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Heavy Metal Exposure and Potential Risks for Breastfed Infants in the Appalachian Coal-Mining Region: A Systematic Review

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Introduction

In this manuscript we will discuss the mountain-top mining process within the Appalachian region and its implications in heavy metal toxicity within the population. More specifically, we will look at the health risks of various heavy metals that are acquired from coal-mining practices and the subsequent consequences on infant development when transmitted via lactation. The recommendations and composition of breast milk and its role as a route of elimination for various toxins like heavy metals is also addressed. Finally, we will discuss some of the means to measure general heavy metal deposition moving forward, both environmentally using bio-accumulators, and biologically via human milk screening and toenail clippings.

The goal of the literature review was to acquire and integrate as much information as possible about heavy metal toxicity, particularly arsenic (As), lead (Pb), mercury (Hg) and cadmium (Cd), which are the most common heavy metals found in coal-mining regions. The literature search was conducted using Virginia Tech Appalachian Research Initiative for Environmental Sciences (ARIES) and Google Scholar using the following keywords: heavy metal contamination, arsenic, lead, mercury, cadmium, mountaintop mining, Appalachian region, breastfeeding, and lactation.

Appalachian Region

Appalachia is a geographical region in the Eastern United States that stretches from New York to northern Alabama and Georgia. The cultural region on the other hand, typically refers to the central and southern portions of the range, from the Blue Ridge Mountains of Virginia to the Great Smoky Mountains of Tennessee. This region is endowed with abundant natural resources but has long struggled and been associated with poverty [1]. To combat poverty, large-scale coal mining firms brought wage-paying jobs and modern amenities to the Appalachian region in the early 20th century and implemented mountaintop removal (MTR) mining [2]. The MTR mining process is a form of surface mining that uses explosives to remove up to 400

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vertical feet of mountain in order to expose underlying coal seams [3]. In an effort to curb pollution associated with coal, the Clean Air Act amendments of 1990 pushed coal mining companies towards low-sulfur coal in order to reduce emissions of sulfur dioxide and oxides of nitrogen [4]. MTR mining in Appalachia skyrocketed as a result, since low-sulfur coal is abundant in this region [4]. While the amendments intended to reduce environmental pollution, the drastic increase in coal mining in the Appalachian Mountains seemed to have the opposite effect. Today, Appalachia remains the second largest coal-producing area in the United States [5]. This review will specifically focus on West Virginia, Kentucky and Virginia due to the prevalence of mining in these areas. West Virginia is the top coal producer in the region, Kentucky is the second top producer and Virginia is the fourth top producer [5].

The Appalachian Mountains are typically thought of as stable and pristine; however, contamination from MTR mining is often difficult to measure and unrecorded levels of toxicities pose a serious threat to the populations surrounding these regions. Mining corporations are not held responsible for cleaning up or monitoring environmental pollution in abandoned or out-of-use mines [5]. In addition, the transportation of coal with diesel burning trucks and trains releases significant quantities of nitrogen oxide and particulate matter into the air [3]. While MTR mining is beneficial for the economy of the region, it creates large-scale disturbances in local air quality, surface water and groundwater [3]. It is a controversial practice as subsequent slurry (residue from cleaning coal) is impounded in ponds or injected into old underground mine shafts [4]. Excess rock and soil are dumped into nearby valleys, which may contain more than 300 million tons of mining debris and extend downstream as far as six miles from the original site [2]. Elevated levels of inorganic acid deposition cause surface water acidification and concerns for potential toxicity [6]. In 2000, a sludge impoundment in Kentucky broke and released 300 million gallons of slurry [5]. This event killed all aquatic life within 20 miles and contaminated drinking water in a majority of the state [5]. The toxic impurities found in coal often find their way into ponds and groundwater, making these areas common sources of heavy metal contaminants for local habitants [1]. For example, several reports show groundwater sampled from domestic wells in unmined areas contain high levels of mine-drainage constituents [7]. In one study, well water samples from 18 homes in the Appalachian region were tested and found to have significant amounts of heavy metals contamination [4]. Additionally, hundreds of homes smelled of hydrogen sulfide gas and concentrations measured in homes were above the tolerable concentration [4].

