180: 0.58 ± 0.35 μg/L Reference site:	
				PCB-28: 0.03 ± 0.14 μg/L PCB-18, PCB-52, PCB-101, PCB-138, PCB-153, PCB-180: not detected	
America					
United States	n = 45	PAHs	GC–MS	Naphthalene: 3.0 ± 20.6 μg/L Acenapthene: 3.2 ± 21.2 μg/L Phenanthrene: 24.1 ± 31.8 μg/L Fluoranthene: 18.3 ± 34.6 μg/L Pyrene: 13.8 ± 26.5 μg/L Benz(a)anthracene: 11.7 ± 35.6 μg/L Chrysene: 11.9 ± 39.4 μg/L Benz(b)fluoranthene: 15.5 ± 42.7 μg/L Benz(k)fluoranthene: 7.9 ± 26.7 μg/L Benzo(a)pyrene: 0.1 ± 0.6 μg/L Indeno[1,2,3-c,d]pyrene: 12.4 ± 40.3 μg/L Benzo(g,h,i)perylene: 25.1 ± 59.6 μg/L Acenaphthylene, fluorene, and anthracene: not detected ΣPAHs: 146.9 ± 239.4 μg/L	(Acharya et al., 2019)
United States	n = 34 (n = 13 from an agricultural region and n = 21 from an urban region)	PCBs	GC-HRMS	Agricultural women:	(Weldon et al., 2011)
				PCB-118: 0.017 μg/L PCB-138: 0.0382 μg/L PCB-153: 0.0436 μg/L PCB-180: 0.683 μg/L Urban women:	
				PCB-118: 0.0928 μg/L PCB-138: 0.183 μg/L PCB-153: 0.242 μg/L PCB-180: 0.239 μg/L	
Asia					
China	n = 42 (electronic-waste site compared to a reference-site)	Dioxins	GC–MS	E-waste site:	(Luo et al., 2021)
				2,3,7,8-TeCDD: 0.00159 ± 0.00219 μg/L 1,2,3,7,8-PeCDD: 0.00221 ± 0.00172 μg/L 1,2,3,4,7,8-HxCDD: 0.0013 ± 0.00156 μg/L 1,2,3,6,7,8-HxCDD: 0.0034 ± 0.00213 μg/L 1,2,3,7,8,9-HxCDD: 0.00131 ± 0.00189 μg/L	

(continued on next page)

Table 5 (*continued*)

Location	Samples (n)	Contaminants	Methods	Main outcomes	Refs.
				1,2,3,4,6,7,8-HpCD: 0.00648 ± 0.00207 μg/L OCDD: 0.042 ± 0.00212 μg/L 2,3,7,8-TeCDF: 0.0051 ± 0.00119 μg/L 1,2,3,7,8-PeCDF: 0.0035 ± 0.00116 μg/L 2,3,4,7,8-PeCDF: 0.0085 ± 0.0012 μg/L 1,2,3,4,7,8-HxCDF: 0.0033 ± 0.00227 μg/L 1,2,3,6,7,8-HxCDF: 0.0052 ± 0.00148 μg/L 2,3,4,6,7,8-HxCDF: 0.0037 ± 0.00113 μg/L 1,2,3,4,6,7,8-HpCD: 0.0064 ± 0.00152 μg/L Total PCDDs: 0.0047 ± 0.00181 μg/L Total PCDFs: 0.0046 ± 0.00127 μg/L Total PCDDs/DFs: 0.0096 ± 0.00145 μg/L Reference site: 2,3,7,8-TeCDD: 0.0006 ± 0.00189 μg/L 1,2,3,7,8-PeCDD: 0.0013 ± 0.00158 μg/L 1,2,3,4,7,8-HxCDD: 0.0009 ± 0.00172 μg/L 1,2,3,6,7,8-HxCDD: 0.0014 ± 0.00173 μg/L 1,2,3,7,8,9-HxCDD: 0.0006 ± 0.00181 μg/L 1,2,3,4,6,7,8-HpCD: 0.003 ± 0.00164 μg/L OCDD: 0.019 ± 0.00191 μg/L 2,3,7,8-TeCDF: 0.0007 ± 0.00174 μg/L 1,2,3,7,8-PeCDF: 0.0005 ± 0.00196 μg/L 2,3,4,7,8-PeCDF: 0.0033 ± 0.00138 μg/L 1,2,3,4,7,8-HxCDF: 0.0022 ± 0.00224 μg/L 1,2,3,6,7,8-HxCDF: 0.0017 ± 0.00185 μg/L 2,3,4,6,7,8-HxCDF: 0.0005 ± 0.00164 μg/L 1,2,3,4,6,7,8-HpCD: 0.0012 ± 0.00208 μg/L Total PCDDs: 0.0025 ± 0.00149 μg/L Total PCDFs: 0.0015 ± 0.00136 μg/L Total PCDDs/DFs: 0.0041 ± 0.0014 μg/L	
China	n = 55	Dioxins	HRGC/MS	Total PCDDs: 0.029 ± 0.026 μg/L Total PCDFs: 0.013 ± 0.0072 μg/L 4Cl-PCDD/Fs: 0.0010 ± 0.0006 μg/L 5Cl-PCDD/Fs: 0.0060 ± 0.0032 μg/L 6Cl-PCDD/Fs: 0.0086 ± 0.0065 μg/L 7Cl-PCDD/Fs: 0.0034 ± 0.0025 μg/L 8Cl-PCDD/Fs: 0.024 ± 0.021 μg/L Total PCDD/Fs: 0.043 ± 0.031 μg/L Total non-ortho PCB: 0.027 ± 0.012 μg/L Total mono-ortho PCBs: 3.179 ± 2.549 μg/L 4Cl-PCBs: 0.006 ± 0.005 μg/L 5Cl-PCBs: 2.525 ± 2.216 μg/L 6Cl-PCBs: 0.634 ± 0.422 μg/L 7Cl-PCBs: 0.041 ± 0.037 μg/L Total dl-PCBs: 3.206 ± 2.259 μg/L Total PCDD/Fs and dl-PCBs: 3.249 ± 2.565 μg/L	(Bao et al., 2020)
Malaysia	n = 21	Dioxins	HRGC/HRMS	2378-TCDD: 0.00017 ± 0.00011 μg/L 12378-PeCDD: 0.00058 ± 0.00091 μg/L 123478-HxCDD: 0.0007117 ± 0.00051 μg/L 123678-HxCDD: 0.00163 ± 0.00178 μg/L 123789-HxCDD: 0.0017 ± 0.00175 μg/L 1234678-HpCDD: 0.00407 ± 0.00718 μg/L OCDD: 0.018 ± 0.019 μg/L 2378-TCDF: 0.00022 ± 0.00016 μg/L 12378-PeCDF: 0.00082 ± 0.00054 μg/L 23478-PeCDF: 0.00085 ± 0.00094 μg/L 123478-HxCDF: 0.00083 ± 0.00102 μg/L 123678-HxCDF: 0.00068 ± 0.00081 μg/L 234678-HxCDF: 0.00087 ± 0.00115 μg/L 123789-HxCDF: 1234678-HpCDF: 0.00112 ± 0.00048 μg/L 1234789-HpCDF: 0.00516 ± 0.01335 μg/L OCDF: 0.0011 ± 0.00084 μg/L PCB77: 0.01228 ± 0.00942 μg/L PCB81: 0.00056 ± 0.00034 μg/L PCB105: 0.49757 ± 0.48762 μg/L PCB114: 0.0714 ± 0.10682 μg/L PCB118: 1.48683 ± 1.41086 μg/L PCB123: 0.02201 ± 0.02853 μg/L PCB126: 0.00693 ± 0.01214 μg/L PCB156: 0.33339 ± 0.43569 μg/L	(Leong et al., 2021)

Table 5 (*continued*)

Location	Samples (n)	Contaminants	Methods	Main outcomes	Refs.
				PCB157: 0.07869 ± 0.11464 µg/L PCB167: 0.09461 ± 0.09625 µg/L PCB169: 0.00523 ± 0.00413 µg/L PCB189: 0.01629 ± 0.018 µg/L Total PCDD/Fs: 0.039 ± 0.030 µg/L Total dl-PCBs: 2.62 ± 2.60 µg/L Total (PCDD/Fs and dl-PCBs): 2.665 ± 2.607 µg/L	
India	n = 150	Dioxins (PCBs)	GC	Bathinda district: PCB101: 11.3 ± 36.7 µg/L PCB52: 7.7 ± 33.6 µg/L PCB28: 4.9 ± 25.04 µg/L PCB180: 9.7 ± 37.2 µg/L Σ PCB: 33.7 ± 67.9 µg/L Ludhiana: PCB101: 8.5 ± 29.5 µg/L PCB52: 6.2 ± 27.1 µg/L PCB28: 5.09 ± 22.2 µg/L PCB180: 4.3 ± 19.2 µg/L Σ PCB: 24.2 ± 48.3 µg/L	(Bawa et al., 2018)
Europe					
Spain	n = 20	Dioxins	HRGC/HRMS	2,3,7,8-TCDD: 0.00029 ± 0.00033 µg/L 1,2,3,7,8-PeCDD: 0.00081 ± 0.00042 µg/L 1,2,3,4,7,8-HxCDD: 0.00050 ± 0.00026 µg/L 1,2,3,6,7,8-HxCDD: 0.00261 ± 0.00203 µg/L 1,2,3,7,8,9-HxCDD: 0.00046 ± 0.00035 µg/L 1,2,3,4,6,7,8-HpCDD: 0.00280 ± 0.00155 µg/L OCDD: 0.0157 ± 0.00611 µg/L 2,3,7,8-TCDF: 0.00018 ± 0.00008 µg/L 1,2,3,7,8-PeCDF: 0.00014 ± 0.0001 µg/L 2,3,4,7,8-PeCDF: 0.00192 ± 0.000111 µg/L 1,2,3,4,7,8-HxCDF: 0.00060 ± 0.00039 µg/L 1,2,3,6,7,8-HxCDF: 0.00064 ± 0.00035 µg/L 2,3,4,6,7,8-HxCDF: 0.00035 ± 0.00021 µg/L 2,3,4,6,7,8-HxCDF: <0.00025 µg/L 1,2,3,4,6,7,8-HpCDF: 0.00092 ± 0.0008 µg/L 1,2,3,4,7,8,9-HpCDF: <0.00025 µg/L OCDF: <0.00025 µg/L PCDDs + PCDFs: 0.0288 ± 0.00948 µg/L I-TEQ: 0.00226 ± 0.00104 µg/L WHO-TEQ: 0.00226 ± 0.00102 µg/L	(Schuhmacher et al., 2019)
Sweden	n = 539	PCBs and dioxins	GC/ECNI/MS	PCB-28: 2.2 ± 3.3 µg/L PCB-105: 1.2 ± 1.1 µg/L PCB-118: 8.5 ± 6.3 µg/L PCB-138: 23 ± 14 µg/L PCB-153: 46 ± 28 µg/L PCB-156: 3.8 ± 2.4 µg/L PCB-167: 1.0 ± 0.73 µg/L PCB-180: 22 ± 13 µg/L Mono-ortho TEQ: 0.00043 ± 0.00029 µg/L PCB-126: 0.033 ± 0.021 µg/L PCB-169: 0.018 ± 0.011 µg/L Non-ortho TEQ: 0.0039 ± 0.0024 µg/L 2,3,7,8-TCDD: 0.000670 ± 0.00044 µg/L 1,2,3,7,8-PeCDD: 0.0018 ± 0.001 µg/L 1,2,3,6,7,8-HxCDD: 0.0057 ± 0.0038 µg/L 2,3,4,7,8-PeCDF: 0.0049 ± 0.0028 µg/L PCDD TEQ: 0.0033 ± 0.002 µg/L PCDF TEQ: 0.0019 ± 0.00097 µg/L PCDD/F TEQ: 0.0052 ± 0.0028 µg/L Total TEQ: 0.0094 ± 0.0052 µg/L	(Gyllenhammar et al., 2021)
Croatia	n = 46	Dioxins	GC-EI/MS/MS	PCB-77: ~0.01725 µg/L PCB-81: ~0.0025 µg/L PCB-126: ~0.0255 µg/L PCB-169: ~0.0125 µg/L SD not indicated	(Šimić et al., 2020)

