Improving Infant Exposure and Health Risk Estimates: Using Serum Data to Predict Polybrominated Diphenyl Ether Concentrations in Breast Milk

ARTICLE *in* ENVIRONMENTAL SCIENCE & TECHNOLOGY · APRIL 2013

Impact Factor: 5.33 · DOI: 10.1021/es305229d · Source: PubMed

5 AUTHORS, INCLUDING:


Judy Lakind
Johns Hopkins University
81 PUBLICATIONS **1,715** CITATIONS

SEE PROFILE

Daniel Naiman
Johns Hopkins University
79 PUBLICATIONS **3,214** CITATIONS

SEE PROFILE


Cheston M Berlin
Pennsylvania State University
75 PUBLICATIONS **1,412** CITATIONS

SEE PROFILE


John F Kenneke
United States Environmental Protection Age…
26 PUBLICATIONS **389** CITATIONS

SEE PROFILE

Environmental Chemicals in Breast Milk☆

SA Marchitti, US Environmental Protection Agency, Athens, GA, USA
EP Hines, US Environmental Protection Agency, Research Triangle Park, NC, USA
JS LaKind, LaKind Associates, LLC, Catonsville, MD, USA; University of Maryland School of Medicine, Baltimore, MD, USA; Penn State College of Medicine, Hershey, PA, USA
CM Berlin Jr., Penn State College of Medicine, Hershey, PA, USA
SE Fenton, National Institute for Environmental Health Sciences, Research Triangle Park, NC, USA
JF Kenneke, US Environmental Protection Agency, Athens, GA, USA

Abbreviations

AAP	American Academy of Pediatrics
BPA	bisphenol A
DDE	dichlorodiphenyldichloroethylene
DDT	dichlorodiphenyltrichloroethane
HCB	hexachlorobenzene
HCH	hexachlorocyclohexane
NIS	sodium–iodide symporter
PBDE	polybrominated diphenyl ether
PCB	polychlorinated biphenyl
PFAA	perfluoroalkyl acid
PFOA	perfluorooctanoic acid
PFOS	perfluorooctane sulfonate
TEF	toxic equivalent factors
TEQ	toxicity equivalency
WHO	World Health Organization

Introduction

Humans are exposed to a variety of chemicals that are present in their environment (environmental chemicals). Exposures to environmental chemicals can occur via contact with environmental media (e.g., air, soil, dust, and water), foods, pharmaceuticals, and personal care products. As a result of these exposures, environmental chemicals have been measured in human tissues and body fluids including blood, breast milk, urine, hair, exhaled breath, nails, cord blood, and meconium. The first reports of

☆*Change History:* May 2013. SA Marchitti and EP Hines updated authors, affiliations, and contact information.
SA Marchitti updated and created new figures.
SA Marchitti, EP Hines, CM Berlin, JS LaKind, SE Fenton, and JF Kenneke substantially updated all text, references, and citations.

 http://dx.doi.org/10.1016/B978-0-12-409548-9.02139-4

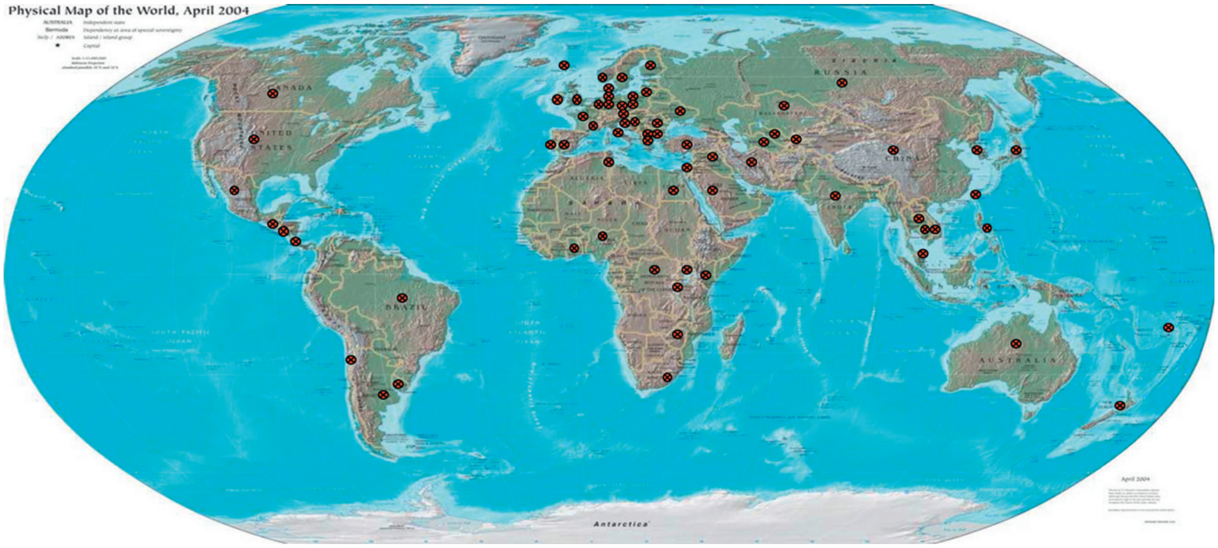

Figure 1 Countries with published data on environmental chemicals in human milk (red circles). These data are not typically nationally representative (in some cases studies included a small number of women from one or more regions in a country), and the data represent varying numbers of environmental chemicals. *Source*: Source of world map: http://en.wikipedia.org/wiki/Image:World-map-2004-cia-factbook-large-1.7m-whitespace-removed.jpg (this work is in the public domain in the United States because it is a work of the United States Federal Government under the terms of Title 17, Chapter 1, Section 105 of the US Code)

environmental chemicals in breast milk appeared in the 1950s; since that time, the published literature on the detection of environmental chemicals in breast milk has expanded enormously, with information now available from a multitude of countries (Figure 1). At the same time, however, the general lack of systematic, nationally or regionally representative breast milk biomonitoring studies has limited our understanding of environmental chemical concentrations in breast milk. Few countries or regions have undertaken this type of effort (with the exception of Canada, Sweden, and Germany, where analyses have focused on a few persistent organic chemicals). The World Health Organization (WHO) has organized five rounds of international human milk sampling and analysis for persistent organic chemicals; although many countries provide data as part of these studies, they typically collect only a limited number of samples due to the resource-intensive nature of this type of research.

Over the past few decades there has been a multi-stakeholder effort to increase the prevalence and duration of breast-feeding and these efforts have been very successful in the United States. To that end, the American Academy of Pediatrics (AAP) has reaffirmed the benefits of breast-feeding and continues to advocate for increasing the incidence of breast-feeding through the education of physicians and the public. The AAP is urging government and industry to provide opportunities for nursing mothers to have adequate postpartum leave and to return to the work force and still continue to breast-feed (AAP, 2012). The AAP Policy Statement (AAP, 2012) supports breast-feeding and emphasizes the unequivocal evidence that breast-feeding protects the infant from a variety of diseases and conditions such as bacteremia, diarrhea, respiratory tract infection, necrotizing enterocolitis, otitis media, urinary tract infection, late-onset sepsis in preterm infants, diabetes, lymphoma, leukemia, and Hodgkins disease, as well as childhood overweight and obesity (AAP, 2012). There are also advantages to the breast-feeding mother including decreased risk of type 2 diabetes mellitus, rheumatoid arthritis, adult cardiovascular disease, hypertension, hyperlipidemia, and breast and ovarian cancers.

The AAP recommends exclusive breast-feeding until 6 months of age, and breast milk to be the only source of milk until 12 months of age or longer. In 1970, approximately 26% of newborn infants in the U.S. were breast-fed, with breast-feeding rates increasing over the years to 75.0% in 2007 (CDC, 2010). The duration of breast-feeding varies by country; in the United States, only 33.5% of infants at 3 months and 13.8% of infants at 6 months are exclusively breast-fed (i.e., no artificial milks or other foods). The extent of breast-feeding influences infant exposure to environmental chemicals during lactation (as well as environmental chemicals from alternative food sources including formula). The growing numbers of studies highlighting the presence of environmental chemicals in breast milk has raised concerns about whether breast milk is still the best food for infants. However, despite the presence of environmental chemicals in breast milk, the preponderance of evidence indicates that breast-feeding not only confers numerous health benefits on the infant and mother, but may also counter effects associated with prenatal chemical exposures (Patandin et al., 1999; LaKind et al., 2008; Pan et al., 2010).

Breast milk monitoring programs in various countries (e.g., Germany, Sweden) have provided valuable information on early life exposures to chemicals in breast milk. These temporal and geographical trends in chemical levels in humans have influenced voluntary and government enforced restrictions of these chemicals. Information on concentrations of environmental chemicals in breast milk also provides data that can be used in exposure and risk analysis for breast-feeding infants.