Heavy Metals

Heavy metals have a relatively high density when compared with other metals that we regularly encounter [8]. They are not decomposable, and are recognized as environmental contaminants that cause cytotoxic, mutagenic and carcinogenic effects in animals- including humans [9]. As, Pb, Cd and Hg are heavy metals that are commonly released into the environment during the MTR mining process. The Agency for Toxic Substances and Disease Registry (ATSDR) ranked As first, Pb second, Hg third, and Cd seventh on their 2019 Substance Priority List (SPL) based on frequency, toxicity and potential human exposure at various hazardous waste sites [10]. The composition of heavy metals found at coal burning sites varies based on the soil and rock makeup [9]. Soils in the Appalachian region that are exposed to MTR mining have been shown to contain Cd levels up to ten times higher than nearby soils in areas exempt from MTR mining [11]. These levels were at or exceeded the maximum contamination levels set forth by the United States Department of Agriculture and U.S. soil scientists [11]. While coal mining operations are common sources of these metals, humans may be exposed in a variety of other ways including air and water contamination, food adulteration, medicine, improper coating of food containers, dental amalgams, ingestion of lead-based paints and other environmental hazards [12]. Particularly, As is often found in rice and inorganic forms of arsenic are easily absorbed in the body if ingested [13]. Pb is often produced in activities like mining, smelting and battery manufacturing, while Hg is often found in amalgam fillings [14]. A highly toxic form of Hg, methylmercury, builds up in fish and shellfish that are then consumed by humans [14]. Cd is found in the production of batteries, dyes, coatings, plastic stabilizers and ironless alloys [14]. It is also prevalent in contaminated soil, manure fertilizer, tobacco leaves, jewelry and toys [14].

Toxic metals harm all living organisms when the bioaccumulation rate is greater than the filtration rate [9]. Heavy metals are bio-accumulated in humans through inhalation, ingestion and absorption [9]. Ample studies have shown that the bioaccumulation of heavy metals in humans has been associated with negative developmental consequences. Elevated serum levels of heavy metals can lead to reduced vital nutrients in the body, which causes harm to the immune system, induces growth delay, reduces psychosocial abilities, causes malnutrition and causes upper gastrointestinal cancer syndromes [9]. Ambient particulate matter containing heavy metals and gaseous air pollutants associated with coal mining have been associated with fetal developmental problems, cognitive anomaly risks, heritable gene mutations, and mutations in fetal DNA [3]. In a study performed by Cordial et al., women in coal mining counties of West Virginia were 16% more likely to give birth to low birth weight infants than women living in non-coal mining counties [2]. According to a published analysis of birth defect data in Kentucky, Virginia and West Virginia, infants in counties with MTR mining activities are associated with an increased risk of birth defects [3]. Similarly, in 2012, births in MTR mining counties had a birth defect prevalence of 0.021 (2.1%) as compared to those of non-mountaintop removal mining counties with a prevalence of 0.015 (1.5%) [15]. The rates for the two groups of counties are significantly different with a significant proportional reporting ratio (PRR) of 1.43 (95% CI; $p<0.001$) [15].

Most toxic substances that humans are exposed to can be excreted naturally via sweat, exhalation, urine and feces. However, for pregnant or nursing mothers, a small amount may be released via breast milk excretions [16]. Both of the latter pose significant threats to the developing fetus and nursing newborns. Heavy metals have been shown to induce oxidative stress in the body that overburdens the placenta in the first two months of gestation [17]. During this period particularly, the placenta has yet to mount its protection against free radicals and thus has little antioxidant capabilities [17]. The negative effects are also magnified in lactating newborns who absorb metals to a greater extent than adults and also have a lower capacity to excrete compounds in the bile, thus decreasing body clearance [14].

Breast Milk and Lactation

The current breastfeeding recommendations established by the American Academy of Pediatrics suggest exclusive breast milk for six months, and then for at least one additional year in combination with supplemental foods [18]. In 2018, the Centers for Disease Control (CDC) released information on breastfeeding rates for newborns born in 2015. The data revealed that the national average in the United States for infants that were ever breastfed was approximately 83.2% [18]. More specifically, 73.9% of infants in Kentucky, 81.7% of infants in Virginia and 68.6% of infants in West Virginia were ever breastfed [18]. This suggests that a high proportion of infants in the Appalachian region were potentially exposed to toxins like heavy metals that may be transferred via mammary secretions.