levels of 3-MCPD and glycerol were detected, being higher than the recommended level depending on the type of oil used for the formula (Beekman et al., 2020; MacMahon and Beekman, 2019). Furthermore, different studies also detected levels of these contaminants in Brazil, Canada, and USA (Beekman and MacMahon, 2020a; de Mendonça Pereira et al., 2020; Leigh and MacMahon, 2017; MacMahon and Beekman, 2019; Wenzl et al., 2015). In Asia, even though benzo(*a*)pyrene was detected in both Iran and China, the values were safe when compared to the TDI concentrations advised by EFSA (Badibostan et al., 2019; Yan et al., 2021). In addition, levels of some other levels of PAHs were detected in these studies as

Table
Levels of heat treatment-products found in infant formula expressed by mean ± SD, or as median:range.

Location	Samples (n)	Contaminants	Methods	Main outcomes	Refs.
America					
Brazil	n = 140	PAHs	ICP-MS	PAHs: 53.68 μg/kg SD not indicated	(de Mendonça Pereira et al., 2020)
Canada	n = 30	3-MCPD, 2-MCPD, and glycidol	GC–MS and LC–MS/MS with APCI	- 3-MCPD: 38.075 μg/kg - 2-MCPD: 16.6 μg/kg - Glycidol: 13.95 μg/kg SD not indicated	(Wenzl et al., 2015)
United States	n = 55	3-MCPD and glycidol	LC-MS/MS	3-MCPD: - Fungal/algal: 380 μg/kg - Blend palm olein: 1290 μg/kg - Canola: 300 μg/kg - Coconut: 55 μg/kg - Corn: 390 μg/kg - MCT: 4 μg/kg - Palm olein: 4080 μg/kg - Safflower: 930 μg/kg - Soybean: 270 μg/kg - Sunflower: 80 μg/kg Glycidol: - Fungal/algal: 64 μg/kg - Blend palm olein: 1480 μg/kg - Canola: 510 μg/kg - Coconut: 690 μg/kg - Corn. 1390 μg/kg - MCT: 43 μg/kg - Palm olein: 4180 μg/kg - Safflower: 360 μg/kg - Soybean: 390 μg/kg - Sunflower: 500 μg/kg SD not indicated	(Beekman and MacMahon, 2020a)
United States	n = 98	3-MCPD, 2-MCPD, and glycidol	GC–MS and LC–MS/MS with APCI	3-MCPD: 318.29 μg/kg Glycidol: 107.29 μg/kg SD not indicated	(Leigh and MacMahon, 2017)
United States	n = 222	3-MCPD and glycidol	GC–MS	Powder: 3-MCPD: 150 μg/kg Glycidol: 61 μg/kg Concentrate: 3-MCPD: 75 μg/kg Glycidol: 8 μg/kg Ready-To-Feed (RTF): 3-MCPD: 88 μg/kg Glycidol: 14 μg/kg SD not indicated	(Beekman et al., 2020; Beekman and MacMahon, 2020a)
Asia					
Iran	n = 27	PAHs	GC–MS	Chrysene: 0.43 ± 0.035 μg/kg Benzo(*a*)pyrene: 0.44 ± 0.324 μg/kg Benzo(*a*)anthracene: <0.11 μg/kg Benzo(*b*)fluoranthene: <0.14 μg/kg	(Badibostan et al., 2019)
China	n = 31	PAHs + PAH-derivative	QuEChERS + GC-QqQ-MS	Stage I (for 0–6 months): 9-FO: 0.41 ± 0.27 μg/kg ATQ: 1.51 ± 0.42 μg/kg BaP: not detected PAH4: 0.44 ± 0.45 μg/kg PAH8: 1.49 ± 1.12 μg/kg EU 15 + 1PAHs: 1.82 ± 1.42 μg/kg 6-ClBaP: 3.63 ± 2.50 μg/kg 7-ClBaA: not detected Σ20 PAHs: 8.37 ± 2.48 μg/kg Stage II (for 6–12 months): 9-FO: 1.46 ± 0.26 μg/kg ATQ: 1.62 ± 0.35 μg/kg BaP: not detected	(Yan et al., 2021)

Table (*continued*)

Location	Samples (n)	Contaminants	Methods	Main outcomes	Refs.
				PAH4: 0.50 ± 0.42 μg/kg PAH8: 1.84 ± 1.07 μg/kg EU 15 + 1PAHs: 2.28 ± 1.39 μg/kg 6-ClBaP: 2.65 ± 0.79 μg/kg 7-ClBaA: not detected Σ20 PAHs: 8.02 ± 1.46 μg/kg Stage III (for 1–3 years): 9-FO: 1.45 ± 0.29 μg/kg ATQ: 1.45 ± 0.30 μg/kg BaP: 0.05 ± 0.13 μg/kg PAH4: 0.59 ± 0.51 μg/kg PAH8: 2.30 ± 1.19 μg/kg EU 15 + 1PAHs: 2.78 ± 1.35 μg/kg 6-ClBaP: 2.16 ± 1.28 μg/kg 7-ClBaA: not detected Σ20 PAHs: 7.85 ± 1.58 μg/kg Stage IV: 9-FO: 1.39 ± 0.24 μg/kg ATQ: 1.61 ± 0.22 μg/kg BaP: not detected PAH4: 1.11 ± 0.92 μg/kg PAH8: 2.13 ± 1.63 μg/kg EU 15 + 1PAHs: 2.94 ± 2.13 μg/kg 6-ClBaP: 1.53 ± 1.58 μg/kg 7-ClBaA: not detected Σ20 PAHs: 7.47 ± 2.38 μg/kg	
China	n = 35	Furan	GC–MS	Furan: 2.53 μg/kg SD not indicated	(Sijia et al., 2014)
Europe					
France	n = 23	Furan	GC–MS	Furan: 3.5-5.7 μg/kg	(Lambert et al., 2018a)
Germany	n = 70	3-MCPD, 2-MCPD, and glycidol	GC–MS and LC–MS/MS with APCI	3-MCPD: 101 ± 19.35 μg/kg 2-MCPD: 44 ± 12.36 μg/kg Glycidol: 87.5 ± 23 μg/kg	(Wöhrlin et al., 2015)
Malta	n = 6	HMF	MP-AES	0-6 months formulae: Room-temperature: 5270 ± 1400 μg/kg 30 °C: 7170 ± 1440 μg/kg 6-12 months formulae: Room-temperature: 1810 ± 880 μg/kg 30 °C: 3570 ± 1050 μg/kg	(Vella and Attard, 2019)
France	n = 140	Acrylamide	LC-MS	Infant formula: Lower bound: 0.60 ± 0.97 μg/kg Upper bound: 2.9 ± 1.5 μg/kg Follow-on formula: Lower bound: 0.14 ± 0.53 μg/kg Upper bound: 2.2 ± 0.80 μg/kg	(Lambert et al., 2018b)
Romania	n = 5	PAHs	GC-ECD	Acenaphthylene: 0.084 ± 0.01 μg/kg Acenaphthene: 0.102 ± 0.018 μg/kg Anthracene: 0.104 ± 0.006 μg/kg Fluorene: 0.048 ± 0.005 μg/kg Pyrene: 0.1 ± 0.02 μg/kg Chrysene: 0.242 ± 0.024 μg/kg Benz[*k*]fluoranthene: 0.1764 ± 0.028 μg/kg Indenol[1,2,3–cd]pyrene: 0.159 ± 0.0182 μg/kg Napththalene, fluoranthene, phenanthrene, benzo(*a*)anthracene, benzo(*a*)pyrene, benzo[*g,h,i*]perylene, dibenzo[*a,h*]anthracene: not detected	(Dobrinas et al., 2016)
Poland	n = 9	5-HMF	RP-HPLC with UV detection	2315 μg/kg SD not indicated	(Czerwonka et al., 2020)

well. In Europe, some levels of hydroxymethylfurfural (HMF) were detected in Malta and Poland (Czerwonka et al., 2020; Vella and Attard, 2019), while different studies performed in European countries such as France, Germany, or Romania led to the detection of different heat treatment pollutants too, including acrylamide (Dobrinas et al., 2016; Lambert et al., 2018a,b; Wöhrlin et al., 2015). Considering the toxicity of all these chemicals, infant formula seems to be safer in these terms in China than breast milk, which is not surprising considering the industrial areas where the studies took place. Furthermore, in the USA, high values of different toxicants have been detected in both types of food. Concerning Europe, and according to these data, it would be safer to administer infant formula than breast milk. However, it is important to consider that the only experiment performed in breast milk was carried out in an industrial city of Spain, so it would not be very representative to the rest of the continent. In addition, it is worth mentioning the number of experiments and samples for both types of matrices, as the experiments performed in breast milk are less and the toxicants studied are also fewer. All these results are compiled in Supplementary Fig. 2.

3.3. Pharmaceuticals

The stories of thalidomide and diethylstilbestrol are still remembered and have set the basis for clinical, regulatory, and public attitudes that involve pregnant and breastfeeding women (Nooney et al., 2021). Studies have shown that breastfeeding women tend to take more medication than pregnant women, mostly multivitamins, nonsteroidal anti-inflammatory drugs, acetaminophen, progestins, antimicrobials, and decongestants (Stultz et al., 2007). However, these medicines used during lactation are considered safe and adverse events of them on breastfed infants are very rare (Saha et al., 2015).

For some of the most used medicines, different adverse events have been reported. For example, amiodarone used to treat some types of arrhythmias is contraindicated during breastfeeding because it can cause hypothyroidism and delayed development. Contraceptives, which are safe for use during lactation, have also been reported to cause breast enlargement in breastfed infants, due to estrogen or decreased weight gain for combined oral contraceptives. For antidepressants, fluoxetine being one of the most used due to its safety as only a small part can reach maternal milk, has been reported to cause gastrointestinal complaint, agitation or colics and even dressed weight (Anderson et al., 2003).