Breast milk is an attractive matrix for monitoring postnatal exposure to environmental chemicals for several reasons. First, the collection procedure is noninvasive and can be done directly by the mother (as opposed to blood collection, which requires a trained individual). Breast milk, unlike urine, is lipid-rich and many of the chemicals of interest are lipophilic and can be readily measured in milk. Finally, unlike data from other matrices, breast milk biomonitoring data provide information on the exposure levels of a particular chemical in the mother and provide insight into potential infant exposure to that chemical. Thus, the use of breast milk in biomonitoring studies provides unique information on adult and infant exposure to environmental chemicals.

This article provides an overview of three fundamental topics related to environmental chemicals in breast milk: (i) identification and concentrations of chemicals detected in breast milk over time and place, (ii) factors associated with the observed levels of chemicals in breast milk, and (iii) the association between environmental chemicals in breast milk and infant health.

Environmental Chemicals in Breast Milk

The detection and measurement of environmental chemicals in breast milk is complicated because breast milk is a complex matrix composed primarily of lipids ($\sim$4%), proteins ($\sim$1%), lipoproteins, immune factors, lactose, and water. A further complicating factor is that milk fat and protein content vary considerably depending on whether the milk is the first (fore) or the last (hind) from the breast (LaKind et al., 2004). Depending on the lipophilicity of the chemical of interest, the sample collection, and analytical procedures vary. Over time, the sensitivity and selectivity of these analytical procedures has improved to the point that the limits of detection for several classes of environmental contaminants in breast milk are now in the low ppb range.

Since milk is a combination of lipid and aqueous phases, it can contain environmental chemicals that are lipophilic and non-lipophilic (or water-soluble). The chemicals that partition into the lipid fraction of milk have been widely studied because they tend to bioaccumulate, have a long half-life in humans, and have been consistently detected in biological matrices over decades. One consequence of a long half-life is that lifetime maternal exposure to these chemicals can contribute to the lactational exposure of these chemicals in infants. More recently, non-lipophilic chemicals can now be readily measured in breast milk due to the development of sufficiently sensitive analytical methods and appropriate collection and storage protocols. Biomonitoring studies are beginning to provide useful information for informing regulators, physicians, new mothers, and children's advocacy groups on the presence of environmental chemicals in breast milk. Here, we describe the trends and concentrations of various persistent and nonpersistent chemicals from studies around the world.

Lipophilic Chemicals

The most extensively studied environmental chemicals detected in breast milk are the persistent organic chemicals, which include dioxins and furans (commonly referred to as 'dioxins'), polychlorinated biphenyls (PCBs), organochlorine pesticides, and the class of flame retardants referred to as polybrominated diphenyl ethers (PBDEs). Owing to their lipophilic nature, the breast milk concentrations of these compounds may be substantially higher than the levels measured in the serum of the donor. Concentrations of dioxins and certain PCBs are commonly reported as toxic equivalents (TEQ), which is the measured concentration (typically on a lipid-adjusted basis) multiplied by a toxic equivalent factor (TEF).

The levels of dioxins in the environment have decreased significantly over the past 20 years and countries that have monitored breast milk concentrations over time (many European countries, Japan, Pakistan, Ukraine, and Vietnam; reviewed by LaKind et al. 2004; **Figure 2**) have observed a corresponding decrease in levels of dioxins from the early 1970s to the late 1980s. A recent comparison of global dioxin levels demonstrates their consistent decrease in breast milk over the past 10 years (LaKind et al., 2007). PCBs have also been measured globally in breast milk (**Figure 3**). Since the United States does not have a national breast milk biomonitoring program, it is not clear from the available data if the levels of dioxins and PCBs have decreased in the breast milk of U.S. women, although data on serum levels of these chemicals in the U.S. population have declined substantially over that time period and a concomitant decline in milk levels would be expected.

The organochlorine pesticides include several compounds for which breast milk data are available: dichlorodiphenyltrichloroethane (DDT) and its metabolite dichlorodiphenyldichloroethylene (DDE), dieldrin, chlordanes (oxychlordane, heptachlor, γ-chlordane, trans-nonachlor), hexachlorocyclohexanes (HCHs), mirex, and endosulfan. These compounds were primarily used for pest control and have been banned or removed from the market in most countries. Although previous assessments indicated that the concentrations of many of these compounds have been decreasing in breast milk over time (LaKind et al., 2004; 2007), the concentrations of certain pesticides in the milk of some women may still be high. For example, in Chelem, Yucatan, Mexico, some breast milk samples were recently found to exceed the JMPR-FAO/WHO (Joint Meeting on Pesticide Residues/Food and Agriculture Organization) acceptable daily intakes (Rodas-Ortíz et al., 2008).

PBDEs, a class of brominated flame retardants, were first reported in milk approximately 15 years ago (Meironyté et al., 1998). Unlike the chemicals previously mentioned, PBDE levels have dramatically increased in breast milk from the 1970s to 2000s, leading to a recent ban (2004) in Europe and a voluntary manufacturing phase-out in the United States for the lower brominated penta- and octa-congeners. These smaller sized congeners are believed to bioaccumulate to a greater extent than the highest brominated congeners. In the United States, PBDE concentrations in breast milk are among the highest in the world with levels

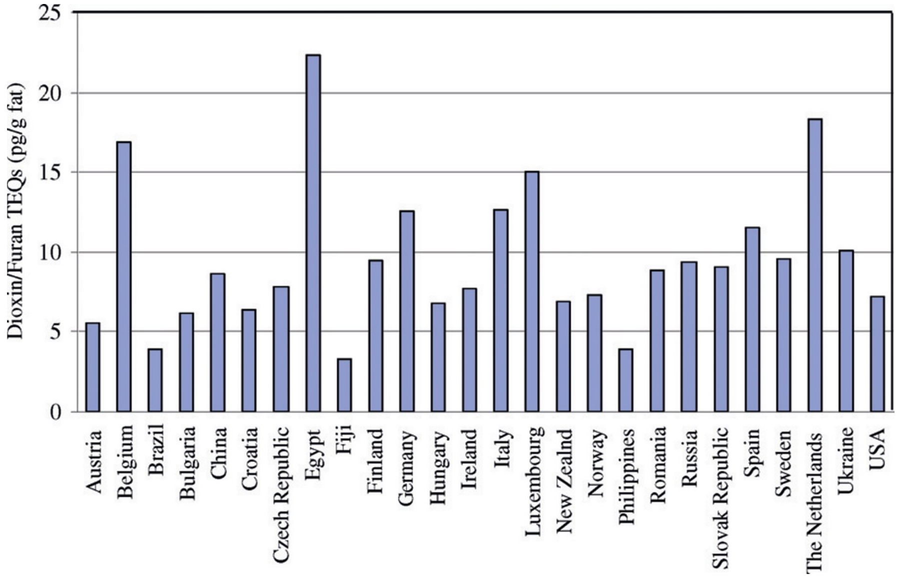

Figure 2 Total dioxins and furans (pg WHO-TEQs per g fat) in breast milk from the World Health Organization-coordinated exposure study (based on data on median levels reported in Malisch and van Leeuwen, 2003).

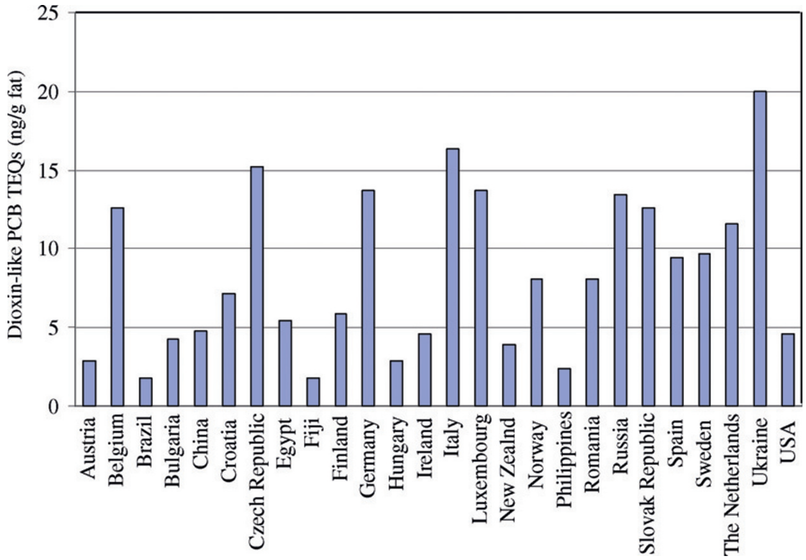

Figure 3 PCBs (pg WHO-TEQs per g fat) in human milk from the World Health Organization-coordinated exposure study (based on data on median levels reported in Malisch and van Leeuwen, 2003).

substantially higher than those reported in Asia and Europe (**Figure 4**).This is likely due to the fact that the U.S. was the primary consumer of the PBDE flame retardant products. In addition, the previous use of PBDEs to meet California TB117 flame retardant standards in furniture has likely contributed to high PBDE exposures in the U.S. compared with other countries. Assessing the impact of recent bans and voluntary withdrawals of these chemicals from the market on levels in breast milk may require a milk sampling and analysis program. However, maternal serum and breast milk PBDE concentrations are highly correlated, indicating that maternal serum levels of PBDEs may be used as a surrogate for estimating breast milk concentrations (Marchitti et al., 2013). For the PBDEs, this approach appears to represent a computational alternative to breast milk biomonitoring, however, further validation and research is needed to see if this approach is applicable to other chemicals measured in serum.