Human milk remains the gold standard of nutrition for infants due to its unique composition and benefits. In general, it is made up of 87% water and the remaining is a mixture of carbohydrates, lipids, proteins, vitamins and minerals that all fluctuate depending on various physiological factors [19]. Breast milk is a bioactive fluid that also contains immunoglobulins, antimicrobials, leukocytes and immune modulators like cytokines that are specifically tailored and created in order to enhance the child's immune system, act as a protective barrier in the gastrointestinal epithelial, and influence intestinal microflora [14].

Immunoglobulins (Ig), or antibodies, in breast milk represent previous maternal antigen exposure and subsequent response of the immune system to protect against future exposure to the same foreign antigen. While there are several classes of immunoglobulins, breast milk primarily contains IgA > IgM > IgG, in that order of concentration [20]. IgM is the first antibody made after an exposure, while IgG remembers the infection and remains in all body fluids for life and IgA is predominantly in mucus membranes [21]. IgA aids in the protective aspect of the epithelial barrier and helps with immunosuppression as needed within the infant's gastrointestinal tract [21].

Cytokines are a group of protein hormones predominantly made by helper T cells (Th) and macrophages that aim to propagate the body's immune response by triggering and initiating other aspects of both the innate and adaptive immune system [22]. They also function in embryonic development and stem cell differentiation [19]. Those that have been detected in human colostrum (the initial mammary gland secretions) and milk include interleukin 2 (IL-2), interferon gamma (INF-γ), and tumor necrosis factor beta (TNF-β) all produced by helper T cells Type 1 (Th1) and IL-4, IL-5, IL-10 and IL-13 produced by helper T cells Type 2 (Th2) [23]. Other cytokines found in breast milk include IL-3, IL-6, tumor necrosis factor alpha (TNF-a) and granulocyte-macrophage colony stimulating factor (GM-CSF) [23]. There is a natural balance between the Th1 and Th2 cytokine profile that is essential for the newborn as their cytokine production mechanisms are not fully functioning directly after birth [19].

Factors that influence the percentages of these elements within breast milk include maternal factors (age, diet, ethnicity, weight gain during pregnancy, environmental pollutants and lifestyle), infant factors (birth weight, caesarean vs. vaginal delivery and biological needs) and specific lactation factors (time of day, stage of nursing, time since last feed and length of lactation) [21]. Lactation typically begins 40 hours after birth, and it is triggered by progesterone, estrogen, prolactin and oxytocin [14]. Physiologically, the composition most markedly changes during the first 21 days post-partum as it transitions from colostrum to transitional milk to mature human milk [24].

While there are many benefits to breastfeeding as identified above, it also acts as a route of elimination for toxic substances such as heavy metals built up in the mother's body. Some heavy metals are even stored in the mother's bones and are unintentionally released when bone turnover is increased to provide calcium for the infant via mammary secretions [25]. The amount of toxin that is actually passed to the infant depends on the chemical and physical features of the toxin as well as its half-life both within the mother and within the breast milk. Depending on its makeup, it can pass from the maternal blood plasma into the breast milk; thus, in theory a higher milk-to-maternal plasma ratio represents a more soluble and lipophilic substance that is more likely to dissolve into the breast milk and be transported to the infant [16]. It is also important to note that milk contamination decreases with duration and frequency of breastfeeding as the mother's body rids itself of the toxins [26]. In a study done by Chao et al. in Taiwan in 2008, 180 human milk samples from four stages of lactation (colostrum, transitional, early mature and mature milk) were taken from 45 healthy lactating women and concentrations of As, Pb, Cd and aluminum (Al) were measured [27]. The overall trend revealed that concentrations of these heavy metals declined rapidly as the lactation period progressed, possibly due to the fact that colostrum has a higher content of protein, lactose and fat than other stages of breast milk [27]. The high protein increases the binding capacity to toxic metals while the lactose and fat levels increase the absorption of the heavy metals within the neonatal gastrointestinal tract [28].

