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REVIEW ARTICLE

The impact of environmental pollution on the quality of mother's milk

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Abstract

Breastfeeding is a gold standard of neonate nutrition because human milk contains a lot of essential compounds crucial for proper development of a child. However, milk is also a biofluid which can contain environmental pollution, which can have effects on immune system and consequently on the various body organs. Polychlorinated biphenyls are organic pollutants which have been detected in human milk. They have lipophilic properties, so they can penetrate to fatty milk and ultimately to neonate digestive track. Another problem of interest is the presence in milk of heavy metals—arsenic, lead, cadmium, and mercury—as these compounds can lead to disorders in production of cytokines, which are important immunomodulators. The toxicants cause stimulation or suppression of this compounds. This can lead to health problems in children as allergy, disorders in the endocrine system, end even neurodevelopment delay and disorder. Consequently, correlations between pollutants and bioactive components in milk should be investigated. This article provides an overview of environmental pollutants found in human milk as well as of the consequences of cytokine disorder correlated with presence of heavy metals.

Keywords Breast milk · Polychlorinated biphenyls · Heavy metals · Cytokine

Introduction

A newborn child is exposed to many factors which may have negative impact on its health. Thus, protection is very important during infancy. One of its elements is breastfeeding, which reduces frequency of diarrhea and the risk of such diseases as necrotizing enterocolitis (NEC). Benefits of breastfeeding can be seen both during infancy and later in adult life (Duijts et al. 2010; Le Huërou-Luron et al. 2010; Martin et al. 2005; Owen et al. 2003). Ingredients contained in milk have many functions, such as providing nutrients and energy; thanks to the presence of specific proteins, or oligosaccharides milk also

Highlights

- Environmental pollutions easily transferred into breast milk and consequently to neonate body.
- The diet of nursing mothers rich in fat-rich foods can be a potential threat to newborns.
- The results of milk analysis from different study shows that this natural food is contaminated by polychlorinated biphenyls, especially when mother have diet rich in fish products and live in industrial areas.
- Harmful factors as heavy metals can disrupt cytokine production.
- A change in cytokine profile (Th1/Th2) can have consequences in child health.
- The milk contamination studies note that the benefits of breastfeeding outweigh its potential risks.

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has bioactive properties as these compounds have an impact on the development of the child's immunity (Gomez-Gallego et al. 2016). Among the compounds associated with the immune system are cytokines, which are polypeptides that operate in a complex network. Connection to a specific receptor produces an immunomodulating effect (Fig. 1) (Garofalo 2010).

In newborn babies, the full-scale production of cytokines begins with a certain delay, and this is why their presence in women's milk is so important. Delivered with mother's milk, they interact with respiratory and digestive tract cells and act as anti-inflammatories and immunomodulators (Meki et al. 2003).

Unfortunately, the effect of negative factors such as stress or toxic compounds (i.e., heavy metals) can cause disruption in the production of cytokines (Kendall-Tackett 2007; Krocova et al. 2000). The recent reports suggest that high concentrations of pro-inflammatory cytokines in milk may be connected to inflammation in the child, and their excess in food can be harmful when the newborn has necrotizing enterocolitis (MohanKumar et al. 2017; Rentea et al. 2017). Monitoring mother's milk is very important both in the search for compounds crucial for a developing organism and in testing for potential contaminants—environmental agents which can disrupt developmental process (Table 1) such as heavy metals, polychlorinated biphenyls, or dioxins (Rebelo and Caldas 2016; Urbaniak et al. 2015). Persistent organic pollutants such as dioxins and polychlorinated biphenyls are very hard to eliminate from the environment. They are lipophilic, i.e., they accumulate in adipose tissue. These compounds could be transferred to infants through breast feeding (Man et al. 2017). For newborns, these substances are particularly dangerous due to the immaturity of internal organs and the nervous system. Maternal exposure to heavy metals as Pb or Hg and persistent organic pollutants were associated with children neurodevelopment delay (Čechová et al. 2017; Kim et al. 2018; Shelton et al. 2014). Environmental pollutants induce changes in structure of immune system and also in function by disturbing the homeostasis. The toxicants cause stimulation or suppression of the immunomodulatory components and can influence indirectly on the various body organs and other system as nervous, reproductive, respiratory, and endocrine (Bahadar et al. 2015; Mokarizadeh et al. 2015).

Human milk monitoring makes it possible to assess the exposure of the mother and the baby. This is a non-invasive way to track environmental pollution (Lopes et al. 2016; Rebelo and Caldas 2016) and it is recommended by WHO.

The aim of this study is to summarize the current knowledge regarding monitoring human milk for the presence of compounds that could pose a threat to the health of both mothers and children, and linking their presence in milk to immunomodulatory compounds. It is important to summarize the latest achievements and current knowledge on pro-inflammatory cytokines in the context of biomarkers of inflammatory conditions in breastfeeding women and their double role: ingredients essential for a vulnerable child (immunomodulatory function) and compounds that may harm infant's digestive tract in case of necrotizing enterocolitis.

Because each of the review points could be a separate and extensive paper, the purpose of our work was to highlight key informations about discussed problems, and show that environmental pollutants can be associated with cytokine profile in breast milk, which can have harmful effect on newborn child.

A systematic review was conducted using PubMed and Scopus databases. Search strategies include keywords as "polychlorinated biphenyls," "PCBs," "human milk," "breast milk," "cytokine," "heavy metals," "lead," "mercury," "cadmium," and "arsenic" in various combination. We limited our paper to articles published in the English language. We performed the last search on 2 December 2018.

Human milk composition

Human milk is referred to as the golden standard of nutrition. It has unique composition: it is in 87% made up of water, and the rest is macro- and micronutrients—7% carbohydrates (mainly lactose), 4% lipids, and 1% proteins and others (vitamins and minerals) (Fig. 2). Milk composition changes with lactation periods, which is caused by physiological factors and also corresponds to the current needs of the infant. At the beginning of the lactation period, colostrum is produced (for 3–4 days), then immature milk (for about 2 weeks), and finally mature milk. Colostrum is rich in protein and vitamins such as A, B_{12}, and K as well as oligosaccharides. Concentration of these compounds in colostrum is higher than in mature milk. Colostrum is intended to provide immune protection to a child against numerous environmental pathogens. In mature milk, concentration of lipids is higher than in colostrum. Milk ingredients not only ensure proper growth and development of the baby, but also due to their bioactive properties they contribute to and support defense mechanisms, and thus they are

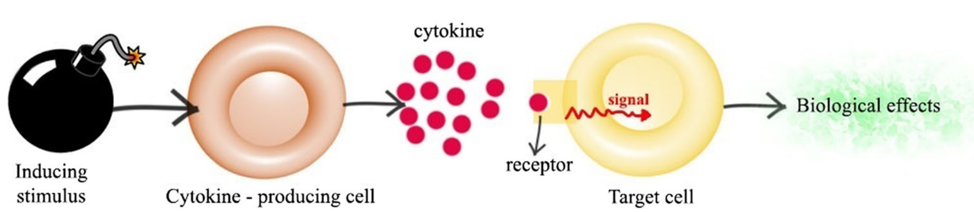


Fig. 1 Mechanism of cytokine production and action

Table 1 Anthropogenic pollutants and examples of toxic effects

Class of compounds	Examples of toxic effects	Literature
Pesticides • Organochlorine pesticides (OCPs) • Organophosphate pesticides (OPPs)	Delayed effects on central nervous system functioning	Ennaceur et al. 2008
	Disruption of endocrine system (hormonal imbalance)	Eskenazi et al. 2006
	Increased risk of cancer	Ribas-Fitó et al. 2006
	Genotoxic effects	Yamazaki et al. 2018
	Abnormal behavior	
	Growth retardation	
Organochlorines • Polychlorinated dibenzo-dioxin (PCDDs) • Polychlorinated dibenzofurnas (PCDFs) • *Polychlorinated biphenyls (PCBs)	Dermatitis	Gascon et al. 2013
	Disorders in the endocrine and reproductive system	Hansen et al. 2014
	Neurological and behavior problems	Passatore et al. 2014
	Metabolic diseases (diabetes, obesity)	Tang-Péronard et al. 2014
	Reduced immune response	Taylor et al. 2013
	Increased risk of asthma	
Bisphenols	Neuroendocrine disorders (e.g., precocious puberty)	Braun et al. 2011
	Obsesity	Rochester 2013
	Diabetes	
	Anxiety	
	Hyperactivity	
Parabens	Endocrine related disorders: (e.g., obesity, thyroid gland disorders, female/male reproduction issues)	Nowak et al. 2018
Phtalates	Adverse neurodevelopmental effects (e.g., autism spectrum disorders)	Benjamin et al. 2017
	Reproductive toxicity (testicular cancer, male infertility, reproductive abnormalities)	Katsikantami et al. 2016
	Asthma and allergic symptoms, overweight, and obesity	
Brominated flame retardants	Endocrine disruption	Műller et al. 2016
	Neurodevelopment and behavioral disorders	
	Potentially increased risk of cancer	
Perofluoroalkyl substances • Perfluorooctane sulfonate (PFOS) • Perfluorooctanoate (PFOA)	Delayed effects on development	Granum et al. 2013
	Decreased antibody response	
*Heavy metals: • Cadmium (Cd) • Arsenic (As) • Lead (Pb) • Mercury (Hg)	Immunotoxicity (weakening of the immune system)	Grandjean and Landrigan 2006, 2014
	Toxic effect on neurodevelopment	Samiee et al. 2019
	Development of autoimmune diseases (i.e., allergies or atropy)	
	Clinical disorders (e.g., anemia, cancer, reproductive disorders, depression	

*One of the main topics described on this paper

essential to the health of the infant. Additionally, milk has antioxidant properties. However, the composition of human milk is affected also by such external factors as mother's diet, lifestyle, and potential environmental pollutants (Andreas et al. 2015; Emmett and Rogers 1997; Gomez-Gallego et al. 2016; Mandal et al. 2014; Matos et al. 2015).