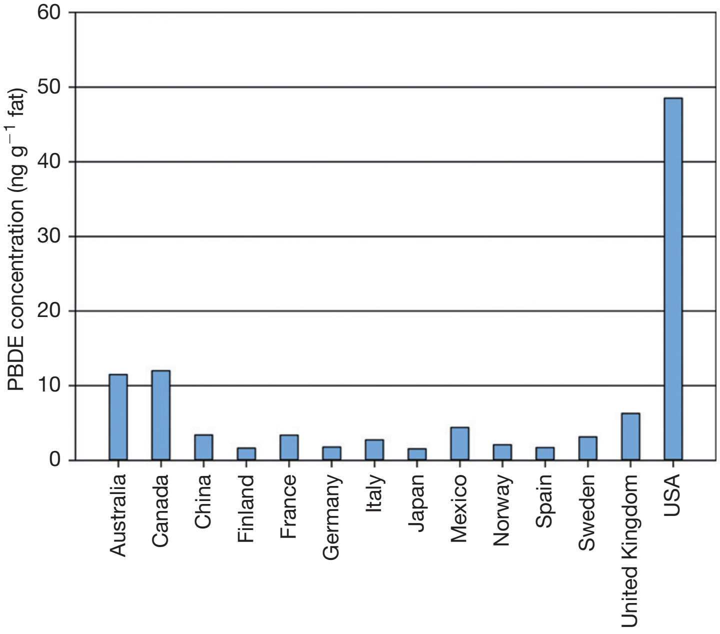

Figure 4 Levels of PBDEs (ng per g fat) in human milk worldwide (based on median values reported in Inoue et al., 2006, and Siddique et al., 2012).

Non-Lipophilic Chemicals

Unlike lipophilic compounds, the non-lipophilic chemicals described here do not accumulate in milk fat and are detected at concentrations at or below those measured in serum or urine of donors. Breast milk concentration data have been published for a small number of non-lipophilic chemicals; the primary reasons for this dearth of data are (i) the difficulty in detecting these chemicals in milk at the low levels found in milk (matrix and volume interactions) and (ii) many but not all of the non-lipophilic compounds have short half-lives. Recently published data for non-lipophilic chemicals measured in breast milk include bisphenol A (BPA), perchlorate, phthalate metabolites, parabens, perfluorinated compounds (PFCs) such as perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), and a number of metals. Because concentration data for non-lipophilic chemicals in breast milk have only recently become available, there is insufficient information to assess geographic or temporal trends.

The phenolic compound BPA, which is used mainly to manufacture polycarbonate plastic and epoxy resins, has been reported in breast milk at a mean value of less than 1 ppb (Sun et al., 2004) and ranging from 0.4 to 1.4 ppb (Mendonca et al., 2012). In a study of a 24 breastfeeding U.S. women, total BPA was detected in 75% of breast milk samples (Mendonca et al., 2012). In breast milk samples with detectable concentrations of BPA, no correlation to the lipid content of milk samples has been found (Sun et al., 2004). As with other short-lived chemicals, BPA concentrations in the milk of the study participants likely reflect the mother's recent BPA exposures.

Phthalates are plasticizers that are used in cosmetics, food containers, medicine coatings, ink and tubing, among other commercial products and are ubiquitous in the environment. In breast milk, esterases metabolize the parent diester phthalates to monoester phthalate metabolites. Thus, it is the phthalate monoester metabolites, rather than diester phthalates, that are measured in studies of breast milk. The monoester phthalate metabolites of these compounds are measureable in breast milk, albeit in less than 10% of measured samples (Hines et al., 2009).

Perchlorate, a component of jet and rocket fuel, is physically transported into milk via the sodium–iodide symporter (NIS) in the cell membrane of the mammary epithelium. The NIS has up to 30-fold greater affinity for perchlorate than iodide (Kirk et al., 2005). Perchlorate has the potential to interfere with the normal transfer of iodide to the breast-feeding infant and has been detected in nearly all human milk samples that have been tested (Kirk et al., 2005).

Parabens, esters of 4-hydroxybenzoic acid, are extensively employed as preservatives in a wide range of personal care products, in canned foods, beverages and pharmaceuticals (Meyer et al., 2007) and have been shown to have estrogenic activity. Few data exist quantifying levels of parabens in breast milk. However, in a study of 54 Swiss women, parabens were detected in approximately 15 to 34% of de-fatted breast milk samples, with the level of detection corresponding to the degree of paraben lipophilicity (methylparaben > ethylparaben > propylparaben) (Schlumpf et al., 2010). The more lipophilic butyl paraben was not detectable in defatted samples; however its presence in milk fat was not determined.

PFCs are chemicals that have both lipophilic and non-lipophilic regions (i.e., amphiphilic). These compounds are water soluble, protein-bound, and typically not found in appreciable concentrations in human lipids. Traditionally used as surfactants for firefighting and in making commercial products water or greaseproof, the most commonly detected PFCs in breast milk are PFOA and PFOS (von Ehrenstein et al., 2009). PFCs bind to proteins and are known to persist in humans for years. By 2002, PFOS was voluntarily phased out of production by its manufacturers due to its bioaccumulative properties. The limited available data suggest that levels of PFCs in human milk have been relatively constant (from 1996 to 2004 in Sweden; Kärrman et al., 2007). Because these compounds have been observed in breast milk in several countries, this class of chemicals should continue to be monitored (Lykissa and Maharaj, 2006).

Several metals, including mercury, cadmium, arsenic, lead, as well as nutrient trace elements such as copper and zinc, have been detected in breast milk from many countries (Al-Saleh et al., 2013; Liu et al., 2013). The environmental sources of metals are typically associated with region-specific dietary preferences or exposure patterns (metals in water/air, food storage containers, cigarette smoking status, drinking water pipe composition).

With each passing year, new analytical methods become available for measuring additional chemicals in breast milk; some recent examples include triclosan, triclocarban, and several volatile organic compounds. Many chemicals are present in cosmetics and personal care products are beginning to be measured in breast milk. Various cosmetics-derived compounds, including UV filters, and synthetic musks, have been found in human milk (Schlumpf et al., 2010; Latini et al., 2009; Ye et al., 2008).

Pharmaceuticals

The first published concern over the appearance of pharmaceuticals and chemicals in human milk was in 1908 (Reed, 1908). For the compounds discussed in this early work, the amount transferred into milk was quite small. Although analytic methods at the time were primitive in comparison to today's capabilities, this observation has been repeatedly confirmed for most pharmaceuticals over the years. Almost all pharmaceuticals measured to date appear in milk to some extent with the milk/plasma ratio almost always between 0.5 and 1.0. (Berlin, 2011). In an attempt to both protect the breast-feeding infant as well as to permit maternal therapy, and continuation of lactation, the Committee on Drugs of the AAP has published statements on the transfer of drugs and chemicals in human milk. The most recent edition was published in 2001 (AAP, 2001). This statement outlines the factors that should be considered before prescribing drugs to lactating women. Some pharmaceuticals or drugs that are contraindicated with breastfeeding include radioactive compounds (e.g., iodine-131, radioactive sodium; breast-feeding may be resumed after radioactivity has disappeared from milk samples), drugs of abuse (e.g., cocaine, heroin), and cytotoxic drugs (e.g., cyclosporine, doxorubicin). The use of oral contraceptives containing estrogen and progestin, either individually or in combination, may significantly decrease milk production in the breast-feeding mother. However, most drugs likely to be prescribed to the breast-feeding mother are compatible with breast-feeding and are not expected to have an effect on milk supply, milk quality, or infant well-being.

The U.S. National Library of Medicine Toxicology Data Network recently launched an internet database called LactMed (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT). It provides information on over 1000 drugs, chemicals, and dietary supplements, such levels in breast milk, infant blood levels, potential effects in breastfeeding infants, the AAP category indicating the level of compatibility of the drug with breastfeeding, and alternate drugs to consider. Additional drugs are continually added and updated with peer review and literature citation.

Factors Influencing Concentrations of Environmental Chemicals in Breast Milk

The levels of environmental chemicals in mother's milk will depend on the levels of those chemicals in her environment as well as the physicochemical properties of the chemical(s). For some chemicals, such as persistent bioaccumulative compounds, her lifetime exposure will be important, whereas for other short-lived chemicals (such as many volatile organic compounds) more recent exposures will strongly influence the levels in milk. Thus, the levels of a given chemical in milk are influenced by a multitude of complex factors making population-based predictions difficult. In general, physiochemical properties that favor the transfer of chemicals into breast milk are (1) low molecular weight, (2) unionized state, (3) low binding to maternal plasma proteins, and (4) lipid solubility.