Heavy Metals in Breast Milk

Arsenic (As). Arsenic is found in the environment in organic forms such as mono-methyl arsenic (MMA), dimethyl arsenic (DMA), arsenobetaine and arsenocholines and in more toxic, inorganic forms such as Arsenite (As^{III}) and Arsenate (As^{V}) [19]. The inorganic forms are water soluble and thus most often spread via contaminated water; however, it may also spread via air in coal burning areas [29]. Inorganic forms and methylated forms (MMA and DMA) are able to cross the placental barrier. A study conducted by Concha et al. in Argentina measured As metabolite concentrations in samples of maternal blood and urine before delivery, and cord blood and placental concentrations at the time of delivery [30]. After delivery, concentrations of As metabolite were measured in maternal blood, maternal urine, infant urine, and breast milk over the course of 4.4 months [30]. The results revealed a high percentage of DMA in the maternal urine before delivery and the first infant urine after birth [30]. This suggests that either DMA is the main form transferred to the fetus in utero or that As methylation occurs throughout pregnancy and converts inorganic forms into DMA [30]. Comparatively, concentrations of As in breast milk were relatively low, despite the ability of As^{III} to leave the body via aquaglyceroporins in mammary glands [30]. A study by Samanta et al. reported a similar finding and found that levels of As in breast milk were much lower than in urine, suggesting that urine is the most efficient way of elimination for the body [31]. This supports the claim from Castro et al. that infants are more likely to be exposed to As from water in formula than through breast milk [32].

There are few studies on the effects of As specifically in infants or via breast milk transmission, as a majority of studies have focused on adult exposure from environmental sources. Studies have suggested however, that health effects in adults and infants are similar and include respiratory, dermal, neurological and cardiovascular symptoms [29]. One study conducted by Bencko et al. reported that children living near an As-high coal burning factory were more likely to have hearing deficits than those living in areas outside of the pollution [33]. While this does not coincide with exposure via breast milk, it may suggest that living in the vicinity of a coal mining area in the Appalachian Mountains presents an environmental hazard to infants.

Lead (Pb). Pb is absorbed into the body via the digestive tract, respiratory tract and transdermally [19]. Pb has both inorganic and organic forms; however, the inorganic forms are most often released into the environment from activities like mining [34]. Prior to stricter Pb regulations in products, the most common form of exposure was via Pb paint and water pipes [35]. 90% of Pb is stored in the bone for the duration of a person's life; however, it is released from bone in pregnant and lactating mothers when their bone turnover increases to release important nutrients like calcium for the child [19]. Chao et al. concluded that lactating mothers greater than 30 years of age had significantly increased Pb concentration in their mammary secretions when compared to younger mothers [27]. Another study reported that the Pb concentrations in breast milk are significantly correlated to the levels of Pb in the mother's blood and umbilical cord at the time of delivery [14]. This observation may provide a novel way to estimate the levels of Pb in a mother's breast milk, and to assess the risk versus reward of breastfeeding over formula use. Despite the limited research on Pb in breast milk, clinicians advise women with Pb blood levels below 40 µg/dL to continue to breastfeed [36].

Like other heavy metal exposure, both prenatally and postnatally, Pb has significant effects on child development. The World Health Organization (WHO) states that infants absorb four to five times more Pb than adults [37]. Infants also have an immature blood brain barrier, making them more susceptible to the neurotoxic effects of exposure [37]. Pb inhibits the production of Th1 cytokines, thus making the newborn more susceptible to infections [19]. Furthermore, prenatal exposure has been correlated to decreased birth weight, birth length and smaller head circumference in newborns as it passively diffuses into placental cells [17]. Once in the placenta, Pb interferes with placental calcium uptake [17]. Exposures postnatally have been shown to decrease IQ and even precipitate the later development of attention deficit disorder (ADD) and aggression [38].