Organic pollutants in milk

Because of high fat content in milk, currently it may be difficult to eliminate from it such lipophilic compounds as dioxins: polychlorinated dibenzo-dioxin (PCDDs), polychlorinated dibenzofurans (PCDFs), and polychlorinated biphenyls (PCBs) (Lopes et al. 2016). The last mentioned group—PCBs—is one of the main topics discussed in this paper. Polychlorinated biphenyls are a group of compounds comprising 209 congeners. They are built of two phenyl rings combined by a C–C bonding (Andersson et al. 1997a). Individual congeners differ by the number of attached chlorine atoms. The arrangement of the rings depends on the number and position of chlorine atoms (Fig. 3). The flat conformation has biphenyl without chlorine in ortho position (non-ortho). Mono-ortho and di-ortho PCBs have similar structures. This group of congeners

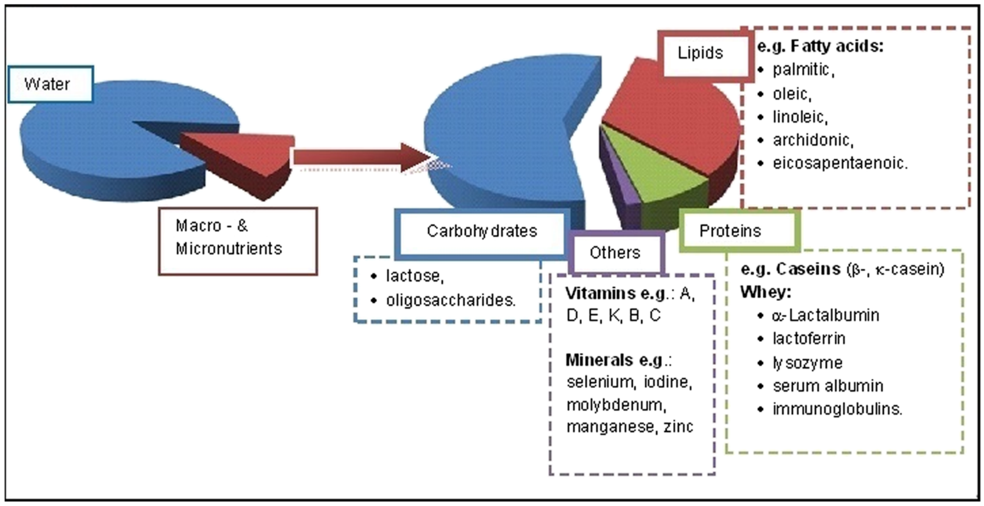


Fig. 2 Composition of human milk

is called dioxin-like PCBs (dl-PCBs 77, 81, 126, 169, 105, 118, 156, 157, 123, 167, 189). The chlorination substitution of PCB rings influences the toxicity of compound. Their structure and toxicity is similar to a very dangerous congener 2,3,7,8-Tetrachlorodibenzo-p-dioxin (2,3,7,8—TCDD), which is the most toxic compound in dioxin class. The toxic and biological effects of these environmental agents (teratogenic and carcinogenic effects) are connected with their tendency to bind with aryl hydrocarbon receptor (AhR), the cellular protein (ligand-activated transcription factor); thus, TCDD currently occupies the first place in the toxic equivalency factor (TEF) table. The Health and Environmental organizations advise to use this factor method for estimating health hazard connected with exposure to these compounds (Parvez et al. 2013). The TEF value is determined for particular compounds as PCBs, which have toxicity and biological effects relative to TCDD (TEF = 1), which is reference substance. It is also possible to assess toxic effect of mixture of dioxins. The total toxic equivalent (TEQ) is calculated by concentration of an individual compounds with TEF, and resulting are summed up as WHO-TEQ (Van den Berg et al. 2006). The non-dioxin-like PCBs (ndl-PCBs: 28, 52, 101, 138, 153, 180) show different toxic properties; however, they are very stable and are the substances most likely to accumulate (Andersson et al. 1997a, 1997b; Faroon et al. 2003; Van den Berg et al. 2013). This group of PCBs is called as indicator PCBs and they occur predominantly in the environment. Polychlorinated biphenyls are very hard to eliminate from the environment; for example, half-lives of the indicator PCBs are PCB 28, 5.5 years; PCB 52, 2.6 years; PCB 101, 2.8 years; PCB 118, 11.5 years; PCB 138, 12 years; PCB 153, 17 years, PCB 180, 15 years (Bányiová et al. 2017; Bu et al. 2015; Ritter et al. 2011).

The consequences of widespread pollution with these compounds and the threat PCBs pose to living organisms are a result of the multitude of ways in which this compound was used for over 50 years. Polychlorinated biphenyls found applications, e.g., in electrical insulation, lubricating and hydraulic fluids, as plasticizers for plastic and paints, and as additives in glue and copy paper (Erickson and Kaley 2011). Commercial production of these compounds was banned in the USA in the late 1970s. Unfortunately, due to PCBs' resistance to decomposition processes, even today, most of the lakes and rivers are polluted (Paliwoda et al. 2016; Rocheleau et al. 2011). Furthermore, illegal burning of hazardous waste, for example, old transformers containing chlorinated hydrocarbons, increases this type of pollution in the environment (Asamoah et al. 2018; Rivezzi et al. 2013). Contamination is carried by atmospheric transport over long

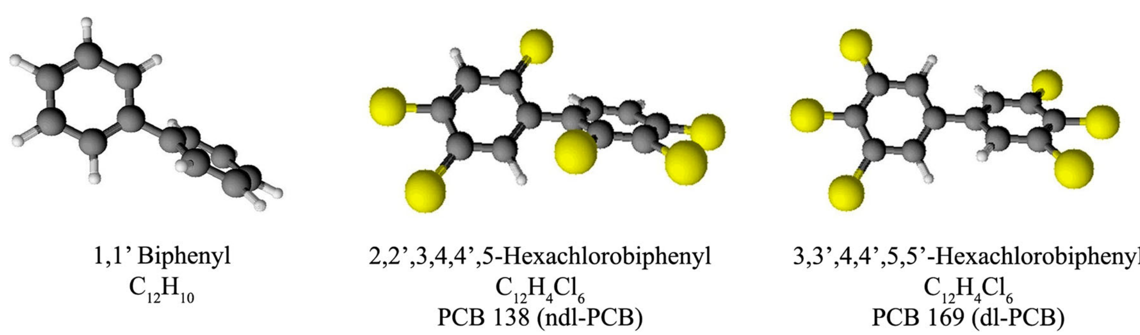


Fig. 3 Structure of polychlorinated biphenyls

distances to the regions which are not in the immediate vicinity of industrial plants (Gevao et al. 1998; Nelson et al. 1998; Norström et al. 2010) . An important problem is penetration of these compounds into water: due to their lipophilic properties, they bioaccumulate in fish. The species at the top of the food chain are the most vulnerable (Fig. 4). The fish are an essential source of omega 3 fatty acids, which are not synthesized by mammals but are necessary for proper metabolism. Consequently, the consumption of fish and fish products by humans and domesticated animals ensures the delivery of docosahexaenoic acid (DHA), yet it also creates the risk of exposure to harmful organic compounds that may be present in such food (Paliwoda et al. 2016).

Research conducted in Spain found that fish products are the main source of PCB, dioxin, and furan consumption, while the contribution from grains and vegetables is small (Marin et al. 2011). Fish consumption can cause accumulation of organic pollutants in tissue, and breastfeeding is the main way of excreting such substances from a woman's body (Uemura et al. 2008). The most polluted species are sardine, red mullet, and mackerel (Perelló et al. 2015), and fish with a lot of fatty tissue (salmon and trout) (Struciński et al. 2013). It is safer to eat fish from lower trophic levels. The big fish are exposed to higher PCB concentrations due to bioaccumulation and biomagnification (Paliwoda et al. 2016). People who have diet low in fish can fill the lack in DHA deficiency with fish oil supplements. Such supplements usually come in the form of microcapsules in which unstable fatty acids are protected against degradation (Barrow et al. 2009). However, there remains a question regarding pollutants in these capsules: Is oil derived from fish and enriched with omega-3 fatty acids also a source of lipophilic impurities? Unfortunately, if the oils have not been cleaned enough, the contents of PCBs or dioxins may exceed the limits, particularly if the oils come from fish that are on the highest trophic level, for example, shark. Another problem are differences in concentrations of these compounds in the product of the same type, but coming from a different manufacturing process (another region or collection season) (Fernandez et al. 2006; Martí et al. 2010; Rawn et al. 2009).

