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Review

Lead, mercury, and cadmium in breast milk

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Abstract

Toxic heavy metals are the major source of environmental pollution in this new millennium. Lead, mercury, and cadmium are the most common toxic heavy metals in the environment. There is no known function of these toxic heavy metals in the human body. In females, toxic heavy metals can be accumulated in maternal body before pregnancy and may be transferred to fetus through placenta and later, via breast milk. Lead previously accumulated in maternal bones can be mobilized along with calcium in order to meet increased calcium needs of the fetus in pregnant women and for the calcium needs in human milk during lactation. Human fetus and infants are susceptible to heavy metal toxicity passing through placenta and breastmilk due to rapid growth and development of organs and tissues, especially central nervous system. However most of the damage is already done by the time the infant is born. Intrauterine lead exposure can cause growth retardation, cognitive dysfunction, low IQ scores on ability tests, and low performance in school. Biological samples, such as umbilical cord blood and breast milk, and less commonly infant hair, are used for biomonitoring of intra-uterine exposure to these toxic chemicals. Although toxic metals and other pollutants may be excreted into breast milk, their effects are unknown and this topic is subject of a growing body of research. Despite the possibility of harm from environmental contaminants in breast milk, breastfeeding is still recommended as the best infant feeding method. In fact, the species-specific components present in breast milk protect infants against infections; promote immune and

neurologic system development; and may decrease the risk of disease, including allergies, obesity, insulin-dependent diabetes mellitus, inflammatory bowel disease, and sudden infant death syndrome. Breastfeeding also facilitates maternal-infant attachment. The potential risk of environmental contaminants that can be transferred from mother to infant via breastfeeding can be alleviated by reducing life-long exposure since toxic chemicals accumulate long before pregnancy and released during gestation and lactation. Thus, management should aim to reduce life-long exposure through precautionary measures such as prevention of exposure to cigarette smoking, use of unleaded gasoline, and prevention of air pollution with an effect at the community level.

Keywords

Lead, mercury, cadmium, breast milk.

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Introduction

From the viewpoint of human evolution, breastfeeding undoubtedly represents the only biological norm in the nutrition and care of infants. However contamination of the breast milk with variety of environmental toxic chemicals in the last 60 years is an increasing concern as it is one of the routes of environmental toxic chemical exposure for the infants. First reports on the presence of quantifiable toxic chemicals were published in 1950s, with DDT (dichlorodiphenyltrichloroethane) being the first toxic chemical found in human breast milk in 1951 [1].

Assessment of the presence and quantity of environmental toxic chemicals in the breast milk does not only provide information on the maternal toxic burden but also serves as a marker for prenatal exposure of the fetus to these chemicals [2]. Measurement of the level of toxic chemicals in the breast milk, and particularly in the colostrum, reflects prenatal exposure to such chemicals, similar to the measurements in certain other tissues and body fluids such as cord blood, infant hair, nail, or meconium. It also reflects the potential exposure risk during postnatal period in breastfed infants. Presence and the levels of certain toxic chemicals in the breast milk is also used for the bio-monitoring of the level of environmental pollution as well as to gauge the effectiveness of the preventive measures [3-5].

Over the years many more lipophilic persistent organic pollutants (POPs) have been reported to be present in human breast milk include polybromide, diphenyl ethers (PBDEs – polybrominated diphenyl ethers), polychlorinated dibenzo-p-dioxins (PCDDs), dibenzofurans (PCDFs), biphenyls (PCBs), hexachlorocyclohexane isomers (HCHs), chlordane compounds (CHLs), and pesticides such as hexachlorobenzene (HCB), dieldrine. Although their use was banned many years ago, residues of POPs can still be detected at high concentrations in human breast milk [6].

Unfortunately human milk is one of the ways of elimination for mother's environmental toxic chemical burden. Breast milk has a rich content of fat. Lifelong maternal exposure to persistent lipophilic chemicals (such as polychlorinated biphenyls [PCBs]) cause gradual accumulation of these substances in the maternal fat tissue that are excreted into the breast milk during milk production after being mobilized from the maternal fat stores. Therefore, a higher concentration of organohalogen lipophilic pollutants may be detected in the breast milk than in maternal blood and cord blood samples [7]. The presence of POPs in human breast milk has been of great concern because these lipophilic chemicals are readily transferred to infants and easily absorbed. In case of dioxins, it is reported that one- to three-month-old infants absorb above 90% of most dioxin congeners containing in their mothers' milk [8-10].