Mercury (Hg). Hg exists in the elemental form (Hg^0), inorganic forms as Hg^+ and Hg^{2+} and various organic forms like methylmercury (MeHg) [39]. It is estimated that 80% of the Hg released from human activities like mining is in the form of Hg^0 [39]. Once absorbed, a majority is oxidized to Hg^{2+} and deposited in the kidneys [19]. Inorganic forms are excreted mainly via urine or feces, and little is currently known about the excretion via breast milk [40]. Bose-O'Reilly et al. conducted a study on 46 breast-feeding women with close proximity to a gold mining area and suggested that breast milk may in fact be a source of inorganic Hg for nursing infants [41]. MeHg is the most toxic form and is readily absorbed into the mother's bloodstream [40]. It's lipophilic properties also allow it to cross the placenta and break down the fetal blood brain barrier [14]. MeHg can be transported to the infant postnatally via breast milk [40]. In a study done by Drasch et al., the concentration of Hg was measured in 70 in breast milk samples from 46 mothers [42]. The results showed a positive correlation between the amount of Hg and the number of dental amalgam fillings and the frequency of fish consumption by the mother [42]. For future analyses and studies of Hg burden, it is important to note that a majority of studies only measure Hg exposure via hair samples; however, Bose-O'Reilly et al. measured Hg burden via breast milk, urine, blood and hair in participants and revealed that levels of Hg in breast milk were sometimes high despite a low Hg hair level [41].

The presence of Hg exposure in the developing fetus and infant inhibits the production of Th1 cytokines and alters the cytokine profile [19]. Many of the effects of Hg exposure are related to the nervous system and include delayed developmental milestones, incoordination, blindness, seizures and muscle weakness [39].

Cadmium (Cd). Cd mainly enters the body via inhalation, and after it binds to proteins it is transported in the blood [19]. In utero, the placenta has been shown to be slightly protective against Cd as levels in human milk are often 5-10% of the levels of Cd in the mother's blood [43]. However, a study by Kippler et al. measured Cd levels in mother's breast milk and erythrocytes and indicated that there is no protective barrier against the transportation of blood Cd to breast milk [44]. Higher breast milk concentrations of Cd have been shown in mothers who smoke [19]. In a study by Honda et al. and several other studies, the concentrations of Cd were inversely related with calcium concentrations—implicating that Cd may affect the secretion of calcium in mammary secretions [45]. This is potentially due to the fact that Cd has physicochemical similarities to calcium [14]. Due to its resemblance, processes that utilize calcium naturally like cell death pathways may also be disrupted [14].

Cd, like many other heavy metals inhibits the production of Th1 cytokines, which negatively affects the developing immune system in neonates [19]. In a study by Wang et al. that measured Cd serum levels in 3254 mothers, there was a significantly higher risk for preterm birth in mothers with elevated Cd serum levels as compared to those with lower concentrations [46]. There have also been associations of elevated Cd levels and the development of asthma [19]. Additionally, Cd has been shown to alter endocrine function in the fetus and effect placental progesterone production [8].

Future Studies

Assessing the risks and health consequences that exposure to As, Pb, Hg and Cd pose to infants in the Appalachian region is of the utmost importance. Risk identification has formerly been divided into four steps: (1) Hazard Identification, (2) Hazard Characterization, (3) Exposure Assessment, and (4) Risk Characterization [14]. While the first two steps are often established by researchers through laboratory and human epidemiological studies, a vast array of methods must be explored to assess the exposure and characterize the risk to nursing infants in the Appalachian mining region [14].

One such method that should be explored is screening breast milk provided to the infant from its mother, or from a human milk bank, which is a place where breast milk can be purchased or sold by individuals or commercial entities [48]. Breast milk is a non-invasive form of detecting environmental contaminants and allows the exposure of both the mother and the baby to be assessed at the same time [14]. The WHO and UNICEF recommend that if the mother's milk is insufficient, that she seek milk from another healthy lactating mother, milk from a human milk bank, or supplement formula [47]. Prospective milk bank donors are commonly screened for recreational drug use through behavioral questionnaires, but are not routinely tested for pharmaceuticals or environmental substances [48]. For example, the Human Milk Banking Association, which is one of the most common milk banks in North America, screens donors for medical and lifestyle risk factors, and tests for select diseases, but does not evaluate the milk for environmental contaminants [49]. Further screening of breast milk, whether provided by the mother or by a regional milk bank, should be screened in areas known to have increased heavy metal contaminants.

