Chemical Contaminants in Breast Milk and Their Impacts on Children's Health: An Overview

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**Human milk is the best source of nutrition for infants. Breast milk contains the optimal balance of fats, carbohydrates, and proteins for developing babies, and it provides a range of benefits for growth, immunity, and development. Unfortunately, breast milk is not pristine. Contamination of human milk is widespread and is the consequence of decades of inadequately controlled pollution of the environment by toxic chemicals. The finding of toxic chemicals in breast milk raises important issues for pediatric practice, for the practice of public health, and for the environmental health research community. It also illuminates gaps in current knowledge including *a*) insufficient information on the nature and levels of contaminants in breast milk; *b*) lack of consistent protocols for collecting and analyzing breast milk samples; *c*) lack of toxicokinetic data; and *d*) lack of data on health outcomes that may be produced in infants by exposure to chemicals in breast milk. These gaps in information impede risk assessment and make difficult the formulation of evidence-based health guidance. To address these issues, there is a need for a carefully planned and conducted national breast milk monitoring effort in the United States. Additionally, to assess health outcomes of toxic exposures via breast milk, it will be necessary to examine children prospectively over many years in longitudinal epidemiologic studies that use standardized examination protocols that specifically assess breast milk exposures. Finally, current risk assessment methods need to be expanded to include consideration of the potential risks posed to infants and children by exposures to chemical residues in breast milk. *Key words:* breast milk, breast-feeding, children's health, chemical contaminants. *Environ Health Perspect* 110:A313–A315 (2002). [Online 13 May 2002] *http://ehpnet1.niehs.nih.gov/docs/2002/110pA313-A315landrigan/abstract.html*

Human milk is, without question, the best source of nutrition for infants. Breast milk contains the optimal balance of fats, carbohydrates, and proteins for developing babies, and it provides a range of benefits for growth, immunity, and development (*1*). Breast milk contains powerful immune factors that help infants fight infections (*2*), and it contains growth factors that appear to influence brain development and increase resistance to chronic diseases such as asthma, allergies, and diabetes. Breast-feeding builds a powerful bond between a mother and her child, and this bond enhances health and well-being across the generations. Recognition of the manifold benefits of breast milk has led to the adoption of breast-feeding policies by numerous health and professional organizations (*3–9*) and stimulated development of the recent "Blueprint for Action on Breastfeeding" by the U.S. Department of Health and Human Services (*10*).

Unfortunately, breast milk is not pristine. Contamination of human milk is widespread and is the consequence of decades of inadequately controlled pollution of the environment by toxic chemicals. Polychlorinated biphenyls (PCBs), DDT and its metabolites, dioxins, dibenzofurans, polybrominated diphenyl ethers (PBDEs), and heavy metals are among the toxic chemicals most often found in breast milk (*11,12*). These compounds are encountered to varying extents among women in industrially developed as well as in developing nations. Some of the highest levels of contaminants are seen among women in agricultural areas of the developing world that are extensively treated with pesticides (*13*) and among women in remote areas, such as the Canadian Inuit, who eat a diet rich in seal, whale, and other species high on the marine food chain that accumulate heavy burdens of persistent organic pollutants (POPs) (*14*).

The finding of toxic chemicals in breast milk raises a series of important issues for pediatric practice, for the practice of public health, and for the environmental health research community.

Lack of data on contaminants. Although much information has been generated on the types of chemicals likely to be found in breast milk, this database is scattered and incomplete. Data have been collected on only a limited number of chemicals, from small samples of women in relatively few geographic locations (*15*). Major need exists for more data on exposure patterns, levels of contamination, and trends.

Lack of consistent protocols. No standardized methodology has been developed in the United States for collecting and analyzing breast milk samples. This makes it difficult to compare data from study to study. Although more data are available in other nations, again, standardized protocols do not exist. Methodologic shortcomings of published studies include inconsistent sampling and analysis protocols, incomplete descriptions of sampling methods, nonrepresentative sampling (in regard to geography, parity, age), limited duration of sampling, small numbers of study participants, and limited number and types of chemicals analyzed (*16*).

Lack of toxicokinetic data. Women may be exposed to lipophilic chemicals from various sources including air, food, water, and occupational and household environments.

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This article is an introduction to the Mini-Monograph on "Chemical Contaminants in Breast Milk." The series of articles in this mini-monograph were developed from ideas developed at the conference on "Chemical Contaminants in Breast Milk: Impacts on Children's Health."

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Lipophilic chemicals can be stored and accumulated over time in body fat and can then be mobilized into milk during lactation. Generally, chemicals enter breast milk by passive transfer from plasma, and their concentration in milk is proportional to their solubility and lipophilicity (*17*). Twenty percent or more of maternal body burden of some persistent pollutants, such as PCBs, can be transferred during 6 months of lactation (*18*). Information on the toxicokinetics of chemicals in breast milk is incomplete.

Lack of data on health outcomes. There are scant data on the health outcomes that may be produced in infants by exposures to chemicals via breast-feeding. Thus far, effects on the nursing child have been seen primarily in high-dose poisonings where the mother was clinically ill (*19*). The prospective epidemiologic studies that are needed to assess chronic outcomes that may occur at lower levels of exposure have been undertaken for only a few chemical contaminants, most notably PCBs. Few data exist on long-term effects or on interactions among chemicals.

Lack of evidence-based health standards. Although most breast-feeding mothers have detectable levels of several environmental agents in their milk, there are no established normal or abnormal values for clinical interpretation that are derived from toxicologic or epidemiologic studies; therefore, evidence-based guidance cannot be provided.

To examine these emerging issues and to chart a course for the future, the Mount Sinai Center for Children's Health and the Environment convened a conference on 5 October 2001 titled "Chemical Contaminants in Breast Milk: Impacts on Children's Health." The stimulus for this conference was a desire to confront the issue of nursing infants' exposure to chemicals in breast milk and to assess the hazards to health and development that may result from those exposures. A group of scientists and clinicians came together to examine what we know and do not know about patterns and trends in infants' exposure to chemicals in breast milk, toxicokinetics, possible health outcomes, research needs, and implications for risk assessment. The following are the major findings and recommendations of this conference.

Breast Milk Monitoring

The conferees agreed unanimously that a need exists for a carefully planned and conducted national breast milk monitoring effort in the United States. A few countries, mainly Sweden and Germany, have systematic breast milk monitoring programs that have tested considerable numbers of women over time using consistent sampling methods (*15*). However, most countries have done little monitoring for pesticides, metals, or industrial chemicals in breast milk. To be nationally representative, such an effort would need to include women of various socioeconomic backgrounds and geographic locations.

Comprehensive breast milk monitoring with standardized protocols for specimen collection and analysis must be expanded worldwide. Only with more reliable and better standardized approaches to selection of subjects, milk sampling and collection, and analytical methods can conclusions be drawn about global patterns of contamination, trends over time, and emerging hazards. Good data on time trends and geographic patterns would aid in generating hypotheses and would lead to more definitive studies. Such information would also provide a sound basis for evidence-based public health policies. Without such data, it is difficult to provide advice to health care professionals and to new mothers on the potential risks and benefits of breast-feeding.

Another need is to study lactating women prospectively to determine rates of decrease in concentrations of chemicals over the course of lactation. It has been recommended that women should donate milk samples on a monthly basis (or more frequently in the first 2 months) and then every 2–3 months if lactation continues (*16*).

It will also be necessary to develop data that will permit comparison of breast milk contamination levels with contaminant levels associated with other infant food sources, such as formula and cow's milk. Such data will permit us to compare the risks associated with each source of infant nutrition. Use of formula feeding does not necessarily result in a child being protected from chemicals in the environment because formula can be diluted with water that is polluted (*15*). Infant formula has been found to be contaminated with toxic metals, bacteria, and other environmental toxicants. Pesticide residues and bovine growth hormone can be found in cow's milk.

Health Outcomes

The conferees agreed that to assess the effects of contaminants in breast milk on child health and development, it will be necessary to examine children prospectively over many years in longitudinal epidemiologic studies that use standardized examination protocols and that specifically assess exposures to environmental contaminants via breast milk. This is the study design envisioned for the National Children's Study, a major prospective epidemiologic study now being planned under the direction of the National Institute of Child Health and Human Development in collaboration with the National Institute of Environmental Health Sciences, the Centers for Disease Control and Prevention, and the U.S. Environmental Protection Agency. The goal of this study will be to examine the influences of multiple exposures—environmental, behavioral, socioeconomic, and genetic—on child and adult health. It will follow as many as 100,000 children in all regions of the United States, from *in utero* to at least 21 years of age (*20*). Companion studies are under development in Canada and possibly in Mexico. The choice of which exposures to measure, which outcomes to assess, what data infrastructure to build, what specimens to store, and what ethical safeguards to impose will be critical to the National Children's Study.

Risk Assessment

The conferees agreed that current risk assessment methods generally do not consider chemical exposures to infants via mother's milk and therefore need to be expanded. In traditional risk assessment, assessment of risk is normally based on adult body weights and food consumption data (*11*).

The level of risk to infants and children of exposure to chemical residues in human milk depends on each mother's food consumption patterns, the nature and levels of chemical residues in her milk, and the toxicologic potency of those chemicals. A comprehensive analysis of the potential health risks to infants and children exposed to chemicals from breast milk will require consideration of all these factors as well as of the unique vulnerabilities of infants and children.

Infants and children may exhibit unique susceptibilities to the toxic effects of chemicals because they are undergoing rapid tissue growth and development (*21*). Infants and children also consume much greater quantities of milk fat and certain foods than do adults on a body weight basis, and thus they may be subjected to proportionately higher levels of exposure to certain chemicals. These exposures occurring earlier in life may predispose infants and children to a greater risk of chronic toxic effects than exposure occurring later in life (*22*). Traditional approaches to health risk assessment need to be expanded to encompass those factors and to adequately protect infants and children. Furthermore, it must be recognized that there are only limited data on the residue levels of chemicals in milk and food consumption patterns of infants and children that are appropriate for use in risk assessment.

Another source of exposure of infants to chemicals that must be considered in risk assessment is drinking water and the water used for mixing formulas. Although water intake is considered in current risk assessment, neither nondietary exposures nor exposures in drinking water are considered in deriving risk estimates for total chemical exposure in infants' milk. Because of these limitations, burden of total exposures to infants and children may be underestimated.