Besides POP's, toxic heavy metals represent in this century a major source of the ever-increasing problem of environmental pollution. Of these, lead (Pb), mercury (Hg), and cadmium (Cd) are the most common toxic heavy metals, with no known function in human body. Pregnant women and children living close to e-waste areas [includes waste cathode ray tube (CRT) televisions, desktops, laptops, CRT monitors, liquid crystal display (LCD) monitors, cell phones, keyboards, computer mice, printers, and copiers] are at high risk for environmental exposure to heavy metals, Pb, Hg, Cd [11].

Heavy metals particularly Pb, Hg and Cd, have been detected in breast milk in many countries around the world. The World Health Organization (WHO) has indicated that the mean and range of these toxic metals detected in breast milk around the world are: Pb 5.0 ppb (0.0-41.1 ppb), Hg 2.7 ppb (0.64-257.1 ppb), and Cd 0.1 ppb (0.1-3.8 ppb) [12]. Mothers are exposed to these toxic metals, throughout their life. Unlike the POPs, metals do not accumulate in maternal fat tissue, and so do not usually achieve higher concentrations in breast milk than in blood. Heavy metals with high plasma protein or erythrocyte binding properties are unlikely to pass into the milk through passive diffusion, leading to a tendency for lower concentrations in the breast milk than in the cord blood [13]. As a result, infants are likely to be exposed to higher levels before birth through placenta and cord blood than during breastfeeding. Because the protein compartment in the maternal blood is far greater than that in breast milk, the amount of protein-bound chemical that enters breast milk is of little concern. Therefore breast milk is not the primary pathway of toxic heavy metal exposure for infants. The fetus is more vulnerable through placental transfer of heavy metals than through milk. Besides intrauterine exposure to heavy metals, has more important health implications than the exposure during breastfeeding. Intrauterine exposure occurring during a period of highest growth and development rate within the framework of fetal programming not only affects the fetal outcome, but also may have long term neurodevelopmental consequences in later stages of the life. Besides being a good marker of prenatal exposure, heavy metals in the breast milk represent another route of infant exposure to heavy metals.

Pb, Hg and Cd have no place in infant nutrition since they are devoid of biological activities, in addition to their toxic effects on the human body. However, maternal milk and infant formulas may contain heavy metals, which potentially have adverse effects on neonates or nursing infants. FAO/WHO proposed a provisional tolerable weekly intake (PTWI) value for toxic metals. Infants are more sensitive to the effects of food contaminated with toxic metals due to a number of factors including high gastrointestinal absorption, reduced efficacy of the blood-brain barrier against toxic metals, high growth rate of organs, immature detoxification systems, immature development of the central nervous system as well as the immune system [14]. The estimated PTWI for Pb in infants and children is 25 μg per kg of body weight [15]. The corresponding value for Cd is 7 μg/kg, and for total Hg is 5 μg/kg (< 3.3 μg/kg for methyl-Hg) [16, 17]. According to World Health Organization, the acceptable ranges in the breast milk for Hg and Pb are 1.4-1.7 ng/g and 2-5 ng/g, respectively [18]. Studies of infants exposed to environmental chemicals through breast milk have not shown clear evidence of adverse health effects to the nursing infant. Besides it is hard to separate whether the adverse effect is caused from prenatal or postnatal exposure.

Lead

Lead is a heavy metal naturally occurring in the earth crust and has no known biological activity. The main sources of exposure include the drinking water, food, dust, soil, paints, enameled soil cookware, soldered metal containers, water pipes, cosmetics, insecticides, cell battery, cigarette, gasoline, and printing houses where Pb is used [19]. Air pollution is a major route of Pb exposure. Coal burning is associated with the contamination of the air by Pb through the ashes (fume, smut). Also, burning of the waste products may release Pb into air. Leaded gasoline represents a major source of urban air pollution and is the primary factor responsible for increased maternal Pb levels among women residing in urbanized areas. Pb particles may travel very long distances and may be mixed with the soil and water through rainfall. In districts close to waste yards, air, drinking water, and food may be contaminated with Pb [20]. The major routes of exposure to Pb include the gasoline with leaded fuel, leaded paints, ceramic cookware glazed with Pb, and the use of leaded water conduits [21].