A major drawback from taking medication during lactation would be the possible exposure of the infant through breast milk. In this sense, only three experiments have been reported where the presence of drugs such as isoflavonoids, antibiotics or phenolic compounds have been detected in breast milk. In this sense, 2 out of the 3 studies were performed in Asia, finding residues of isoflavonoids and phytoestrogens in China, and antibiotic residues in Syria (Smadi et al., 2019; Zhou et al., 2020). Concerning Europe, a study performed in Poland led to the detection of residues of different isoflavonoids as well, accounting for higher levels and more subtypes in this last case (Nalewajko-Sieliwoniuk et al., 2020). These studies are compiled in Table 7. It is important to notice that these levels can also be detected as a consequence of the type of diet of the subjects. In this sense, a diet with a high fruit, nuts, or soy content would lead to the detection of levels of both isoflavonoids and phytoestrogens (Liggins et al., 2000), while some antibiotic residues can be transferred to humans by the consumption of animal meat or milk (Moga et al., 2021).

Concerning the levels of pharmaceuticals found in infant formula, most of them were antibiotics, although some other medication was also found. In Asia, only one experiment was performed, by measuring a battery of veterinary drugs in China, finding levels of amphenicols, avermectins, benzimidazoles, non-ionophore coccidiostats, ionophore coccidiostats, miscellaneous anthelmintics, miscellaneous veterinary drugs, lincosamides and macrolides, non-steroidal anti-inflammatory drugs, quinolones, and sulfonamides (Zhan et al., 2013). In addition, levels of different antibiotics

Table 7
Levels of pharmaceuticals found in infant formula expressed by mean ± SD, or as median: range.

Location	Samples (n)	Contaminants	Methods	Main outcomes	Refs.
Asia					
China	n = 9	Isoflavonoid phytoestrogens	UHPLC-ESI-MS/MS	0.5 h: Daidzein: 0.71 ± 0.16 μg/L Genistein: not detected3 h: Daidzein: 13.25 ± 4.86 μg/L Genistein: 49.83 ± 9.56 μg/L6 h: Daidzein: 104.2 ± 12.51 μg/L Genistein: 98.67 ± 13.34 μg/L9 h: Daidzein: 6.86 ± 3.59 μg/L Genistein: 12.48 ± 5.32 μg/L12 h: Daidzein: 3.24 ± 1.43 μg/L Genistein: 1.24 ± 0.38 μg/L24 h: Daidzein: 0.52 ± 0.18 μg/L Genistein: not detectedFormononetin and biochanin A: not detected	(Zhou et al., 2020)
Syria	n = 120	Antibiotics residues	LC-MS/MS, GC–MS/MS	Oxytetracycline: 5.04 μg/L (in 4 contaminated samples) Ampicillin, sulfamethazine and tetracycline: not detected SD not indicated	(Smadi et al., 2019)
Europe					
Poland	n = 13	Isoflavonoids	LC-ESI-MS/MS	Gallic acid: 31.8 ± 1.3 μg/L Daidzein: 3.61 ± 5.93 μg/L Caffeic acid: 54.4 ± 24.3 μg/L Quercetin: 12.4 ± 5.61 μg/L Genistein: 3.63 ± 3.40 μg/L Naringenin: 1.89 ± 1.57 μg/L Hesperetin: 1.243 ± 1.31 μg/L Epicatechin, epicatechin gallate, epigallocaechin gallate, and kaempferol: not detected	(Nalewajko-Sieliwoniuk et al., 2020)

Table 8
Levels of pharmaceuticals found in infant formula expressed by mean ± SD, or as median: range.

Location	Samples (n)	Contaminants	Methods	Main outcomes	Refs.
Asia					
China	n = 30	Veterinary drug residues and other contaminants	UHPLC-HRMS	Progesterone: 0.45–8.3 μg/kg Lincomycin: 5.1 μg/kg (1 sample) Enoxacin: 2.0 μg/kg (1 sample) Coffein: 0.55-150 μg/kg (5 samples)	(Zhan et al., 2013)
China	n = 20	Veterinary drugs including antivirals, anticoccidials, macrolides, sulfonamides, beta-agonists, sedatives, thyreostats, nonsteroidal anti-inflammatory drugs, and other pharmacologically active substances	UHPLC-HRMS	Regulated compounds: All below or equal to corresponding MRLs Banned and nonauthorized compounds: <LOD	(Zhang et al., 2020)
Europe					
Switzerland	n = 20	23 β-lactam antibiotics	LC–MS/MS	Amoxicillin: 16 μg/kg Ampicillin: 16 μg/kg Aspoxicillin: 100 μg/kg Cefalonium: 40 μg/kg Cefacetril: 200 μg/kg Cefadroxil: 200 μg/kg Cefalexin: 200 μg/kg Cefapirin: 40 μg/kg Cefazolin: 200 μg/kg Cefquinome: 40 μg/kg Ceftiofur: 200 μg/kg Cefuroxime: 200 μg/kg Cloxacillin: 40 μg/kg Desacetylcefapirin: 80 μg/kg Dicloxacillin: 40 μg/kg Nafcillin: 20 μg/kg Oxacillin: 40 μg/kg Penicillin G: 16 μg/kg Penicillin V: 40 μg/kg Piperacillin: 40 μg/kg Sulbactam: 100 μg/kg Tazobactam: 100 μg/kg	(Bessaire et al., 2018)

were found in infant formula in Switzerland (Bessaire et al., 2018), as can be observed in Table 8.

According to all this data, breast milk was safer than infant formula in general. However, it is important to take some variables into account. First, that the medication intake is much regulated during both pregnancy and lactation. Second, the traces measured, as only one study measured levels of antibiotic residues in breast milk. Third, the type of pharmaceutical found, as they will not cause the same harmful effect in children. These results are represented on Supplementary Fig. 3.

3.4. Mycotoxins

Mycotoxins are secondary metabolites produced by some filamentous fungi or molds, which can grow under suitable humidity and temperature conditions on various food and feeds, being a human and animal risk (Zain, 2011). Human exposure to mycotoxins may result from consumption of contaminated-plant-derived foods, the carry-over of mycotoxins and their metabolites in animal products such as meat and eggs (CAST, 2003) or exposure to air and dust containing toxins (Jarvis, 2002). During lactation, the infants can be exposed to different mycotoxins after ingestion of contaminated foods by lactating mothers, as they can be transferred in unaltered or metabolized forms into breast milk (Sengling Cebin Coppa et al., 2019). Among the most common mycotoxins in food products, the presence of aflatoxins, ochratoxin A, patulin, fumonisins, zearalenone, and deoxynivalenol is of relevance (Sengling Cebin Coppa et al., 2019). From them, aflatoxins (AFs) are qualified as carcinogenic, mutagenic, teratogenic, and immunosuppressive (Eaton and Gallagher, 1994). This group contains the AFB1 and its metabolite AFM1, which are classified as carcinogenic (group 1) by the IARC (Cherkani-Hassani et al., 2020). In general, mycotoxins have demonstrated to be able to cross the placental barrier and exert effects on the fetal systems (Alvito and Pereira-Da-silva, 2022). These mycotoxins can impact in children health through different mechanisms, and depending on the type, they can cause different effects, including hepatotoxicity, dermatotoxicity, neurotoxicity, carcinogenic, and estrogenic effects (Memiş et al., 2021). In fact, AFB1 has been associated with growth impairment in children and modifications of the immune function (Alvito and Pereira-Da-silva, 2022; Eze et al., 2018). These effects have also been associated with maternal exposure during pregnancy, an exposure that continues in the lactating phase, but could result in early problems at birth such as low weight and neonatal jaundice, or even anemia in pregnancy, being one of the principal causes of maternal mortality during childbirth in Asia and Africa (Eze et al., 2018). These conditions reflect significant malnutrition, which could even lead to kwashiorkor, a very common disease in African countries due to lack of proper nutrition (Bryden, 2007). More effects have been described; however, it is not known if they would be due to the exposure to these mycotoxins or if they are a direct consequence of this malnutrition (Khlangwiset et al., 2011). Other mycotoxins, such as fumonisins, cause mostly neural tube defects such as spina bifida and meningio-myeloceole, reported for early maternal exposure during gestation (Eze et al., 2018).

Concerning the studies detecting levels of these pollutants on breast milk, AFM1 has been found in all the samples collected from Morocco and Nigeria, in Africa, and in Bangladesh, in Asia, with levels that are above those recommended by the EFSA (Cherkani-Hassani et al., 2020; Ekeanyanwu et al., 2020; Islam et al., 2021). There is only one study performed in America screening levels of mycotoxins on breast milk and, although no levels of AFM1 were detected (Coppa et al., 2021). These studies are gathered in Table 9. Concerning the levels found in the infant formula, also AFM1 is the mycotoxin found in more samples in dangerous levels. In this regard, Mexico was the only country where these levels were measured in America, finding higher values than those recommended (Quevedo-Garza et al., 2020). This mycotoxin has also been found in excess in different Asiatic countries, such as Iran and Jordan (Dehcheshmeh et al., 2021; Omar, 2016). In contrast, no dangerous levels of mycotoxins were found in Africa or Europe. These studies can be found in Table 10. When comparing the quality of both types of food, in Africa, although high levels of AFM1

Table 9
Levels of mycotoxins found in breast milk expressed by mean ± SD, or as median: range.

Location	Samples (n)	Contaminants	Methods	Main outcomes	Refs.
Africa					
Morocco	n = 82	AFM1	ELISA	AFM1: 0.00575 ± 0.00344 μg/L	(Cherkani-Hassani et al., 2020)
Nigeria	n = 225	AFM1	HPLC, AAS	AFM1: 0.00402 ± 0.00112 μg/L	(Ekeanyanwu et al., 2020)
America					
Brazil	n = 74	AFM1, FBs, OTA, DON, ZEN and some of their metabolites	LC-MS/MS	FB1: 2.200-3.400 μg/L OTA: 0.360 μg/L AFM1, DON, ZEN: not detected SD not indicated	(Coppa et al., 2021).
Asia					
Bangladesh	n = 62	AFM1	ELISA	AFM1: 0.00442 ± 0.00056 μg/L	(Islam et al., 2021)

were found on breast milk, also some other mycotoxins were found which levels have not been established yet. However, in America, high values of AFM1 were found only on infant formula. Concerning Asia, although relevant levels were found in both, breast milk and infant formula, more studies reported the presence of mycotoxins on infant formula, while only studies performed on infant formula were found in this regard, not existing, to our knowledge, on breast milk in the last decade. Thus, although infant formula demonstrated to contain more types of mycotoxins, it is also worth to mention the number of studies performed in both types of samples. The distribution of the detection of mycotoxins in both breast milk and infant formula can be found in Supplementary Fig. 4.

