Global Pediatrics 2 (2022) 100017

Contents lists available at ScienceDirect

Global Pediatrics

journal homepage: www.elsevier.com/locate/gpeds

Chemical contaminants in breast milk: a brief critical overview☆

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ARTICLE INFO

Keywords:
Breast milk
Milk
Environmental contaminants
Endocrine disruptors

ABSTRACT

Breast milk is the reference food for the infant both for its content in nutrients, necessary for normal growth and development, and for the presence of biologically active substances that provide protection from infections and a lower susceptibility to several non-communicable diseases typical of adulthood. However, substances that the mother assimilates from the environment, and which can be potentially harmful, can be concentrated in breast milk. In fact, for a long time, breast milk has been considered a reliable biomarker of the environment. The huge increase in the production and use of chemicals that has occurred in recent decades with consequent wide dispersion in the soil, water and air makes it necessary to carefully evaluate the levels of contamination. Based on a synthetic review of current knowledge, it can be confirmed that breast milk is always the first choice. However, various aspects remain to be clarified based on more robust scientific data. This review aims to stimulate further research, managed by multi-disciplinary teams which, with the use of the most modern chemical analysis tools, determine the presence of exogenous chemicals in longitudinal studies during pregnancy and lactation, clarifying their metabolic fate and evaluating them in the 'scope of global exposure (exposome). To this end, the gaps present in the studies conducted so far are also highlighted to make future scientific approaches increasingly robust.

1. Introduction

A recent review has highlighted some significant data on chemical contaminants that have effects of on human health[1].

- in the last decades the industrial production of chemicals has increased significantly and the number estimated varies from 140,000 to over 350,000;
- about 220 billion tons are dispersed into the environment every year;
- these substances are ubiquitous, they spread in the atmosphere, in the soil, in the water and have been found in uninhabited regions, on mountain peaks, at the poles and in the oceans;
- population studies have revealed their presence in various tissues of the human body.

Many of these substances can be hazardous to health even in small doses and the toxicity of many is yet unknown[2].

In USA the presence of 36 environmental chemicals has been tested in children aged 6–18 years through five National Health and Nutrition Examination Survey (NHANES) cycles (2003–2012). Chemicals have

Abbreviations: PAHs, polycyclic aromatic hydrocarbons; BM, breastmilk; DOHaD, developmental origi ns of adult health and disease; FASD, fetal alcohol spectrum disorders; WHO, World Health Organization; EDCs, Endocrine disrupting chemicals; Mg, manganese; Zn, zinc; Mo, molybdenum; Cu, copper; Se, selenium; Pb, lead; Cd, cadmium; Hg, mercury; As, arsenic; MTL, maximum tolerable limits; POPs, Persistent Organic Pollutants; PCBs, polychlorinated biphenyls; BFRs, brominated flame retardants; OCPs, organochlorine pesticides; BPA, bisphenols; PBs, parabens; BPs, benzophenones; MADI, Maximum Acceptable Daily Intake; PFOS, perfluorooctane sulfonic acid; PFOA, perfluorooctanoic acid; PFHxS, perfluorohexane sulfonic acid; CDC, Centers for Disease Control and Prevention; DDTs, dichloro diphenyl dichloro- ethylenes.

☆ The Authors of this Special Issue are all part of the Safe Food for Infant Sino-European project (SAFFI), funded from the European Union's Horizon 2020 research and innovation programme under grant agreement N°861917.

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https://doi.org/10.1016/j.gpeds.2022.100017

Available online 7 May 2022

been detected in 93% of sujects and the 5 most represented categories were metals, phenols, pesticides, phthalates, and polycyclic aromatic hydrocarbons (PAHs)[3].

In other words, the development of chemistry has brought considerable benefits to humanity and has favored its development from many points of view, however, one cannot ignore "the other side of the moon" and possible negative effects on human health must be considered also and understood.

The main aim of this overview, since exogenous chemicals are found in breast milk, is to stimulate greater interest in both clinical and basic research to better understand how contaminants may interfere with the positive biological actions of breast milk and the mechanisms that could affect the triad mother-breast milk-child,[4] especially in the long term to avoid any risks to the baby's and mother's health.