Stockholm Convention

The conference concluded by noting that there is some encouraging news for nursing mothers. On 22 May 2001, the United States and 119 other nations signed an international treaty in Stockholm to phase out use and production of 12 POPs worldwide and established a procedure to add additional chemicals to the list of banned pollutants (*15*). The treaty also promotes action to minimize the release of biologically persistent industrial byproducts such as dioxins and furans. Over the last several decades, individual nations have banned certain chemicals, effectively reducing the threat that these chemicals pose. For example, the United States has banned DDT and PCBs. Countries that have banned certain POPs are likely to have lower levels of pollutants in mother's milk. However, even with the signing of the treaty, newly emerging hazards such as PBDEs and nonyl phenols must be monitored (*12*). Breast milk remains the best source of nutrition for babies, but constant vigilance is needed to keep it pure.

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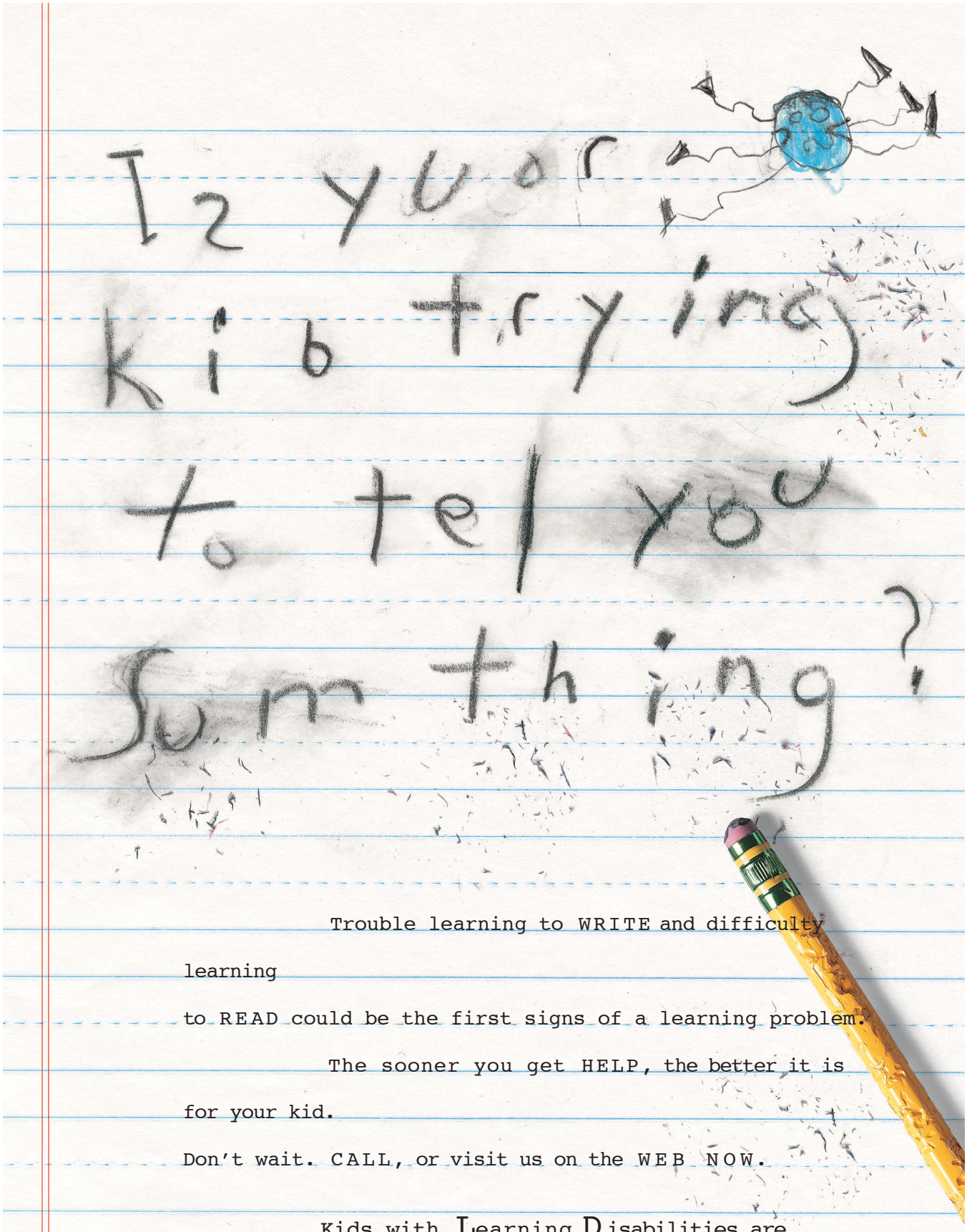

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Analytic Considerations for Measuring Environmental Chemicals in Breast Milk

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The presence of environmental chemicals in human breast milk is of general concern because of the potential health consequence of these chemicals to the breast-fed infant and the mother. In addition to the mother's exposure, several features determine the presence of environmental chemicals in breast milk and their ability to be determined analytically. These include maternal factors and properties of the environmental chemical—both physical and chemical—such as its lipid solubility, degree of ionization, and molecular weight. Environmental chemicals with high lipid solubility are likely to be found in breast milk; they include polyhalogenated compounds such as polychlorinated biphenyls, polychlorinated dibenzo-*p*-dioxins, polychlorinated dibenzofurans, organochlorine insecticides, and polybrominated diphenylethers. These fat-soluble chemicals are incorporated into the milk as it is synthesized, and they must be measured in accordance with the fat content of the milk to allow for meaningful comparisons within an individual and among populations. Although the analytic approach selected to measure the environmental chemical is predominantly determined by the characteristics of the chemical, the concentration of the chemical in the milk sample and the existence of structurally similar chemicals (e.g., congeners) must be considered as well. In general, the analytic approach for measuring environmental chemicals in breast milk is similar to the approach for measuring the same chemicals in other matrices, except special considerations must be given for the relatively high fat content of milk. The continued efforts of environmental scientists to measure environmental chemicals in breast milk is important for defining the true contribution of these chemicals to public health, especially to the health of the newborn. Work is needed for identifying and quantifying additional environmental chemicals in breast milk from the general population and for developing analytic methods that have increased sensitivity and the ability to speciate various chemicals. ***Key words*****: analytic, chemical, environment, human breast milk, measurement, toxicant.** ***Environ Health Perspect*** **110:A317–A324 (2002). [Online 13 May 2002]**
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Breast milk is unique as a matrix for biomonitoring because, in addition to serving as a matrix for the many uses of biomonitoring, it also serves as a food source for a segment of the human population; thus, the analyses of breast milk for environmental chemicals as well as for nutrients are of wide scientific interest. One of the earliest reports of the measurement of an environmental chemical in breast milk was by Laug et al. in 1951 (*1*). They reported that the breast milk from 32 women from the general population of Washington, DC, contained 1,1,1-trichloro-2, 2-bis(4-chlorophenyl)ethane (*p,p′*-DDT or DDT) at an average concentration of 0.13 ppm. Laug et al. (*1*) attributed the primary source of DDT to their diet. Over the years, many more chemicals have been measured in human breast milk, our understanding of the interaction between lactation and exposure to environmental chemicals has grown, and our analytic methods have become more sophisticated. Because the fat content of milk is relatively high, most of the chemicals that have been monitored in milk are those that have high lipid solubility, in particular, polyhalogenated chemicals. These chemicals tend to degrade slowly in the environment, to bioaccumulate and bioconcentrate in the food chain, and to have long half-lives in humans. Certain adverse health and reproductive outcomes have been attributed to these chemicals in laboratory animals and in wildlife, as well as in humans. Therefore, public health officials, environmental regulators, and scientists are concerned about their sources, their presence in our ecosystems and in people, and finally the relation between exposure and adverse health outcomes. Scientists develop and apply methods to measure these chemicals in human specimens, such as breast milk, and also in other matrices, both environmental and biological. These methods present challenges, such as the need for overcoming the relatively high fat content of milk while still maintaining all of the characteristics of state-of-the-art analytic methods. In this paper we note those characteristics and means of ensuring that they are met; we also describe in summary how breast milk is made, how environmental chemicals are incorporated into the milk, and factors that influence the levels of these chemicals in milk.

Incorporation of Environmental Chemicals into Breast Milk

Following human exposure, environmental chemicals can be absorbed into the bloodstream by three routes: ingestion, inhalation, and dermal contact. These chemicals circulate in the bloodstream, either bound to carrier proteins such as albumin and lipoproteins or in their free form, and distribute among tissue compartments throughout the body (*2*). Initially, the rate of distribution of chemicals within the body is a function of tissue perfusion, which is the rate of blood flow through the various tissues. Highly vascular organs accumulate the chemicals first. Then, as equilibrium states are reached, the chemicals redistribute, and chemicals with high lipid solubility concentrate in tissues with higher fat content, such as adipose tissue, brain, liver, kidney, and, in the case of lactating women, breast milk.

In lactating women, lactogenesis begins about 40 hr after the birth of their offspring. During the first 3–5 days after delivery, the milk is low in volume and in fat (lipid) content (2.9%) and is called "colostrum." Over the next 2–6 weeks, the transitional milk matures and increases in fat content to about 4%. The lipids are important for infant brain development; the major class of lipids in milk is the triglycerides, which are made from fatty acids such as arachidonic and docosahexaenoic acids (*3*). Breast milk is made up of several other components including carbohydrates, proteins, and minerals, especially calcium. Milk is synthesized in the mammary alveolar gland; to synthesize milk, milk components and their precursors pass through a membrane that separates the blood flowing in capillaries from the alveolar epithelial cell of the breast. However, during this process certain environmental chemicals present in the blood also can pass through the membrane and be incorporated into the breast milk at concentrations comparable to the

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chemicals' levels in other fatty compartments in the body (*4,5*). The most common mechanism for the passage of environmental chemicals is passive transport, which in general allows passage of lipophilic components of molecular weight < 800 Da; thus, lipid solubility of a chemical is a primary factor for its incorporation into breast milk. Factors that affect the lipophilic character of a chemical include its chemical structure and its degree of ionization (pKa) in the body compartments. For example, in general, halogens increase the lipophilic nature of a chemical. Also, chemicals in their nonionized state are more lipophilic than when in their ionized state and hence are more likely to diffuse into breast milk when in their nonionized state. Because the pH of plasma is 7.40, weakly acidic chemicals tend to exist primarily in their ionized form and thus are less likely than weak bases to pass through the membrane and into milk, which has a pH of 7.0–7.25 (*6*).

However, the passive transport mechanism for lipid-soluble chemicals is not the only mechanism for chemicals to cross cell membranes. For example, low molecular weight (< 200 Da) water-soluble chemicals can cross cell membranes with the bulk transfer of water. On the other hand, chemicals of high molecular weight (> 800 Da) tend not to pass through the membrane and likely do not enter breast milk to a measurable degree. Also, chemicals (e.g., heavy metals) that are highly bound to either plasma proteins or erythrocytes are unlikely to passively diffuse into milk (*7*). Overall, the amount of protein-bound chemical that enters milk is of little concern because the protein compartment in the blood is far greater than that in breast milk.