Urban pollution and industrial activities also influence the Pb content of the food. Fish represent a primary nutritional source of Pb exposure. Pb in the water may contaminate the fish. However, Pb is not biomagnified; in other words, it does not incrementally accumulate in the food chain in water or soil. Older organisms accumulate higher amounts of Pb due to more prolonged duration of exposure [20]. Studies have shown more than 15-fold higher Pb concentrations as compared to Hg in fish [22-24]. Approximately 3 to 10% of the water-soluble Pb is absorbed by the adult intestines. However, this figure may reach 40 to 50% in small children and pregnant women [20, 21].

Once absorbed, Pb is transported to the brain, lungs, spleen, renal cortex, teeth and the bones through the circulation with highest concentrations

in the bone [25]. In adults, approximately 94% of the Pb burden is found in the osseous tissues, mainly in the Pb-carbonate and Pb-phosphate forms [26, 27]. The half-life of Pb in the blood is 30 days vs. 27 years in the bone [20]. Therefore, girls exposed to Pb since infancy reach the reproductive age with significant Pb burden [28]. Even exposure to Pb discontinues, the stored Pb may lead to persistently high blood Pb levels [29, 30].

Much of the Pb in breast milk does not come from the mothers' exposure during lactation. It comes from Pb stored in the mothers' bones. Maternal blood, cord blood, and breast milk Pb concentrations are greatly influenced by maternal bone metabolism rather than the absorption of dietary Pb. During the calcium mobilization occurring in the maternal bones at the second half of the pregnancy for fetal skeletal development, Pb enters to maternal blood circulation. In women with low dietary calcium intake (less than 500 mg per day), 79% of the Pb in the cord blood originates from the Pb mobilized from maternal bones [31]. Increased maternal bone resorption for meeting the increased calcium needs during lactation result in the transfer of Pb from maternal bone stores into the blood and breast milk. On the other hand, calcium supplementation during pregnancy or postpartum period (1 g/day) was unable to prevent Pb mobilization from maternal bone stores [32].

Prenatal exposure to Pb has been reported to be associated with preterm birth, low birth weight, still birth, or abortus [19, 25, 33]. Intrauterine Pb exposure impairs cell differentiation and proliferation, synaptic growth, and apoptosis during brain development [34-36]. Chronic intrauterine exposure may Pb to growth retardation, cognitive impairment, lower IQ scores, and lower scores in ability tests, attention deficits, lower academic performance, and behavioral changes in the later stages of life [19, 37-40].

The breast milk Pb concentrations reported in previous studies from a number of countries range between 0.5 and 126.55 μg/L. Higher breast milk Pb levels have been observed in polluted urban centers as compared to less polluted areas in some studies, while others failed to detect a difference. In Italy, breast milk Pb concentration was 126.55 μg/L in urbanized areas vs 46 μg/L in other regions. In extremely polluted urban areas, the average breast milk Pb concentrations were between 48 and 62 μg/L, while much lower Pb levels were reported (0.7-0.8 μg/L) in less polluted areas [41]. Leotsinidis et al. [42] found higher breast milk Pb concentrations in mothers residing in city centers as compared to those from urban areas.

There have been no reports of toxicity occurring due to breast milk Pb. To decrease both intrauterine exposure and postnatal exposure via breast milk, the likelihood of Pb exposure in both pregnant and lactating women should be minimized. Accordingly, educational and preventive programs implemented in a geographical location with very high Pb exposure and Pb glazing practices led to significantly lower maternal blood and breast milk Pb concentrations [43].

Mercury

Mercury is naturally occurring liquid, odorless, colorless, silvery heavy metal found in the earth's crust. It is utilized in industrial processes, in the production medical devices (blood pressure measurement devices, thermometers), fluorescent lamps, and amalgam tooth fillings. Amalgam, a durable tooth filling material, is composed of a mixture of silver, tin, copper, and Hg, with Hg comprising 45 to 50% of the mixture [44].