2. Advantages of breastfeeding

According to the World Health Organization[5], the American Academy of Pediatrics[6] and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)[7] breastmilk (BM) is the first choice for feeding infants in the first six months of life and in addition to complementary food up to two years of age. This statement was based on several evidence supporting that BM contains macro and micro-nutrients able to guarantee both normal statural-ponderal growth and normal psycho-motor and intellectual development.

Moreover, the bio-active factors contained in BM (oligosaccharides, stem cells, microRNAs, growth factors, hormones, antioxidants, cytokines) are able to perform a wide range of biological actions (still not fully explainable). Actions are both direct and indirect through, for example, changes in the microbiome. These actions are aimed at safeguarding the state of health both in the short and long term.[8].

It is well known in fact that the anti-inflammatory[9], antioxidants[10] and probiotic[11] properties can give to the breast milk an immunological protective effect which, in the poorest Countries, has contributed to the reduction of mortality from infectious diseases in the first years of life[12]. Regarding the long-term effects, there is evidence that BM could help to prevent chronic diseases such as overweight and obesity, hypertension, type 2 diabetes and atopic diseases during adolescence and adulthood[12].

In conclusion, "Breastmilk can be considered a "**live tissue**" which composition varies among women and changes over the course of lactation[13].

It should be remembered also that breastfeeding has benefits for the mother and is associated with less postpartum blood loss and lower risk of breast cancer and cardiovascular disease.

3. Reasons for infant's susceptibility to chemicals

The mammary gland acts as an excretory organ of substances taken by the mother which are transferred into the milk. Since the 1950s BM has been used as a biomonitoring matrix to assess exposure to contaminants in humans, in particular to establish the levels of exposure in the mothers, and pre-natal exposure, and understand transfer of contaminants to the infant through breast feeding[14].

Subsequently, medical research has sought to identify substances in BM that can be harmful for mothers and their infants, however, data at present are scarce.

In the first years of life, infants are particularly sensitive to the possible toxic action of chemicals because of some fundamental differences compared with adults. Infancy is characterized by elevated longitudinl growth, rapid changes in body composition, in numerous metabolic mechanisms and in the various organs. For example, in the first 3 months after birth the brain volume incfeases by over 60% and the brain, lungs, and immune system continue to develop through to the age of 6 years and beyond[15]. Infants eat more food and drink more water per unit of body weight and their respiratory minute ventilation adjusting for weight is greater than in adults[16]. Children's behavior and activity patterns are also much different than that of adults and exposure to contaminents may play an important role[17]. The metabolic processes required for detoxification are immature[18].

Finally, in accordance with the developmental origins of adult health and disease' (DOHaD) hypothesis it has been proven that a contact with different chemicals during pregnancy and the first years of postnatal life can contribute, through epigenetic mechanisms, to favor the onset of metabolic and cardiovascular diseases in later ages[19, 20].

4. Chemical contaminants

4.1. Drugs, therapeutic agents, alcohol, cigarette smoking

In the past years a series of studies have focused on the mother's bad habits (smoking cigarettes, alcohol), on the use of therapeutic drugs and on the problems related with drug addiction.

Briefly, the following pointa summarise current knowledge and indications:

- for the use of therapeutic drugs one can refer to the indications provided by the scientific societies[21].
- the use of illicit.drugs is generally considered a contraindication to breastfeeding[22, 23].
- as far as alcohol is concerned it is is well established that during pregnancy it can harm the unborn baby and be responsible for physical and neurobehavioral damage. These conditions are referred to as fetal alcohol spectrum disorders (FASD).

The possible effects of acohol on breastfed infant is less studied and more controversial. According to some researches, the use of alcohol during lactation can damage neuropsychic development regardless of whether or not there was an exposure in the prenatal period also, and thus should be discouraged[24]. This is also the recommendation of the World Health Organization(WHO)[25]. Other Authors has come to different conclusions after a review of the literature and they argue that there seem to be no risks[26]. Most likely these discrepancies are related with the amount of alcohol consumed the mothers. In the absence of more robust evidence, the Australian guideline recommendation "The evidence does not indicate a safe amount of alcohol that pregnant women and breastfeeding mothers can drink, therefore not drinking is recommended as the safest option"[27] can be supported.