Other factors that affect the presence of a chemical in breast milk are its degree of biotransformation and its elimination rate. Frequently, the biotransformation processes, Phase I and Phase II, produce a metabolite that is more water soluble than the parent chemical and is readily eliminated through the kidney into the urine; hence, the chemical is not available for incorporation into breast milk. Less frequently, the metabolite is sustained in the blood and tissues, including breast milk, and is more readily measured than the original chemical (e.g., aldrin is metabolized to dieldrin and DDT is metabolized to DDE). With regard to the elimination rate, chemicals with a slow elimination rate have a long half-life, which allows for more time in the body and hence more time for bioaccumulation in breast milk. Many halogenated compounds, including the organochlorine insecticides (e.g., DDT and cyclodienes), polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs), polychlorinated dibenzo-*p*-dioxins (PCDDs), and polychlorinated dibenzofurans (PCDFs), have long biological half-lives and are persistent in the environment and in humans because of their resistance to oxidative degradation and metabolism. The number of halogen atoms and the position of the halogen atoms on the molecule modulate these enzymatic processes (*8*). For example, the reported biological half-life for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) is 7.2 years, whereas the reported estimates for other dioxins are 3.7 years for 1,2,3,4,6,7,8-heptachlorodibenzo-*p*-dioxin and 15.7 years for 1,2,3,7,8-pentachlorodibenzo-*p*-dioxin (*9*).

For many of these long-lived environmental chemicals in lactating women, breast milk may be a major route of their elimination (*10*). Lipid-soluble chemicals are transported from adipose tissue stores to the lipids in breast milk and then eliminated from the body during breast-feeding. Thus, during a single lactation period or after several children and lactation periods, the concentration of a persistent chemical tends to decrease, assuming only background exposures to that chemical. This process of decreasing levels of chemicals during the breast-feeding period is known as "depuration" (*11*). For example, the half-life of total PCBs and DDT in human milk has been estimated to be approximately 6 months (*12*).

The Role of Breast Milk in Biological Monitoring Programs

In the body, lipophilic chemicals are stored and equilibrated in tissue compartments with high fat content (e.g., breast milk and adipose tissue). In actuality, adipose tissue, breast milk, and blood or its components have been used for biological monitoring for assessing human exposure to lipophilic chemicals. Biological monitoring of these chemicals has several advantages over environmental monitoring because the former measures the internal dose rather than the exposed dose, and accounts for exposure from all sources (residential and work), all environmental pathways (through air, water, food, soil, surfaces), and all routes of absorption (ingestion, dermal, inhalation). However, biological monitoring may or may not yield information about specific sources, routes, and pathways that are important for risk management purposes. The most common reason for large-scale national biomonitoring programs is to monitor a population's exposure to chemicals, such as organochlorine insecticides, industrial chemicals and by-products (PCBs, PCDDs, PCDFs, lead), and solvents, and to determine whether a population's exposure to these chemicals is changing over time. The consequence of such information assists in the determination of directed efforts in research, regulation, and policy design to improve public health care and safety.

In the United States, breast milk has not recently been used to a large degree in biomonitoring programs. The largest biomonitoring studies involving breast milk in the United States were conducted at Colorado State University. The first, conducted from 1974 to 1976, comprised 1,436 nursing women in hospitals; their milk samples were analyzed for selected chlorinated hydrocarbon insecticides and later for PCBs (*13*). The second national study, conducted from 1977 through 1983 by the same laboratory, comprised a total of 1,842 milk samples, which also were collected from women residing throughout the United States and were analyzed for the same organochlorine insecticides and PCBs (*13*). Also, in 1980 the U.S. Environmental Protection Agency (EPA) reported qualitative and semiquantitative data on levels of volatile organic compounds and semivolatile organic compounds in milk samples collected from lactating women in five U.S. cities (*14*). Despite these earlier initiatives, milk has not been routinely monitored in recent national surveys, such as the National Human Adipose Tissue Survey (*15*), which analyzed adipose tissue, and the National Health and Nutrition Examination Surveys (*16*) and the piloted National Human Exposure Assessment Survey (*17*), which both monitored blood and urine. However, breast milk has been more widely used in biomonitoring programs in Europe and Canada (*18*). For example, Norén and Meironyte (*19*) in Sweden and Fürst et al. (*20*) in Germany reported that the milk levels of PCDDs, PCDFs, and PCBs decreased dramatically from the early 1970s to the late 1990s. In contrast, Norén and Meironyte (*19*) reported a dramatic increase in milk levels of selected polybrominated diphenylethers (PBDE) congeners over this period. The World Health Organization (WHO) European Centre for Environment and Health is conducting its third field study, which is designed to assess levels and changes in levels of PCDDs, PCDFs, and selected PCBs in breast milk in countries worldwide (*21*).

Breast milk is a convenient specimen for biomonitoring programs because relatively large volumes (50–100 mL) can be collected noninvasively. This makes it a suitable matrix to be sampled in a large and easily identified population, albeit a selected population of women of reproductive age who are lactating. Because only this specific sample demography can be used, the use of mother's milk in a probability-based survey, the results of which are intended to be extracted to the general population, is questionable. Nevertheless, exposure in this segment of the

population obviously is important to monitor, and milk is important to monitor for contaminants because breast milk is a human food and is the major route of exposure to these contaminants by the breast-feeding newborn.

Another reason to monitor breast milk is that it reflects the maternal total body burden for lipophilic chemicals. Furthermore, concentrations of lipophilic chemicals in breast milk indicate the levels of these chemicals in the mother's fat stores during pregnancy and, consequently, provide a dosimeter of prenatal exposure to these chemicals. If used for this purpose, the milk should be collected in a narrow window of time as soon postpartum as possible to reduce the effects of depuration. However, any fat-containing matrix could be sampled from the mother and used for this dosimeter because lipophilic compounds partition within the body primarily on the basis of the fat content of the tissue. The average fat content of mature breast milk is about 4%. In contrast, serum contains 0.5–0.6% lipids and adipose tissue may range in lipids from 65% to > 90%, depending on the location in the body from where it is taken and the method used for procuring it (e.g., surgical, needle biopsy, or liposuction). The lipid-partitioning effect was demonstrated in a study of a population exposed to varying levels of TCDD (*22*). Patterson et al. (*22*) reported that, on average, levels of TCDD were 158 times higher in adipose tissue than in serum, but when each matrix was adjusted for its lipid content, the levels of TCDD were comparable in each matrix. Thus, tissue perfusion and the lipid partition coefficient [or bioconcentration factor (*23*)] play important roles in the distribution of chemicals in the body. In the case of PBBs, their concentrations in breast milk were reported to be 0.7–0.9 times that of adipose tissue when results from both were reported on a lipid-adjusted basis; in the same study the lipid-adjusted adipose tissue and breast milk concentrations were 107–119 times that of plasma, when results from the latter matrix were reported on a whole weight basis (*24*).

However, the level of fat and the level of environmental chemicals in breast milk require consideration of several factors beyond the degree and duration of exposure, the effects of depuration, and the time of sampling during lactation. These include characteristics of the mother. Maternal features that affect these levels include the health of the mother during pregnancy and during the lactation period, presence and levels of other xenobiotics (including environmental chemicals and pharmaceutical agents) that may alter metabolism, change in body mass index during pregnancy and lactation, diet, other factors that may mobilize fat, parity and length of previous lactation, number of children being breast-fed at one time, maternal age, and maternal body mass index. Also of importance is the variation of the fat content during lactogenesis and during the course of feeding (*25–27*). We have already mentioned that the fat content during lactogenesis tends to increase from about 2.9% during the first few days and then stabilizes at around 4% after 2–6 weeks. During the actual time of breast-feeding, the foremilk can have a fat content of about 1% and the hindmilk can have a fat content of up to 12%; levels of fat can also differ between the two breasts. Also, if an infant empties the milk content of one breast, the foremilk from the second breast is generally higher in fat content than the foremilk was from the first breast. For monitoring surveys, breast milk should be collected once the fat content has stabilized; the protocol of WHO-Europe calls for sampling 2 weeks to 2 months after delivery (*21*); however, more studies need to be conducted to determine whether the milk is comparable during this 8-week period.

The Role of Breast Milk Monitoring in Epidemiologic Studies

In addition to monitoring breast milk purely for exposure assessment purposes, researchers have analyzed breast milk to determine the relation between concentrations of environmental chemicals and adverse effects in humans; thus, the determination of potential health consequences of contaminated breast milk to the infants and their mothers is another important reason to conduct biological monitoring in breast milk. Several incidents have been reported of women being exposed to chemicals, then breast-feeding their children with contaminated milk, and the children having adverse effects, especially neurodevelopmental effects. These reported chemicals include PCBs (*28–31*), PCBs/PCDDs/PCDFs (*32–34*), PBBs (*35*), hexachlorobenzene (*36*), methylmercury (*37,38*), and DDT (*25*). Although transplacental exposure is generally believed to be more consequential to the health outcomes than exposure through breast milk, this has been debated (*39,40*). If these measurements in breast milk had not been conducted, such information about contributory effects on health outcome would not have been recognized. Nevertheless, because the significant nutritional and immunologic benefits from breast-feeding outweigh the limited adverse health effects from the presence of environmental chemicals in breast milk, the American Academy of Pediatrics continues to recommend breast-feeding in most circumstances (*41*).

Concerns have been raised about the levels of environmental chemicals in breast milk and other human tissues and effects on the mother. Women with a higher DDE concentration in their breast milk have a shorter duration of lactation than do those with a lower concentration (*42,43*). Another concern is for the occurrence of breast cancer with exposure to organochlorine chemicals (e.g., DDE, DDT, PCBs). This association has not been consistently demonstrated (*44*).

Analytes Monitored in Breast Milk

Before describing the analytic considerations for analyzing breast milk for environmental chemicals, we need to list the analytes of interest.

Organohalogens. The first class of chemicals generally discussed in breast milk monitoring programs is the organohalogens, which include the organochlorine insecticides, PCDDs, PCDFs, PCBs, PBBs, and PBDEs. On the basis of analytic chemistry methods, these chemicals are considered to be semivolatile and are generally measured by gas chromatographic methods after an extraction process.