3.5. Pesticides

Pesticides are chemical compounds designed to protect agricultural products from undesirable insects, plants, or fungal diseases, which led to a noticeable increase in crop yields and food production (WHO, 1986). These chemicals are applied annually in millions of tons of yields worldwide (Dar et al., 2020; De et al., 2014; US EPA, 2008). Despite being an agricultural advantage, the overuse of these pesticides leads to high toxicity, affecting soil, water, and natural resources where they can be present, which leads to several environmental, animal, and human health issues (Bhardwaj et al., 2018; Toni et al., 2006). Due to their perdurability, these compounds can be found after a long period (Asghar et al., 2016; Tago et al., 2014). Based on their chemical structure, pesticides can be divided into organochlorines, organophosphorus, carbamates, pyrethroids, and neonicotinoids (Vankayalapati, 2016).

Organochlorine pesticides (OCPs) have been some of the most important pesticides used worldwide and, although most of them have been banned in the past several years, some levels can still be found in environmental and physiological samples (Costa, 2015). Among the most used, it is relevant to mention the chlorinated ethane derivative 1,1,1-trichloro-2, 2-bis (4-chlorophenyl) ethane (DDT) and its analogs, including methoxychlor; the cyclodienes, including chlordane, dieldrin, aldrin, heptachlor, and endrin; and the benzene hexachlorides (BHC) including lindane (Costa, 2015). These compounds act mainly by affecting sodium channels and GABA receptor-gated chloride channels. However, due to their environmental persistence and high lipophilicity, most of them have been banned in most countries in the last decades (Costa, 2015).

Organophosphate pesticides (OPPs) are extensively applied in agriculture, horticulture, domestic purposes, veterinary medicine, and control of disease vectors (Dar et al., 2020). Their use increased due to their high effectiveness against target pests and their relatively low toxicity to non-target organisms compared to other pesticides (Singh and Walker, 2006; Vijayalakshmi, 2012). General population may be exposed to pesticide residues in food and drinking water daily or to pesticide drift in residences close to spraying areas (Damalas and Eleftherohorinos, 2011; Damalas and Koutroubas, 2016). The bioaccumulation process usually is the consequence of the runoff from pesticide-contaminated agricultural land areas into the waterbodies such as streams, rivers, and oceans (Dar et al., 2020). Thus, these contaminants are ingested by fish and accumulate into the food chain, reaching humans (Dar et al., 2020; Maurya and Malik, 2016). Thus, OPPs have been found in blood, urine, semen, breast milk, amniotic fluid, adipose tissue, and umbilical cord blood from humans (Kumar et al., 2016). These compounds act by inhibiting irreversibly the acetylcholinesterase activity, leading to neurotoxicity and developmental neurotoxicity (Burke et al., 2017). Among these compounds, is especially relevant the presence of chlorpyrifos (CPF) (Hinojosa et al., 2020). Same mechanism of action but with a reversible effect would be the one caused by carbamates, reducing the toxic effects in non-target organisms (Dhouib, 2016; Gupta et al., 2017).

On the other hand, pyrethroids (PYR) are synthetic organic insecticides derived from pyrethrins (Tang et al., 2018). Due to their high effectiveness and their low toxicity in comparison with other pesticides, they have become one of the most important types of pesticides in the last decades (Tang et al., 2018; Yoo et al., 2016). Compared to the rest of pesticides, these compounds have less potential to pollute the environment, although they can still reach humans through the food chain (Tang et al., 2018). Among their characteristics, they are very lipophilic, which is the reason for their finding in breast milk.

As some of the most used pesticides nowadays, it is also relevant to study the levels of neonicotinoids. These compounds are insecticides that act through the activation of the nicotinic acetylcholine receptors (nAChRs) (Loser et al., 2021a). They have been demonstrated to have high species specificity, although some studies have reported possible effects on developmental neurotoxicity (Loser et al., 2021a; Loser et al., 2021b).

Taking all of this into consideration, it is also important to notice the effects during development. In this sense, due to this worldwide but uneven distribution of these pesticides, exposures are very different and can lead to different results on the infant. However, considering that the main mechanisms of action for these pollutants are related to neurotoxic effects of plagues, the main side effects are related to this mechanism (Shelton et al., 2014). The nervous system is the target organ for most of these toxicants, being the developing brain of infants and the fetus, especially vulnerable. Although the dose of exposure may be too low to cause visible effects on adults, they can cause permanent damage on the brain function, due to the lack of proper defenses at those early stages of development (Dalsager et al., 2019). Nonetheless, pesticides not only result in developmental neurotoxicity but also can generate carcinogenicity, have endocrine disruptive properties and have been found to be associated with certain cancers and leukemia. In this sense, maternal exposure to pesticides such as OPPs or OCPs has been linked to an increase in the incidence of brain tumor and digestive cancer (Mostafalou and Abdollahi, 2017). In addition, the exposure to different organophosphates has been linked with risk of neural tube defects, low birth weight and length, hypospadias, spina bifica and some other anomalies (Mostafalou and Abdollahi, 2017). For pyrethroids, some studies indicate that they can have an association with behavioral disorders, cognitive deficits and learning disorders and ADHD (Qi et al., 2022) and even an association with ASD and development delay, including cognitive, memory, visual, verbal, behavioral, and motor dysfunctions, when there is maternal exposure during pregnancy that can continue into the breastfeeding phase (Shelton et al., 2014). Organophosphates have also been

Table 10
Levels of mycotoxins found in infant formula expressed by mean ± SD, or as median: range.

Location	Samples (n)	Contaminants	Methods	Main outcomes	Refs.
Africa					
Nigeria	n = 137	3-Nitropropionic acid, AFB1, AFB2, alternariol, beauvericin, chloramphenicol, citrinin, deoxynivalenol, HT-2 toxin, moniliformin, nivalenol, T-2 toxin, ZEN	LC-MS/MS	3-Nitropropionic acid: 21.1 ± 2.0 μg/kg AFB1: 4.2 ± 0.0 μg/kg AFB2: 0.5 ± 0.0 μg/kg Total aflatoxins: 4.6 ± 0.0 μg/kg Alternariol: 0.7 ± 0.0 μg/kg Beauvericin: 4.7 ± 7.5 μg/kg Chloramphenicol: 4.1 ± 6.7 μg/kg Citrinin: 3.6 ± 0.0 μg/kg Deoxynivalenol: 31.6 ± 6.3 μg/kg HT-2 toxin: 18.8 ± 0.0 μg/kg Moniliformin: 13.0 ± 4.2 μg/kg Nivalenol: 20.5 ± 2.2 μg/kg T-2 toxin: 59.6 ± 83.2 μg/kg ZEN: 3.2 ± 2.1 μg/kg	(Ojuri et al., 2018)
America					
Mexico	n = 55	AFM1	IACC-HPLC with FD	AFM1: 0.04 ± 0.099 μg/L	(Quevedo-Garza et al., 2020)
Brazil	n = 140	AFM1 and OTA	ICP-MS	OTA: 0.0351-0.6895 μg/L AFM1: not detected	(de Mendonça Pereira et al., 2020)
Asia					
Qatar	n = 69	AFB1, AFG1, AFB2, AFG2, AFM1, OTA, DON, ZEN, FB1, FB2, T2 and HT2	LC-MS/MS and HPLC	AFB1: 22 % of samples (mean <0.04 μg/kg) AFM1: 33 % of samples (mean <0.010 μg/kg) OTA: 31 % of samples (mean <0.05 μg/kg) DON: 27 % of samples (mean <20 μg/kg) ZEN: 4 % of samples (mean <1.00 μg/kg) FB2: 10 % of samples (mean <20 μg/kg) T2: 2 % of samples (mean 1.00–9.99 μg/kg) AFG1, AFB2, AFG2, FB1, HT2: Not detected SD not indicated	(Ul Hassan et al., 2018)
Iran	n = 29	AFM1	HPLC	Only one sample with AFM1 (0.043 μg/kg)	(Hooshfar et al., 2020)
Iran	n = 80	AFM1	GFAAS and ELISA	AFM1: 0.444 ± 0.044 μg/kg	(Dehcheshmeh et al., 2021)
Jordan	n = 20	AFM1	ELISA	AFM1: 0.12026 ± 0.03354 μg/kg	(Omar, 2016)
Europe					
Portugal	Breakfast cereals primarily marketed for children, from six different generic brands (n = 20) and three different name-brands (n = 6)	21 mycotoxins and metabolites (AFB1, AFB2, AFG1, AFG2, AFM1, OTA, FB1, FB2, ZEA, NIV, NEO, DAS, FUS-X, DON, 15-ADON, 3-ADON, HT-2, T-2, VER)	UPLC-MS/MS, HPLC-FD	AFM1: 0.017 μg/kg AFB1: 0.013 μg/kg AFB2: 0.004 μg/kg AFG1: 0.013 μg/kg OTA: 0.040 μg/kg DON: 91.5 μg/kg NIV: 15.1 μg/kg FB1: 12.5 μg/kg FB2: 12.5 μg/kg ZEA: 0.7 μg/kg	(Martins et al., 2018)
Austria and Czech Republic	n = 59	46 mycotoxins and key metabolites: AFB1, AFB2, AFG1, AFG2, AFM1, AFM2, AFP1, AFQ1, AFB1-N7-Gua, AFL, STC, OTA, OTB, OTα, CIT, DH-CIT, NIV, DON, T-2, HT-2, FB1, FB2, ZEN, α-ZEL, β-ZEL, BEA, EnnA, EnnA1, EnnB, EnnB1	LC-MS/MS	Aflatoxicol: not detected AFB1: not detected Sterigmatocystin: <LOQ - 0.2 ZEN: <LOQ - 0.7 DON: not detected NIV: <LOQ – 19 T-2: not detected Beauvericin: not detected EnnA: not detected EnnA1: not detected EnnB: not detected EnnB1: <LOQ FB1: <LOQ	(Braun et al., 2021)

correlated to increase of prevalence of ASD, observing positive associations between ASD and prenatal exposure for residential proximity to organophosphates (Shelton et al., 2014) and several studies support an association between OPs and ADHD (Tessari et al., 2022). Organochlorine pesticides have not been as closely associated with ADHD as OPs and pyrethroids, but some authors have found a correlation between high levels of β-hexachlorocyclohexane in breast milk and increased odds of ADHD in childhood (Tessari et al., 2022).

In this regard, many studies have been performed analyzing the levels of these pesticides on both breast milk and infant formula. Concerning breast milk, as can be seen in Table 11, levels of different OCPs have been found in Tanzania and Tunisia, in Africa, being DDT derivatives and HCH

Table 11
Levels of pesticides found in breast milk expressed by mean ± SD, or as median: range.