- as far as cigarette smoking is concerned an extensive review of the data collected confirms that smoke is associated with a reduced content of macronutrients, decreased antioxidant properties and altered immune status in human milk. However, there is a need both to deepen the results obtained and above all to place them in a broader context of risk factors[28].

4.2. Metals

Another group of substances worthy of attention is that of metals (some of them also might act as endocrine disrupting chemicals (EDCs) (See next chapter).

Some metals present in trace in BM [(like manganese (Mg), zinc (Zn), molybdenum (Mo), copper (Cu), and selenium (Se)], are necessary for a normal development of the infants.

Others such as lead (Pb), cadmium (Cd), mercury (Hg), and arsenic (As) do not play any biological role, and may cause adverse health effects. Generally, Cd, As and Pb are considered as potential carcinogens and are associated with many diseases affecting cardiovascular and nervous systems and the function of various organs such as liver, kidney, bladder, and bone[29]. Therefore, international organizations such as the WHO have given indications of the maximum tolerable limits (MTL)[30].

In general, the belief has always prevailed that, a part for events (natural and/or industrial disasters), there are no indications for the

suspension of breastfeeding. The widespread diffusion of chemical substances in the environment, the displacement of populations with profound changes in lifestyles and eating habits including eating more prepared food, the industrialization of large areas has stimulated in the last few years, also thanks to more modern chemical analysis skills, the dosage of metals in breast milk in different geographical areas.

The results obtained are heterogeneous[31].

Several studies have focused on one single metal. The determination of lead in breast milk in Moroccan women has, for example, highlighted a mean values of 23.08 μg / L with a very wide range (1.38 - 515.39). Moreover, about 80% of the samples had a Pb content higher than 5 μg / L which is considered the MTL[32].

This wide variability is also found in other Countries of the Mediterranean and other geographical areas with a range between values higher than those in Morocco (31.67 in Saudi Arabia) to values lower than the MTL as in Portugal, Slovakia, and Austria.

Different results have also been reported in the same Country (Italy and Greece in Mediterranean area[32] and in 15 chinese cities[33]. demonstrating the need to carry out, if necessary, a specific biomonitoring in the geographical areas considered to be at greatest environmental risk.

The importance of the place where the mother lives also also turns out to be important in studies that have evaluated the presence in BM of several minerals. In a specific area in Spain, rich in industries and mines, all the mineral elements were present in BM exceeding the MTL with fluctuations from 6% for Cadmium to 60% for Selenium up to a maximum of 92% for Chromium[34].

Higher levels of lead in human milk have been reported in women that live close to industrial or urban areas[35]. The highest levels of arsenic in breast milk were found in a district in West Bengal in India where arsenic in water was above 50 mg/L[36].

However, it should be remembered that various other environmental factors can affect the presence of metals in BM, among these different eating habit. For example, a Norwegian study showed that Hg concentrations were correlated with a high seafood intake as in other Countries (Greece, Italy, Croatia, Slovenia[34],[37]. The European Food Safety Authority recommended that each country should consider its own pattern of fish consumption since 2014[38].

Another example is the correlation between lead levels and the use of lipstick in mothers[39].

4.3. Endocrine Disruptors (EDCs)

Almost 800 chemicals are considered to be Endocrine Disruptors (EDCs) defined as "exogenous substances or mixtures that alters function (s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations "[40]. Furthermore, EDCs can cause metabolic disorders and may play an important role in the global epidemic of metabolic diseases. For this reason, for some of these it has also been proposed to use the definition of 'metabolism disrupting chemicals (MDCs)[41].

However, only a small fraction of these chemicals have been tested for their safety or toxicity concern[42].

EDCs are widespread in the environment. They are found in everyday products (toys, personal care products, food and beverages containers, detergents, flame retardants, pesticides, metals). It is therefore not surprising that epidemiological studies have found the presence of EDCs in large populations of adults, children and pregnant women[43, 44] and in the fetus[45]. A wide range of research has shown that EDCs can affect multiple vital mechanisms in the animal world as well as in humans[46, 47] and particularly in the child[48, 49].

The presence of EDCs has also been documented in breast milk.