Volatile organic compounds. In the U.S. EPA's analyses of breast milk collected from five U. S. cities, 26 halogenated hydrocarbons, 17 aldehydes, 20 ketones, 11 alcohols, 2 acids, 3 ethers, 1 epoxide, 14 furans, 26 other oxygenated compounds, 4 sulfur-containing compounds, 7 nitrogen-containing compounds, 13 alkanes, 12 alkenes, 7 alkynes, 11 cyclic hydrocarbons, and 15 aromatic compounds were found, including significant amounts of hexanal, limonene, and dichlorobenzene (*14*). These chemicals are generally measured by gas chromatographic methods following a purging or headspace sampling process.

Metals. Heavy metals, including lead, mercury, and cadmium, are seldom monitored in breast milk; one reason is that their levels are only about 20% of their levels in maternal blood. These metals can be present either in their inorganic forms or as organometallics. They are generally measured by atomic absorption spectroscopy (AAS), inductively coupled argon plasma spectroscopy, or mass spectrometry (MS), often following a digestion process.

Other chemicals. As in most cases, the "other chemical" category contains a variety of chemicals ranging from contemporary pesticides, polycyclic aromatic hydrocarbons, nicotine, ethanol, phthalates, musk xylenes, and phytoestrogens, such as genestein. These chemicals are generally determined by either gas chromatography (GC) or high performance liquid chromatography methods (HPLC).

The Analytic Method

The major methodologic goals of analyzing breast milk for environmental chemicals are the same as for analyzing any other biological sample or, for that matter, any environmental sample for those environmental chemicals. The goals of the method are built around specificity, sensitivity, robustness, ruggedness, accuracy, precision, ability to measure multiple analytes, and high throughput. However, the analytic approach for analyzing milk for environmental chemicals must take into account the fat content of milk. This leads to some general (e.g., specimen collection, preparation) and specific (e.g., congeners) considerations for measuring environmental chemicals in breast milk.

Specimen Collection

The sample must be collected under a well-designed protocol; this includes signed consent forms and approval by an Office for Human Research Protection-approved Institutional Review Board. Key issues of breast milk collection are the adherence to the protocol, administration of a well-designed questionnaire, accurate labeling of all containers, avoidance of contamination, and the adequacy of the specimen. The breast and hands should be clean, yet soap should be avoided as much as possible. The use of creams or ointments on the nipples should be used outside the sampling time for the analysis, but if this is not possible because of tenderness, the breasts should be washed thoroughly and rinsed with copious amounts of water before sampling. The milk can be expressed either manually or by a breast pump, but if a pump is used, it must be free of contamination. Some groups recommend collecting the milk specimen from one breast using an electric pump while the baby feeds on the other breast in order to take advantage of the let-down reflex. The collecting bottle must be provided free of contamination and should be washed, rinsed with water, and rinsed with acetone before being given to the mother. If the analysis calls for inorganic elements, the collecting bottle is generally acid rinsed. At least 50 mL of milk should be collected in a wide-necked glass bottle; if the milk is expressed manually, avoid contact between the breast and the jar. In general, glass; Teflon; certain plastics, such as polyethylene; and aluminum foil (if only organic chemicals are measured) are suitable to come in direct contact with the specimen. Certain plastics, such as polyvinyl chloride, and metal containers are to be avoided because their constituents can interfere with certain detectors interfaced with the analytic instrument. Aluminum foil (dull side down) or Teflon is generally used as liner material for the lid.

Specimen Storage and Transport

If the breast milk is collected several times over a 72-hr period, then the milk in the collection container should be stored in the home freezer or in a home refrigerator. Tablets of potassium dichromate, a preservative, may be added if necessary. If volatile organic chemicals are not intended to be measured, the milk specimen should be warmed to 38°C and inverted several times to mix the cream layer, and then divided into aliquots into several bottles to minimize the effects of freeze–thaw cycles. These bottles should have labels that will remain intact and readable throughout transport and storage (*45*). The bottles containing the samples should be placed in a thermoinsulated box with dry ice; the bottles should not contact each other or the dry ice. The laboratory staff should be notified of the shipping of the samples and given all information about the shipping. When the samples arrive, the laboratory staff should remove the bottles from the shipping box; note the condition of the labels, the bottles, and the milk; and relay this information back to the shipper. For the measurement of most analytes, the samples can be stored indefinitely at –70°C.

General Analytic Approach

Several methods exist for measuring environmental chemicals in breast milk. Of course, as mentioned above, the specific method depends on the analytes of interest; therefore, specific methods are not practical to discuss without listing the specific chemicals or at least classes of chemicals. We classify the environmental chemicals as either inorganic chemicals (including organometallic compounds) or organic compounds, which are further divided into volatile or semivolatile classes. The measurement process of the chemicals of concern consists of four primary steps: lipid determination; sample preparation; instrumental analysis, which usually involves a chromatographic step; and data analysis and evaluation. Before the measurement process, the samples to be analyzed in an analytic run or batch should be removed from the freezer, checked for proper labeling, brought to 38°C (unless they are to be analyzed for volatile chemicals), and mixed by gentle inversion. The number of samples that can be analyzed by an analyst or a team of analysts in 1 day generally determines the number of samples included in an analytic run. Into this batch are added quality control samples that consist of milk that has been fortified with the analytes and/or milk that has not been fortified, as well as a solvent blank, which is often purified water that is analyzed in the same manner as the milk samples. The quality control samples can consist of bench or internal quality control samples and external or blind quality control samples. Generally, both of these samples are prepared in a bulk manner and then the milk is transferred by pipette to the container so that the quality control samples are identical in appearance to the unknown samples. In our study, both the bench and the blind quality control samples have been analyzed by the laboratory numerous times, and the mean values and control limits have been determined for the analyses. Laboratory personnel know the positions of the bench quality control sample and of course the quality of the blank in the analytic run, but they do not know the position of the blind quality control sample. We also recommend analysis of standard or certified reference materials, if they are available, for the particular analytes in breast milk.

Sample Preparation and Lipid Determination

Semivolatile organic compounds. The purposes of the sample preparation step and lipid determination step are to extract the fat components and the analytes of interest from the remainder of the milk sample, to determine the fat content of the milk sample, and to further prepare the extract for instrumental analysis. The lipid content may be measured in the entire amount of sample or in an aliquot of the milk specimen. In either case, the homogenized milk sample is treated with a denaturing agent such as ethanol, sodium oxalate, or formic acid, and the lipids are extracted into an organic solvent. The extract is sometimes passed through a column containing a drying agent such as sodium sulfate to remove traces of water. The solvent is concentrated to dryness and the lipid weight is determined gravimetrically. The percentage of the lipid content of the specimen is determined especially when lipophilic compounds such as PCBs and organochlorine insecticides are measured because, most frequently, the concentrations of the analytes of interest are reported on a lipid-adjusted basis as well as on a whole-weight basis. The lipid-adjusted basis normalizes the concentrations of the lipophilic environmental chemicals to the different lipid contents of the milk, both within a mother and among mothers. The lipid-adjusted concentrations of lipophilic compounds are used for population estimates of these chemicals in the mothers and for defining infant intake of these chemicals. These chemicals must be accurately and precisely measured on a whole-weight basis to adjust their concentrations to a lipid basis. This lipid determination step, however, is critical, and because of the potential for incomplete extraction, incomplete concentration of the sample, and weighing errors, the overall error is often more associated with the

measurement of the lipids than with the measurement of the analytes. This was demonstrated in the first WHO-sponsored interlaboratory study for measuring PCBs, PCDFs, and PCDDs in breast milk (*46*). In addition to the liquid/liquid extraction method, milk samples have also been prepared for further analysis by using lyophilization or freeze drying of the milk.

The goal of the sample preparation step is to prepare the sample for instrumental analysis while maintaining the high recovery of the analytes but separating them from the lipids and from other coextracted potential interferants. The method used for the sample preparation step (sometimes called the "cleanup step") is determined by the physical and chemical nature of the analytes and instrumentation available to the laboratory. This concept sounds straightforward but can often tax the ability of analytic chemists. For example, as we mentioned, human milk is generally 3–4% lipids, but the analytes of interest, such as PCDD and PCDF congeners, PCB congeners, and organochlorine insecticides, are generally present at parts-per-quadrillion, parts-per-billion, and parts-per-billion concentration levels, respectively. Thus, the method needs to extract the lipids and the analytes and separate all of these components from other components of the milk sample with high efficiency and specificity. To carry this one step further, the PCDDs, PCDFs, and coplanar PCBs must also be separated from the "regular" PCBs and organochlorine insecticides before instrumental analysis. The specificity, sensitivity, precision, accuracy, "ruggedness," and robustness of the analytic method are highly related to the ability of this step to meet its goal.

Some methods used for cleanup for the measurement of semivolatile analytes include column chromatography, thin-layer chromatography, sweep codistillation, and gel permeation chromatography. More recently, chromatographic techniques such as solid phase extraction (SPE) have been used in the cleanup of many semivolatile chemicals, including pesticides and organochlorine compounds. A variety of sorbents are commercially available for solid phase extraction (SPE). These sorbents can be used in combination with the specific properties of the analytes to selectively isolate the compounds of interest from other components of the sample. SPE can be used in two different modes: the first is to initially retain the analytes on the column packing, thereby allowing potential interferants to pass through the column, and then elute the analytes with the prescribed eluent; the second is to retain the interfering substances, thereby allowing the analytes to pass initially through the column. If the second mode is used, typically an additional preparation step is employed to isolate the components from the matrix. Another technique, which has the potential for extracting lipophilic compounds directly from milk, is stir bar sorptive extraction.

Volatile organic compounds. To analyze breast milk for volatile analytes, the sample preparation step is based on volatization of the analyte, which can include a process based on volatilization of the analyte into the headspace above the sample or by a similar process followed by a purge of the headspace by an inert gas, then trapping of the analytes onto an adsorbent. The adsorbent is reheated and the analytes are released as part of the instrumental analysis process. A separate aliquot of the milk sample is generally used for lipid determination.

Inorganic chemicals. To analyze breast milk for metals, the sample preparation step is generally based on a digestion of the proteins in the milk, thereby releasing the metal to be measured by an instrumental analysis process. Lipid content may or may not be determined because the metals are generally not partitioned into the lipids.