Mother's milk is a non-invasive matrix, which contains information about exposition to organic pollution. For instance, one study (Chen et al. 2015) showed that concentration of impurities in milk is correlated with levels of impurities in the feces of a neonate who has been fed this milk.

In order to assess the exposure of milk to these compounds, a number of factors should be considered that may influence their deposition in the body. These factors include mother's age, BMI before pregnancy, weight gain during pregnancy, her weight at birth (Lignell et al. 2013), smoking habit, area of residence (a neighborhood with industrial plants has the biggest impact) (Černá et al. 2010; Schuhmacher et al. 2007), and a detailed diet description, e.g., in the case of fish consumption, it is important how frequently the fish are eaten and what they are (fat or lean, fresh or frozen, local or imported) (Skrbić et al. 2010). Quantity and time of sampling from one mother are also very important factors, because organic pollutants such as PCBs and PCDD/Fs can be present in milk until the end of lactation (Vigh et al. 2013). Therefore, the best way is to conduct analysis during at least two or three stages of lactation (Uemura et al. 2008; Wang et al. 2008). Analysis of environmental pollutions in women's milk has been conducted by many researchers from the whole world, and in the most cases they focused on specific areas of the following states: Sweden (Lignell et al. 2013), Spain

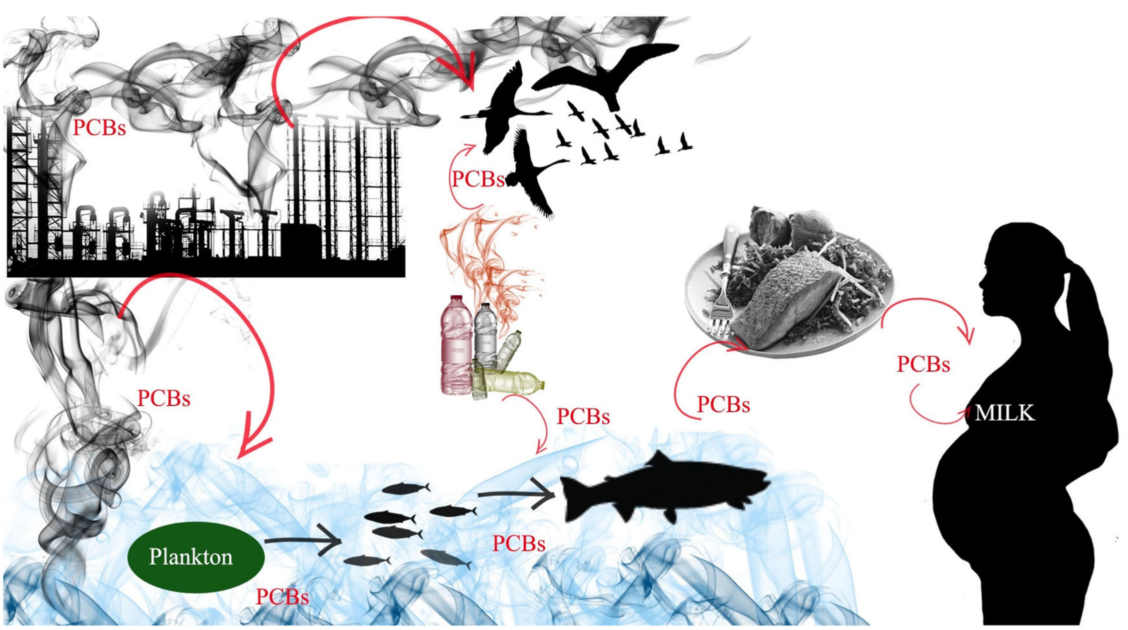


Fig. 4 Sources of exposition and bioaccumulation of PCBs

(Schuhmacher et al. 2007), the Czech Republic (Bencko et al. 2004; Černá et al. 2010), Hungary (Vigh et al. 2013), Slovakia (Čechová et al. 2017; Chovancová et al. 2011), Russia (Mamontova et al. 2017; Polder et al. 2008), Ireland (Pratt et al. 2012), Poland (Szywrińska and Lulek 2007; Škrbić et al. 2010), Greece (Costopoulou et al. 2006), Tunisia (Hassine et al. 2012), Canada (Ryan and Rawn 2014), and China (Deng et al. 2012; Zhang et al. 2016; Zhang et al. 2017), Ghana (Asamoah et al. 2018), Netherlands, Norway (Čechová et al. 2017), The Republic of Moldova (Tirisina et al. 2017), France, Denmark, Finland (Antignac et al. 2016), Croatia (Klinčić et al. 2016). Generally, the number of published papers between 1979 and 2017 (searching in Scopus database; using keywords as "polychlorinated biphenyls," "breast milk," "human milk," and "monitoring") are 169, which include documents by country USA (38), Japan (20), Germany (19), Sweden (15), and China (13) (top five) (Scopus database, 8.04.2018). The amount of research on milk is justified as milk is the first natural food for a baby, which is a very important source of essential compounds; however, when the mother is exposed to organic pollutants, her milk can be also a source of this impurities. The tolerated daily intake of PCDD/PCDF/PCB (according to WHO) should not exceed 1–4 pg/kg bw/day, equivalent milk level 0.2–0.9 pg/g lipids (Van den Berg et al. 2017).

PCBs conformation influences on the tendency to bind with aryl hydrocarbon receptor (AhR), where the highest properties have a dioxin-like polychlorinated biphenyls. Non-dioxin-like polychlorinated biphenyls have effects on the immune system, for example, can cause production of reactive oxygen species (ROS) in human neutrophil granulocytes, which was investigated by Bernsten et al. (2016). Their research shows that three PCBs (52, 153, and 180) induced the production of ROS. Long-term exposure to organic pollutants can lead to serious health consequences such as dermatitis, disorders in the endocrine (e.g., impact on the thyroid function), and reproductive system, and neurological problems (Passatore et al. 2014). Maervoet and co-workers (Maervoet et al. 2007) presented the results of research on relationships between organochlorine pollutions and thyroid hormone levels in cord blood (n = 198 neonates). The conclusion of this paper is that impurities such as PCBs may affect triiodothyronine (fT3) and free thyroxine (fT4) hormones and consequently the thyroid system of infants. This is why care is necessary during children's development, especially in the case of vulnerable newborns, whose immunological system is still forming. Weakness of the immune system can lead to allergy, asthma, and infection (Gascon et al. 2013; Lignell et al. 2013). The PCB compounds have been also linked with behavioral problems in children; i.e., prenatal exposure to PCB 153 is associated with anxiety and attention deficits among children, which was researched by Verner and co-workers (Verner et al. 2015) in epidemiological studies. In the Norwegian Mother and Child Cohort Study (including 1024 children) conducted by Caspersen et al. 2016a and Caspersen et al. 2016b, the results show that low-level maternal exposure (PCB 153 was 0.8 ng/kg bw/day; range 0.1–17) to PCB with six chlorine atoms such as 153 is associated with girls' poorer expressive language skills in early life. Language development delay in girls and problems with using complete grammar structures (44,092 children included in the study) were correlated with intake of PCB 153 (median 11 ng/kg bw/day to 5–28 ng/kg). The results of milk analyses from different countries are given in Table 2, which shows the number of samples and comments. In most cases, the dominant forms of accumulated PCBs are biphenyls with six or more chlorine atoms No. 138, 153, 180 (Černá et al. 2010; Chovancová et al. 2011; Hassine et al. 2012; Lignell et al. 2013; Schuhmacher et al. 2007). Unfortunately, such number of chlorine atoms causes resistance to being metabolized and results in greater accumulation (Faroon et al. 2003; Skrbić et al. 2010). Comparison of these data is very difficult, because in every case the sample have different parameters as period of lactation, years, volume, and sample preparation method. Furthermore, in Table 2, we include result obtained for total analyzed PCB. In one, researchers investigated only indicator PCBs, in other more than seven PCBs. The aim was to show on what scales these tests can be conducted. In our opinion, study performed for indicator PCBs are enough, because these congeners have been used as indicators of the total PCBs content. The non-dioxin-like PCBs are used on the basis environmental analysis. Indicator PCBs were selected as representatives for all PCBs, they occur predominantly in biotic and abiotic matrices (Baars et al. 2004).