Despite these complexities, however, many factors thought to be important in determining breast milk concentrations have been investigated, and some generalizations can be made. These factors include geography, previous lactation and length of lactation, diet, age, weight loss, body mass index, and lifestyle. It should be noted that special caution should be taken during collection and analysis of media for ubiquitous environmental chemicals including the PCBs, PBDEs, PFCs, BPA and the phthalates because these chemicals can be accidentally introduced into biological media during collection and analysis, contributing to spurious concentrations. In this regard, matrix blanks and special care to awareness of composition of laboratory plastics, machine filters, tubing, and dust levels are very important in controlling for background contamination and interpretation of results (Calafat et al., 2009; Ye et al., 2013).

This section summarizes the results of several studies that have examined factors that influence the levels of environmental chemicals in breast milk. Because most of the breast milk research has focused on persistent organic chemicals, the following sections address these chemicals.

Geography

Many environmental chemicals, including persistent bioaccumulative compounds, such as PCBs, dioxins, and PBDEs and heavy metals such as lead, are globally distributed and have been found in breast milk in virtually all samples tested from around the world. It is important to recall that these data are typically based on a limited number of samples from one or a few regions in a country and are not likely to be representative of the country as a whole. This makes an assessment of the influence of geography much more difficult to discern. Despite this, there are sufficient data to note instances where geography influences the concentrations of environmental chemicals in breast milk. For example, DDT was banned in most Western countries in the 1970s, but was only recently banned in other countries and is still used for malaria control in certain parts of the world. Thus, countries with more recent DDT use may still exhibit higher milk levels of DDT and its metabolites compared to countries with longer-term bans in place. The use and release of PCBs and dioxins were severely curtailed during the 1970s and 1980s, and levels of these chemicals in breast milk have declined sharply. However, they can still be detected in breast milk samples, and the concentrations vary by country (country-specific data for dioxins and PCBs are shown in **Figures 2** and **3**, respectively). Point sources of exposure like Agent Orange and its co-contaminant dioxin from application in Vietnam can lead to regional spikes in environmental chemicals in breast milk in subpopulations. Atmospheric and oceanic transport can distribute chemicals far from their original site of production or use. For example, Inuit women are believed to have the highest body burdens of organochlorine pesticides in the world, which is thought to occur from background environmental exposure related to climate or oceanic transport factors and a diet rich in lipid-laden sea mammals (Dewailly et al., 1993). Coastal living and associated consumption of certain fishes has been associated with higher levels of PCBs in breast milk (Falk et al., 1999).

Lactation History

Past studies have reported decreases in breast milk concentrations of persistent organic chemicals over the course of lactation (reviewed by LaKind et al., 2001), and it has been hypothesized that as the mother breast-feeds, she transfers some of her lifetime stores of these chemicals from her adipose tissue to milk, and then to the breast-fed infant. More recent studies have not observed significant declines in these chemicals in breast milk over lactation, including dioxins (LaKind et al., 2009) (**Figure 5**). In some cases, levels of these persistent organic chemicals appear to increase for some women (LaKind et al., 2009; Sasamoto et al., 2006). The PBDEs and other persistent chemicals such as HCB and some PCBs appear to remain relatively constant over the course of lactation (Sjödin et al., 2005) (**Figure 6**). This may be related to the balance between current low-level dietary exposures and elimination during breast-feeding (Sjödin et al., 2005).

At present, elimination of chemicals during lactation is still poorly characterized and additional research is needed to draw clear conclusions. A recent study of ten Norwegian mothers has reported the depuration rates for PFOS and PFOA in breast milk as being 3.8% and 7.8% per month, respectively (Thomsen et al., 2010). Some studies have found an association between increasing parity and a decrease in levels of persistent organic compounds in milk (reviewed by LaKind et al., in 2004; Nakamura et al., 2008). However, a study from a lactating population in the Yucatan peninsula of Mexico found no significant difference in the levels of PCBs or organochlorine pesticides as a function of age or number of births (Rodas-Ortíz et al., 2008).

Other Factors

Humans are exposed to persistent organic chemicals throughout their lives; these compounds tend to accumulate in human lipids. It is thus believed that as age increases, so do levels of persistent organic chemicals in the body. Several (but not all) studies have

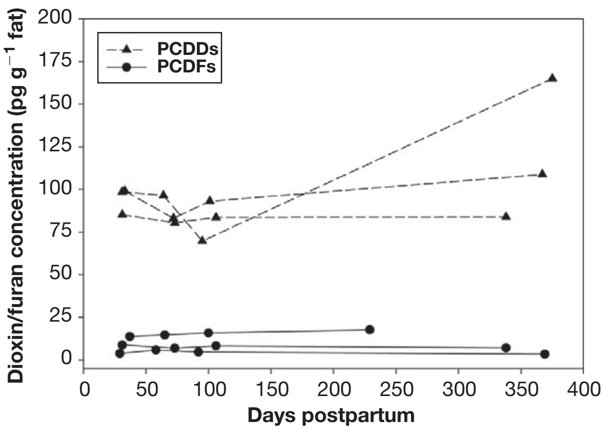

Figure 5 Examples of changes in concentrations of dioxins (PCDDs) and furans (PCDFs) in human breast milk during lactation over 350 days postpartum for 3 participants (data from LaKind et al., 2009).

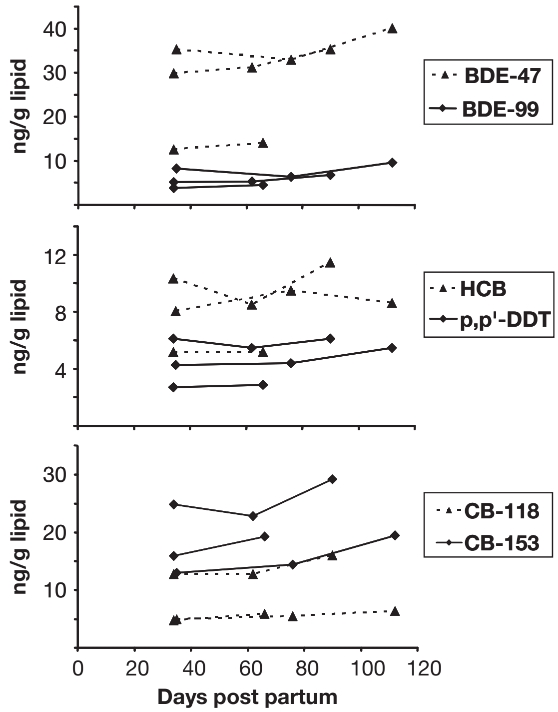

Figure 6 Changes in concentrations of two PBDEs (BDE-47 and BDE-99), HCB, DDT, and two PCBs (CB-118 and CB-153) in human milk during lactation over 120 days postpartum for 3 participants (Sjödin et al., 2005).

shown a relationship between increasing age of the mother and level of some persistent organic chemicals in breast milk (reviewed by LaKind et al. 2004).

Several studies have examined the relationship between diet and levels of environmental chemicals in milk (reviewed by LaKind et al. 2004). In general, it appears that there is a positive association between consumption of fatty foods and levels of persistent organic chemicals in breast milk (Dewailly et al., 1994). Studies exploring relationships between consumption of fish and shellfish and levels of chemicals in milk have yielded inconsistent results. However, those people who consume large amounts of locally caught fish, including some indigenous populations, have been found to have higher levels of certain persistent organic chemicals in milk. The consumption of vegetables may also be positively correlated with higher levels of certain pesticides in milk (Schinas et al., 2000). A recent study of levels of persistent organic chemicals in the breast milk of 29 Hong Kong residents reported significant correlations between DDTs, DDE, and PCBs in breast milk and the consumption of fish (Tsang et al., 2011). Levels of these chemicals were also associated with maternal age.

Neither body mass index nor weight loss appear to be correlated with levels of persistent organic chemicals in breast milk, and conflicting results have been published regarding associations between a mother's cigarette smoking status or alcohol consumption and levels of persistent organic chemicals in her milk (reviewed by LaKind et al., 2004).

Levels of UV filters such as 4-MBC (4-methylbenzylidene camphor) and OCT (octocrylene) and benzophenone-3 in breast milk have been found to be directly correlated with consumer habits in terms of the extent of use of certain cosmetics and personal care products while no correlations were found with mother's age, body weight, or nutrition (Schlumpf et al., 2010).

Health Effects

The association between environmental chemicals in breast milk and potential for adverse health effects in the breast-feeding infant has been studied in epidemiologic research. While many data gaps exist, the epidemiologic research has not demonstrated adverse health effects in breastfed children. However, it is important to note that information from laboratory animal studies suggest that this issue requires continued investigation.