Instrumental Analysis and Quantification

Once the specimen has been prepared for instrumental analysis, the analytes of interest can be further separated from each other and from remaining potential interferants by high-resolution chromatographic techniques such as capillary column GC or HPLC. The method is selected depending on the physical and chemical properties of the chemical (e.g., volatility, thermal stability). Following separation, the analytes are detected using a variety of analytic instruments, including mass spectrometers, although historically halogenated, semivolatile organic compounds have been detected by electron capture detectors. Once detected, these particular compounds are quantified by two primary methods, the external standard method and the internal standard method. The external standard method is generally the less accurate of these two quantitative techniques. It relies on a standard curve consisting of the detector responses of the analyte (y-axis) versus the varying concentrations of the analyte in standard solutions (x-axis) and generally makes no amends for losses of the analyte during the analysis of each unknown; however, recovery losses can be estimated by using one of two approaches. The first approach is to incorporate a surrogate compound in the milk sample and monitor its recovery throughout the analytic process; for example, the analyst may add a PCB congener that is generally not detected in human milk to the milk sample and monitor its recovery. The recovery of the analytes of interest can be inferred from the recovery of the added PCB, although no adjustments for losses are made when reporting the concentration levels of the analytes. The second approach is to spike a milk pool with known amounts of the analytes of interest, analyze the milk pool many times, and calculate and average the recovery of the analytes over time. The analyst then assumes that during the analyses of the actual samples, the analytes are recovered to a similar degree, but again the analyst does not take this into account during the reporting of the concentration levels of the analytes.

The internal standard method involves the addition of one or more compounds (the internal standards) that ideally are recovered to the same degree (but at least to a consistent relative degree) as the analytes during the analytic method; this relative behavior is determined by previous analyses of milk pools spiked with the analytes and the internal standards. The internal standards should be added and equilibrated into the sample before the extraction step. Therefore, any losses of the analytes during the analytic method are accompanied by similar losses (or at least defined losses) of the internal standards. The quantitative result for a given analyte in a milk sample is calculated from a standard curve consisting of the ratio of the detector responses of varying concentrations of that analyte divided by the detector responses for a constant concentration of its internal standard (y-axis) versus the varying concentrations of the analyte in standard solutions (x-axis).

The isotope dilution MS technique for quantification is essentially the same as the internal standard quantification method with two exceptions. The first exception is that the internal standard is actually the same chemical (differing only in isotopes) as the analyte; therefore, the stable isotopically labeled internal standard should chemically and physically mimic the analyte, and any loss of the analyte during the analytic process should be accompanied by a similar loss of its internal standard. Its use allows for a complete accounting of any loss of analyte and thus "adjusts" the recovery to 100%; therefore, as with the internal standard method, no recovery calculations have to be made. The concentration level of the analyte is calculated in a similar manner as described for the internal standard method. The second exception is that because the analyte and internal standard are the same chemical (differing only in isotopes), their primary difference is only in mass, which means that the instrumental detector must be able to distinguish the analyte from the internal standard on the basis of mass (i.e., a mass spectrometer must be used). For increased sensitivity that is often required in milk analysis, the mass spectrometer generally monitors only selected ions. The use of the isotope

dilution quantification technique and the combination of specificity and sensitivity of mass spectrometry, especially when used in the selective ion monitoring mode, can provide the basis for "definitive" methods in analytic chemistry. The only pertinent weakness, besides the expense of instrumentation and the labeled standards, is the inability to qualitatively distinguish among certain isomers that have similar chromatographic properties and mass spectral fragmentation patterns (i.e., structural isomers that coelute); in such cases, Fourier-transform infrared spectroscopy can be used, even though it does not have the same inherent sensitivity as MS in the selected ion monitoring mode. However, with the advent of many more widely varying chromatographic columns, including those based on chirality, this weakness is seldom relevant. From a quantitative viewpoint, the major sources of error in IDMS are in the purity of the native (unlabeled) standards and sometimes the labeled standard, and the inaccurate addition of the prescribed amount of the solution containing the labeled standard. A fourth method of quantification, the spiked addition method, is seldom used because repeated analyses are required for each sample. The first analysis involves the analysis of the sample without the addition of any native standard to the sample, but each successive analysis involves the addition of increasing amounts of labeled standard. A calibration plot is constructed from the areas of the spiked samples, and the *x*-intercept is representative of the concentration of the analyte in the milk sample.

The mass spectrometers used for measuring environmental chemicals in milk can range in price from the relatively inexpensive mass selective detectors (around $100,000 U.S.) to tandem mass spectrometers (around $300,000 U.S.) to high-resolution mass spectrometers with various designs and configurations (range from $500,000 to $1,000,000 U.S.). With proper laboratory technique, the use of pure standards, and IDMS, the instrumental analysis step seldom leads to imprecise and/or inaccurate measurements.

Data Analysis and Evaluation

Most laboratories use computers to better track the status of samples from their delivery into the laboratory to reporting of the data, to control the instruments for analyzing the sample, and to calculate the results. This generally results in fewer laboratory errors. Nonetheless, laboratory personnel must be aware of the potential for errors, must properly set up each of the computers, and must check the output of each step. They should help determine which data output parameters are necessary and their specifications for determining the quality of the data and for determining whether the results for an individual sample and/or for the entire analytic run are "in control." The determination of whether the entire analytic run is in control is based, to a large degree, on the results of the quality control samples. These quality control samples also evaluate the performance of the analytic method in a given laboratory over time. The determination of whether the results for a particular milk sample are in control is generally based on other factors relevant to the type of analyses. For example, for GC/MS methods, these quality control factors may include the retention times of the analytes and the internal standard; the degree of resolution of the analyte from other analytes or contaminants; the percent recovery of the internal standard; and, particularly if halogenated (chlorinated or brominated) compounds are being measured, the ion ratios of the halogen atoms (e.g., if the analyte contains one chlorine, the contribution of ^{37}Cl should be about one-third that of ^{35}Cl). If compounds not containing halogen atoms are being measured, certain ion(s) can be used for quantification and another for confirmation in much the same manner.

Of particular concern in trace analysis is how to report and statistically treat concentration levels that are below the limit of detection (LOD). The LOD is defined by the lowest concentration of chemical that the analytic method can measure. It is determined by the measured value that differs in a statistically significant manner from having "zero" chemical in the specimen (*47*). The efficiency of the analytic method in preparing extracts free of potential interferants (but still recovering a high percentage of the analytes of interest) and the sensitivity of the instrumental system affect the LOD for the method. The LOD should be determined in each laboratory for each instrument (instrumental LOD) and for each method (method LOD); frequently, the method LOD is calculated for each and every sample analysis. When measurements are calculated to be < LOD, the concentrations are generally reported as "nondetectable" with the LOD given. However, for parametric statistics, a number must be assigned for each sample. To circumvent this problem, values ranging from the most "conservative" value of zero to one-half of the detection limit concentration, to the detection limit divided by $\sqrt{2}$, to the most "liberal" value—the detection limit itself (*48*)—have been used. More sophisticated modeling methods have also been used to estimate the concentration levels for nondetectable results (*49*). From a laboratory perspective, our general policy is to statistically use all values determined by MS that are at or above the LOD and that pass the quality control criteria (for the run; for the sample; and if the analysis is for multiple analytes, then also for individual analytes within the sample). However, what about reporting concentrations when they are below the LOD? Two scenarios exist: For the first, all of the quality control criteria are again met except that the calculated concentration value is below the LOD; in this case, we report the calculated value with the caveat that the result is below the LOD—for statistical purposes in our epidemiologic studies, we believe that this is the most accurate value to use for that sample. For the second scenario, the quality control criteria for the analytic run are met but no signal for a particular analyte is discernible; those results are reported as below the LOD, and no number above zero can be assigned to them. Other researchers treat both scenarios as the same and report all results below the LOD as nondetectable and then assign, for statistical purposes, a number as described above (e.g., one-half the LOD). Because our analytic methods have become much more sensitive, concentrations of targeted chemicals in the breast milk from exposed populations, as well as from the general population, are seldom calculated as being below the LOD; however, we are still faced with this problem. As shown by many researchers, our exposure to many environmental chemicals is decreasing (fortunately), and their milk concentration levels may not continue to be sufficient for detectable measurements. Another scenario that can lead to nondetectable results is that we often measure multiple analytes in an analytic run, and the more analytes that we measure in an analytic run, the lower the sensitivity for the measurement process of all of the analytes, either because of instrumental reasons or for recovery reasons. Therefore, the use of multianalyte methods has many advantages, but generally they have higher LODs than single analyte methods.

One approach to help ensure the availability of an adequate volume of milk for measuring low levels of environmental chemicals is to combine individual samples of similar demographic or presumed-exposure characteristics into a single sample to prepare a "pooled sample." This practice is widely used to decrease the number of samples to be analyzed and consequently it allows for a larger number of mothers to be represented in the survey; in addition, it saves laboratory resources. Another benefit of pooling specimens is the use of small volume specimens that would otherwise be excluded from analysis. However, some issues should be considered when specimens are pooled: the loss of direct association with the donors; the inability to perform statistical analysis between pooled populations because of the loss of variability within the pooled population; the reporting of estimated instead of

actual measurements of the analyte in the population; and the disproportionate weighting of the measurements because of dilution. The creation of subgroups within each pool can establish a variance for the pool to allow for comparison between pools. Additional consideration needs to be given for the variability in lipid content relative to time of breast-feeding among the donors before the specimens are pooled. Therefore, whether the volume of each sample to be pooled should be based on a given volume per sample or a given amount of lipids per sample becomes questionable. Although the latter method may be preferred, it is seldom used because it requires the additional measurement of the lipid content of the samples before pooling.

Analytic Issues with Specific Chemicals

PCDDs, PCDFs, and certain PCBs. The PCDDs, PCDFs, and certain PCB congeners represent classes of many compounds that exhibit similar mechanisms of toxic actions. There are 75 congeners of PCDDs, 135 congeners of PCDFs, and 209 PCB congeners. All of these congeners could potentially be dispersed into the environment. However, not all of the congeners bioaccumulate in the food chain and hence are not found in the fatty stores in humans. For example, we generally consider that only 7 of the PCDDs and 10 of the PCDFs are stored in the fatty tissues of the human body. That is the good news. The bad news is that these 17 are the most toxic members of these two classes of chemicals. The most toxic congeners have four or more chlorine atoms substituted (for hydrogen) on the aromatic rings, and all four of the lateral positions (the 2, 3, 7, and 8 positions) must be substituted with a chlorine atom. Because of their dioxin-like activity, 12 PCBs are generally reported along with the PCDDs and PCDFs; 4 of these PCBs (the coplanar PCBs or non-*ortho*-substituted PCBs) have no chlorine substitution in either of the four *ortho*-positions (the 2, 2′, 6, or 6′-positions) and 8 of these PCBs (the mono-*ortho*-substituted PCBs) have only one of these four positions substituted with a chlorine. Therefore, approximately 30 different chemicals are reported as dioxin-like chemicals in humans. Because so many congeners need to be monitored for dioxin-like activity, methods to facilitate the interpretation and reporting of the data (as well as to establish regulatory limits) were adopted. In short, the reported value for dioxin-like chemicals is frequently condensed to one value—the toxic equivalency (*50*).