The dominant method used for detection and identification of polychlorinated biphenyls and dioxins is gas chromatography with electron capture detector (Hassine et al. 2012; Polder et al. 2008; Skrbić et al. 2010), and mass spectrometry (Bencko et al. 2004; Černá et al. 2010; Chovancová et al. 2011; Deng et al. 2012; Ryan and Rawn 2014; Schuhmacher et al. 2007; Vigh et al. 2013; Zhang et al. 2016). Techniques used for sample preparation include classical liquid-liquid extraction (LLE) (Bencko et al. 2004; Černá et al. 2010; Chovancová et al. 2011; Hassine et al. 2012; Ryan and Rawn 2014), solid phase extraction (SPE) (Dmitrovic and Chan 2002; Lin et al. 2016), and accelerated solvent extraction (ASE) (Deng et al. 2012; Vigh et al. 2013; Zhang et al. 2016). It is important to improve the sample preparation stage and search for a method which will make it possible to analyze a lot of samples in a short time, with small amounts of solvents. An interesting approach was a QuEChERS technique (Luzardo et al. 2013; Asamoah et al. 2018) where the extract was cleaned by dispersive solid phase extraction (dSPE).

Table 2 Monitoring of organic pollutants—PCBs in human milk

Number of tested PCBs	Country	Number of mothers	Years	Concentrations (ng/g lipid)	Comments	Reference
Di-ortho PCBs	Sweden	413	1996–2010	$\sum_{3}$ 15–363	The higher concentration of PCBs, the higher weight of the baby after birth.	(Lignell et al. 2013)
35 PCBs	Czech Republic	90	1999–2000	$\sum_{35}$ 293–13.754	High concentrations found in milk from mothers who live in industrial areas, PCB concentrations increased with mother's age.	(Černá et al. 2010)
33 PCBs	Spain	20	2012	$\sum_{33}$ 121–471	Concentration of POPs was higher in milk from women living in urban areas than in industrial areas. The author suggests this may be caused by urban women eating a larger number of fish dishes.	(Schuhmacher et al. 2007)
19 PCBs	Hungary	22 (3× at 5, 12, 84 lactation days)	2012	$\sum_{19}$ Mean 5 days, 37.45; 12 days, 30.66; 84 days, 30.08	PCB concentration decreased during lactation. The biggest fall occurred between day 5 and 12.	(Vigh et al. 2013)
12 PCBs	Slovakia	33	2006–2007	$\sum_{12}$ 2.7–32.0 TEQ pg/g	In milk from women who live in industrial areas, concentration of POPs exceeded TDI limit (WHO).	(Chovancová et al. 2011)
8 PCBs	Tunisia	36	2010	$\sum_{8}$ 16.4–1360.2	PCB concentration was positively correlated with the age of mothers, who gave birth for the first time Mothers with second-born and following children - no correlation.	(Hassine et al. 2012)
18 PCBs	China (Shenzhen)	60	2007	$\sum_{12\ \text{dl-PCBs}}$ 1.964–13.967 $\sum_{6\ \text{indicate PCBs}}$ 0.0034–0.0392	Body burden of PCBs was positively correlated with the period of residence in Shenzhen and fish consumption. Positive correlation between mother's age and body burden for DL-PCBs and PCBs.	(Deng et al. 2012)
7 PCBs	Ghana	128	2014–2016	$\sum_{7\text{indicate PCBs}}$ 3.64	In an electronic waste hot spot area, mean concentration of PCB was much higher than in non-spot area (4.43/0.03)	Asamoah et al. 2018

Cytokines in milk

It is well known that breastfeeding provides bioactive ingredients for proper development of a child. The unique composition of human milk was highlighted in many papers (Andreas et al. 2015; Bode 2012; Gao et al. 2012; Lönnerdal 2016; Walker 2010). These bioactive ingredients include cytokines, which in newborns are not produced in sufficient amounts. Because milk cytokines work not only through the digestive tract but also get into the bloodstream of the newborn, they compensate for this deficit.

Cytokines are a group of protein, which shows important functions in regulating inflammation (Quaqliato and Nardi 2017). These compounds have pleiotropic properties and work in complicated network. Depending on the target cell, a single cytokine may cause or inhibit signal (Arai et al. 1990). These small proteins are present in the most biological processes as disease pathogenesis, specific response to antigen or non-specific response to infection, embyronic development and stem cell differentiation, and other major pathways (Dinarello 2007). These signaling molecules include chemokines, interleukins interferons, and growth factors (Agarwal et al. 2011). Their presence in human milk provides anti-inflammatory protection and immunomodulating effect—activation and retention of the immune response at the right time (Amsen et al. 2009; Bryan et al. 2016; Meki et al. 2003). Unfortunately, it is risk that cytokines after infection does not return to their normal state and still are present in body fluids with high concentrations. Consequently, disregulation of cytokine production can have harmful effects on organism function (Dinarello 2007). Therefore, we should ask a question: What are the effects of the imbalance of cytokine production and their high concentration in milk?

When studying the literature, it becomes clear that cytokines can be a double-edged sword. They play a key role in child's development, but they also can be harmful when a newborn has necrotizing enterocolitis (NEC), and they can theoretically affect the development of gluten intolerance (MohanKumar et al. 2017; Olivares et al. 2015; Rentea et al. 2017).

Depending on the lactation period and factors such as the course of pregnancy, gestational age, and vaginal or caesarean *delivery,* there are changes in milk composition and cytokine concentration, whose expression is dynamic (Chollet-Hinton et al. 2014). Cytokine concentration is also included in this biological rhythm. Morais et al. (2015) suggested that cytokines are characterized by chronobiological fluctuations. The study showed that the concentration of IL-6 was highest in colostrum in the diurnal phase and TNF-α also was in higher amount in colostrum compared to mature milk.

The amount of these compounds is higher at the beginning of lactation than in mature milk as a result of changes taking place in a woman's body during pregnancy and childbirth. However, when complications such as pre-eclampsia occur, high cytokine levels in mother's milk may persist up to 30 days postpartum. This may be a consequence of a still active inflammatory reaction (Erbağci et al. 2005). In milk from a mother with allergies, one can observe higher concentration of cytokines produced by lymphocytes Th2 (IL-4, IL-13, IL-5, IL-10) and lower TGF-β (Hrdý et al. 2012; Prokesová et al. 2006; Ragib et al. 2009; Zizka et al. 2007).

The higher concentrations of pro-inflammatory cytokines, where Th1 cytokines are predominant is observed in functional disorders of the mammary gland such as mastitis, particularly in women with systemic syndromes (Buescher and Hair 2001; Mizuno et al. 2012). Mastitis affects form 2 to 33% of nursing women and it is inflammation of breast tissue. This is a potentially serious illness, cause by milk stasis and infection (Angelopoulou et al. 2018) (Table 3). Depression, stress, or posttraumatic pain may also contribute to increased levels of pro-inflammatory cytokines (Kendall-Tackett 2007). Increased cytokine concentrations in milk (mainly IL-1β) correlate with the occurrence of jaundice in newborns, though the mechanism which is still unexplained (Apaydin et al. 2012; Zanardo et al. 2007). The extreme cases of overactive cytokine-induced inflammatory response may hypothetically contribute to sudden death of neonates. However, this has not been confirmed by enough cases (Vennemann et al. 2012). Cytokines are essential in the formation of the immune system, and they contribute to the mechanisms of many diseases. Disturbed balance between Th1 and Th2 can lead to long-lasting health consequences since the window between beneficial and damaging levels is very narrow. Crossing this limit may trigger pathophysiological mechanisms leading to immune dysfunctions (Zanardo et al. 2005). The absence of clear description of the consequences of higher/lower levels of cytokines in human milk is a result of the limitations of the research conducted, e.g., the lack of follow-up monitoring of the children as they grow, so many interpretations are still based on suppositions. The reason of the non-clear conclusion, obtained from research study are also a small number of sample, unknown volume of milk, non-constant collection times between studies, differences in population, and lack of standardized methods used to detect a cytokines.

The procedure of cytokine identification and quantification must deal with a highly heterogeneous matrix as biological sample. Furthermore, cytokines are present in milk in low concentrations, so the method must be highly selective and specific. We need to keep in mind the high number of cytokines and how they work in a complex network of relationships (Liu et al. 2016).