Location	Samples (n)	Contaminants	Methods	Main outcomes	Refs.
Africa					
Tanzania	n = 47	OCPs	HRGC-LRMS; CALUX, HPLC-MS/MS	p,p′-DDE: 113 μg/L p,p′-DDD: 6.61 μg/L ΣDDTs: 117 μg/L ΣOCs: 146 μg/L	(Müller et al., 2019)
Tunisia	n = 36	OCPs	GC-ECD/GC–MS	p,p′–DDE: 508.7 ± 570.1 μg/L p,p′–DDD: 218.1 ± 363.5 μg/L p,p′–DDT: 437.2 ± 519.9 μg/L ΣDDTs: 1163.9 ± 1005 μg/L β-HCH: 39.7 ± 43 μg/L Lindane: 36.5 ± 32 μg/L HCB: 286.8 ± 272.6 μg/L Dieldrin: 9.1 ± 13.9 μg/L ΣHCHs: 76.2 ± 62.2 μg/L α-HCH, oxychlordane, c-chlordane, t-nonachlor: not detected	(Hassine et al., 2012)
America					
Brazil	n = 34	OCPs	GC–MS	β-HCH: 0.66 ± 0.00 μg/L δ-HCH: 1.52 ± 0.77 μg/L Σ-HCH: 1.55 ± 0.87 μg/L Heptachlor: 1.62 ± 1.40 μg/L Aldrin: 9.56 ± 4.41 μg/L Dieldrin: 56.18 ± 33.23 μg/L Endosulfan I: 20.22 ± 14.39 μg/L DDE: 2.37 ± 2.22 μg/L DDT: 2.09 ± 0.00 μg/L Methoxychlor: 102.17 ± 73.68 μg/L	(Souza et al., 2020)
Mexico	n = 167	OCPs	GC-ECNI-LRMS	Rural: HCB: 15 μg/L β-HCH: 5 μg/L op′DDT: 17 μg/L pp′DDT: 49 μg/L pp′DDE: 1008 μg/L ΣDDT: 1079 μg/L Urban: HCB: 8 μg/L β-HCH: 5 μg/L op′DDT: 15 μg/L pp′DDT: 44 μg/L pp′DDE: 44 μg/L ΣDDT: 827 μg/L SD not indicated	(Chávez-Almazán et al., 2020)
United States	n = 34 (n = 13 from an agricultural region and n = 21 from an urban region)	OCPs, PYR, OPPs	GC-HRMS	Agricultural women: Chlorpyrifos: 0.028 μg/L *cis*-Permethrin: 0.103 μg/L *trans*-Permethrin: 0.176 μg/L Hexachlorobenzene: 0.223 μg/L β-hexachlorocyclohexane: 0.443 μg/L o,p′-DDT: 0.0624 μg/L p,p′-DDT: 0.102 μg/L o,p′-DDE: 0.00517 μg/L p,p′-DDE: 3.490 μg/L Dacthal: 0.003.3 μg/L Urban women: Chlorpyrifos: 0.0245 μg/L *cis*-Permethrin: 0.0819 μg/L *trans*-Permethrin: 0.0931 μg/L Hexachlorobenzene: 0.191 μg/L β-hexachlorocyclohexane: 0.220 μg/L o,p′-DDT: 0.0366 μg/L p,p′-DDT: 0.107 μg/L o,p′-DDE: 0.00565 μg/L p,p′-DDE: 3.170 μg/L Dacthal: 0.00279 μg/L SD not indicated	(Weldon et al., 2011)
Asia					
China	n = 97 (pooled)	Neonicotinoids	HPLC-MS/MS	Acetamiprid metabolite: 0.161 ± 0.188 μg/L	(Chen et al., 2020b)

Table 11 (*continued*)

Location	Samples (n)	Contaminants	Methods	Main outcomes	Refs.
				Imidacloprid: 0.0410 ± 0.0243 μg/L Thiamethoxam: 0.0203 ± 0.0149 μg/L Acetamiprid: 0.0191 ± 0.0281 μg/L Clothianidin: 0.0130 ± 0.0109 μg/L Nitempyran: 0.00777 ± 0.0186 μg/L	
China	n = 55	OCPs, PYRs, OPPs	GC–MS	HCB: 29.4 ± 30.0 μg/L β-HCH: 32.0 ± 59.0 μg/L p,p′-DDE: 85.2 ± 105.1 μg/L PYRs: not detected OPPs: not detected	(Kuang et al., 2020)
China	n = 46	OCPs	GC-μECD	Total OCPs: 1003.8 μg/L 4,4′-DDE: 655.4 μg/L β-HCH: 172.5 μg/L HHCB: 17.7 μg/L	(Zhou et al., 2012)
China	n = 142	OCPs	GC	ΣDDTs: 316 ± 279 μg/L ΣEndosulfan: 4.4 ± 10.1 μg/L ΣDrins: 2.8 ± 5.6 μg/L ΣHeptachlor: 1.4 ± 4.1 μg/L ΣHCHs: 41.5 ± 60.7 μg/L ΣChlordane: 5.6 ± 16 μg/L ΣOCPs 423 ± 543 μg/L	(Lu et al., 2015)
China	n = 54	Carbamates	GC/MS	Syn-DP: 1.64 ± 3.15 μg/L Anti-[DP-1Cl]: 0.156 ± 0.163 μg/L Anti-DP: 3.91 ± 5.75 μg/L ΣDPs: 5.65 ± 8.30 μg/L CB-28: 8.31 ± 7.86 μg/L CB-99: 5.97 ± 5.00 μg/L CB-118: 14.9 ± 15.0 μg/L CB-153: 16.9 ± 12.9 μg/L CB-138: 14.3 ± 13.8 μg/L CB-187: 2.77 ± 1.90 μg/L CB-180: 5.15 ± 53.7 μg/L	(Pan et al., 2020)
Jordan	n = 120	OCPs	GC/ECD	HCHs: not detected DDTs: 320 μg/L Cyclodienes: 200 μg/L	(al Antary et al., 2021)
India	n = 150	OCPs	GC	Bathinda district: DDTs: 519.2 ± 1017.4 μg/L HCHs: 46.6 ± 106.9 μg/L Heptachlor: 5.9 ± 35.8 Heptachlor epoxide: 6.6 ± 42.04 μg/L Endosulfan sulfate: 5.1 ± 25.4 μg/L Methoxychlor: 11.4 ± 89.3 μg/L Ludhiana: DDTs: 415.3 ± 846.3 μg/L HCHs: 35.5 ± 87.3 μg/L Heptachlor: 5.9 ± 15.1 μg/L Heptachlor epoxide: Not detected Endosulfan sulfate: 6.4 ± 28.6 μg/L Methoxychlor: 2.09 ± 12.8 μg/L	(Bawa et al., 2018)
India	n = 153 among four zones: - I: Subtropical - II: Sub-humid foothills - III: Wet temperate high hills - IV: Dry temperate high hills	OPPs, OCPs	GC, GC–MS	Zone I: DDT: 11 μg/L Zone II: DDT: 10 μg/L Zone III: DDT: 1 μg/L Zone IV: DDT: not detected CPF not detected in any of the zones SD not indicated	(Sharma et al., 2020)
Japan	n = 45	PYR	GC–MS	S-421: 0.026 μg/L	(Maekawa et al., 2017)
Saudi Arabia	n = 206	OCPs	AAS, GC–MS, AMA	DDD: 0.319 ± 0.562 μg/L DDE: 0.972 ± 1.211 μg/L DDT: 1.957 ± 1.254 μg/L	(Al-Saleh et al., 2019)
Saudi Arabia	n = 50	OCPs	GC–MS/MS	HCB: 117 ± 46.9 μg/L Alpha-HCH: 40.4 ± 24.0 μg/L Beta-HCH: 70.2 ± 30.0 μg/L Gamma-HCH: 14 ± 3.88 μg/L Delta-HCH: 104 ± 30.1 μg/L Σpp, opDDT: not detected Σpp, opDDE: 79.9 ± 26.3 μg/L Σpp, opDDD: 12.4 ± 8.04 μg/L Alpha-chlordane: 3.52 ± 2.51 μg/L Gamma-chlordane: 1.77 ± 1.25 μg/L	(EL-Saeid et al., 2021)

(*continued on next page*)

Table 11 (*continued*)

Location	Samples (n)	Contaminants	Methods	Main outcomes	Refs.
				Aldrin: 11.2 ± 3.78 μg/L Dieldrin: 5.07 ± 2.43 μg/L Endrin: 9.46 ± 4.03 μg/L Heptachlor: 4.48 ± 2.99 μg/L Mirex: 4.03 ± 2.55 μg/L Methoxychlor: 3.05 ± 3.05 μg/L	
Syria	n = 120	OPPs	LC-MS/MS, GC–MS/MS	Methamidophos: 2.198 μg/L Chlorpyrifos: 2.05 μg/L SD not indicated	(Smadi et al., 2019)
Taiwan	n = 68	OCPs	HRGC/LRMS	Aldrin: 0.168 ± 0.455 μg/L ΣHCH (the sum of α, β, γ, and δ-HCH): 0.839 ± 0.557 μg/L ΣCHL (the sum of cis- and trans-CHLs): 0.161 ± 0.284 μg/L 4,4′-DDD: 0.161 ± 1.64 μg/L 4,4′-DDE: 8.07 ± 6.53 μg/L 4,4′-DDT: 0.360 ± 0.798 μg/LΣDDT (the sum of DDD, DDE, and DDT): 9.81 ± 7.52 μg/L Dieldrin: 0.170 ± 0.500 μg/L Σendosulfan (the sum of endosulfan I, II, and sulfate): 0.290 ± 0.776 μg/L Σendrin (the sum of endrin aldehyde and ketone): 0.381 ± 0.701 μg/L Σheptachlor (the sum of heptachlor and heptachlor epoxide): 0.645 ± 0.995 μg/L Methoxychlor: 0.0388 ± 0.145 μg/L	(Chen et al., 2018)
Taiwan	n = 55	OCPs	HRGC/MS	α-HCH: 0.236 ± 0.310 μg/L β-HCH: 0.208 ± 0.241 μg/L γ-HCH: 0.128 ± 0.113 μg/L δ-HCH: 0.148 ± 0.122 μg/L *cis*-CHL: 0.113 ± 0.129 μg/L *trans*-CHL: 0.131 ± 0.268 μg/L 4,4′-DDD: 1.00 ± 1.43 μg/L 4,4′-DDE: 10.3 ± 6.76 μg/L 4,4′-DDT: 0.715 ± 0.745 μg/L Endosulfan I: 0.194 ± 0.353 μg/L Endosulfan II: 0.151 ± 0.367 μg/L Endosulfan sulfate: 0.147 ± 0.179 μg/L Endrin: 0.313 ± 0.208 μg/L Endrin ketone: 0.112 ± 0.146 μg/L Endrin aldehyde: 0.152 ± 0.265 μg/L Heptachlor: 0.660 ± 0.685 μg/L Heptachlor epoxide: 0.365 ± 0.388 μg/L Dieldrin: 0.352 ± 0.422 μg/L Methoxychlor: 0.106 ± 0.149 μg/L	(Kao et al., 2019)
Europe					
Belgium	n = 206	OCPs	GC-ECNI-MS, GC-EI-MS/MS	p,p′-DDT: 4.40 ± 0.43 μg/L p,p′-DDE: 52.23 ± 3.10 μg/L HCB: 5.57 ± 0.15 μg/L β-HCH: 2.91 ± 0.27 μg/L γ-HCH (lindane), p,p′-DDT, and chlordane group: not detected	(Aerts et al., 2019)
Sweden	n = 539	OCPs	GC/ECNI/MS	p,p′-DDT: 6.7 μg/L p,p′-DDE: 92 μg/L HCB: 12 μg/L β-HCH: 9.6 μg/L Oxychlordane: 3.4 μg/L *trans*-Nonachlor: 6.1 μg/L	(Gyllenhammar et al., 2021)
Switzerland	n = 3	Neonicotinoids	UHPLC-MS/MS	Thiamethoxam: BDL-0.002 μg/L Clothinidin: BDL-0.006 μg/L Imidacloprid: BDL-0.0065 μg/L Acetamiprid: BDL-0.009 μg/L Thiacloprid: not detected Total neonicotinoids: 0.015 ± 0.0065 μg/L	(Lachat and Glauser, 2018)