Among the longest-evaluated substances are Persistent Organic Pollutants (POPs) that include polychlorinated biphenyls (PCBs), brominated flame retardants (BFRs) and organochlorine pesticides (OCPs). These may all persist for many years in the environment and may bio-accumulate in animals and humans (food chain). In addition, to the endocrine effects, especially at the level of the reproductive system, they can cause damage to the central nervous system and be carcinogenic. In 2004, the Stockholm Convention banned their production[50]. In the following years a series of international surveys monitored the presence of POPs in breast milk[51]. Over the years there has been a downward trend in exposure to POPs but, according a recent survey, levels of PCBs have exceeded the toxicologically safe levels in breast-fed infants in all of the reported 51 countries[52].

In addition to POPs, other EDCs may be present in BM. The most studied are reported in Table 1.

In a systematic review that examined 50 scientific publications (over 3000 samples of breast milk) bisphenols (BPA), parabens (PBs), and benzophenones (BPs) were detected in about half of the samples of BM, and this is in agreement with epidemiological data of a wide diffusion in the population. The concentrations of these substances are variable ranging from 0,1 to 3,9 ng/mL of BPA and from 0.5 to>73.5ng/mL of BP-3. This variability can be explained both by methodological differences for the detection, and by the different geographical areas in which the research took place (Asia, America and Europe) and, at least partially, by other several unspecified variables. For instance, higher breast milk concentrations of BPA were observed in multiparous women, in those living in a rural area, and in those with a higher annual household income. Higher concentrations of some PBs were associated with a greater use of plastic food containers or consumption of canned beverages[53].

Although phthalates are one of the categories of chemical substances most produced worldwide and their monoesters were dosed in BM many years ago[54], very few studies have evaluated the presence of both their parent and degradation compounds in breast milk. In a high percentage of samples (up to 100%), however, measurabla amounts of phthalate diesters and / or monoesters have been confirmed and the ingested daily amount recorded was much lower than the Maximum Acceptable Daily Intake (MADI) proposed by European organizations[55].

Per- and polyfluoroalkyl substances (PFASs) represent a group of several thousand substances widely diffused in the environment. Some of these, in particular perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), and perfluorohexane sulfonic acid (PFHxS) are included in the Stockholm Convention on Persistent Organic Pollutants (POPs). The presence of these substances has been documented in studies carried out in different continents and it is interesting to note that over time their detection rate has decresed but has been replaced by other contaminants which toxicological risk is largely unknown. Finally, the concentrations in milk are lower than those found in maternal blood and in the umbilical cord due to a (protein) mechanism that would hinder the passage into the maternal breast[56].

Table 1
Specific endocrine disruptors and their known main sources.

Endocrine disrupting chemicals	Main sources
Benzophenones	cosmetics sunscreen, food packaging
Bisphenol A (BPA)	polycarbonate for plastic products (drinking bottles, food packaging, toys, medical devices) and epoxy resins (food/beverage containers, electronic devices)
Parabens	food and cosmetic preservatives
Paraffins	flame retardants, metal-cutting fluids, plasticizers and additives in lubricants.
Phthalates	humectants, emollients, or skin penetration enhancers in personal care products. Plasticizers in toys, bags, shoes, cosmetics, food packaging, medical equipment, and building materials.
Per- or polyfluoroalkyl substances (PFAS)	food packaging, cookware, clothing, carpets, fire extinguishers.

4.4. Infant health risks

On the basis of the data reported above, it can therefore be concluded that in a significant percentage of BM samples it is possible to dose chemical substances attributable to general chemical pollution. The point to be addressed is what damage can this cause to human health?

On the basis of current knowledge, there are no definite scientific proven elements that discourage the use of breast milk by weighing advantages and theoretical risks[57].

Therefore, the recommendation that has prevailed is that, beyond events (natural and / or industrial disasters), there is no indication to suspend breastfeeding[58, 59]. The views of the Centers for Disease Control and Prevention (CDC) go in this direction stating that although human milk contamination is a known issue, breastfeeding is recommended and fully endorsed[10]. The same conclusion is reached after an extensive revision of the literature stating that the evaluation of the relationship between the undoubted advantages of breast milk and the possible toxicological disadvantages leads to the conclusion that the former is clearly superior[59].