The tests most commonly used for cytokine determination are the commercially available ELISA (Bryan et al. 2016; Hawkes et al. 2001; Zizka et al. 2007) and PCR (Hrdý et al. 2012). A disadvantage of immuno-enzymatic assays such as ELISA and ELISASPOT is the problem they have with rapid and accurate determination of multiple cytokines at the same

Table 3 Example of study where cytokine were detected in milk and correlated with mastitis or allergy mother's problem

Diseases	Samples	Investigated cytokines*	Comments	Literature
Clinical mastitis	*N* = 8 (women with clinical mastitis)	Selected pro-inflammatory cytokines (IL-6, IL-1β, TNF-α) Selected endogenous cytokines control molecules (sIL-6R, SIL-1RII, STNFRI)[1]	• TNF-α were evaluated in 6 from 8 samples, whereas IL-6 5/8 and Il = 1β 3/8.	Buescher and Hair 2001
	N = 17 Group A, body temperature was > 38.5 °C Group B, without systemic symptoms	IL-6[1]	• Level of IL-6 is higher in mastitic milk than milk from healthy mothers. If the women had a systemic symptoms, these differences are more significant.	Mizuno et al. 2012
Subclinical mastitis	*N* = 110 (56 from left breast and 54 form right breast collected from 44 healthy women)	25 cytokines IL-2, IL-2R, IL12p40/70, IL-15, IFN-α, IFN-γ, MIG, IP-10, IL-4,IL-5, IL-13,IL-7, IL-17, GMCSF, IL-10, EPO, IL-1RA, TNF-α, IL-6, IL-8, IL-1β, RANTES, EOTAXIN[2]	• Factors associated with inflammation (e.g., TNF-α, IL-6, Il-8, IL-17) were significantly increased in SCM samples. • Only IL-4 from Th2 in higher concentrations in SCM samples • The Th1/Th2 ratio; predominant elevation of cytokines that belong to the Th1 –lymphocyte	Tuaillon et al. 2017
	N = 108 Categorized as SCM (Na:K > 0.6); non-SCM (Na:K < 0.6)	IL-1β IL-6 IL-8 TNF-α[3]	• IL-8 and TNF-α where higher in SCM mothers (most notably in transitional milk)	Li et al. 2018
Allergy	Colostrum milk (3 days after delivery) Allergic (*n* = 15–44) and non-allergic mothers (*n* = 15–64)	IL-4, IL-6, IL-8, IL-10, _IL-12, IL-13, IFN-γ, TGF-β1, eotaxain, GRO-α, RANTES, TNF-α, EGF[1]	• Cytokines present in colostrum with high quantities (mediana > 100 pg/mL): IL-4, IL-5, IL-10, IL-13, INF-γ, TGF-β, TNF-α, MCP-1, GRO-α, EGF • Colostrum form allergy mothers: IL-5, IL-10, and IL-4; higher levels compared to healthy mothers	Zizka et al. 2007
	9 healthy mothers 11 allergic mothers	IL-2, IL-4, IL-8, IL-10, IL-13, IFN-γ, TGF-β1, EGF[1,4]	• Expression of IL-4, IL-13, and EGF was higher and levels of IFN-γ decreased in the colostral cells of allergic mothers compared to healthy.	Hrdý et al. 2012
	13 allergic mothers 9 healthy mothers Colostrum (3 days) Mature milk (1 month)	IL-10, TGF-β1[1]	• TGF-β concentration had a significant difference between colostrum and mature milk in milk from allergy mothers. • Compared to a mature milk form two groups of mothers, the TGF-β concentration was significantly lower in allergy mother's milk. • No significant differences of IL-10 within the same group • 46% children form allergy mothers presented atopic dermatitis symptoms, none from controls (6-month observation)	Rigotti et al. 2006
	21 allergic 21 healthy mothers Colostrum (4 days) Mature milk (3, 6, 12 months)	IL-4, IL-5,IL-6,IL-10, IL-13. IFN-γ, TGF-β[1]	• The tendency to higher concentration of IL-4 and IL-10 in milk from allergy mothers • In mature milk, higher IL-4 concentration and different dynamic of IL-10 in allergy mother's milk	Prokesová et al. 2006

*Detected by following method:

[1] ELISA

[2] Multiplex microbeads assay

[3] MILLIPLEX MAP Human High Sensitivity Cytokine panel

[4] PCR

time. A wider range of analytical tools is offered by immunological multiplex tests, e.g., BI-PRO™ Human Cytokine 21-plex Assay (Bio-Rad Laboratories, Milan, Italy) (Kemp et al. 2015; Radillo et al. 2013) (Table 3). They consist of a bead on which specific capture antibodies are immobilized. This method is very sensitive and allows the researchers to determine analytes at low concentration levels (pg/ml). In addition, these tests also require smaller sample volumes (Keustermans et al. 2013). Cytokine detection was the subject of several reviews (Keustermans et al. 2013; Liu et al. 2016; Stenken and Poschenrieder 2015).

Immunotoxicity of heavy metals

Metallic elements that are characterized by relatively high density and toxicity at low concentrations are known as heavy metals. These elements include cadmium, lead, mercury, and arsenic (Shaban et al. 2016). Heavy metals are external factors which can influence cytokine production. They are able to cross placenta and blood-brain barrier, and they can be present in women's milk as well. This poses a potential risk for newborns (Rebelo and Caldas 2016).

The proven toxic effects of heavy metals on brain, kidney, and liver are particularly dangerous in situations when more than one metal is present. For instance, in a study carried out on laboratory animals (mice), simultaneous exposure to lead, cadmium, and mercury led to degradation of neurons in the brain. Addition of arsenic caused renal tubular necrosis (Cobbina et al. 2015). Heavy metal influences also on neurodegerative diseases as Alzheimer's (Tan et al. 2014; Hussien et al. 2018).

Immunotoxicity of heavy metals includes changes in the immune system (Rowley and Monestier 2005). Changes in cellular and humoral responses caused by metals may contribute to the development of autoimmune diseases, atopy, and allergies; they may disrupt sleep and also play a part in causing depression (Elenkov et al. 2005; Heo et al. 1997). These changes are reflected in the production of cytokines—hormone-like peptides, which are produced by lymphocytes Th (as a result of inflammatory action). Cytokines work in a complex networks (Elenkov et al. 2005). They are necessary for the initiation and regulation of the immune response (specific and non-specific), and they also influence the nature of such reactions (Kaiser et al. 2004). Even low concentrations of heavy metals can cause changes in cytokine productions (Låg et al. 2016). Lymphocytes Th1 produce interleukin 2 (IL-2), interferon gamma (IFNγ), and tumour necrosis factor-beta (TNF-β), while cytokines such as IL-4, IL-5, and IL-13 are produced by lymphocytes Th2. Both lymphocytes Th1 and Th2 produce IL-3, IL-6, IL-10, tumour necrosis factor-alpha (TNF-α), and granulocyte-macrophage colony-stimulating factor (*GM-CSF*) (Fig. 5) (Heo et al. 1996).

As a result of the presence of heavy metals, the production of cytokine Th1 may increase whereas the production of cytokine Th2 may be inhibited (or the other way round) (Krocova et al. 2000). In their research, Heo et al. (1996) showed that lead increased the amount of IL-4 produced, and decreased IFNγ. Disregulation occurs due to the dominance of cytokines produced by Th2. Krocova et al.

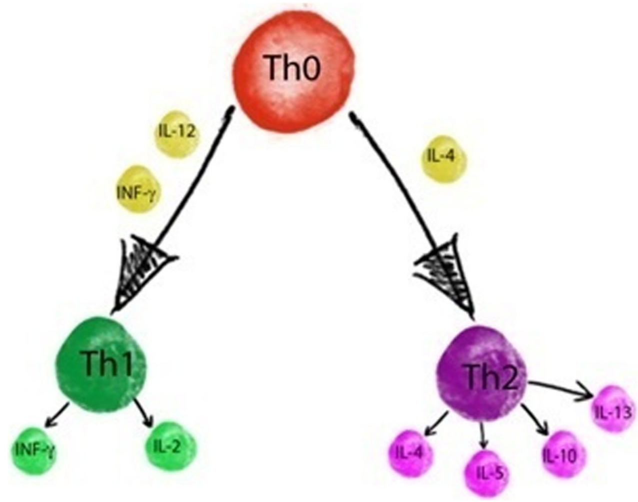


Fig. 5 Production and interactions of cytokines

(2000) also showed that production of cytokines Th2 was preferred during their study on the effects of lead and cadmium on mouse cells. A change in cytokine profile (Th1/Th2) can have dangerous consequences to fast and effective immune response. An example of such negative action was presented by Slovak scientists (Dvorožňáková et al. 2016), who showed that lead and cadmium inhibit the production of cytokines Th1. The metals suppress defense mechanisms and make it possible for an infection to spread rapidly, e.g., in the case of a parasitic infection. Not only the immune system is exposed to harmful effect on heavy metals and cytokine modulation. Cytokines play a crucial role in development of the central nervous system (CNS). Kasten-Jolly et al. (2011) conducted research on post-natal-day 21 mice, where Pb modulated IL-6, TGF-β1 and IL-18 protein expression in brain. Overexpression of IL-6 and TGF-β1 may harmfully affect neuronal growth and cell differentiation. Another heavy metal as mercury induced effect on neuroimmune signaling, mercury exposure cause increase in TNF-α expression in hippocampus and cerebellum (test in prairie voles) (Thomas Curtis et al. 2011). Interesting studies have been conducted by Gump et al. 2014. They showed that increasing blood Hg (9–11 children) was correlated with lower concentration of TNF-α in whole blood and shorter sleep duration.

There is no doubt that compounds like cytokines play a key role in proper functioning of the immune system, particularly a developing one. It is also known that any impairment of any function of the body can lead to irreversible damage caused by pathogens. Cytokines are essential to the immune response, and heavy metals can lead to cytokine production disorder and cause health problems. The hazard posed by heavy metals, including sources of exposure, mechanism of absorption, and metabolism of four metals—arsenic, mercury, cadmium, and lead—is described in more detail in "Heavy metals" section.