Future research should also focus on measuring the heavy metal concentrations in local water supplies and cow's milk in order to characterize the risk and assess the exposure to infants and weigh the benefits of breastfeeding. Infant formula prepared with local water has been found to have higher amounts of heavy metals than breast milk in some areas [28]. Akayezu et al., reported that cow's milk is often a source of Hg, Pb, and lipophilic organochlorine pesticides for infants [50]. A variety of other methods to assess exposure risk of heavy metals exist by utilizing environmental and biological methods. For example, plant species which act as bioaccumulators can be used to monitor heavy metal pollutants in the air in MTR mining regions and could indicate whether a population is at risk. These pollutants are measured when deposition occurs on the plant canopy or air pollutants accumulate in and on leaves [9]. Mosses may also be able to assist in monitoring these pollutants because they have high cation exchange capacity, which causes them to be hyper-accumulants of metals and metal complexes [51]. Another method to monitor contaminant accumulation may be through toenail clippings, which have shown to be successful in assessing environmental exposures to trace elements like heavy metals [52]. Due to the slow rate of toenail growth, toenail measurements represent exposures over three to twelve months and remain relatively stable [53]. Toenail samples could be collected from women of childbearing age in the Appalachian region as a potentially less invasive way to detect chronic exposures to heavy metals.

Conclusion

Infants being breastfed in the Appalachian region are at an increased risk of heavy metal contamination from an unlikely source - their own mothers and the life-giving milk that they provide. Many studies presented in this report have shown how heavy metals accumulate in the human body and are subsequently transferred to infants through breast milk. The health effects resulting from heavy metal exposure are clear: pre- and post-natal birth defects that have severe developmental consequences. This paper suggests that screening breast milk of the mother and milk provided by milk banks located in the Appalachian region could be a useful tool in assessing an infants' exposure and characterizing the risk to heavy metals. It also suggests that this can be done by monitoring concentrations of heavy metal contamination in local water supplies, cow's milk and through bioaccumulation in plants and toenail clippings. While breastfeeding will likely remain the gold standard for infant nutrition, heavy metal exposure to breastfed infants as a result of MTR mining practices in the Appalachian region requires additional study.