derivatives the most common ones (Hassine et al., 2012; Müller et al., 2019). This situation was also found in America, where levels of OCPs were found in Brazil, Mexico, and USA (Chávez-Almazán et al., 2020; Rodrigues and de Souza, 2018; Weldon et al., 2011). Levels of these contaminants have been also found in Asia in many countries, such as China, Saudi Arabia, Taiwan, Jordan, and India, being different studies with different cohorts in the case of the first three countries mentioned (al Antary et al., 2021; Bawa et al., 2018; Han et al., 2021; Kao et al., 2019; Kuang et al., 2020; Lu et al., 2015; Pan et al., 2020; Sharma et al., 2016; Zhou et al., 2012). Concerning Europe, only studies in Belgium and Sweden have been performed, also detected levels of OCPs (Aerts et al., 2019; Gyllenhammar et al., 2021). The studies detecting other types of pesticides on breast milk are scarcer. In this sense, levels of OPPs and pyrethroids have been found in USA, being higher the levels of these pesticides on samples collected from agricultural areas than in urban areas (Weldon et al., 2011). The levels of these pesticides have also been studied in China, although the presence of these compounds was not detected (Kuang et al., 2020). Also in China, levels of carbamates have been detected (Pan et al., 2020), while levels of pyrethroids have been detected in Japan (Maekawa et al., 2017). In India, also the presence of the pesticide CPF was measured, but again, no significant levels were detected in any of the zones measured (Sharma et al., 2016). Only in Syria, levels of the OPPs CPF and metamidophos were detected (CDC, 2017). However, it is important to mention that the use of metamidophos has been banned in Europe since 2009, and the use of CPF since 2019 (Hernandez and Hougaard Bennekou, 2019). Concerning neonicotinoids, only two studies have reported their measurement and presence in breast milk, one carried out in China (Chen et al., 2020a), and one carried out in Switzerland (Lachat and Glauser, 2018). In both, levels of imidacloprid, clothianidin, and thiamethoxam were detected. Nonetheless, their use has been banned in Europe outdoors due to their dangerous effects on bees (EFSA, 2021).

Regarding the levels of pesticides found in infant formula, as can be found in Table 12, only two studies have been performed in America, leading to the detection of glyphosate and different OCPs in Brazil (de Mendonça Pereira et al., 2020; Rodrigues and de Souza, 2018). In Asia, five studies have been reported. In this sense, the presence of OCPs was measured in a study performed in India (Sharma et al., 2016) and in one performed in Turkey (Kilic et al., 2018), where no levels of these contaminants were found. In Europe, only one study concerning the levels of OCPs have been performed in Romania, leading to the detection of heptachlor epoxide and endosulfan sulfate (Dobrinas et al., 2016). In the same study, levels of different OPPs were also detected, such as CPF or parathion-methyl, among others. Regarding these pesticides and pyrethroids, no levels were detected in India (Sharma et al., 2016).

Taking all of this into account, the presence of pesticides has been detected in more breast milk samples than in infant formula, which is not surprising. This is due to the regulation in the production of the infant formula, and the persistence of these pesticides in nature, reaching the mother through both the food chain and air pollution. It is also worth mentioning that most of the pollutants detected in breast milk samples are already banned from the European Union, and that mothers from agricultural areas are more exposed to these pesticides than urban mothers. A more visual representation of the detection of pesticides can be found in Supplementary Fig. 5.

3.6. Packaging materials

Concerning the contaminants proceeding from food packaging, the most common ones in both breast milk and infant formula samples were per- and polyfluoroalkyl substances (PFAS). Among them, perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) stand out (Zheng et al., 2021). However, the use of PFOA has been banned from USA and Europe (Zheng et al., 2021), leading to their replacement for PFAS with shorter carbon chains. In addition to these, the presence of phthalates has also been reported. These compounds are used as plasticizers in a variety of plastics, including those used for packaging materials, and most of them have demonstrated to have endocrine disruption features, affecting neurodevelopment (Dong et al., 2019). In addition, the presence of bisphenol A (BPA), which is a monomer of polycarbonate plastics and epoxy resins, has also been detected (Gao et al., 2021). The addition of this compound has been banned in some baby products (Bolognesi et al., 2015; Gao et al., 2021). However, BPA is still used in foodstuffs, environment, and human body, despite demonstrating to cause neurotoxicity and reproductive toxicity (Gao et al., 2021). To avoid this toxicity, some BPA analogs have been used to replace it, such as BPF, BPS, BFAF, BPB, etc., as they present lower toxicity (Liao and Kannan, 2013).

Besides being considered some of them as endocrine disruptors, bisphenols and PFAs have been studied after the exposure under laboratory conditions in different experimental models such as *C. elegans*, fish, or rodents. However, no human studies have found a correlation between

Table 12
Levels of pesticides found in infant formula expressed by mean ± SD, or as median: range.

Location	Samples (n)	Contaminants	Methods	Main outcomes	Refs.
America					
Brazil	n = 140	Glyphosate and OCPs	ICP-MS	Glyphosate: 0.00003-0.00108 μg/kg OCPs: 0.002-0.026 μg/kg	(de Mendonça Pereira et al., 2020)
Brazil	n = 105	Glyphosate and AMPA residues	LC	Glyphosate: 30-1080 μg/kg AMPA residues: 20-170 μg/kg	(Rodrigues and de Souza, 2018)
Asia					
India	n = 14	OCPs, OPPs, PYR	QuEChERS/GC	α-HCH, β-HCH, γ-HCH, δ-HCH, dicofol, p,p′-DDE, p,p′-DDD,p,p′-DDT,α-endosulfan, β-endosulfan, endosulfan sulfate, fenpropathrin, fluvalinate I and II, deltamethrin, bifenthrin, α-cypermethrin, fenvalerate I and II, chlorpyrifos, quinalphos, profenofos, triazophos, dimethoate, methyl demeton, phosphamidon, malathion, ethion and acephateand synthetic pyrethroids: not detected	(Sharma et al., 2016)
Turkey	n = 29	OCPs	ICP-MS, GC–MS/MS	Chlorobenzilate, chlordane-cis, chlordane-trans, o,p-DDD, p,p-DDD, o,p-DDE, p,p-DDE, o,p-DDT, p,p-DDT, dieldrin, endosulfan-α, endosulfan-β, endosulfan-sulfate, endrin, HCH-α, HCH-β, HCH-δ, HCH-γ (lindane), heptachlor, heptachlorepoxide-cis, heptachlorepoxidetrans, methoxychlor, nitrofen, and quintozene: not detected	(Kilic et al., 2018)
Europe					
Romania	n = 5	OCPs and OPPs	GC-ECD	OCPs: Aldrin, endrin, α-HCB, β-HCB, γ-HCB, λ-HCB, heptachlor, p,p′-DDD, p,p′-DDE, p,p′-DDT, α-endosulfan, β-endosulfan: not detected Heptachlor epoxide: BDL-2 μg/kg Endosulfan sulfate: 1-3 μg/kgOPPs: Dichlorvos: not detected Ethoprophos: 1-14 μg/kg Chlorpyrifos: BDL-5 μg/kg Prothiofos: BDL-0.9 μg/kg Guthion: BDL-0.8 μg/kg Disulfoton: BDL-2 μg/kg Fenchlorophos: BDL-0.4 μg/kg Parathion-methyl: BDL-0.2 μg/kg	(Dobrinas et al., 2016)

Table 13
Levels of food packaging residues found in breast milk expressed by mean ± SD, or as median: range.

Location	Samples (n)	Contaminants	Methods	Main outcomes	Refs.
Africa					
Tanzania	n = 47	PFAs	HRGC-LRMS; CALUX, HPLC-MS/MS	PFOA: 0.21 μg/L PFNA: 0.17 μg/L PFDA: 0.14 μg/L PFOS: 0.50 μg/L Dioxin-like activity: 30.2 μg/L	(Müller et al., 2019)
America					
United States	n = 50	PFAS	UPLC- MS/MS	PFHxA (C6): 0.00969 μg/L PFHpA (C7): 0.0061 μg/L PFPeS (C5), 4:2 FTS (C6), PFDS (C10), PFTeDA (C14): BDL Σshort-chain: 0.0172 μg/L PFHxS (C6): 0.00655 μg/L PFHpS (C7): 0.00105 μg/L PFOS (C8): 0.0304 μg/L PFOA (C8): 0.0139 μg/L PFNS (C9): 0.00044 μg/L PFNA (C9): 0.00598 μg/L PFDA (C10): 0.0074 μg/L PFUdA (C11): 0.00443 μg/L PFDoA (C12): 0.00526 μg/L PFTrDA (C13): 0.00316 μg/L Σlong-chain: 0.0996 μg/L ΣPFAS: 0.121 μg/L	(Zheng et al., 2021)
Asia					
China	n = 109	BPA and secondary metabolites	UPLC-MS/MS	BPA: 2.5 μg/L BPS: 0.19 μg/L BPAF: 0.092 μg/L BPF: Not detected SD not indicated	(Jin et al., 2018)
China	n = 174	PFAS	HPLC -MS/MS	PFBA: 0.024 μg/L PFPeA: 0.0068 μg/L PFHxA: 0.041 μg/L PFOA: 0.087 μg/L PFNA: 0.012 μg/L PFDA: 0.012 μg/L PFUnA: 0.013 μg/L PFHpA, PFTrA, and PFTeA: not detected PFHxS: 0.025 μg/L 6:2 FTOH: 0.014 μg/L 8:2 FTOH: 0.009 μg/L 10:2 FTOH: 0.010 μg/L 6:2 Cl-PFES: 0.028 μg/L 8:2 Cl-PFES: 0.0021 μg/L ΣPFASs: 0.203 μg/L SD not indicated	(Jin et al., 2020)
China	n = 149	BPA	UHPLC-MS/MS	BPA: 0.053 μg/L	(Gao et al., 2021)
South Korea	n = 221	Bisphenol A and phthalate metabolites	LC-MS/MS	MEP: 0.17 ± 2.37 μg/L MnBP: 0.83 ± 3.16 μg/L MiBP: 0.47 ± 3.19 μg/L MBzP: 0.06 ± 1.37 μg/L MEHP: 1.44 ± 6.00 μg/L MiNP: 0.10 ± 2.84 μg/L BPA: 0.12 ± 2.91 μg/L	(Kim et al., 2020)
Europe					
Poland	n = 21	Bisphenols	LC-MS/MS	Sampling point 1: BPA: 1.91 μg/L BPS: 0.16 μg/L BPAF: 0.07 μg/L BPF: not detected Sampling point 2: BPA: 1.41 μg/L BPS: 1.20 μg/L BPAF: 0.07 μg/L BPF: not detected Sd not indicated	(Czarczyńska-Goślińska et al., 2021)
Spain	n = 10	Bisphenols	UPLC-MS/MS	BPA: BDL-1.62 μg/L BPF: BDL-0.32 μg/L BPS: BDL-0.37 μg/L	(Dualde et al., 2019)