Main industrial fields involving Hg use are mining and furnace, chloride-alkaline manufacturing, cement production, and paper production [45]. In addition, Hg may be released into the environment through the burning of medical or urban waste. Hg may be found in insecticides, pesticides, fertilizers, adhesives, cosmetics, plastic material, batteries, drugs (laxatives, suppositories), printer ink, solvents, polishing material, and paints [46]. In the last century, the environmental Hg level has almost tripled due to common use of Hg in industry [44].

Mercury evaporates without being heated at normal room temperature and is mixed with the ambient air. Hg vapors are toxic. In addition to gastrointestinal absorption, Hg may also be taken into the body through inhalation [25]. Inorganic Hg found in air and soil as well as the earth's crust may be mixed with water resources through industrial activities and may be transformed into the organic mercury (methylmercury) by methylation by planktons in the sea. Organic mercury taken up by simple organisms such as larvae pass onto the small fish and subsequently to larger fish, causing increasing rates of bioaccumulation in the food chain in the water; this process is referred to as biomagnification [47]. The type of food with highest bioaccumulation potential is fish.

Mercury has no known biological activity and toxic for human. The effects of Hg exposure

in children and adults have long been known for centuries. On the other hand, a much higher awareness regarding the toxic effects of Hg exposure has been attained after the disasters in Minamata Japan and in Iraq. Both epidemics of Hg toxicity showed that exposure to high concentrations of Hg leads to neurological injury [48].

Following maternal exposure, placental transfer of Hg to the fetus may occur. Although no cut-off values, below which no neurodevelopmental effects occur have not been defined, a cord blood Hg concentration more than 5.8 μg/L has been shown to be associated with neurodevelopmental effects [49]. Exposure to low Hg doses during the intrauterine period may Pb to a number of problems in later stages of life including attention deficit, learning difficulty, speech disorders, memory problems, impaired motor skills, and growth and developmental problems [44, 48-50]. High doses of intrauterine exposure, however, causes mental retardation, cerebral palsy, movement disorders, visual disturbance, speech disturbance, and impaired hearing [51-54].

Breast milk levels of Hg are usually lower than levels of breast milk Pb. Moreover, Hg levels in the mother's blood are generally about three times higher than the levels in milk: thus, Hg does not accumulate in breast milk [55]. Studies on human breast milk have reported Hg levels between 0.235 and 5.5 mg/L. Two major forms of Hg can enter breast milk. The most hazardous, methylmercury, does not enter breast milk at high rates because it is attached to red blood cells. However even the small amounts of organic Hg in breast milk may be readily absorbed by the infant. The second form, inorganic Hg, enters breast milk easily but is not well absorbed in the infant's gastrointestinal system [56]. Consumption of food contaminated with Hg, and mainly the consumption of fish by the mother and exposure to Hg vapor during tooth filling with amalgam or removal of amalgam fillings during pregnancy and lactation, skin lightning creams represent risk factors for high concentrations of Hg in the breast milk [46].

In a study multivariate analysis maternal Fe deficiency anemia, consumption of viscera (eating liver, brain of bovine, sheep) and active/passive smoking during pregnancy are related to higher breast milk Hg levels [57]. Dorea [58], in his review on Hg and Pb during breastfeeding, mentioned that farming practices in industrialized countries increasingly utilized animal by-products as ingredients fed to animals used as food for human consumers. Hg can thus also pass to eggs, milk, meat, and farmed fish fed fishmeal containing diets. Therefore, fish may not be the endpoint of Hg contamination in the human food chain. Kacmar et al. [59] reported that the long-term ingestion of Hg with feed Pb to a pronounced Hg accumulation in the viscerals (kidneys and liver) of sheep. Industrial farming practices that will transmit toxic chemicals through food chain should be avoided. The concentration of Hg in breast-milk and its relation with the infant's development during the exclusive breastfeeding period are not clear.

However a recent study in 155 healthy mother-infant pair, lactational exposure to Hg has been shown to induce oxidative stress in breast-fed infants. Metal toxicity usually involves the production of reactive oxidative species (ROS) that can damage DNA, lipids in membranes, or proteins or enzymes in tissues. Both urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG) and malondialdehyde (MDA) were measured in mothers and infants as biomarkers of oxidative stress. Hg in the breast milk of mothers and in the urine of infants affected the excretion of urinary MDA and 8-OHdG, respectively, in a dose-related manner suggesting induced oxidative stress in breast-fed infants [60].