Disclosures

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References

1. Hendryx M (2009) Mortality from heart, respiratory, and kidney disease in coal mining areas of Appalachia. Int Arch Occup Environ Health. 82: 243-249.
2. Cordial P, Riding-Malon R, Lips, H (2012) The effects of mountaintop removal coal mining on mental health, well-being, and community health in Central Appalachia. Ecopsychology. 4: 201-208.
3. Ahern MM, Hendryx M, Conley J, Fedorko E, Ducatman A, et al. (2011) The association between mountaintop mining and birth defects among live births in central Appalachia, 1996-2003. Environmental Research: Elsevier. 11: 838-46.
4. Holzman DC (2011) Mountaintop removal mining: digging into community health concerns. Environ Health Perspect. 119: a476–a483.
5. Lashof DA, Delano D, Devine J. Finamore B, Hammel D, et al. (2007) Coal in a changing climate. Natural Resources Defense Council.
6. Olson C (2018) Susceptibility of Appalachian mountain streams to non-point source contamination. (Unpublished masters dissertation). Middle Tennessee State University, Tennessee, United States.
7. McAuley SD, Kozar MD (2006) Ground-water quality in unmined areas and near reclaimed surface coal mines in the northern and central Appalachian coal regions. Geological Survey Scientific Investigations Report. 2006-5059.
8. Caserta D, Graziano A, Monte GL, Bordi G, Moscarini M (2013) Heavy metals and placental fetal-maternal barrier: a mini-review on the major concerns. Eur Rev Med Pharmacol Sci, 17: 2198-2206.
9. Sardar K, Ali S, Hameed S, Afzal S, Fatima S, et al. (2013) Heavy metals contamination and what are the impacts on living organisms. Greener Journal of Environmental management and public safety. 2: 172-179.
10. Agency for Toxic Substances and Disease Registry (ATSDR). 2019. Substance Priority List. U.S. Department of Health and Human Services.
11. Slagle A, Skousen J, Bhumbla D, Sencindiver J, McDonald, L (2004) Trace element concentrations of three soils in Central Appalachia. Soil Survey Horizons. 45: 73-85.
12. Rather IA, Koh WY, Paek WK, Lim J (2017) The sources of chemical contaminants in food and their health implications. Frontiers in pharmacology. 8: 830.
13. Hojsak I, Braegger C, Bronsky J, Campoy C, Colomb V, et al. (2015) Arsenic in rice: a cause for concern. Journal of pediatric gastroenterology and nutrition. 60: 142-145.
14. Rebelo FM, Caldas ED (2016) Arsenic, lead, mercury and cadmium: Toxicity, levels in breast milk and the risks for breastfed infants. Environmental Research: Elsevier. 151: 671-688.
15. Lamm SH, Li J, Robbins SA, Dissen E, Chen R (2015) Are residents of mountain-top mining counties more likely to have infants with birth defects? The West Virginia experience. Birth Defects Research Part A: Clinical and Molecular Teratology. 103: 76-84.
16. Anderson HA, Wolff MS (2000) Environmental contaminants in human milk. Journal of Exposure Science & Environmental Epidemiology. 10: 755-760.
17. Gundacker C., Hengstschlager M (2012) The role of the placenta in fetal exposure to heavy metals. Wien Med Wochenschr. 162: 201-206.
18. Centers for Disease Control and Prevention (2018) Breastfeeding Report Card.
19. Pajewska-Szmyt M, Sinkiewicz-Darol E, Gadzała-Kopciuch R (2019) The impact of environmental pollution on the quality of mother's milk. Environmental Science and Pollution Research. 26: 7405-7427.
20. Butler J, Kehrli Jr M (2004). Immunoglobulins and immunocytes in the mammary gland and its secretions. Mucosal immunology.
21. Hurley WL, Theil PK (2011) Perspectives on immunoglobulins in colostrum and milk. Nutrients. 3: 442-474.
22. Garofalo R (2010) Cytokines in human milk. The Journal of pediatrics. 156: S36-S40.
23. Dawod B, Marshall JS (2019) Cytokines and soluble receptors in breast milk as enhancers of oral tolerance development. Frontiers in immunology. 10: 16.
24. Institute of Medicine, National Research Council. Subcommittee on Nutrition During Lactation, Institute of Medicine (US). Subcommittee on Nutrition during Lactation, Institute of Medicine (US). Subcommittee on Lactation, United States. Health Resources, Services Administration, ... & Lactation. (1991). Nutrition during lactation. Henry Holt and Company.
25. Bentum JK, Sackitey OJ, Tuffuor JK, Essumang DK, Koranteng-Addo EJ, et al. (2010) Lead, cadmium, and arsenic in breast milk of lactating mothers in Odumanse-Atua community in Manya Krobo district of eastern region of Ghana. Journal of Chemical and Pharmaceutical Research. 2: 16-20.
26. Gundacker C, Pietschnig B, Wittmann KJ, Lischka A, Salzer H, et al. (2002) Lead and mercury in breast milk. Pediatrics. 110: 873-878.
27. Chao HH, Guo CH, Huang CB, Chen PC, Li HC, et al. (2014) Arsenic, cadmium, lead, and aluminium concentrations in human milk at early stages of lactation. Pediatr Neonatol. 55: 127-134.
28. Dorea JG (2004) Mercury and lead during breast-feeding. British Journal of Nutrition. 92: 21-40.
29. Vahter M (2008) Health effects of early life exposure to arsenic. Basic & clinical pharmacology & toxicology. 102: 204-211.
30. Concha G, Vogler G, Lezcano D, Nermell B, Vahter M (1998) Exposure to inorganic arsenic metabolites during early human development. Toxicological sciences. 44: 185-190.
31. Samanta G, Das D, Mandal BK, Chowdhury TR, Chakraborti D, et al. (2007) Arsenic in the breast milk of lactating women in arsenic-affected areas of West Bengal, India and its effect on infants. Journal of Environmental Science and Health, Part A. 42: 1815-1825.