Studies evaluating environmental chemicals in breast milk on the health of the breast-feeding infant have been conducted for a limited number of chemicals (DDT and metabolites, PCBs, dioxins). However, no clear evidence of adverse effects has been reported for breast-feeding infants. As with any epidemiological study, studies on environmental chemicals in breast milk and infant health have limitations that preclude making definitive all-encompassing statements about the impact of environmental chemicals in breast milk on infant health. These limitations include measurements on only a limited number of chemicals, reported effects that are not statistically significant, cohort sizes that are too small to detect health effects, studies that follow infants for only a small portion of their life with later health outcomes undetermined, inability to separate effects that may arise due to postnatal breast-feeding exposure from prenatal exposure, and lack of data on other sources of exposure to the infant including transdermal, oral, and respiratory routes. Despite these limitations, studies to date examining numerous health end points have consistently concluded that breast-feeding is recommended despite the presence of environmental chemicals in breast milk (see, for example, Jorissen, 2007 and LaKind et al., 2008). This conclusion, however, is not applicable to certain rare events such as poisonings, certain occupational exposures, or instances involving drugs of abuse.

Several large-scale prospective cohort studies are studying the influence of the environment on infants' health. The National Children's Study is currently underway in the U.S. and plans to study the influence of the environment from birth through age 21 in a large cohort of infants (see National Children's Study website). Similarly, the Cooperative Environment and Childhood Research Network in Spain is studying children up to 6 years of age (Fernandez et al., 2007). These and other studies should provide more detailed and complete information on the levels of environmental chemicals in milk and their potential influence on infant health.

Key infant organ systems and effects that have been the major focus of studies are briefly summarized below. In addition, one maternal outcome affecting infant health – duration of lactation – is described. Other end points have been explored for a limited number of chemicals, including effects on the respiratory and immune systems, and research has generally shown a lack of significant clinical effects on those systems.

Growth

In a prospective longitudinal study of children from the general U.S. population born between 1978–1982 (the North Carolina Infant Feeding Study), DDT and PCB compounds in breast milk had no effect on infant weight during the first year of life (Rogan et al., 1987) or on children's development at 18 or 24 months of age (Rogan and Gladen, 1991). Further work with this cohort found no effects of lactational exposure to DDE or PCBs on growth (height and body weight) at puberty (Gladen et al., 2000). A study analyzing data collected from the Pregnancy, Infection and Nutrition (PIN) Babies Study in central North Carolina during 2004–2006 reported similar results for PCBs, DDTs, and DDE (Pan et al., 2010). In this study, breast feeding for 6 months or longer, with lactational exposure to PCBs, DDT, and DDE at low background level concentrations, resulted in no measureable influence on infant growth in the first 12 months. In a German cohort, an association was reported between DDE concentrations in milk and reduction in growth (average of 1.8 cm in height) in girls (but not boys) at 8 years of age; this reduction was no longer observed at 10 years of age (Karmaus et al., 2002). No similar effect was observed for PCBs. Other studies have reported no effects of lactational PCB or DDE exposure on the ages at which puberty stages were attained (Gladen et al., 2000).

Neurodevelopment

In a Dutch study on PCBs and dioxins, over 400 children were studied for neurological development in the newborn period (10–21 days postpartum) (Koopman-Esseboom et al., 1994). Increased levels of PCBs in milk were associated with higher incidences of infant hyptotonia and reduced neurological 'optimality' (Huisman et al., 1995a) but these effects were not found when the children were reexamined at 18 months of age (Huisman et al., 1995b). Ribas-Fitó et al. (2003) observed a negative association with DDE cord serum levels and mental and psychomotor development at 1 year of age. Only a marginal association was found with PCBs and there was no correlation with hexachlorobenzene (HCB). However, long-term breast-feeding was associated with better performance of both the mental and psychomotor scales. This may reflect the positive advantages of breast-feeding outweighing potential negative effects associated with exposure (including prenatal exposure) to these chemicals. In a recent study, no consistent associations between lactational exposure to PCBs, DDT, or DDE and infant neurodevelopment (cognitive and motor function as assessed by the Mullen Scales of Early Learning) at 12 month were observed, using data from the PIN Babies Study, 2004–2006 (Pan et al., 2009).

Neurotoxic effects from exposure to PBDEs in animal studies have been reported at concentrations comparable to those found in humans (Blanco et al., 2013); however, more research is needed to better understand if these studies can be extrapolated to humans. Some research has suggested that children's neurodevelopment can be affected by PBDE exposure in utero or during childhood (Eskenazi et al., 2013). Results from the limited data available from lactational studies of PBDE exposure are difficult to interpret and suggest the need for additional research (Chao et al., 2011; Hoffman et al., 2012).

A U.S. cohort consisting of infants of mothers who consumed fish contaminated with high levels of PCBs was studied in the early 1980s. Maternal exposure levels were determined by mothers recalling the amounts of fish eaten, and by measuring PCBs in cord blood and breast milk for a portion of the cohort. At 7 months of age, postnatal exposure was not associated with visual recognition (Jacobson et al., 1985), but at 4 years of age, a postnatal exposure effect on activity was found, with the effect characterized as 'subtle' with 'uncertain clinical significance' (Jacobson et al., 1990). Re-analysis of the data dichotomizing the children into those who were breastfed less than or greater than 6 weeks revealed that the PCB-related decrement in cognitive function was only seen in the group of children who were breastfed less than 6 weeks (Jacobson et al., 2002). No IQ deficits related to breast-feeding were found in the children up to 11 years of age.

A study (Wilhelm et al., 2008) of a German cohort of 232 mother/infant pairs did not show any association between breast milk concentrations of PCBs, lead, mercury, cadmium, or selenium exposure (pre- and postnatal) and thyroid function, neurological, and development status in infants up to 24 months of age.

Studies from the Faroe Islands and the Seychelles Islands on maternal fish ingestion (including fish containing methylmercury) and infant health showed a better neurodevelopment outcome in breastfed babies despite the presence of methylmercury in breast milk (Grandjean et al., 1995, Davidson et al., 1998). These data, in accordance with other research results, support the possible offset of potential harm from exposure to environmental chemicals prenatally and by breast-feeding, especially breast-feeding for long periods.

In 2007, Ribas-Fitó et al. studied the role of breast-feeding on cognitive function among preschoolers, taking prenatal DDT exposure into account, and found that children ($n = 391$) who were breast-fed longer than 20 weeks had better cognitive performance regardless of their in utero exposure to DDT. The authors concluded that breast-feeding for long periods should continue to be recommended as the best infant-feeding method.

Thyroid Function

Thyroid hormones are critical to the development of the human brain both in utero and during the neonatal period. All newborns born in the United States are screened for thyroid function so that, if necessary, prompt intervention can occur. In addition, maternal thyroid status is important for proper lactation. Some environmental chemicals, such as PFCs, may interfere with thyroid function or with thyroid hormone-binding proteins and thyroid hormone receptor binding (Zoeller, 2005). The lower brominated PBDEs and their metabolites are structurally similar to the thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3), and in vivo studies have indicated that prenatal or neonatal exposure of rodents to PBDEs disrupts thyroid hormone balance (Shy et al., 2012). The implications of this research to humans are not well understood. High serum levels of PFCs in adults have been associated with thyroid disease in the U.S. (Melzer et al., 2010). However, breast milk levels of PBDEs, as analyzed from 239 Norwegian women who were part of the "Norwegian Human Milk Study" (HUMIS) during 2003–2006, are not associated with levels of thyroid-stimulating hormone (TSH) in infants (Eggesbo et al., 2011). A similar lack of significant findings have been reported in the U.S. in a large California cohort (Chevrier et al., 2011). Further, to date, research on pre- and postnatal infant exposure to PCBs and dioxins have found no clinically significant effects on thyroid hormone levels (e.g., Koopman-Esseboom et al., 1994; Wilhelm et al., 2008; Dallaire et al., 2008; LaKind et al., 2008).

Environmental Chemicals and Lactation Duration

Both the AAP and the WHO recommend that infants should be exclusively breast-fed for the first six months of life to achieve optimal growth, development and health. In addition, breast-feeding should continue (along with nutritionally adequate and safe complementary foods) until up to two years of age or beyond. Whether the presence of environmental chemicals in breast milk has an effect on lactation duration is unclear. In 1987, Rogan et al. observed that high concentrations of DDT and metabolites were associated with decreased duration of lactation, and suggested that the compounds could act as estrogen agonists and shorten the duration of lactation. Two more recent studies in Mexico, where breast milk levels of DDT and its metabolites are comparatively high (due to more recent use of DDT for malaria control), gave conflicting results regarding whether levels of DDT and metabolites are associated with a shortened duration of lactation (Gladen and Rogan 1995; Cupul-Uicab et al., 2008). In multiparous women from the Danish National Birth Cohort (1996–2002), PFOA and PFOS have been shown to be associated with decreased duration of breastfeeding (Fei et al., 2010). However, this association was not seen among primiparous women. A mechanistic underpinning for a potential relationship between PFC compounds and shortened duration of lactation is provided by rodent studies in which PFCs have been associated with elevated serum progesterone in peri-pubertal rodents (Zhao et al., 2010) and impaired mammary gland development in lactating rodents (White et al., 2007). However, given the contradictory findings in humans, additional research is needed.