The toxic equivalency is a weighting factor derived by multiplying the concentration of each of approximately 30 individual dioxin-like chemicals by their respective toxic equivalency factor and then summing these values. The toxic equivalency factor is a relative factor based on ability of each chemical (relative to the most toxic congener, TCDD) to induce cytochrome P450 1A1 and its affinity for the aryl hydrocarbon (Ah) receptor. The toxic equivalency approach allows for a meaningful comparison of the toxicologic contribution of each dioxin-like compound and a comparison of the concentration of each of these compounds within a biological or environmental sample and between samples. Some of the limitations to this approach include the nonadditive antagonistic effect of various chemical mixtures (*51*) and mechanisms of toxicity not appreciated by either the Ah receptor or cytochrome P450 activity (*52*).

Another approach that has been developed recently for measuring dioxin-like total equivalents is the chemical-activated luciferase gene expression (CALUX) bioassay (*53*). This method, based on the Ah receptor agonistic activity of these chemicals, is less expensive and has higher throughput than methods based on GC/MS. However, the method still requires an extraction, lipid determination, and cleanup of the milk sample. Furthermore, the final result is only a toxic equivalent and thus gives no information about the dioxin pattern of exposure, which yields information about the exposure scenario, including the source. Also, frequently this method overestimates the concentration of PCDDs, PCDFs, and dioxin-like PCBs because other components in the breast milk may possess Ah agonistic activity. Nonetheless, this method is suitable for screening of samples to estimate dioxin levels and for prioritizing those samples for dioxin analysis by GC/MS.

Another area of interest in measuring chemical classes with many congeners, such as PCBs, is the interpretation of residue data. The toxic mechanism of action for most of the PCB congeners is different from that of dioxins; in fact, the 209 PCB congeners can act through a variety of toxic mechanisms. So, from a toxicologic standpoint it is important to be able to separate and quantify each of the congeners that appear in breast milk. Of course, not all of the congeners are present in any specimen, environmental or biological; the number of congeners identified depends not only on the exposure scenario but also on the analytic method. Over the years, as technology and methods have improved, so has the ability to chromatographically resolve more compounds and to measure them with improved sensitivity. Thus, PCBs are now frequently reported as individual congeners, although the individual congeners themselves are frequently summed to give total PCBs; this is done to allow for direct comparison with historical data and for ease of correlation with health end points, although this approach may be flawed for both uses. Historically, total PCBs were calculated from comparison to the commercial material that chromatographically was most similar to the chromatographic pattern of the extract from the biological sample; however, little or no information was available for individual congeners. Methods were developed for calculating total PCBs from these chromatograms. However, these methods of interpretation led to an over estimation of the actual measurement of the chemical class compared with analytic methods that can resolve all the congeners (*54*). Thus, the comparison of data among laboratories with different abilities to resolve many congeners can be problematic. Data sets can be best compared from laboratories that can identify and quantify a similar number of congeners using similar techniques.

Heavy metals. Heavy metals appear in milk at smaller concentrations than the lipid-soluble chemicals and are about 20% of the level found in blood from the same person. This is attributed to their low lipid solubility and high binding to erythrocytes. The amount of heavy metal exposure to the infant from breast milk appears to be low in comparison with other sources; further information is needed about the pharmacokinetics of the heavy metals (especially lead) as they go from mother to infant. An area of concern regarding the analysis of heavy metals is the identification of the various species of metals (especially for mercury and arsenic). This is important because different species of metals have varying toxic effects. For example, methylmercury, which binds to sulfhydryl groups, is a central nervous system toxicant and inorganic mercury is a nephrotoxicant. Thus, the need to be able to measure individual species of the heavy metals becomes apparent. AAS is commonly used to detect heavy metals, which can be speciated by using selective specimen preparation methods. The LOD with AAS can be decreased with flameless (e.g., electrothermal) atomizers.

Future Trends

The assessment of exposure to environmental chemicals in breast milk from the general population needs to pursue the measurement of environmental chemicals that have not been well characterized and have potential adverse health effects (e.g., pesticides, such as organophosphates; xenoestrogens; brominated aromatic hydrocarbons; solvents; and polycyclic aromatic hydrocarbons). In addition, breast milk monitoring needs to be increased in populations that may be unduly exposed to certain chemicals that are easily measured in breast milk. As mentioned previously, breast milk is a

unique biomonitoring matrix in that it is also a human food, and although the exposure lasts for a relatively short and limited time, the amount of chemical intake on a daily basis may far exceed the public health criteria, which are generally based on an exposure period of 70 years. Public health officials need to recognize this. In addition, chemists need to measure these chemicals in an accurate and precise manner. Therefore, the chemist must be kept abreast of laboratory criteria in order to help ensure the quality of the data. An increasing number of laboratories will have to demonstrate quality through such programs as the Clinical Laboratory Improvement Amendment of 1988 (*55*) and interlaboratory studies. The chemists are responsible for providing accurate and precise analytic data for assessing exposure so that the relationship between exposure and adverse health outcomes can be made most accurately; this in turn should lead to improvements in legislation and regulation that protect people but not to an unwarranted degree.

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Infant Exposure to Dioxin-like Compounds in Breast Milk

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We used a one-compartment, first-order pharmacokinetic model to predict the infant body burden of dioxin-like compounds that results from breast-feeding. Validation testing of the model showed a good match between predictions and measurements of dioxin toxic equivalents (TEQs) in breast-fed infants, and the exercise highlighted the importance of the assumption of the rate of dissipation of TEQs in the infant. We evaluated five nursing scenarios: no nursing (i.e., formula only), and nursing for 6 weeks, 6 months, 1 year, and 2 years. We assumed that an infant weighs 3.3 kg at birth and is exposed to a total of 800 pg TEQ/day by consumption of breast milk, leading to an estimated body weight-based dose of 242 pg TEQ/kg-day, which drops to 18 pg TEQ/kg-day after 1 year. This decline is due to declines in dioxin concentration in mother's milk and infant body weight increases. This range is significantly higher, on a body-weight basis, than adult TEQ exposure, which has been estimated to average about 1 pg TEQ/kg-day. For the nursing scenarios of ≥ 6 months, we predict that body burdens (expressed as a body lipid concentration) peak at around 9 weeks at 44 ppt TEQ lipid. We predict that the body burden of the formula-fed infants will remain below 10 ppt TEQ lipid during the first year. These results compare to the current adult average body burden of 25 ppt TEQ lipid. We also found that an infant who had been breast-fed for 1 year had an accumulated dose 6 times higher than a 1-year-old infant who had not been breast-fed. For a 70-year lifetime, individuals who had been breast-fed had an accumulated dose 3–18% higher than individuals who had not been breast-fed. *Key words:* breast milk, dioxin-like compounds, dioxins, furans, infant exposure, pharmacokinetic modeling. *Environ Health Perspect* 110:A325–A332 (2002). [Online 13 May 2002]
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Several researchers have shown that infant exposure to dioxin-like compounds can be significant by the breast milk pathway (*1–4*). Ayotte et al. (*1*) used data on the concentrations of dioxin-like compounds [including dioxin and furan congeners as well as the dioxin-like polychlorinated biphenyls (PCBs)] in breast milk of Inuit populations in Nunavik (the Arctic region of Quebec, Canada) with a median concentration of 48 pg dioxin toxic equivalents (TEQ)/g lipid, to calculate an infant dose of 226 pg TEQ/kg-day. They applied a pharmacokinetic (PK) model to evaluate the impact of breast-feeding of dioxin TEQs on infant body burdens and on lifetime (up to 75 years) body burdens of TEQs. By studying the accumulation of dioxin-like compounds in humans over time, Patandin et al. (*2*) showed that 6 months of breast-feeding during the first 25 years of life could contribute 12% of the total dose of these compounds during those 25 years for men and 14% for women. Kreuzer et al. (*3*) and Lakind et al. (*4*) combined estimates of 2,3,7,8-tetrachlodibenzo-*p*-dioxin (TCDD) dose received by the infant via breast-feeding with PK models to demonstrate the initial significant elevation in infant body burdens of TCDD as a result of this exposure. Their models predicted that initially high body burdens declined as a result of infant body weight increases, depuration of residues, and reduced doses due to declines of residues of TCDD in mother's milk.

In this paper, we build on the efforts of other researchers (*1–4*) to model the impacts of breast-feeding on body burdens of dioxin-like compounds. We express body burdens in terms of picograms of dioxin TEQs per gram body lipid or parts per trillion TEQ lipid; these compounds are known to accumulate in lipid, and TEQ concentrations in mother's milk, blood, and other organs are often expressed on a lipid basis.

In this paper we focus on dioxin-like compounds expressed as a dose or concentration of dioxin TEQs. The TEQ concentration is the sum of the concentrations of the individual dioxin-like compounds multiplied by their respective toxicity equivalency factors (TEFs). The TEF scheme we used is the one promoted by the World Health Organization in 1998 (*5*). We use TEQ to signify the 29 compounds assumed to have dioxin-like toxicity, including the 7 polychlorinated dibenzo-*p*-dioxin (PCDD) and 10 dibenzofuran (PCDF) congeners, as well as the 12 dioxin-like coplanar PCBs, unless otherwise stated. We treat TEQs as a single compound. Even with the principal uncertainty of this approach, the limited validation and general comparison of modeled results with the measured values suggest that this may be a reasonable approach for evaluating trends in exposure to dioxin-like compounds via breast-feeding.

In this paper we describe and validate a simple pharmacokinetic model for evaluating the impact of breast-feeding on infant body burdens. We then apply the model to five scenarios: formula only, and nursing times of 6 weeks, 6 months, 1 year, and 2 years. We also performed another sensitivity analysis test that doubled the dose received by the infant and also doubled the infant's initial body burden at birth to determine how these parameters affect model predictions.

Modeling the Impact of Breast-Feeding on Infant Body Burden

To better evaluate the impact of nursing on infants, we used a one-compartment non-steady state PK model to predict dioxin tissue levels in infants. The PK model is based on the following differential equation describing the mass balance of dioxin in lipids (*6*):

$$\partial a(t)/\partial t = abs\ D(t) - k(t)a(t) \qquad [1]$$

$$c(t) = a(t)/[1{,}000\ V(t)], \qquad [2]$$

where $a(t)$ is the total mass of dioxins in lipid (picograms) at time t; t is time (days); abs is the fraction of ingested dose that is absorbed into the lipid compartment (unitless); $D(t)$ is the ingested dose of TEQs (picograms per day) at time t, $k(t)$ is the elimination rate function (per day) at time t; $c(t)$ is the concentration of dioxins in lipid (picograms per gram) at time t; and $V(t)$ is the lipid weight (kilograms) at time t.