On the other hand, in two studies with long-term follow up of children exposed to methylmercury during breastfeeding failed to detect any effects, and surprisingly breastfed children performed better in developmental tests. In that study from Seychelles, better developmental test scores in children exposed to Hg via breastfeeding was accounted for by the "beneficial effects of breastfeeding that prevented or compensated the potential harmful effects of methylmercury" [61]. In another study from Faroe Islands, children exposed to Hg via breastfeeding performed better at age 7 in neuropsychological tests [62].

Fish is a source of omega-3 fatty acids and docosahexaenoic acid (DHA), which is important for brain development and visual acuity. In the last period of pregnancy, DHA intake is of clinical significance due to increased DHA intake in the brain. Pregnant women are recommended to avoid from consuming fish with high Hg concentrations. In 2014, FDA (Food and Drug Administration) recommended that pregnant women and women of reproductive age should avoid consuming big hunter fish such as tilefish, shark, swordfish, or mackerel due to high organic mercury content; also recommending that women

who might become pregnant along with pregnant and breastfeeding women should eat adequate quantities of fish at least eight ounces and up to 12 ounces weekly, which is two to three servings [63]. Also, in pregnant women and children, the recommended weekly intake for other types of fish including tuna fish is below 350 g [51].

Cadmium

Cadmium is a silver-white, soft and shiny metal and represents one of the most common environmental pollutants with a biological half-time of 10 to 30 years in human body [64, 65]. It occurs naturally at high concentrations in the earth's crust, water, and soil. Forest fires and volcano eruptions release a certain amount of Cd into the air. It may span very long distances before returning to the nature in dust, rain, or snow. The major source of Cd contamination is human activity [66]. One of the toxic substances within the ash (fume, smut) released into the atmosphere by coal burning is Cd [67].

Cadmium was first discovered in early 1800s. Commercial Cd production started only at the beginning of the 20th century, and is used in industrial processes in the last 50-year period. Cd and Cd-containing alloys are used in certain consumer or industrial products such as nickel-Cd batteries, storage batteries (78% of Cd use), paints used for plastic or ceramic materials (12% of Cd use), stabilizers providing heat and light resistance to PVC (polyvinyl chloride) (8% of Cd use), metal alloys, and others (0.5% of Cd use) [66, 68].

Each year, approximately 25,000 to 30,000 tons of Cd are thought to be released into environment [64]. Cd in urban and industrial waste (especially e-waste) are the main sources of Cd contamination in soil through sewage water and fertilizers [69-71]. Cd in the soil may be passed onto the water and taken up by plants. The tobacco plant naturally accumulates relatively high concentrations of Cd in its leaves. Thus, smoking tobacco is an important source of exposure. Higher concentrations of Cd have been detected in certain species of oysters, scallops, mussels and crustaceans and liver or kidney of mammals fed with Cd-rich diets as compared to other seafood or meat [72].

Cadmium has no known beneficial function in the human body. Absorbed Cd is eliminated from the body primarily in urine. The rate of excretion is low, probably because Cd remains tightly bound to metallothionein, which is almost completely reabsorbed in the renal tubules [73]. Due to slow excretion, Cd accumulates in the body over a lifetime and body burden increases with age. Cd bioaccumulation in mother's body may start at an early age. The kidneys and liver together contain about 50% of the body's accumulation of Cd [74]. Irrespective of the route of exposure, the absorbed Cd is stored mainly in the liver and kidneys after distribution in the body. Its half-life is 6-38 years and 4-19 years in the liver and kidneys, respectively [75]. Cd also accumulates in muscle and bone. Besides urinary excretion, Cd taken up by the mother may also be removed from mother's body by the placental route as well as the breast milk [64].

A major factor responsible for Cd exposure during pregnancy is cigarette smoking. Sorkun et al. reported that smoking increased the placental Cd concentration [76]. Butler et al. [77] reported that the level of Cd in the blood of mothers who were moderate smokers (1-8 cigarettes per day) and heavy smokers (48 cigarettes per day) was 7.4-fold higher and 12.5-fold higher, respectively, than in nonsmokers. In addition, they detected Cd in 26% of all cord samples, with a geometric mean of 0.08 μgL. Cd level in breast milk is also significantly associated with cigarette smoking [78]. Örün et al. [79] reported that the level of Cd in breast milk increased in active and/or passive smokers during pregnancy (0.89 μgL and 0.00 μgL, respectively; $p = 0.023$). Kutlu et al. [80] studied a group of pregnant women (30 non-smokers and 90 smokers) and reported that the placental level of Cd and Pb was higher in the smokers than in the non-smokers. Cigarette smoke is an important source of Cd exposure, not only for active smokers but also for passive smokers. In a recent study maternal exposure to ETS during pregnancy was associated with higher levels of Cd in newborn hair [57].