Breast Cancer

Several studies have explored whether being breast-fed as an infant is associated with altered risk of breast cancer later in life. These studies have consistently found that having been breast-fed does not result in increased risk of breast cancer (with a possible decreased risk of breast cancer for premenopausal women who had been breast-fed), nor do breast-fed infants appear to be at greater risk for childhood cancer as compared with formula-fed infants (reviewed by LaKind et al. 2007).

Studies have also examined whether future breast cancer risk is altered in women who have breastfed their children. Previous studies have indicated that breast-feeding protects against breast cancer for women who gave birth before age 25 (Enger et al., 1998). More recent studies, however, have shown that women who have breastfed are protected against breast cancer regardless of when they gave birth (Lord et al., 2008).

Effects Associated with Pharmaceuticals

Similar to other environmental chemicals, it is difficult to definitively attribute an adverse reaction to a pharmaceutical detected in breast milk. In 2003, in a comprehensive review of the literature on adverse effects to the breast-feeding infant, Anderson et al. (2003) examined 100 case reports from 1966 to 2002. Of these, 53 were 'possibly' related to the pharmaceutical used by the mother, 47 were 'probably' related to the pharmaceuticals and none were 'definite.' In infants younger than 1 month of age, 63 cases were reported and in infants older than 6 months, only 4 were reported.

Published reports on the excretion of pharmaceuticals in human milk have several problems that limit application to a larger breast-feeding infant population: (i) the series are usually small (often single patients); (ii) studies are frequently done only in early lactation and usually do not include mothers on long term medication; (iii) studies are not repeated in the same patients at different times of lactation; and (iv) long-term (throughout childhood) studies are lacking. The AAP's Committee on Drugs provides guidance for the use of maternal medications during breastfeeding. They provide a framework that first inquires as to whether the drug therapy is necessary. Next, they suggest using the safest drug possible if multiple options are available. Then, if there is a possibility that a drug may present a risk to the infant, "consideration should be given to measurement of blood concentrations in the nursing infant." Finally, pharmacokinetic principles dictate that the mother can minimize drug exposure to the breast-feeding infant by taking medications immediately after she has breastfed or just before the infant is expected to have an extended period of sleep (AAP, 2001). The general consensus is that a great proportion of drugs given to the mother are safe enough to be given directly to the breast-feeding child for therapeutic reasons in doses that far exceed the amount that appears in milk after maternal administration. It is of course essential that the breastfeeding mother consult with her health care practitioner regarding the use of pharmaceuticals during lactation.

Conclusions

The amount of Data on levels of environmental chemicals in breast milk has expanded substantially since the 1950s in terms of the types of chemicals measured and the number of countries for which data exist. While research has focused on persistent organic chemicals in milk, several emerging chemicals of interest are now receiving more attention. Many factors appear to influence the levels of environmental chemical in milk, but further research is needed. Current analytic techniques allow measurement of extremely small amounts of many chemicals in breast milk, and it is unlikely that any milk sample collected from women in either industrialized or non-industrialized countries will be free of environmental chemicals. However, studies to date examining numerous health end points have consistently concluded that breast-feeding is recommended despite the presence of environmental chemicals in breast milk. Information on risks and benefits regarding breast-feeding versus using infant formula will need to be continually updated and disseminated. Currently, the WHO (2007) has noted that "evidence for the health advantages of breastfeeding and scientific evidence to support breastfeeding has continued to increase ..." and "breastfeeding reduces child mortality and has health benefits that extend into adulthood."

Further Reading

AAP (2001) The transfer of drugs and chemicals in human milk. *Pediatrics* 108: 776–789.

AAP (2012) The transfer of drugs and other chemicals into human milk. *Pediatrics* 129: e827–e841.

Al-Saleh I, Abduljabbar M, Al-Rouqi R, Elkhatib R, Alshabbaheen A, and Shinwari N (2013) Mercury (hg) exposure in breast-fed infants and their mothers and the evidence of oxidative stress. *Biological Trace Element Research* 153(1–3): 145–154.

Anderson PO, Pochop SL, and Manoguerra AS (2003) Adverse drug reactions in breastfed infants: Less than imagined. *Clinical Pediatrics* 42: 325–340.

Berlin CM (2011) The excretion of drugs and chemicals into human milk. In: Yaffe SJ and Aranda JV (eds.) *Neonatal and pediatric pharmacology*, 3rd ed., pp. 210–220. Philadelphia: Lippincott Williams & Wilkins.

Blanco J, Mulero M, Heredia L, Pujol A, Domingo JL, and Sanchez DJ (2013) Perinatal exposure to BDE-99 causes learning disorders and decreases serum thyroid hormone levels and BDNF gene expression in hippocampus in rat offspring. *Toxicology* 318C: 122–128.

Calafat AM and Needham LL (2009) What additional factors beyond state-of-the-art analytical methods are needed for optimal generation and interpretation of biomonitoring data? *Environmental Health Perspectives* 117(10): 1481–1485.

CDC (Centers for Disease Control and Prevention), Breastfeeding report card – United States, (2010), www.cdc.gov/breastfeeding/data/reportcard/reportcard2010.htm.

Chao HR, Tsou TC, Huang HL, and Chang-Chien GP (2011) Levels of breast milk PBDEs from southern Taiwan and their potential impact on neurodevelopment. *Pediatric Research* 70(6): 596–600.

Chevrier J, Harley KG, Bradman A, Sjodin A, and Eskenazi B (2011) Prenatal exposure to polybrominated diphenyl ether flame retardants and neonatal thyroid-stimulating hormone levels in the CHAMACOS study. *American Journal of Epidemiology* 174(10): 1166–1174.

Cupul-Uicab LA, Gladen BC, Hernández-Ávila M, Weber JP, and Longnecker MP (2008) DDE, a degradation product of DDT, and duration of lactation in a highly exposed area of Mexico. *Environmental Health Perspectives* 116(2): 179–183.

Dallaire R, Dewailly E, Ayotte P, Muckle G, Laliberte C, and Bruneau S (2008) Effects of prenatal exposure to organochlorines on thyroid hormone status in newborns from two remote coastal regions in Quebec, Canada. *Environmental Research* 108(3): 387–392.

Davidson PW, Myers GJ, Cox C, et al. (1998) Effects of prenatal and postnatal methylmercury exposure from fish consumption on neurodevelopment. *Journal of the American Medical Association* 280: 701–707.

Dewailly E, Ayotte P, Bruneau S, Laliberte C, Muir DCG, and Norstrom RJ (1993) Inuit exposure to organochlorines through the aquatic food chain in arctic Quebec. *Environmental Health Perspectives* 101: 618–620.

Dewailly E, Ryan JJ, Laliberte C, et al. (1994) Exposure of remote maritime populations to coplanar PCBs. *Environmental Health Perspectives* 102(Suppl.1): 205–209.

Enger SM, Ross RK, and Bernstein L (1998) Breastfeeding experience and breast cancer risk among postmenopausal women. *Cancer Epidemiology, Biomarkers & Prevention* 7(5): 365–369.

Eggesbo M, Thomsen C, Jorgensen JV, Becher G, Odland JO, and Longnecker MP (2011) Associations between brominated flame retardants in human milk and thyroid-stimulating hormone (TSH) in neonates. *Environmental Research* 111(6): 737–743.

Eskenazi B, Chevrier J, Rauch SA, Kogut K, Harley KG, Johnson C, Trujillo C, Sjodin A, and Bradman A (2013) In utero and childhood polybrominated diphenyl ether (PBDE) exposures and neurodevelopment in the CHAMACOS study. *Environmental Health Perspectives* 121(2): 257–262.

Falk C, Hanranhan L, Anderson HA, Kanarek MS, Draheim L, Needham L, and Patterson D (1999) Body burden levels of dioxin, furans, and PCBs among frequent consumers of great lakes sport fish. *Environmental Research* 80: S19–S25.

Fei C, McLaughlin JK, Lipworth L, and Olsen J (2010) Maternal concentrations of perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) and duration of breastfeeding. *Scandinavian Journal of Work, Environment and Health* 36(5): 413–421.

Fernandez MF, Sunyer J, Grimalt J, et al. (2007) The Spanish environment and childhood research network (INMA study). *International Journal of Hygiene and Environmental Health* 210: 491–493.

Gladen BC and Rogan WJ (1995) DDE and shortened duration of lactation in a northern Mexican town. *American Journal of Public Health* 85(4): 504–508.

Gladen BC, Ragan NB, and Rogan WJ (2000) Pubertal growth and development and prenatal and lactational exposure to polychlorinated biphenyls and dichlorodiphenyl dichloroethene. *The Journal of Pediatrics* 136(4): 490–496.