On the other hand, we cannot forget that some studies report a correlation between EDCs in BM and some clinically evaluable negative consequence in infants like a reduced weight and/or length gain related with BPA[60] or PFAS[61] exposure.

Moreover, many authors agree on the need to deepen the topic with methodologies that take into account the limits of the studies carried out so far[31, 53].

5. Gaps to consider for future research

Some gaps are often found not only in studies that evaluate BM contamination but also in those that more generally take into consideration the possible impact of the environment on human health.

- Many researches are in fact based on the determination of a specific chemical product and they do not evaluate the possible interaction among several categories of chemicals that can act in a synergistic or antagonistic way and the possible presence of substances not foreseen a priori. In real life, one is more likely to come into contact with a mixture of substances. For example, the application of the so-called nontargeted analysis detected the presence 172 halogenated and nonhalogenated cyclic and aromatic compounds in BM and proved that 85% of 40 prioritized contaminants are not typically monitored in breast milk surveys[14].
- To obtain a robust risk assessment it is necessary to assess not only the exposure to the chemicals mixtures but more generally to identify the so-called exposome which on the one hand includes the set of stimuli (environmental and personal) that can come into play and on the other (especially with metabolomics) the ways in which individuals react to such stimuli. It is a difficult task that requires the joint action of specialized teams (epidemiologists, analytical chemists, biologists, biochemists, geneticists and statisticians) but which will allow to pass from simple epidemiological results to the identification of specific biomarkers, to establish a link between the presence in the biological fluids and tissues of various substances and the causality of specific diseases[62].
- There is a need for more longitudinal studies performed from pregnancy (and pre-pregnancy) and to be continued in postnatal life for different reasons: 1) in real life we are continuously in contact with many substances which, even if in small doses, can be harmful even after a distance of time[63]; 2) the presence of a chemical in breast milk can be the expression of a previous accumulation as for Pb which concentration in BM correlates with the amount accumulated in the maternal bones during pregnancy[64]; 3) a single time analysis may not highlight the presence of substances such as BPA which are quickly washed out.

Some other gaps focus more specifically on the features of previous BM studies:

- BM samples must be analyzed repeatedly over time because the concentration of chemicals such as lead, cadmium, aluminium, and arsenic metals has been shown to differ in colostrum, transition milk and mature milk[65]. Many EDCs (polychlorinated biphenyls (PCBs), perfluorooctanoic acid (PFOA), dichloro diphenyl dichloro- ethylenes (DDTs), parabens) are also more present in colostrum[66].
- Comparative studies between cohorts of children who are breast-fed or formula-fed in similar environmental situations would be useful
- Many studies do not specify the type of breast milk tested (pasteurized? fresh?) and whether spot or mixed samples were used. Some substances pass quickly into the milk (BPA) while others have a much slower passage (Pb)
- In general, some reviews of the literature have highlighted a low quality of research[53].

Currently, the European LIFE-MILCH project is ongoing, coordinated by the University of Parma (www.lifemilch.eu)[67] to assess the levels of thirteen different EDCs in breastmilk in relation to maternal life- and diet habits and in formula milk studying the relationships with infant growth, body fat distribution and developmentfrom birth up to the age of 12 months.

6. Conclusions

As already underlined in the light of current evidence, breast milk is the reference food for newborns and infants and breastfeeding must be encouraged and supported by private and public initiatives.

The demonstration of the presence in breast milk of a wide range of potentially harmful chemicals, even if not classifiable as risk factors for health, must in any case stimulate a preventive work which is based above all on avoiding, during pregnancy and breastfeeding, the contact with these substances. This means, in particular, to pay attention to the origin of food, its handling and storage, reducing/avoiding the use of personal care products that often contain EDCs, decreasing indoor pollution and reducing contact with the outdoor pollution as much as possible.

Finally, research in this field should be stimulated and privileged, and consistent with current knowledge to better define signals of risks and to clarify the effects including epigenetic mechanisms.

Declaration of Competing Interest

The corresponding author states on behalf of the co-authors that all Authors have no conflict or competing of interests to declare.

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