This modeling framework, as well as the parameter assignments we used in this study, derive heavily from the efforts of Lakind et al. (*4*) and Kreuzer et al. (*3*). Lakind et al. (*4*) also used a first-order, single compartment model to predict the accumulation of TCDD and dichlorodiphenyldichloroethane (DDE) in infants from breast-feeding. Lakind reviewed the literature to assign critical model parameters that are also required in our study, such as the absorption of ingested

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dose. Lakind et al. (*4*) assumed a 95% absorption of TCDD, whereas the literature that we reviewed for this work suggests a lower absorption for TEQ intakes (80%). Lakind et al. (*4*) also reviewed the literature to develop a model of declining concentrations in mother's milk. We used the same justification in this study to consider this decline. A key input to the Lakind model (*4*), as in our model, is a first-order rate of elimination; Lakind et al. (*4*) used an elimination rate derived by Kreuzer et al. (*3*). The Lakind model, like our model, does not model any specific process of TCDD elimination; it simply requires assignment of a first-order elimination rate. Kreuzer et al.'s model (*3*) was slightly more complex and more physiologically based than the model of Lakind et al. (*4*) and the one we used in this study. Specifically, ingested TCDD is deposited into body adipose tissue, from which it partitions into richly perfused tissue (a single compartment composed of brain, kidney, intestines, liver, and spleen) and instantaneously into muscle tissue. Elimination of TCDD is modeled as the sum of metabolic (breakdown) and nonmetabolic (fecal elimination) pathways. We estimated fecal elimination as the product of the lipid tissue concentration and the mass of lipids excreted over time. Using physiologic data on the mass of lipids in fecal samples that varied with age, Kreuzer et al. (*3*) found that the overall half-life of TCDD in infants was driven by fecal elimination. This overall half-life was on the order of weeks at infancy, and it increased through infancy until the metabolic pathway dominated in adulthood. The overall half-life of TCDD in adults was more on the order of years rather than weeks.

One key assumption of this simplistic framework is that dioxins are instantaneously distributed to all body lipids. This is a common assumption for TCDD PK modeling in humans, adopted in multicompartment (*7*) and single-compartment (*3,4,8*) models. The model of Carrier et al. (*9,10*) alternately has a nonlinear response to doses, with different partitioning to the liver and other body lipids as a function of body concentration: when the overall body concentration is high, more of the dioxin dose is partitioned to the liver, whereas at lower body concentrations, the partitioning to the liver is lower.

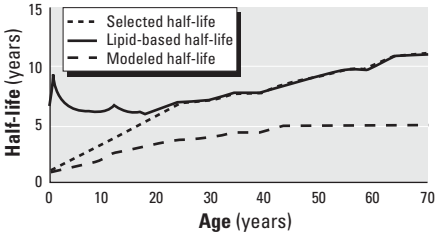

Figure 1. Comparison of the selected half-life of TEQs in the body with lipid-based half-life (*6*) and modeled half-life (*3*) for TCDD.

The other key assumption in our model is that a dioxin TEQ dose behaves as a single compound in humans and is described by a single dissipation half-life. Ayotte et al. (*1*) modeled TEQ body burdens from infancy to adulthood, but it was unclear whether they modeled individual congeners or TEQs as one compound. Campbell et al. (*8*) used a framework similar to the one we used and modeled individual congeners for an industrial exposure study.

An elimination rate function, $k(t)$, for TCDD has been modeled as a function of the percent body fat, k(fat) (*6,11,12*). This empirical function, k(fat), was curve-fit from data on Vietnam veterans (*11*) who had approximately 25% body fat. As the percentage of body fat increases, the elimination rate is modeled to decrease (equivalently, the half-life is modeled to increase) significantly. Given a range of body fat over a lifetime, from a low of 15% (teenage years) to a high of over 40% (elderly females), these relationships suggest a half-life of TCDD ranging from approximately 6 years to > 20 years, with a general trend toward an increase in half-life as individuals age (because the percentage of body fat increases with age).

None of these efforts, however, identified processes or factors critical for infants. With a body fat of around 15% at birth, the half-life of TCDD is approximately 6 years using these k(fat) relationships. Kreuzer et al. (*3*), however, developed a procedure for modeling the overall elimination half-life for TCDD in infants that considers metabolic (t_m; breakdown by enzymes) and nonmetabolic (t_f; fecal elimination) processes. Other key parameters included total body lipid mass and liver volumes, which change over time, and a reference half-life for an adult. For their "reference adult" at 40 years of age, Kreuzer et al. (*3*) cited an overall half-life of 5 years, based on information from Geyer et al. (*13*). The Kreuzer et al. (*3*) model showed a rise in half-lives from a low of < 0.5 years at birth to a high of 5 years at an adult body fat mass of 20 kg. Thus, the model of Kreuzer et al. (*3*) is different than the k(fat) models (*6,11,12*): the model of Kreuzer et al. (*3*) predicts half-lives that never exceed 5 years, whereas the other approaches predict half-lives that never go below 6 years.

For purposes of this assessment, we assumed that the overall half-life for the early years of life more closely follows the trend as derived in the modeling exercises by Kreuzer et al. (*3*). For later years, we believe that the k(fat) model is more valid. Therefore, for this study, we adopted a hybrid of these assumptions, as shown in Figure 1; point estimates of the half-life [the model parameter, $k(t)$, equal to 0.693/half-life] are shown in Table 1. The half-life at birth starts at the low value of 0.4 years and then slowly rises to the levels predicted by the k(fat) models by approximately 25 years of age. The half-life assumptions remain an obvious uncertainty for this type of modeling approach. Not only is there a disparity in the literature with regard to this critical assumption, but the literature was only specific to TCDD, not TEQs.

Using the estimated dioxin concentration in breast milk, the dose to the infant was modeled as follows:

$$D(t) = C(t)\, f\, IR, \qquad [3]$$

Table 1. Parameters used for modeling the impact of breast-feeding on body burden and lipid concentrations of TEQs from infancy to adulthood.

	PK modeling parameters			Dioxin TEQ dose (pg/day)				
					Breast-fed			
Age	BW (kg)	Lipid[a]	Half-life (years)[b]	Formula	6 weeks	6 Months	1 Year	2 Years
Birth	3.3	0.14	0.40	54	800	800	800	800
1 Month	4.3	0.16	0.50	54	733	733	733	733
2 Months	4.6	0.18	0.60	54	667/54	667	667	667
3 Months	6.0	0.20	0.70	54	54	600	600	600
4 Months	6.7	0.22	0.75	54	54	533	533	533
5 Months	7.4	0.23	0.80	54	54	467	467	467
6 Months	7.9	0.25	1.00	54	54	400	400	400
7 Months	8.4	0.25	1.00	54	54	54	367	367
8 Months	8.8	0.24	1.05	54	54	54	333	333
9 Months	9.2	0.24	1.08	54	54	54	300	300
10 Months	9.4	0.23	1.10	54	54	54	267	267
11 Months	9.8	0.23	1.12	54	54	54	233	233
1 Year	11.3	0.23	1.14	54	54	54	200	200
2 Years	13.3	0.20	1.39	54	54	54	54	200
5 Years	19.7	0.15	2.12	59	59	59	59	59
11 Years	41.1	0.15	3.60	64	64	64	64	64
18 Years	65.1	0.13	5.33	65	65	65	65	65
34 Years	71.5	0.21	7.70	65	65	65	65	65
55 Years	73.8	0.27	9.76	65	65	65	65	65

BW, body weight.
[a]Fraction of body weight that is lipid. [b]Half-life of dioxin residues in body.

where $D(t)$ is the ingested dose of TEQs (picograms per day) at time t, $C(t)$ is the concentration in milk fat (picograms per gram), f is the fraction of fat in breast milk, IR is the ingestion rate of breast milk (kilograms per day), and t is time. The dose term, $D(t)$, can easily be converted to a body weight-based dose term by dividing by infant body weight. The milk fat concentration and the infant body weight were modeled to vary over time; we assumed that the rate of ingestion of mother's milk and the fraction of fat in the mother's milk were constant over the duration of breast-feeding.

Smith (*14*) reported that studies in Great Britain and Houston, Texas, found that the breast milk ingestion rate for 7- to 8-month-old infants ranged from 677 to 922 mL/day and 723 to 751 mL/day, respectively, and that breast milk ingestion rates remain relatively constant over an infant's life. Smith (*14*) also assumed that mother's milk has a 4% fat content and that 80% of the ingested dioxins in mother's milk are absorbed. We adopted these assumptions for the modeling exercise described in this paper: abs = 0.80, IR = 0.8 kg/day (which assumes 1 L milk weighs 1 kg), and f = 0.04. Lakind et al. (*4*) reviewed additional literature to support a selection of 95% for absorption of TCDD from breast milk ingestion. However, there is evidence that the absorption is lower as the degree of chlorination increases, particularly for the highest chlorinated congener, octachlorodibenzo-*p*-dioxin (OCDD), with an absorption measured to be between 2% and 15% (*15*). Because TEQ doses are dominated by the lower chlorinated congeners, the low absorption of higher chlorinated congeners may be less critical, justifying the selection of 0.80 for abs for TEQ doses.

The lipid weight of the individual, $V(t)$, was calculated as the product of the fraction of body lipid and the full body weight of the individual. A typical infant (average of male and female) weighs about 3.3 kg at birth, 7.9 kg at 6 months, and 11.3 kg at 1 year of age (*16,17*). For dose calculation and PK modeling in this study, we averaged monthly average weights for males and females for the first 12 months of life and then for later years into adulthood (*16*). The body lipid fraction is about 0.15 at birth. It then increases to > 0.20 within 6 months, decreases into childhood, and increases again through adulthood to > 0.30 after 60 years of age (*17*). Point estimates of full body weight and lipid fraction as a function of age are shown in Table 1.

The last parameter for the model is the initial body burden in infants at birth. We assumed that this initial body burden is 10 ppt TEQ lipid, reasonably similar to the 11.9 ppt TEQ lipid found in stillborn adipose tissue by Kreuzer et al. (*3*), although their TEQ concentration included only dioxin and furan congeners.