Heavy metals

Arsenic

Arsenic (As) exists in the environment in inorganic forms (iAs) as A^{sIII} and As^{V} and in such organic forms as monomethylarsenic (MMA) or dimethylarsenic (DMA), arsenobetaine, and arsenolipids (Rebelo and Caldas 2016). Inorganic forms of arsenic are soluble in water, whence the spread of arsenic in the environment. Consequently, this causes soil contamination and leads to accumulation of arsenic in food (rice and other grains and their products) (Cubadda et al. 2017; Ohno et al. 2007). In products of marine origin, arsenic is present in organic form (Taylor et al. 2017). Arsenic is rapidly absorbed by the digestive tract (As^{III} and As^{V}). Arsenic in state V of oxidation reduces to III, followed by methylation using SAM (S-adenosylmethioninie) in the presence of GSH (glutathione). This leads to less toxic products such as DMA and MMA, which are excreted mainly with urine (Fig. 6). This is a detoxification process; however, in this pathway, reactive intermediates such as MMA^{III} and DMA^{III} may arise, which can have genotoxic effects (Beyersmann and Hartwig 2008; Gomez-Gaminero et al. 2001; Sattar et al. 2016; Vahter 2002). Exposure to arsenic during pregnancy is associated with the lower body of newborn child, weakening of cognitive functions, and even in extreme cases with fetal death (Carignan et al. 2015). The cross-sectional research (n = 190) revealed that exposure to arsenic can be associated with respiratory diseases such as asthma and with tachycardia (the detected concentrations of As were in the range of 36.6–82.7 μg/g creatinine) (Bortey-Sam et al. 2018).

In studies conducted on human milk (Table 4), no observed arsenic concentration would cause anxiety, even from mothers who lived near a contaminated area (for 187 samples tested, in 154 As was below LOD) (Sternowsky et al. 2002). However, it is worth it to pay attention to the research (Islam et al. 2014) where not only milk was analyzed but also urine from mothers and children. In contrast to low concentrations of arsenic in milk, in urine, its level was higher. It was suggested that exposure to this metal may be due to factors other than breastfeeding, for example, the presence of arsenic in water. It is *important to highlight* the fact *that* neonates who are breastfed are less exposed to arsenic than children who eat formula feed (as water is needed to prepare such milk) (Carignan et al. 2015; Castro et al. 2014; LaKind et al. 2001).

In the studies where the sample of milk was analyzed more than for one period of lactation, the arsenic concentrations were decreased. The higher mean concentration was presented in milk from Lebanon (Africa), this can be connected with drinking water contamination (Table 4).

Mercury

Mercury occurs in the environment in organic and inorganic forms as well as in the elemental form (Hg^{0}). The last one is found predominantly in the atmosphere. Water environment is rich in mercury in the second oxidation state (Hg^{2+}). As a result of methylation of inorganic mercury, methylmercury is formed (Wong 2017). The main sources of mercury in milk include diet rich in fish (especially marine) (Grzunov Letinić et al. 2016), amalgam fillings (Drasch et al. 1998; Drexler and Schaller 1998; Grzunov Letinić et al. 2016), and residence in mining areas (Bose-O'Reilly et al. 2008). The findings of epidemiological studies (98 infertile female patients and a control group of 43) conducted by Maeda and co-workers (Maeda et al. 2019) suggest that methylmercury may affect female fertility.

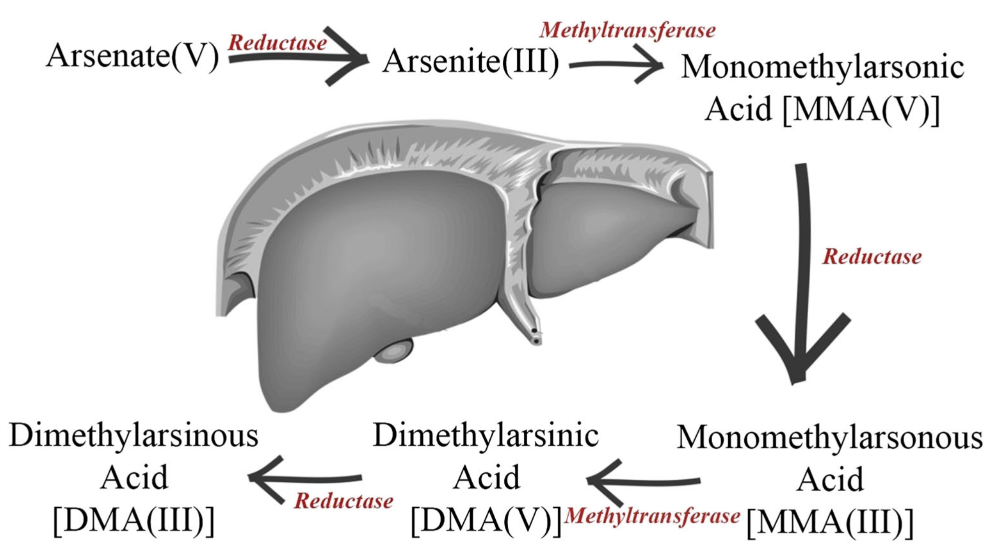


Fig. 6 Metabolism of arsenic

Table 4 Arsenic in human milk

Country	Lactation day (no. of samples)	Mean*/geometric mean**/(range μg/L)	Comments	Reference
Germany	Day 2 (18)	0.20** (0.15–1.1)	187 samples tested, in 154 As was below LOD (0.3 μg/L).	(Sternowsky et al. 2002)
	Day 5 (93)	0.21 (0.15–2.5)		
	Day 15 (18)	0.16 (0.15–0.8)	Low concentration of arsenic in milk from mothers who live in a contaminated area suggests that breastfeeding does not contribute to the exposure of newborns to this metal.	
	Day 30 (11)	0.54 (0.15–2.8)		
	Day 45 (11)	0.19 (0.15–2.0)		
	Day 60 (12)	0.20 (0.15–0.9)		
	Day 75 (11)	0.16 (0.15–0.3)		
	Day 90 (13)	0.17 (0.15–0.8)		
Bangladesh	Month 1 (29)	1.12* (0.5–8.90)	In mother's milk, the content of arsenic compared to the mother's and baby's urine was low (e.g., mean As content in milk:child urine:mother urine (μg/L) 1.12:157.8:18.1).	(Islam et al. 2014)
	Month 6 (25)	0.78 (0.5–2.32)		
	Month 9 (19)	0.70 (0.5–1.68)		
Chile (Arica, Santiago)	Arica (24), mine tailing deposition	0.36** (0.04–2.82)	In drinking water, concentration of arsenic was higher than in milk; as a result, children who are breastfed are less exposed.	(Castro et al. 2014)
	Santiago (11), control area	0.23** (0.08–0.61)		
Taiwan	Days 1–4	1.50	As lactation period progressed, the amount of arsenic in milk was decreasing.	(Chao et al. 2014)
	Days 5–10	0.68		
	Days 30–35	0.27		
	Days 60–65	0.16		
Sweden	Days 14–21 (60)	0.55* (0.041–4.6)	–	(Björklund et al. 2012)
Japan	Month 3 (9)	(0.18–4.20)	–	(Sakamoto et al. 2012)
Cyprus	50 samples	0.73* (0.03–1.97)	No significant correlation between moldy food consumption or the residential area	(Kunter et al. 2017)
Lebanon	74 nursing mothers (3–8 weeks of delivery)	*2.36 (0.08–11.32)	Arsenic was found in 63.51% of samples and this contamination was associated with cereal and fish intake.	(Bassil et al. 2018)

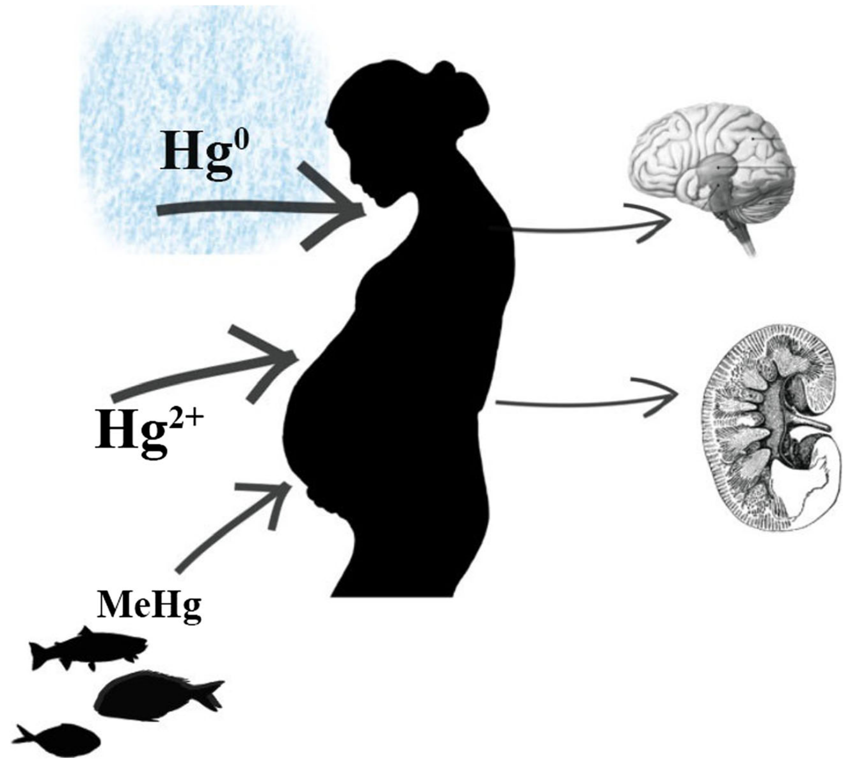
Hg^0 is absorbed into the body mainly via the respiratory track, and on a lesser scale via the digestive track or transdermally. After absorption, Hg oxidizes to Hg^{2+}. To a large extent, mercury ions are deposited in the kidneys. The organic forms of mercury are very well absorbed by the digestive as well as respiratory track. After absorption, MeHg is quickly transported to tissues with high density of fat (Fig. 7). Ionic mercury is removed from the body with urine and feces, while MeHg is secreted with bile (Akerstrom et al. 2017). The high lipophilicity of the organic mercury leads to easy breakdown of the blood-brain barrier and facilitates its transport to placenta (Holmes et al. 2009). Exposure to Hg during lactation affects oxidative stress and can contribute to the pathogenesis of health problems. This is particularly dangerous during neuronal development (Al-Saleh et al. 2013). The results of milk analyses from different countries are presented in Table 5.