Grandjean P, Weihe P, and White RF (1995) Milestone development in infants exposed to methylmercury from human milk. *Neurotoxicology* 16: 27–34.

Harris CA, Woolridge MW, and Hay AHM (2001) Factors affecting the transfer of organochlorine pesticide residues to breastmilk. *Chemosphere* 43: 243–258.

Hines EP, Calafat AM, Silva MJ, Mendola P, and Fenton SE (2009) Concentrations of phthalate metabolites in milk, urine, saliva, and serum of lactating North Carolina women. *Environmental Health Perspectives* 117(1): 86–92.

Hoffman K, Adgent M, Goldman BD, Sjodin A, and Daniels JL (2012) Lactational exposure to polybrominated diphenyl ethers and its relation to social and emotional development among toddlers. *Environmental Health Perspectives* 120(10): 1438–1442.

Hori S (1993) Levels of PCDDs, PCDFs, co-PCBs and PCBs in human breast milk at different times of lactation. *Organohalogen Compounds* 13: 65–67.

Huisman M, Koopman-Esseboom C, Lanting CI, et al. (1995a) Neurological condition in 18-month-old children perinatally exposed to polychlorinated biphenyls and dioxins. *Early Human Development* 43: 165–176.

Huisman M, Koopman-Esseboom C, Fidler V, Hadders-Algra M, van der Paauw CG, Tuinstra LG, Weisglas-Kuperus N, Sauer PJ, Touwen BC, and Boersma ER (1995b) Perinatal exposure to polychlorinated biphenyls and dioxins and its effect on neonatal neurological development. *Early Human Development* 41: 111–127.

Inoue K, Harada K, Takenaka K, Uehara S, Kono M, Shimizu T, Takasuga T, Senthilkumar K, Yamashita F, and Koizumi A (2006) Levels and concentration ratios of polychlorinated biphenyls and polybrominated diphenyl ethers in serum and breast milk in Japanese mothers. *Environmental Health Perspectives* 114(8): 1179–1185.

Jacobson JL (2000) Behavioral effects of development exposure to fishborne contaminants. *Neurotoxicology* 21: 619–620.

Jacobson SW, Fein GG, Jacobson JL, Schwartz PM, and Dowler JK (1985) The effect of intrauterine PCBs on visual recognition memory. *Child Development* 56: 523–532.

Jacobson JL, Jacobson SW, and Humphrey HEB (1990) Effects of exposure to PCBs and related compounds on growth and activity in children. *Neurotoxicology and Teratology* 12: 319–326.

Jacobson JL and Jacobson SW (2002) Association of prenatal exposure to an environmental contaminant with intellectual function in childhood. *Journal of Toxicology. Clinical Toxicology* 40(4): 467–475.

Jensen AA and Slorach SA (1991) *Assessment of infant intake of chemicals via breast milk: Chemical contaminants in human milk*. Boca Raton, FL: CRC Press.

Jensen RG (ed.) (1995) *Handbook of milk composition*. San Diego, CA: Academic Press.

Jorissen J (2007) Literature review: Outcomes associated with postnatal exposure to polychlorinated biphenyls (PCBs) via breast milk. *Advances in Neonatal Care* 7: 230–237.

Karmaus W, Asakevich S, Indurkhya A, Witten J, and Kruse H (2002) Childhood growth and exposure to dichlorodiphenyl dichloroethene and polychlorinated biphenyls. *Journal of Pediatrics* 140: 33–39.

Kärrman A, Ericson I, van Bavel B, et al. (2007) Exposure of perfluorinated chemicals through lactation: Levels of matched human milk and serum and a temporal trend, 1996–2004, in Sweden. *Environmental Health Perspectives* 115: 226–230.

Kirk AB, Martinelango PK, Tian K, Dutta A, Smith EE, and Dasgupta PK (2005) Perchlorate and iodide in dairy and breast milk. *Environmental Science and Technology* 39: 2011–2017.

Koopman-Esseboom C, Morse DC, Weisglas-Kuperus N, et al. (1994) Effects of dioxins and polychlorinated biphenyls on thyroid hormone status of pregnant women and their infants. *Pediatric Research* 36: 468–473.

Technical workshop on human milk surveillance and research on environmental chemicals in the United States. LaKind JS (ed.) (2002) *Journal of Toxicology and Environmental Health* 65(22): 1829–1935.

Technical workshop on human milk surveillance and biomonitoring for environmental chemicals in the United States. LaKind JS (ed.) (2005) *Journal of Toxicology and Environmental Health* 68(20): 1681–1831.

LaKind JS (2007) Recent global trends and physiologic origins of dioxins and furans in human milk. *Journal of Exposure Science & Environmental Epidemiology* 17: 510–524.

LaKind JS, Berlin CM, and Naiman DQ (2001) Infant exposure to chemicals in breast milk in the United States: What we need to learn from a breast milk monitoring program. *Environmental Health Perspectives* 109: 75–88.

LaKind JS, Wilkins AA, and Berlin CM (2004) Environmental chemicals in human milk: A review of concentrations, determinants, infant exposures and health, and guidance for future research. *Toxicology and Applied Pharmacology* 198: 184–208.

LaKind JS, Wilkins AA, and Bates MN (2007) Breast biomonitoring and environmental chemicals: Use of breast tissues and fluids in breast cancer etiologic research. *Journal of Exposure Science & Environmental Epidemiology* 17: 525–540.

Lakind JS, Berlin CM, and Mattison DR (2008) The heart of the matter on breastmilk and environmental chemicals: Essential points for healthcare providers and new parents. *Breastfeeding Medicine* 3(4): 251–259.

LaKind JS, Berlin CM, Sjodin A, Turner W, Wang RY, Needham LL, Paul IM, Stokes JL, Naiman DQ, and Patterson DG (2009) Do Human Milk Concentrations of Persistent Organic Chemicals Really Decline During Lactation? *Chemical Concentrations During Lactation and Milk/Serum Partitioning. Environmental Health Perspectives* 117(10): 1625–1631.

Landrigan PJ, Sonawane B, Mattison D, McCally M, and Garg A (2002) Chemical contaminants in breast milk and their impacts on children's health: An overview. *Environmental Health Perspectives* 110: A313–A315.

Latini G, Wittassek M, Del Vecchio A, Presta G, De Felice C, and Angerer J (2009) Lactational exposure to phthalates in Southern Italy. *Environment International* 35(2): 236–239.

Lawrence RA and Lawrence RM (1999) *Breastfeeding: A guide for the medical profession*, 5th ed. St Louis, MO: Mosby.

Liu KS, Hao JH, Xu YQ, Gu XQ, Shi J, Dai CF, Xu F, and Shen R (2013) Breast milk lead and cadmium levels in suburban areas of Nanjing China. *Chinese Academy of Medical Sciences. Chinese Medical Sciences Journal* 28(1): 7–15.

Lord SJ, Bernstein L, Johnson KA, Malone KE, McDonald JA, Marchbanks PA, Simon MS, Strom BL, Press MF, Folger SG, Burkman RT, Deapen D, Spirtas R, and Ursin G (2008) Breast cancer risk and hormone receptor status in older women by parity, age of first birth, and breastfeeding: A case–control study. *Cancer Epidemiology, Biomarkers & Prevention* 17(7): 1723–1730.

Lykissa ED and Maharaj SVM (2006) Total platinum concentration and platinum oxidation states in body fluids, tissue, and explants from women exposed to silicone and saline breast implants by IC-ICPMS. *Analytical Chemistry* 78: 2925–2933.

Malisch R and van Leeuwen R (2003) Results from the WHO-coordinated exposure study on the levels of PCBs, PCDDs and PCDFs in human milk. *Organohalogen Compounds* 60–65.

Marchitti SA, Lakind JS, Naiman DQ, Berlin CM, and Kenneke JF (2013) Improving infant exposure and health risk estimates: Using serum data to predict polybrominated diphenyl ether concentrations in breast milk. *Environmental Science and Technology* 47: 4787–4795.

Meironyté D, Bergman Å, and Norén K (1998) Analysis of polybrominated diphenyl ethers in human milk. *Organohalogen Compounds* 35: 387–390.

Melzer D, Rice N, Depledge MH, Henley WE, and Galloway TS (2010) Association between serum perfluorooctanoic acid (PFOA) and thyroid disease in the US national health and nutrition examination survey. *Environmental Health Perspectives* 118(5): 686–692.

Mendonca K, Hauser R, Calafat AM, Arbuckle TE, and Duty SM (2012) Bisphenol a concentrations in maternal breast milk and infant urine. *International Archives of Occupational and Environmental Health*. [Dec 5 epub ahead of print].

Meyer BK, Ni A, Hu B, and Shi L (2007) Antimicrobial preservative use in parenteral products: Past and present. *Journal of Pharmaceutical Sciences* 96: 3155–3167.