32. Castro F, Harari F, Llanos M, Vahter M, Ronco AM (2014) Maternal–Child Transfer of Essential and Toxic Elements through Breast Milk in a Mine-Waste Polluted Area. American journal of perinatology. 31: 993-1002.

33. Bencko V, Symon K (1977) Test of environmental exposure to arsenic and hearing changes in exposed children. Environmental health perspectives. 19: 95-101.

34. Alexander J, Benford D, Boobis A, Ceccatelli S, Cravedi JP, et al. (2010) Scientific Opinion on Lead in Food EFSA Panel on Contaminants in the Food Chain (CONTAM). EFSA JOURNAL. 8.

35. Currie J (2009) Socioeconomic status, child health, and future outcomes: lessons for Appalachia. University of Kentucky Center for Poverty Research Discussion Paper Series. University of Kentucky, Kentucky, United States.

36. Barrett JR (2014) Lead transfer during breastfeeding: a start toward filling in the data gaps. Environmental health perspectives. 122: A26.

37. World Health Organization. Exposure to Lead: A major public health concern (2010). World Heal. Organ, 6.

38. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. (2006). Inorganic and organic lead compounds. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. 87: 1.

39. ATSDR U (1999) Toxicological profile for mercury. Atlanta: Agency for Toxic Substances and Disease Registry, US Department of Health and Human Services.

40. Bernhoft RA (2012) Mercury toxicity and treatment: a review of the literature. Journal of environmental and public health. 2012.

41. Bose-O'Reilly S, Lettmeier B, Roider G, Siebert U, Drasch G (2008) Mercury in breast milk–A health hazard for infants in gold mining areas?. International journal of hygiene and environmental health. 211: 615-623.

42. Drasch G, Aigner S, Roider G, Staiger E, Lipowsky G (1998) Mercury in human colostrum and early breast milk. Its dependence on dental amalgam and other factors. Journal of trace elements in medicine and biology, 12: 23-27.

43. ATSDR U (1999) Toxicological profile for cadmium. Atlanta: Agency for Toxic Substances and Disease Registry, US Department of Health and Human Services.

44. Kippler M, Lönnerdal B, Goessler W, Ekström EC, El Arifeen S, et al. (2009) Cadmium interacts with the transport of essential micronutrients in the mammary gland—a study in rural Bangladeshi women. Toxicology. 25: 64-69.

45. Honda R, Tawara K, Nishijo M, Nakagawa H, Tanebe K (2003) Cadmium exposure and trace elements in human breast milk. Toxicology. 186: 255-259.

46. Wang H, Liu L, Hu YF, Hao JH, Chen YH, et al. (2016) Association of maternal serum cadmium level during pregnancy with risk of preterm birth in a Chinese population. Environmental Pollution. 216: 851-857.

47. World Health Organization (WHO) (2003) Global strategy for infant and young child feeding. Geneva, Switzerland.

48. Palmquist AEL, Perrin MT, Cassar-Uhl D, Gribble KD, Bond AB, et al. (2019) Current trends in research on human milk exchange for infant feeding. Journal of Human Lactation. 35: 453-477.

49. Donor Milk Safety. Human Milk Banking Association of North America.

50. Akayezu JM, Hansen WP, Otterby DE, Crooker BA, Marx GD (1997) Yield response of lactating Holstein dairy cows to dietary fish meal and bone meal. J Dairy Sci 80. 2950-2963.

51. Schilling JS, Lehman ME (2002) Bioindication of atmospheric heavy metal deposition in the Southeastern US using the moss Thuidium delicatulum. Atmospheric Environment. 36: 1611-1618.

52. He K (2011) Trace elements in nails as biomarkers in clinical research. European journal of clinical investigation. 41: 98-102.

53. Garland M, Morris JS, Rosner BA, Stampfer MJ, Spate Vl, et al. (1993) Toenail trace element levels as biomarkers: reproducibility over a 6-year period. Cancer Epidemiology and Prevention Biomarkers. 2: 493-497.