In the study in Brazil (2013) and Indonesia, Tanzania, and Zimbabwe, mercury was presented in the highest concentrations. However, in another research from Brazil, but from different regions, mercury concentration was much lower (Table 5).

Lead and cadmium

Among the metals prevalent in nature and dangerous for living organisms, lead also occupies a prominent position. Ninety percent of lead is accumulated in the bones (Gulson et al. 2003). This metal can get into organism in three ways: through the digestive and respiratory system and transdermally. It is transported by red blood cells into the liver and kidneys; the nervous system is also at risk. Lead is excreted from the body with urine, feces, and sweat; it also deposits in hair. Unfortunately, mother's milk is one of the ways of eliminating this heavy metal from a female body (Babayigit et al. 2016; Wani et al. 2015) (Fig. 8). Lead contributes to the production of reactive oxygen in the body, which in turn contributes to the destruction of the existing molecules such as enzymes, proteins, and even DNA (Flora et al. 2012). Lead shows high affinity to the thiol group (-SH), which is involved in the destruction of proteins (Needleman 2004). Exposure to lead stems mainly from the place of residence, as milk from women living in urban areas contains higher concentrations of lead than the milk from women from rural areas (García-Esquinas

Fig. 7 Mercury accumulation



et al. 2011; Leotsinidis et al. 2005). According to the World Health Organization (WHO 2010), the pediatric effects of Pb at various blood levels are developmental toxicity (10 μg/dL), increased nerve conduction velocity (20 μl/dL), decreased hemoglobin synthesis (40 μg/dL), and death when dosage exceeded 150 μg/dL. Moreover, in the blood of children from an industrialized area ($n = 266$), higher concentration of Pb in blood was detected (mean, 65.89 μg/L) than in the blood of children from a reference town ($n = 264$). Furthermore, this exposure can affect the nervous system and intelligence quotient scores, which was suggested in cross-sectional investigation about exposure of children to heavy metals (Pan et al. 2018). The presence of lead in milk does not necessarily result from mother's direct exposure during pregnancy or lactation period. This heavy metal has a tendency to deposit in bones, where it remains for life. A proof of this is higher concentration of lead in milk of women aged over 30 (Chao et al. 2014). This compound may be released into body and milk as a result of bone resorption (changes during pregnancy and lactation) (Gulson et al. 2003).

Smoking is also a source of exposure to lead (Grzunov Letinić et al. 2016) as well as to another heavy metal, cadmium (Cd) (Chao et al. 2014; García-Esquinas et al. 2011; Grzunov Letinić et al. 2016). The exposure to this metal is dependent on lifestyle, diet, and place of residence, and recorded values of daily intake range from 10 μg to more than 200 μg (Mezynska and Brzóska 2018).. Cadmium gets into the body mainly through respiratory track and less through digestive track. It has harmful impact on internal organs (Zalups and Ahmed 2003). After binding to proteins (albumin and metallothionein, MT), cadmium is transported with blood. The primary affected organ is liver ($CdCl_2$), but kidneys are also exposed to long-term accumulation. This is a consequence of strong affinity to the MT protein (complex Cd-Mt). Cadmium is excreted from the body with feces and urine (Godt et al. 2006; Sarkar et al. 2013; Sinicropi et al. 2010; Waalkes 2000) (Fig. 9). Unfortunately, cadmium is one of the metals which are associated also with asthma prevalence; urinary concentrations of Cd in the control ($n = 551$) and case group ($n = 551$) were found to be 0.49 μg/g and 0.62 μg/g creatinine, respectively (Huang et al. 2016). Wang and co-workers (Wang et al. 2016) found that this metal may contribute to preterm birth. Their data ($n = 3254$) showed the serum Cd concentration with a range between 0.04 and 8.08 μg/L. Higher levels of cadmium were positively correlated with risk of preterm birth. The results of milk analyses from different countries are given in Table 6.

In these two heavy metals, lead is predominant, which was detected in sample with higher concentration than cadmium (Table 6). This difference can be a result of strong accumulation of Pb on bone. Lactation may be associated with bone resorption, as a result to calcium demand for breastfed infants. The highest concentration was found in Lebanon and Spain. In both examples, the consumption of potato was associated with amount of lead.

Table 5 Mercury in milk

Country	Lactation day (no. of samples)	Mean*/geometric mean**/(range μg/L)	Comments	Reference
Germany	Days 2–7 (70)	(0.2–6.86)	Presence of mercury was linked with the number of amalgam fillings the mother had. The average content was below 0.2 μg/L; when mother had 1–4 fillings, 0.57 μg/L; if more than 7, the content was 2.11 μg/L. Diet rich in fish also had an influence on mercury concentration in milk.	(Drasch et al. 1998)
	Week 1 (116) Month 2 (84)	1.37* (< 0.25–20.3) 0.64 (0.25–11.7)	Number of amalgam fillings in mother's teeth and eating habits (fish diet) influence mercury concentration in milk. The concentration of mercury in milk after 2 months (mature milk) was lower than shortly after birth.	(Drexler and Schaller., 1998)
Indonesia Tanzania Zimbabwe	Any day (46)	8.11* (< 1.0–149.60)	Area of residence where mercury is present may be a source of hazard. Mercury may be present in a woman's milk at high concentrations, even if its content in her hair is low.	(Bose-O'Reilly et al. 2008)
Spain (Madrid)	Week 3 (100)	0.53** (0.03–2.63)	Concentration of Hg increased with number of amalgam fillings and amount of consumed fish and seafood.	(García-Esquinas et al. 2011)
Japan	Month 3 (9)	(0.28–0.77)	–	(Sakamoto et al. 2012)
Brazil (Brasilia)	Σ(147) Day 15 Day 30 Day 45 Day 60 Day 74 Day 75 Day 76 Day 90	 THg 6.66* 6.03 6.02 5.31 6.01 6.52 7.29 7.89	In the first three months after birth, mercury content in milk was not correlated with the amount of fish consumed by the mother. Intentional introduction of salmon into the diet (on day 75 of lactation) caused an increase in concentration of this metal in milk.	(Cunha et al. 2013)
Cyprus	50 samples	0 (0–0.01)	No significant correlation between moldy food consumption or the residential area	(Kunter et al. 2017)
Brazil	224 samples	THg 2.56* (< 0.76–8.40)	The limitation of this research was lack of information about time of sample collection, lack of food consumption information, or the number of amalgams of mothers. The levels of mercury including MeHg aren't dangerous.	(Rebelo et al. 2017)
Korea Seoul (mega city) Anyaig (a residental city) Ansen (industrial complex) Jeju (mid-sized city)	207 samples Day 15 Day 30	0.94* (0.08–5.66) 1.19 0.79	Mercury concentration was higher in milk form primipara mothers, and women over 30 years age, which are living in a big city. In the 15th day, sample levels of mercury was higher than in the 30-day breast milk sample. Mercury was detected in 100% sample.	(Park et al. 2018)

Absorption of metals in newborn babies is more intense than in adults. Lack of mature defense system and still developing organs reduce the body's ability to excrete toxic compounds with bile (Chao et al. 2014). Monitoring of milk from a single mother at different lactation stages (starting with the first days) reveals that concentration of heavy metals in milk shows a decreasing trend (Chao et al. 2014; Islam et al. 2014; Krachler et al. 1998; Leotsinidis et al. 2005) It is suggested that this trend is caused by the changes in the amount of milk protein that bind metals and fat content during the lactation (Sowers et al. 2002; Park et al. 2018) It is not possible to clearly evaluate factors contributing to and the degree of