Iron deficiency is associated with an increased gastrointestinal absorption of Cd [81]. Women, with lower iron status, are believed to be at risk for greater absorption of Cd after oral exposure [82]. In animal studies, low dietary calcium, protein or iron, or high dietary fat were found to augment Cd absorption [64]. In animal studies, younger ages were also associated with a 20-fold increased intestinal Cd absorption as compared to adults [83]. Cd absorption is also increased during pregnancy. In mice exposed to Cd during pregnancy and lactation, a 2.5-fold increased intestinal Cd absorption was found [84].

The main organs affected in chronic Cd toxicity are kidneys, bone and lungs. However, Cd has toxic

effects in almost all body systems. High intake of Cd can lead to disturbances in calcium metabolism and the formation of kidney stones. Softening of the bones and osteoporosis may occur in those exposed through living or working in Cd-contaminated areas. In an area of Japan where soil has been contaminated with Cd from zinc/lead mines, Itai-itai disease used to be widespread and is still seen in women over 50 years of age. It is characterized by osteomalacia, osteoporosis, painful bone fractures and kidney dysfunction. Although Cd accumulates in bone, the bone disease that results from excessive Cd exposure is believed to be secondary to changes in calcium metabolism due to Cd-induced renal damage [81]. Skeletal effects appear to be secondary to increased urinary calcium and phosphorus losses due to Cd-induced renal effects. These effects are compounded by inhibition of renal hydroxylation of vitamin D, which eventually leads to a deficiency of its active form [85].

Some investigators believe Cd also exerts an inhibitory effect on calcium absorption from the gastrointestinal tract [73]. There is a significant association between breast milk Cd concentration and calcium secretion in breast milk. Increased Cd in the breast milk appeared to decrease the amount of calcium secreted in the breast milk, indicating maternal Cd exposure may result in insufficient levels of calcium in the breast milk [86].

Due to the presence of many reports showing an association between lung cancer and Cd exposure, Cd is considered a primary carcinogen [87]. Cd has an effect on a number of cellular activities such as proliferation, differentiation, and apoptosis. It also effects gene transcription and translation [88].

Provisional tolerable monthly intake (PTMI) The Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Expert Committee on Food Additives (JECFA) recently (in 2010) established a provisional tolerable monthly intake for Cd of 25 μg/kg body weight. Drinking-water should contain less than 3 μg/l, and air less than 5 ng/m^3 (annual average) Cd [89].

Placenta provides only a partial barrier against fetal Cd exposure. In a Chinese birth cohort study, higher Cd exposure in cord blood (> 0.6 μg/L) was associated with a 4-point Full-Scale IQ deficit at preschool age: this result was obtained after adjustment for cord blood Pb levels [90].

Previous reports suggested a human breast milk Cd concentration of 0.05-24.6 μg/L. In a study exposure of infants to Cd from soy infant formula is about 20-fold higher than the levels generally found in breast milk [55]. Instructions for pregnant and lactating women such as preventing exposure to environmental tobacco smoke, ensuring good nutrition and adequate iron and calcium intake, maintaining good industrial hygiene such as keeping away from e-waste areas will minimize further exposure to Cd.