Table 13 (*continued*)

Location	Samples (n)	Contaminants	Methods	Main outcomes	Refs.
Spain	n = 82	PFAS	UHPLC-MS/MS	PFHxA: 0.00158 μg/L PFHpA: 0.01939 μg/L PFOA: 0.00717 μg/L PFNA: 0.00259 μg/L PFDA: <0.00072 μg/L PFUnDA: <0.00074 μg/L PFDoDA: <0.00077 μg/L PFTrDA: 0.00169 μg/L PFBS: <0.0008 μg/L PFHxS: <0.00066 μg/L PFHxS: <0.00086 μg/L	(Serrano et al., 2021)

exposure to these packaging materials and developmental toxicity (Golub et al., 2010; Qiu et al., 2019). Nonetheless, according to Street and Bernasconi (Street and Bernasconi, 2020), children's exposure to phthalates leads to a reduced IQ and a decrease in the psychomotor development index in humans (Yesumanipreethi et al., 2021). In fact, as explained in the review performed by Yesumanipreethi et al. (2021), phthalates have been associated with different neurological disorders in humans, causing similar behaviors than the one seen in ADHD or ASD. Furthermore, these phthalates have also demonstrated to have reproductive consequences in humans, leading to effects on male genital development in newborn boys after maternal exposure during the first trimester of the pregnancy (Swan et al., 2015), or to changes in placental size and shape (Zhu et al., 2018).

Regarding this, and as can be seen in Table 13, the only study performed in the USA led to the detection of higher levels of PFAs in total than those recommended by EFSA (Zheng et al., 2021). Furthermore, only one study has been performed in Africa, where levels of different PFAs were detected in Tanzania (Müller et al., 2019). PFAs have also been detected in China, Asia, leading also to high levels of these pollutants, accounting for almost double of those found in the USA (Gao et al., 2021; Jin et al., 2020). In addition, in Spain, Europe, also high levels of these contaminants have been found in breast milk, leading also to dangerous concentrations (Serrano et al., 2021). Concerning the presence of phthalates, they have only been reported in samples of breast milk from Asia, in China and South Korea. In this sense, different kinds of phthalates have been found in China, leading to very high levels compared to the recommended by the EFSA (Jin et al., 2020). However, in South Korea, even though levels of different phthalates were found, no toxic values were reported (Kim et al., 2020). In addition, concerning the presence of bisphenols, three studies have been performed in Asia and two in Europe. In this regard, the most studied was BPA, which was detected in two studies in China and in South Korea, although not dangerous levels were reported (Jin et al., 2020; Kim et al., 2020). Concerning Europe, one study was performed in Poland (Czarczyńska-Goślińska et al., 2021) and one in Spain (Dualde et al., 2019), and although they detected different types of bisphenols, no dangerous concentrations of these pollutants were found.

With respect to the levels found in infant formula, as can be found in Table 14, the presence of PFAs have been searched only in South Africa, finding higher levels than those recommended by EFSA (Macheka et al., 2021). However, the presence of phthalates and bisphenols has been more studied. In this regard, the presence of different phthalates has been detected in one study in Brazil and in two in Italy, leading to higher levels in one of the studies performed in Italy (Cirillo et al., 2015). In addition, the presence of bisphenols has also been reported in a study carried out in Brazil, two studies in Italy and in one in India. From them, dangerous levels of BPA have been found in the study performed in Brazil (de Mendonça Pereira et al., 2020), and in one of the Italian studies (Cirillo et al., 2015), while the other studies reporting levels in Italy and India led to concentrations within the range established by EFSA (del Bubba et al., 2018; Karsauliya et al., 2021).

Thus, as there was only one study performed in Africa on infant formula, while there are no available studies on breast milk, it would not be correct to assess that breast milk is safer than formula in this case. Concerning the studies carried out in America, only one study performed in USA was found measuring levels of food packaging contaminants that led to high levels of PFAs, while two studies were performed on Brazilian infant formula that led to high levels of BPA, so the safety of both types of food would depend on the country in this case. Regarding the studies performed in Asia, only one study was found on infant formula leading to no toxic concentrations of these pollutants, while different studies were found in breast milk detecting dangerous levels of bisphenols, phthalates, and PFAs. Thus, although infant formula seems to be safer in this term, it is also worth mentioning the lack of the studies in this regard. However, according to the studies available measuring the levels of these contaminants in both breast milk and infant formula, no toxic levels were found in breast milk, while one study led to high concentrations of BPA in Italy on infant formula, being safer, thus, breast milk in this case. In order to visualize the findings in a simpler way, the data can be found in Supplemental Fig. 6.

3.7. Other environmental pollutants

Once the main groups of contaminants have been described, it is also worth mentioning the presence of some compounds that do not fit in any of those groups. According to this, they have been divided into six groups: chlorinated paraffins (CPs), flame retardants (BFRs, HBCDD, TBBPA and PBDEs), parabens, benzophenones, and mineral oil hydrocarbons (MOHs), whose inclusion is justified for several reasons. First, CPs are considered as a group of emerging contaminants, and a cause of an increasing concern due to their environmental persistence and their toxicity to humans (Wu et al., 2020). The same way, flame retardants are a group of contaminants that is getting attention nowadays since the prolonged exposure to them has been described lately due to household products and building materials, and it is associated with many adverse health effects (Killilea et al., 2017). Other chemicals of emerging concern are parabens, since they are widely used as preservatives in food and personal care products, and they can act as endocrine-disrupting chemicals (Wei et al., 2021). Benzophenones have been included for similar reasons, since they are emerging human and environmental contaminants mostly used in sunscreens and personal care products (DiNardo and Downs, 2018). Lastly, MOHs have also gotten the attention because some new studies have found unexpected MOHs sources (Grob, 2018).

Regarding PBDEs, most of them are widely used as brominated flame retardants (BFRs). These chemicals are a group of compounds used to prevent or stop the dissemination of fire (U.S. Department of Health and Human & Services, 2004). For this purpose, they are used in hard plastics and polyurethane foam, being present in many daily products, which leads to an increased human exposure-risk (Birnbaum and Staskal, 2004; Darnerud et al., 2001). These compounds compile 209 chemicals, being BDE-47, BDE-99, BDE-100, and BDE-153 the most detected in humans (Hites, 2004). In addition to these flame retardants, BFRs, HBCDD, and TBBPA should be also considered. As described above, BFRs are used to mitigate the spread of fire, although within this category, some of them have been banned over the past decade, such as penta- and Octa-BDEs (Listing of POPs in the Stockholm Convention, n.d.). Therefore, the present studies focus on the analysis of those BFRs that are produced at high levels or are

Table 14
Levels of food packaging residues found in breast milk expressed by mean ± SD, or as median: range.

Location	Samples (n)	Contaminants	Methods	Main outcomes	Refs.
Africa					
South Africa	n = 9	PFAS	UHPLC-MS/MS	PFBA: 0.19 μg/kg PFPeA: 0.07 μg/kg PFHxA: 0.01 μg/kg PFHxS: 0.01 μg/kg PFOA: 0.01 μg/kg PFNA: 0.05 μg/kg PFOS: 0.02 μg/kg PFDA: 0.17 μg/kg PFUdA: 0.36 μg/kg PFDS: 0.01 μg/kg PFDoA: 0.67 μg/kg PFTrDA: 0.38 μg/kg PDTeDA: 0.16 μg/kg L-PFBS and PFHxA: not detected SD not indicated	(Macheka et al., 2021)
America					
Brazil	n = 140	Perchlorate	ICP-MS	Perchlorate: 7.83 μg/kg	(de Mendonça Pereira et al., 2020)
Asia					
India	n = 68	Bisphenols	UPLC-MS/MS	BPA: 5.46 μg/kg BPS: 0.58 μg/kg BPZ: 1.64 μg/kg BPAF, BPC, BPE, and BPFL: not detected SD not indicated	(Karsauliya et al., 2021)
Europe					
Italy	n = 4	Phthalates	ICP-MS, GC–MS/MS	DEHP: 18–75 μg/kg MEHP: 35–72 μg/kg DiBP: 18–25 μg/kg MiBP: 5.7–43 μg/kg MiNP: 10–23 μg/kg DMP, DEP, DPP, DiPP, DBP, DPeP, DHP, DHepP, BzBP, DOP, DiNP, DNP, DDP, DUP, DDoP, MEP, MBP, MEHP, and MBzP: not detected	(del Bubba et al., 2018)
Italy	n = 50	Phthalates, BPA	HPLC	DEHP: 906 μg/kg DnBP: 53 μg/kg BPA: 15 μg/kg	(Cirillo et al., 2015)

highly present in the environment, such as hexabromocyclododecane isomers (HBCDD) and tetrabromobisphenol A (TBBPA) (Smythe et al., 2022). These flame retardants have been suggested to possibly cause developmental effects in humans, in terms of correlation with lower birth weight and length, lower head and chest circumference and developmental delays in cognition, together with poorer attention, fine motor coordination and cognition (Chao et al., 2007, 2011; Costa et al., 2014).

Concerning CPs, they have a wide usage spectrum, being used for plasticizers, sealing materials, flame retardants, and lubricants, among others (Glüge et al., 2016). These chemicals are classified according to their carbon chain length as short-chain CPs (SCCPs), medium-chain CPs (MCCPs), and long-chain CPs (LCCPs) (Yuan et al., 2019). In terms of public health, the most concerning ones are SCCPs and MCCPs due to their persistence, toxicity, and bioaccumulation (G. L. Wei et al., 2016).

Meanwhile, parabens are a group of p-hydroxybenzoic acid (PHBA), with methylparaben (MP), ethylparaben (EP), n-propylparaben (PP), and n-butylparaben (BP), being the most used in the cosmetic industry (EUR-Lex, 2009). These compounds have shown to increase the risk of several diseases, such as breast cancer, melanoma, allergy, and reproductive disorders (Matwiejczuk et al., 2020). Benzophenones are also a large and diverse group of compounds found in many pharmacologically active natural products, and they are widely used in synthetic products (Surana et al., 2018). One of the most concerning benzophenones nowadays is benzophenone-3 (BP-3), which is used in sunscreen products, and has been shown to be present in 97 % of the population tested (DiNardo and Downs, 2018). The last group of contaminants analyzed is MOHs. Mineral oils are certain fractions derived from petroleum refining, and they can contain open-chain hydrocarbons, commonly named as paraffins, hydrocarbons with saturated rings (MOSH), and aromatic hydrocarbons (MOAH) (Weber et al., 2018). Concerning the effects of the maternal exposure to these compounds and possible effects on the offspring, some studies have reported prenatal exposure to parabens and benzophenoles to be related to cognitive impairment in children (Jiang et al., 2019). Furthermore, Barkoski et al. (2019) reported prenatal phenol and parabens to be possibly linked to ASD.