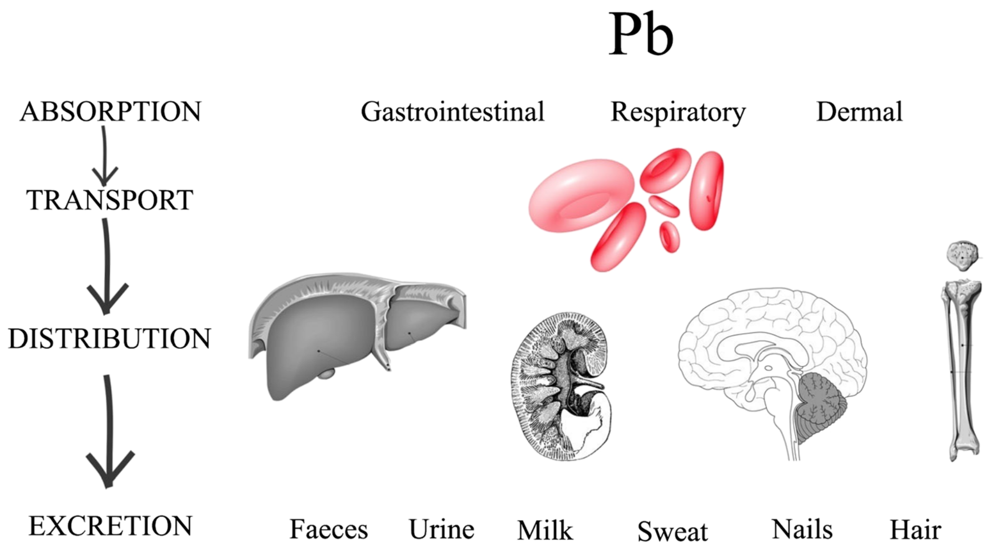


Fig. 8 Lead absorption, distribution, and excretion

exposure to heavy metals. Recently conducted studies are focused on specific areas, where such factors may be different. Milk monitoring requires a sampling plan and a detailed interview regarding potential sources of exposure. Furthermore, it is desirable to analyze samples from more than one stage of lactation for each woman. In most cases metal analysis uses atomic absorption spectrometry (AAS) (Al-Saleh et al. 2013; Chao et al. 2014; Costopoulou et al. 2006; Drasch et al. 1998; Goudarzi et al. 2013; Islam et al. 2014; Winiarska-Mleczan 2014) and inductively coupled plasma mass spectrometry (ICP-MS) (Grzunov Letinić et al. 2016; Kunter et al. 2017).

Breastfeeding: a threat or the gold standard of nutrition?

The problem of widespread environmental pollution and the ease with which it penetrates into human milk may lead to risks for the mother and newborn. From a scientific point of view, the double role of cytokines is very interesting. Their impaired secretion can lead to autoimmune diseases. Their presence in milk and long-term health consequences are still nor fully investigated. While their role is undeniable as the necessary immunomodulators, is breastfeeding the best food for a newborn? To answer this question, we should look at the benefits of breastfeeding (Andreas et al. 2015; Kulinich and Liu 2016; Lönnerdal 2016; Mandal et al. 2014; Nonqonierma and FlitzGerald 2015). Table 7 shows the main milk ingredients with their functions in the newborn's body.

World Health Organization (WHO) recommends to exclusively breastfeed infants for 6 months at minimum. In many milk contamination studies, it is noted that the benefits of breastfeeding outweigh its potential risks (Chao et al. 2014; Islam et al. 2014; Leotsinidis et al. 2005). Formula feeds which are commercially available have less essential ingredients than natural milk. Furthermore, the former also may contain pollution as the water that is used to dissolve the powder may be contaminated. Consequently, formula feeding also can be a reason of imbalance of cytokine production (Akhtar et al. 2017; Castro et al. 2014; Chao et al. 2014; Dabeka et al. 2011; LaKind et al. 2001; Tripathi et al. 1999; Winkler et al. 2015).

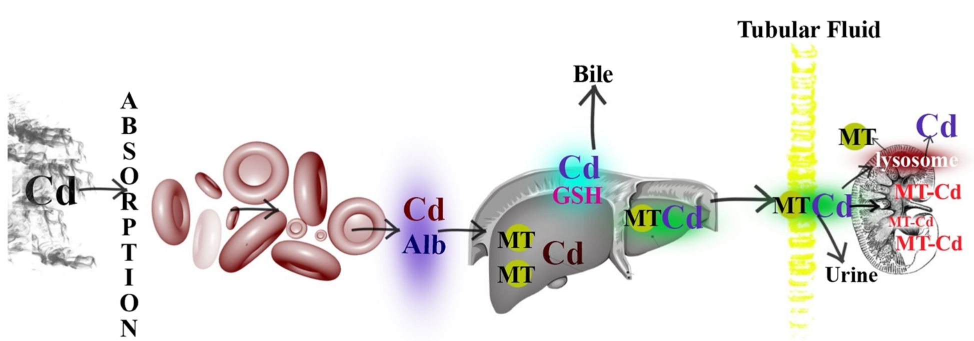


Fig. 9 Absorption, distribution, and metabolism of cadmium

Table 6 Cadmium and lead in milk

Country	Lactation day (no. of samples)	Mean*/geometric mean**/(range µg/L)	Comments	Reference
Croatia	Day 4 Days 5–10 Days 20–30 (107)	Pb 2.4–10 1.9–12 1.7–7.2 Cd 0.6–1.4 0.58–1.4 0.59–1.6	Smoking is a source of lead and cadmium intake.	(Grzunov Letinić et al., 2016)
Spain	Week 3 (100)	Pb 15.65 **(12.92–18.72) Cd 1.31* (1.15–1.48)	Concentration of lead increased with the amount of potatoes consumed. Amount of cadmium increased with frequency of smoking.	(García-Esquinas et al. 2011)
Greece	Day 3 (180)	Pb 0.48* Cd 0.19*	Women from urban areas were more exposed.	(Leotsinidis et al. 2005)
Poland	323 milk samples	Pb 6.33* Cd 2.11*	Higher concentrations of heavy metals were determined in milk from smokers and older women (aged 30+).	(Winiarska-Mleczan 2014)
Japan	Month 3 (9)	Pb (0.18–4.20) Cd (0.40–1.80)	–	Sakamoto et al. 2012
Cyprus	50 samples	Pb 1.19* (0–4.91) Cd 0.45* (0.12–0.80)	No significant correlation between moldy food consumption or the residential area	Kunter et al. 2017
Lebanon	74 samples	Pb 18.17* (1.38–62.61) Cd 0.87* (0.05–5.00)	Cadmium was detected in 40.54% of samples and was significantly associated random smoke exposure. Lead was detected in 67.61% of samples and contamination was correlated with residence near cultivation activities, smoking habits before pregnancy, and potato consumption.	Bassil et al. 2018
Korea Seoul (mega city) Anyaig (a residental city) Ansen (industrial complex) Jeju (mid-sized city)	207 samples Day 15 Day 30	Pb 8.79* 18.3 9.55	The highest level of lead was detected in breastmilk sample from a residential city in both sample dates (15 and 30 days) Lead concentration were not be correlated by age or smoking. Lead was detected in 77% of sample.	Park et al. 2018

Table 7 Ingredients of human milk and their main functions

Ingredient	Functions
Proteins	• Nutritional (binding of essential ingredients, absorption through the intestinal mucosa) • Immunomodulatory and anti-inflammatory action • Anti-microbial effect • Normal bone formation • Growth promoters
Non-protein nitrogen	• Key role in cellular processes, i.e., changing enzymatic activity • Participation in the development, maturation, and repair of the digestive tract • Neurotransmitters
Lipids	• The largest source of energy • Formation of the nervous system incl. brain and spinal cord • Participation in neurobehavioral development • Correct retinal growth and visual acuity
Oligosaccharides	• Supporting growth of beneficial organisms (probiotics) • Nutritional microflora of the digestive tract • Protection against gastrointestinal infections • Prevention of diarrhea and respiratory infections

Conclusion

Organic and inorganic pollutants which are present in the environment can penetrate into living organisms. They are lipophilic and thus can accumulate in tissues, which can cause negative health consequences in the future. A newborn organism, which is still developing its organs and defense mechanisms, is particularly vulnerable. These compounds may get into a neonate's body with mother's milk. However, because human milk is the gold standard of nutrition and milk composition is unique, it is not recommended to give up this food. Furthermore, human milk as a non-invasive matrix is a tool used to analyze environmental pollution and serves also as a disease marker for the mother and child. In further research, attention should be paid to the consequences that can result from exposure to pollution, e.g., the effect of impurities on nutrients and immunomodulators as well as cytokine disregulation. The studies in this field are often limited by the sample size. It is important to develop a method of determination that will be both sensitive and efficient. Furthermore, it is necessary to conduct more coordinated research using an interdisciplinary approach to understand the role of environmental impurities such as PCBs and heavy metals in developmental process of an infant, especially with regard to the role of cytokines. For these reasons, the crucial and the first point is to propose a specific analytical tool (i.e., innovative adsorbents as molecularly imprinted polymers (MIPs) and sensor for analysis of these compounds in human milk. The combination of new tools with modern instrumentation techniques will allow quick and reliable assessment of both the level of milk contamination and the content of cytokines. Moreover, it will be of critical importance to conduct a cohort research with a representative number of samples. The integration of such different fields as chemistry, biology, and medicine with statistical analysis can help understand the influence of environmental agents on human milk quality and consequently on children's health.

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