Breastfeeding

Breastfed infants are at the top of the food chain because, the source of their nutrition is another human who is already at the top of the food chain. Therefore chemical contamination of human breast milk is of concern for child health care practitioners. The scientific evidence indicates that neurodevelopmental benefits of breastfeeding surpass the potential effects of environmental exposure to neurotoxic substances, in terms of immunologic, physiologic, nutritional, and psychological advantages provided by the breast milk. As discussed in a review by Mead [91], breastfeeding provides the infant with a number of nutrients and substances that protect and facilitate the growth of the brain including selenium, glutathione, vitamin E, cysteine, tryptophan, choline, taurine S100B protein, sialic acid, and polyunsaturated fatty acids. Secretory IgA (SIgA), lactoferrin, lysozyme, bifidus factor, oligosaccharides, lipids and leukocytes found in the breast milk have immune protective effects. Also, breast milk contains several growth factors and bioactive substances such as epidermal growth factor (EGF), nerve growth factor (NGF), insulin like growth factor (IGFs) tumor necrosis factor-alpha (TNF-α), transforming growth factor-alpha (TGFα), transforming growth factor-beta (TGFβ), granulocyte colony–stimulating factor (G-CSF), interleukins (IL-1β, IL-6, IL-8, IL-10), prostaglandins, and the basic fibroblast growth factor (bFGF). Hormones found in the breast milk include pituitary hormones (e.g., prolactin, growth hormone, thyroid-stimulating hormone, follicle-stimulating hormone, lutenizing hormone, adrenocorticotropic hormone, oxytocin), hypothalmic hormones (e.g., thyroid-releasing hormone, somatostatin, prolactin inhibiting and releasing factors) thyroid and parathyroid hormones (e.g., thyroxine, triiodothyronine, calcitonin, parathormone, parathyroid hormone–related peptide), steroid hormones (e.g., estradiol, estriol, progesterone, testosterone, 17-ketosteroids, corticosterone, vitamin D), gastrointestinal peptides (e.g., vasoactive intestinal peptide, gastrin, gastric

inhibitory peptide). Furthermore, peptides such as somatomedin C, amino acids, casomorphins, and complement factors represent other components of the breast milk. Immunomodulator and anti-inflammatory agents found in the breast milk have a protective effect on potential future conditions such as asthma, dermatitis, rheumatoid arthritis, diabetes, cardiovascular disease, certain cancers, and obesity [91]. Thus, breast milk with such a rich assortment of beneficial elements can even be considered to represent a type of tissue transplantation, rather than being a sole source of nutrition.

Furthermore, the concerns for environmental contamination in the breast milk should also be raised for the bottle feedings. There is no guarantee that the formula and other alternative food sources will reduce the exposure risk once the baby is weaned from breastfeeding.

Additionally, infant formulas are associated with the risk of eliminating the positive bio-psycho-social development provided by the substances in breast milk protecting and developing the brain as well as those provided by the bond between the mother and the infant. Infant formula may contain more Hg, Cd and Pb than the breast milk [92]. Cow's milk used for the production of infant formula may not only contain heavy metals, but also those substances referred to as lipophilic persistent organic pollutants. The use of fish-derived food products in the feeding of cows may be associated with much higher levels of contamination with Pb as well as the lipophilic organo-chloride pesticides in the cow's milk than in human breast milk [58]. Many studies have clearly documented the presence of much higher levels of Pb in infant formula than in breast milk. In addition, water used for diluting the formula may have been contaminated with heavy metals such as Hg and Pb [93].

Feeding bottles produced industrially in workplaces contaminated with toxic agents may also raise a risk of toxicity. Plastic feeding containers may have "endocrine disruptors" such as phthalates, nonylphenols, and bisphenol-A. For all these reasons, efforts to encourage breastfeeding should be continued, and precautions to reduce the risk of exposure to toxic substances should be taken before and during pregnancy, as well as during lactation. Risk management should thus aim to reduce life-long exposure particularly during the prenatal period and pregnancy since toxic chemicals accumulate long before pregnancy and released during gestation and lactation. Prevention of exposure to cigarette smoking, use of unleaded gasoline, prevention of air pollution are some of the examples for precautionary measures with an effect at the community level. Pregnant or lactating women should maintain a high level of awareness regarding environmental chemical agents. In addition, an increased level of awareness regarding the harmful effects of environmental pollution should be targeted in the general population. Presence of toxic substances in the breast milk is an indication for the fact that the baby has already been exposed to these substances during intrauterine life, which already may have significant adverse effects on infant development.

Studies on child health outcomes in highly polluted areas are still better for the breastfed infants and current scientific evidence does not support altering WHO's recommendation for exclusive breast-feeding for 6 months as a global public health recommendation and the provision of safe and appropriate complementary foods, with continued breastfeeding for up to 2 years of age or beyond [94].

Declaration of interest

The Author declares that there is no conflict of interest.

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