Nakamura T, Nakai K, Matsumura T, Suzuki S, Saito Y, and Satoh H (2008) Determination of dioxins and polychlorinated biphenyls in breast milk, maternal blood and cord blood from residents of Tohoku, Japan. *Science of the Total Environment* 394(1): 39–51.
Pan IJ, Daniels JL, Goldman BD, Herring AH, Siega-Riz AM, and Rogan WJ (2009) Lactational exposure to polychlorinated biphenyls, dichlorodiphenyltrichloroethane, and dichlorodiphenyldichloroethylene and infant neurodevelopment: An analysis of the pregnancy, infection, and nutrition babies study. *Environmental Health Perspectives* 117(3): 488–494.
Pan IJ, Daniels JL, Herring AH, Rogan WJ, Siega-Riz AM, Goldman BD, and Sjodin A (2010) Lactational exposure to polychlorinated biphenyls, dichlorodiphenyltrichloroethane, and dichlorodiphenyldichloroethylene and infant growth: An analysis of the pregnancy, infection, and nutrition babies study. *Paediatric and Perinatal Epidemiology* 24(3): 262–271.
Patandin S, Lanting CI, Mulder PG, Boersma ER, Sauer PJ, and Weisglas-Kuperus N (1999) Effects of environmental exposure to polychlorinated biphenyls and dioxins on cognitive abilities in Dutch children at 42 months of age. *The Journal of Pediatrics* 134(1): 33–41.
Ramos L, Hernández LM, and González MJ (1997) Variation of PCB congener levels during lactation period and relationship to their molecular structure. *Archives of Environmental Contamination and Toxicology* 33: 97–103.
Reed CM (1908) A study of the conditions that require the removal of the child from the breast. *Surgery, Gynecology & Obstetrics* 6: 514–526.
Ribas-Fitó N, Cardo E, Sala M, et al. (2003) Breastfeeding, exposure to organochlorine compounds, and neurodevelopment in infants. *Pediatrics* 111: e580–e585.
Ribas-Fitó N, Júlvez J, Torrent M, Grimalt JO, and Sunyer J (2007) Beneficial effects of breastfeeding on cognition regardless of DDT concentrations at birth. *American Journal of Epidemiology* 166: 1198–1202.
Rodas-Ortíz JP, Ceja-Moreno V, González-Navarrete RL, Alvarado-Mejía J, Rodríguez- Hernández ME, and Gold-Bouchot G (2008) Organochlorine pesticides and polychlorinated biphenyls levels in human milk from Chelem, Yucatan, Mexico. *Bulletin of Environmental Contamination and Toxicology* 81(6): 543–547.
Rogan WJ, Gladen BC, McKinney JD, Carreras N, Hardy P, Thullen J, et al. (1986) Polychlorinated biphenyls (PCBs) and dichlorodiphenyl dichloroethene (DDE) in human milk: Effects of maternal factors and previous lactation. *American Journal of Public Health* 76: 172–177.
Rogan WJ and Gladen BC (1991) PCBs, DDE and child development at 18 and 24 months. *Annals of Epidemiology* 1: 407–413.
Rogan WJ, Gladen BC, McKinney JD, et al. (1987) Polychlorinated biphenyls (PCBs) and dichlorodiphenyl dichloroethene (DDE) in human milk: Effects on growth, morbidity, and duration of lactation. *American Journal of Public Health* 77: 1294–1297.
Sasamoto T, Horii S, Ibe A, Takada N, and Shirota K (2006) Concentration changes of PCDDs, PCDFs, and dioxin-like PCBs in human breast milk samples as shown by a follow-up survey. *Chemosphere* 64(4): 642–649.
Schinas V, Leotsinidis M, Alexopoulos A, Tsapanos V, and Kondakis XG (2000) Organochlorine pesticide residues in human breast milk from southwest Greece: Associations with weekly food consumption patterns of mothers. *Archives of Environmental Health* 55: 411–417.
Schlumpf M, Kypke K, Wittassek M, Angerer J, Mascher H, Mascher D, Vokt C, Birchler M, and Lichtensteiger W (2010) Exposure patterns of UV filters, fragrances, parabens, phthalates, organochlor pesticides, PBDEs, and PCBs in human milk: Correlation of UV filters with use of cosmetics. *Chemosphere* 81(10): 1171–1183.
Shy CG, Huang HL, Chao HR, and Chang-Chien GP (2012) Cord blood levels of thyroid hormones and IGF-1 weakly correlate with breast milk levels of PBDEs in Taiwan. *International Journal of Hygiene and Environmental Health* 215(3): 345–351.
Siddique S, Xian Q, Abdelouahab N, Takser L, Phillips SP, Feng YL, Wang B, and Zhu J (2012) Levels of dechlorane plus and polybrominated diphenylethers in human milk in two Canadian cities. *Environment International* 39(1): 50–55.
Sjödin A, LaKind JS, Patterson D, et al. (2005) Current concentrations and changes in concentrations of PBDEs, persistent pesticides, and PCBs in human milk. *Organohalogen Compounds* 67: 1745–1748.
Sonawane BR (1995) Chemical contaminants in human milk: An overview. *Environmental Health Perspectives* 103(S6): 197–205.
Sun Y, Irie M, Kishikawa N, Wada M, Kuroda N, and Nakashima K (2004) Determination of bisphenol A in human breast milk by HPLC with column-switching and fluorescence detection. *Biomedical Chromatography* 18: 501–507.
Thomsen C, Haug LS, Stigum H, Froshaug M, Broadwell SL, and Becher G (2010) Changes in concentrations of perfluorinated compounds, polybrominated diphenyl ethers, and polychlorinated biphenyls in Norwegian breast-milk during twelve months of lactation. *Environmental Science and Technology* 44(24): 9550–9556.
Tsang HL, Wu S, Leung CK, Tao S, and Wong MH (2011) Body burden of POPs of Hong Kong residents, based on human milk, maternal and cord serum. *Environment International* 37(1): 142–151.
von Ehrenstein OS, Fenton SE, Kato K, Kuklenyik Z, Calafat AM, and Hines EP (2009) Polyfluoroalkyl chemicals in the serum and milk of breastfeeding women. *Reproductive Toxicology* 27(3–4): 239–245.
White SS, Calafat AM, Kuklenykik Z, Villanueva L, Zehr RD, Helfant L, Strynar MJ, Lindstrom AB, Thibodeaux JR, Wood C, and Fenton SE (2007) Gestational PFOA exposure of mice is associated with altered mammary gland development in dams and female offspring. *Toxicological Sciences* 96: 133–144.
Wilhelm M, Wittsiepe J, Lemm F, et al. (2008) The Duisburg birth cohort study: Influence of the prenatal exposure to PCDD/Fs and dioxin-like PCBs on thyroid hormone status in newborns and neurodevelopment of infants until the age of 24 months. *Mutation Research, Reviews in Mutation Research* 659(1–2): 83–92.
World Health Organization (WHO) (2000) *Levels of PCBs, PCDDs and PCDFs in human milk: Protocol for third round of exposure studies, march*. Geneva, Switzerland: World Health Organization European Centre for Environment and Health.
World Health Organization (WHO) (2002) Infant and young child nutrition. Global strategy on infant and young child feeding. Report by the Secretariat, 16 April; WHO, Geneva, Switzerland.
World Health Organization (WHO) (2007) *Fourth WHO-coordinated survey of human milk for persistent organic pollutants in cooperation with UNEP. Guidelines for developing a national protocol* (revised 28 February 2007); WHO, Geneva, Switzerland.
Ye X, Bishop AM, Needham LL, and Calafat AM (2008) Automated on-line column-switching HPLC-MS/MS method with peak focusing for measuring parabens, triclosan, and other environmental phenols in human milk. *Analytica Chimica Acta* 622(1–2): 150–156.
Ye X, Zhou X, Hennings R, Kramer J, and Calafat AM (2013) Potential external contamination with bisphenol A and other ubiquitous organic environmental chemicals during biomonitoring analysis: an elusive laboratory challenge. *Environmental Health Perspectives* 121(3): 283–286.
Zhao Y, Tan YS, Haslam SZ, and Yang C (2010) Perfluorooctanoic acid effects on steroid hormones and growth factor levels mediate stimulation of peripubertal mammary gland development in C57Bl/6 mice. *Toxicological Sciences* 115: 214–224.
Zoeller RT (2005) Environmental chemicals as thyroid hormone analogues: New studies indicate that thyroid hormone receptor are targets of industrial chemicals? *Molecular and Cellular Endocrinology* 242: 10–15.

Relevant Websites

http://www.cdc.gov/breastfeeding/; Centers, for Disease Control and Prevention. Breastfeeding.
http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT; LactMed, United State Library of Medicine Toxicology Network.
http://www.nationalchildrensstudy.gov/; National Children's Study.
http://www.who.int/topics/breastfeeding/en/; World Health Organization. Breastfeeding.