Regarding the results found in breast milk, as can be seen in Table 15, only PBDEs were found in one country in Africa, in Uganda, in safe concentrations, while no other contaminants related were studied (Matovu et al., 2019). These contaminants were also found in Asia, both in China and in Japan, although the levels detected are within the established by the EFSA (Maekawa et al., 2017; Pan et al., 2020). However, in China, some other pollutants were also measured, which led to higher levels of CPs than those recommended by the EFSA (Xu et al., 2021), and to the detection of several flame retardants (Huang et al., 2020). Concerning Asia, levels of parabens and triclosan were also measured in Korea, leading to their detection in two different studies (Kim et al., 2020; Park et al., 2019). In addition, these types of pollutants have also been found in Europe. In this sense, levels of parabens have been detected in Spanish and Polish breast milk-samples (Czarczyńska-Goślińska et al., 2021; Dualde et al., 2019), while levels of PBDEs were detected in Sweden and Belgium (Aerts et al., 2019; Gyllenhammar et al., 2021). Furthermore, levels of phytochemical phenolic compounds were detected in Poland (Nalewajko-Sieliwoniuk et al., 2020).

Respecting the pollutants found in infant formula, as can be found in Table 16, only one study has been performed in America, which led to the detection of different benzophenones on Brazilian samples (Galindo et al., 2021). Concerning the reports from Asia, only China has published, to our knowledge, the presence of these contaminants, including MOH and CPs (Han et al., 2021; Li et al., 2020; Sui et al., 2020). The only study

Table 15
Levels of other pollutants found in breast milk expressed by mean ± SD, or as median: range.

Location	Samples (n)	Contaminants	Methods	Main outcomes	Refs.
Africa					
Uganda	n = 50 (urban vs rural)	PBDEs	GC–MS	Nakaseke (rural): BDE-28: not detected BDE-47: 0.21 μg/L BDE-49: not detected BDE-66: not detected BDE-77: 0.12 μg/L BDE-99: 0.06 μg/L BDE-100: not detected BDE-138: not detected BDE-153: 0.11 μg/L BDE-154: 0.05 μg/L BDE-183: not detected BDE-209: not detected Kampala (urban): BDE-28: 0.03 μg/L BDE-47: 0.83 μg/L BDE-49: 0.09 μg/L BDE-66: 0.04 μg/L BDE-77: 0.13 μg/L BDE-99: 0.15 μg/L BDE-100: 0.13 μg/L BDE-138: 0.04 μg/L BDE-153: 0.37 μg/L BDE-154: 0.26 μg/L BDE-183: 0.15 μg/L BDE-209: 0.92 μg/L SD not indicated	(Matovu et al., 2019)
Asia					
China	n = 42 (pooled) (rural vs urban)	CPs	GC x GC-ECNI-MS	MCCP: Urban areas: 445.09 μg/L Rural areas: 527.72 μg/L SCCP: Urban areas: 370.09 μg/L Rural areas: 426.91 μg/L SD not indicated	(Xu et al., 2021)
China	n = 20	CPs	GC-ECNI-LRMS	ΣSCCP: 117.1 μg/L ΣMCCP: 40.3 μg/L SD not indicated	(Liu et al., 2020)
China	n = 111	BFRs, HBCDD	HPLC-MS/MS	α-HBCDD: 5.4 ± 4.37 μg/L β-HBCDD: 0.127 ± 0.27 μg/L γ-HBCDD: 2.06 ± 3.22 μg/L ΣHBCDD: 7.58 ± 6 μg/L	(Huang et al., 2020)
Korea	n = 260	Parabens	LC-MS/MS	MP: 0.619 ± 2.50 μg/L EP: 1.03 ± 2.01 μg/L PP: 0.174 ± 0.641 μg/L BP: 0.048 ± 0.118 μg/L Σparabens: 1.87 ± 4.26 μg/L	(Park et al., 2019)
Korea	n = 221	Parabens and triclosan	LC-MS/MS	Methyl-paraben: 0.33 ± 5.61 μg/L Ethyl-paraben: 0.46 ± 5.23 μg/L Propyl-paraben: 0.21 ± 3.30 μg/L Triclosan: 0.04 ± 2.62 μg/L	(Kim et al., 2020)
China	n = 54	PBDEs	GC/MS	BDE-28: 0.666 ± 0.827 μg/L BDE-47: 1.15 ± 1.15 μg/L BDE-100: 0.361 ± 0.324 μg/L BDE-99: 0.552 ± 0.749 μg/L BDE-154: 0.757 ± 0.816 μg/L BDE-153: 4.95 ± 4.71 μg/L BDE-183: 1.37 ± 1.73 μg/L BDE-209: 5.77 ± 4.04 μg/L ΣPBDEs: 13.6 ± 10.3 μg/L	(Pan et al., 2020)
Japan	n = 45	PBDEs	GC–MS	BDE-28: 0.001 μg/L BDE-47: 0.011 μg/L BDE-99: 0.001 μg/L BDE-100: 0.003 μg/L BDE-153: 0.014 μg/L BDE-154: 0.001 μg/L	(Maekawa et al., 2017)

(continued on next page)

Table 15 (*continued*)

Location	Samples (n)	Contaminants	Methods	Main outcomes	Refs.
				BDE-183: not detected BDE-197: 0.005 μg/L BDE-207: 0.006 μg/L BDE-209: 0.022 μg/L SD not indicated	
Europe					
Poland	n = 13	Phenolic compounds (phytochemicals)	LC-ESI-MS/MS	Gallic acid: 31.8 ± 1.3 μg/L Daidzein: 3.61 ± 5.93 μg/L Caffeic acid: 54.4 ± 24.3 μg/L Quercetin: 12.4 ± 5.61 μg/L Genistein: 3.63 ± 3.40 μg/L Naringenin: 1.89 ± 1.57 μg/L Hesperetin: 1.243 ± 1.31 μg/L Epicatechin, epicatechin gallate, epigallocatechin gallate, kaempferol: not detected	(Nalewajko-Sieliwoniuk et al., 2020)
Belgium	n = 206	PBDEs	GC-ECNI-MS, GC-EI-MS/MS	PeCB: not detected HexaBB: not detected BDE-28: not detected BDE-47: 0.24 ± 0.02 μg/L BDE-99: 0.10 ± 0.01 μg/L BDE-100: not detected BDE-153: 0.46 ± 0.02 μg/L BDE-154: 0.13 ± 0.01 μg/L	(Aerts et al., 2019)
Poland	n = 21	Parabens	LC-MS/MS	Sampling point 1: MP: 1.02 μg/L EP: 0.32 μg/L PP: 0.25 μg/L BP: 0.04 μg/L Sampling point 2: MP: 1.52 μg/L EP: 0.27 μg/L PP: 0.64 μg/L BP: 0.04 μg/L SD not indicated	(Czarczyńska-Goślińska et al., 2021)
Spain	n = 10	Parabens	UPLC-MS/MS	MP: 1.59 μg/L EP: 0.671 μg/L PP: 0.197 μg/L BP: 0.051 μg/L	(Dualde et al., 2019)
Sweden	n = 539	PBDEs and HBCDDs	GC/ECNI/MS	BDE-47: 1.5 ± 1.6 μg/L BDE-99: 0.33 ± 0.45 μg/L BDE-100: 0.30 ± 0.39 μg/L BDE-153: 0.63 ± 0.49 μg/L BDE-209: 0.10 ± 0.12 μg/L HBCDDs: 0.33 ± 0.41 μg/L	(Gyllenhammar et al., 2021)

performed with Polish samples of infant formula led to the detection of different PBDEs in 16 samples (Pietron et al., 2021). Last, only two studies regarding the presence of nitrogen compounds in infant formula have been found that were performed in the last decade. The first one was carried out in Austria by Beganović et al. (2020), who used a handheld Raman spectrometer (HRS) to quantify melamine in 7 samples of infant formula, finding that the values were correct according to EU limits. The second one was the study developed by de Mendonça Pereira et al. (2020) that has been mentioned before in other sections. They found a melamine concentration of 0.15-1.0 mg/kg, which is safe under the law. These results can be perceived visually in Supplementary Fig. 7.

4. Conclusion

To sum up, breast milk has demonstrated to be a good biomarker for exposure to maternal environmental contamination, and it is a powerful tool to predict also infant exposure, especially in polluted areas. In this sense, the presence of the different pollutants varies from each continent, and the place of residence, as mothers living in industrial areas present higher levels of toxics on breast milk, such as metals, pesticides, or packaging products, in which infant formula seems to be a good alternative. However, infant formula is not exempt from being exposed to different contaminants during the process of fabrication, handling, or manufacturing, also including metals, heat-treatment products, pharmaceutical residues, mycotoxins, or packaging products. Taking all of this into account, as breast milk also has beneficial properties for the infant in terms of microbiota, immune, and nervous system, a professional approach would be required to make the decision of combination of breast milk and infant formula and, in very specific bad scenarios, avoiding breast milk depending on the maternal conditions.

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CRediT authorship contribution statement

I. Martín-Carrasco: Methodology, Writing – original draft. **P. Carbonero-Aguilar:** Methodology. **B. Dahiri:** Methodology, Writing – original draft. **I.M. Moreno:** Conceptualization, Resources, Writing – review & editing. **M. Hinojosa:** Conceptualization, Writing – review & editing.

Table 1
Levels of other pollutants found in breast milk expressed by mean ± SD, or as median: range.

Location	Samples (n)	Contaminants	Methods	Main outcomes	Refs.
America					
Brazil	n = 25	Benzophenones	HPLC-FLD-DAD	BP: 322.57 ± 12.92 μg/kg BP-1: 512.47 ± 81.26 μg/kg BP-3: 232.88 ± 7.61 μg/kg BP-8: 163.60 ± 10.15 μg/kg BP-12: 71.95 ± 3.99 μg/kg	(Galindo et al., 2021)
Asia					
China	n = 51	MOH (MOAH and MOSH)	GC-FID/MS	MOAH: 800 μg/kg MOSH: 2100 μg/kg SD not indicated	(Sui et al., 2020)
China	n = 42	MOH	GC-FID/MS and consumption surveys	MOAH: 550 μg/kg MOSH: 1560 μg/kg SD not indicated	(Li et al., 2020)
China	n = 23	CPs	AG-CMS	Skimmed milk: SCCPs: 3.21 μg/kg MCCPs: 2.29 μg/kg Whole milk: SCCPs: 16.3 μg/kg MCCPs: 11.8 μg/kg SD not indicated	(Han et al., 2021)
Europe					
Poland	n = 16	PBDEs	HRGC-HRMS	BDE-28: 0.09 μg/kg BDE-47: 0.71 μg/kg BDE-49: 0.31 μg/kg BDE-99: 0.88 μg/kg BDE-100: 0.31 μg/kg BDE-138: 0.09 μg/kg BDE-153: 0.07 μg/kg BDE-154: 0.31 μg/kg BDE-183: 0.31 μg/kg BDE-209: 11.3 μg/kg ΣPBDEs: 14 ± 7.0 μg/kg	(Pietron et al., 2021)

Data availability

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

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2023.162461.

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