Impact of Breast-Feeding on Infant Body Burden and a Limited Model Validation

Kreuzer et al. (*3*) presented data on adipose tissue and liver from 3 stillborn infants and 17 infants who had died from sudden infant death syndrome (SIDS). Nine of the 17 infants had been breast-fed for some portion of their lives, whereas the other 8 infants were formula-fed. Average congener and TEQ adipose tissue concentrations for these three groups are shown in Table 2. The highest TEQ concentrations were found in the infants who had been breast-fed, with lipid concentrations of 15.9 ppt TEQ (PCDD/PCDF only), compared to formula-fed infants who had concentrations of 4.3 ppt TEQ lipid. All congener concentrations in breast-fed infants were higher than those for formula-fed infants. The concentrations from breast-fed infants included 4 infants who were weaned several weeks before their deaths from SIDS. This may have generally led to reductions in their body burdens because their higher daily intake from breast-feeding was reduced after weaning. The average TEQ concentration for the 5 infants who died while still breast-feeding was 20.1 ppt TEQ lipid. The highest concentration found, 35 ppt TEQ lipid, was for the infant who was breast-fed the longest (19 weeks) and who died at that time. Other breast-fed infants, however, did not have as much impact: infants who died at 12 and 16 weeks, while still breast-feeding, had concentrations of 9 and 7.5 ppt TEQ lipid, respectively. Kreuzer et al. (*3*) concluded that breast-fed infants had elevated TEQ concentrations compared to formula-fed infants; they also observed that breast-fed infants had lipid TEQ concentrations that were within the range or lower than the values published for adults.

Table 2. Average adipose tissue concentrations of dioxins and furans in stillborn, formula-fed, and breast-fed infants (pg/g lipid).

Compound	Stillborn (n = 3)	Formula-fed (n = 8)	Breast-fed (n = 9)
TCDD	1.6	0.4	1.7
1,2,3,7,8-PentaCDD	3.4	1.1	4.9
1,2,3,4,7,8-HexaCDD	2.5	1.0	4.0
1,2,3,6,7,8-HexaCDD	8.8	4.0	19.9
1,2,3,7,8,9-HexaCDD	1.3	0.7	3.7
1,2,3,4,6,7,8-HeptaCDD	12.9	5.0	25.2
OCDD	51.2	29.1	91.6
2,3,7,8-TCDF	1.4	1.9	1.1
1,2,3,7,8,-PentaCDF	0.2	1.0	0.5
2,3,4,7,8-PentaCDF	9.2	3.1	10.6
1,2,3,4,7,8-HexaCDF	3.7	1.7	3.5
1,2,3,6,7,8-HexaCDF	2.4	1.0	2.8
2,3,4,6,7,8-HexaCDF	1.0	0.2	1.1
1,2,3,7,8,9-HexaCDF	0.1	0.1	0.1
1,2,3,4,6,7,8-HeptaCDF	3.6	1.6	3.8
1,2,3,4,7,8,9-HeptaCDF	0.4	0.1	0.1
OCDF	2.1	1.8	1.6
TEQ	11.9	4.3	15.9

Data from Kreuzer et al. (*3*). Average congener concentrations were calculated by assuming that nondetects equal one-half the detection limit.

Abraham et al. (*18*) reported a study in Germany in which blood samples from 80 breast-fed infants between 4 and 11 months of age were sampled for 17 dioxin-like PCDD/PCDFs. Of these 80 infants, 27 were from a region where a copper recycling plant led to elevations in the mother's milk. The TEQ blood concentration in this group of 80 children at 11 months of age ranged between 2 and 107 ppt lipid, with a median of 25.3 ppt; these TEQs were based only on PCDD/PCDF and were calculated using the older international toxicity equivalency scheme (*18*). Of these children, 6 had TEQ concentrations > 50 ppt lipid, and 5 of these 6 were from the region affected by the copper recycling plant. From a control group of 21 children who had been formula-fed, individual dioxin measurements were performed in 5 children. Concentrations ranged from 1.9 to 3.2 ppt TEQ lipid at 11 months of age.

Patandin et al. (*19*) studied the plasma levels of 4 PCBs in 173 Dutch children who were 3.5 years of age, 91 of whom had been breast-fed and 82 formula-fed. Children in the breast-fed group had significantly higher median PCB levels in plasma ($p < 0.0001$) than children in the formula-fed group. The four PCBs measured by Patandin et al. (*19*) were PCBs 118, 138, 153, and 180. The median sums of these four PCBs in the two groups of children were 0.75 µg/L in the breast-fed group versus 0.21 µg/L in the formula-fed group. By means of an extensive questionnaire on dietary history combined with data on concentrations of dioxin and

PCBs in food provided by the Dutch National Institute of Public Health and the Environment, they were able to determine that the TEQ intake via diet was virtually indistinguishable in the two groups. They found that PCB levels in the breast-fed children were significantly correlated with the period of breast-feeding (r = 0.63), milk PCB levels (r = 0.39), and the total TEQ in breast milk (r = 0.36). Patandin et al. (*19*) concluded that PCB levels in Dutch children are the result of exposure through breast milk and *in utero* exposure and that the influence of dietary intake of PCBs after weaning is small compared to the intake during breast-feeding.

Abraham et al. (*20,21*) sampled blood from formula-fed and breast-fed infants for dioxins, furans, and PCBs. Results showed that the body burden of dioxin-like compounds was more than an order of magnitude higher for the breast-fed infants than the formula-fed infants during both time periods. PCDD/PCDF TEQ concentrations ranged from 34.7 ppt lipid (11 months) to 43.9 ppt lipid (25 months) in breast-fed infants compared to 2.7–3.3 ppt TEQ lipid for the formula-fed infants. Dioxin-like PCB concentrations were also an order of magnitude different, with the breast-fed infants having a concentration of 31.4 ppt TEQ lipid compared to 2.5 ppt TEQ lipid for the formula-fed infants at 11 months. (PCB 126 was not measured at 25 months, so a comparison for that age is not informative.) The increase in the lipid-based PCDD/PCDF TEQ concentration in the blood of the 25-month-old breast-fed infants was attributed to the relative decrease in body fat mass during the period between sampling and slight increases in body burden concentrations.

These studies demonstrate the impact of breast-feeding, but they do not contain the type of information needed for model validation. For the data to be appropriate for model validation, breast milk concentrations should be taken at the same time infant body burden measurements are taken. The breast milk concentrations are used to provide the "independent" model driving term (the dose term), and the body burden measurements provide the "dependent" model prediction (the infant body lipid concentration).

One study included this type of data. Abraham et al. (*22*) studied PCDD/PCDF/PCB levels in blood of six breast-fed infants and breast milk from the infants' mothers. A portion of this data was reported in their earlier articles (*20,21*). In our analysis, we focus on the PCDD/PCDF TEQ concentrations reported in Abraham et al. (*22*) because PCB concentrations were not uniformly available for mother's milk and infant blood for all six mother/child pairs.

Two of the infants were the second children from mothers whose first child was also tracked by Abraham and colleagues (*20,21*). For these two second children, both the mothers' milk and the infants' body burdens were significantly lower; specifically, the comparison of first and second children, respectively, were 34.7 ppt TEQ lipid compared to 11.9 ppt TEQ, and 44.2 ppt TEQ compared to 18.8 ppt TEQ. The comparison of the mothers' milk from the first to second children was similarly disparate: the first mother had concentrations ranging from 14 to 24 ppt TEQ lipid for the first child, but 13 to 14 ppt TEQ lipid for the second child. The other mother showed a range of 15–27 ppt TEQ lipid for the first child, but 13–18 ppt TEQ lipid for the second child. Apparently, breast-feeding of the first child resulted in higher body burdens for this infant compared to the second infant and a lower body burden for the mother when the second infant was born.

Table 3 shows the results of the model validation excercise based on data reported by Abraham et al. (*22*). Abraham et al. (*22*) measured concentrations in breast-milk two times for 5 of 6 children. The one child whose mother had only one measurement was breast-fed for only 7 weeks; all other children were breast-fed for 26–32 weeks. We linearly extrapolated concentrations within the breast-feeding period from the two available data points. For example, for the first mother/child pair listed in Table 3, the mother's milk was analyzed during month 2 and month 11 after the child's birth; TEQ concentrations were 23.5 and 14.0 ppt TEQ lipid, respectively. We extrapolated these concentrations backward to give an estimated concentration of 24.6 ppt TEQ at birth. Likewise, forward extrapolation gave an estimated TEQ concentration of 22.4 ppt TEQ for month 3, assuming linear decline. The infant body burden was determined by blood measurements at approximately 1 year of age for each child. Abraham et al. (*22*) also provided the amount of time of full breast-feeding (Table 3).

For modeling the infant body burden, we assumed that the *IR* for mother's milk is 800 mL/day. After weaning, we assumed that the infant's dose was 54 pg TEQ/day. This is the dose developed for the age range of 1–5 years by the U.S. EPA (*23*). Little information is available on the dioxin content of baby formula and baby food; therefore, it is not known whether the dioxin dose consumed by infants in formula or other foods after weaning may be higher or lower than the assumed 54 pg/TEQ/day.

The rate of dissipation of dioxin residues is a principal uncertainty for this model. Two possibilities include the rapid dissipation (half-life < 1 year) of TCDD residues in infants (*3,4*) and the much longer half-life of around 7 years, based on a model of half-life as a function of body fat (*6,11,12*). This model validation exercise tested the appropriateness of the lower half-life approach adopted in this model, as shown in Figure 1, against an assumption of a constant 7-year half-life for TEQs during the first year of life.

As shown in Table 3, the model predictions at the selected dissipation rate (half-life < 1 year) were significantly nearer to observations than the predictions with the longer half-life. The average predicted concentration for the rapid dissipation rate for the six infants was 26 ppt TEQ lipid compared to the average observed concentration of 23.5 ppt TEQ lipid. With a 7-year half-life, the predicted concentrations were all higher, with an average of 39 ppt TEQ lipid. The model, applied with the shorter half-life, also seemed adequately responsive to lower or higher exposures in infants. For the infant who was breast-fed for only 7 weeks with a low concentration in the mother's milk, the blood concentrations were 5.0 ppt TEQ lipid at 13 months of age compared to a predicted 10 ppt TEQ lipid. The infant who was exposed to the highest dioxin concentration in breast milk had the highest body burden measurement (44.2 ppt TEQ lipid) and also the highest predicted concentration (36 ppt TEQ lipid).

Table 3. Model validation data and results (pg TEQ/g lipid).

	Observed data[a]				Model predictions, child TEQ C[b]	
	Milk TEQ[c]				Selected HL	Long HL
Description	1st	2nd	Child TEQ[b]	Weeks BF[d]	< 1 year[e]	7 years[f]
Mother 1, 1st child	23.5 (2)	14.0 (11)	34.7 (11)	26	34	51
Mother 1, 2nd child	13.7 (2)	12.7 (5)	11.9 (11)	29	27	39
Mother 2, 1st child	26.5 (2)	15.2 (11)	44.2 (12)	30	36	56
Mother 2, 2nd child	18.3 (2)	13.1 (6)	18.8 (12)	32	27	41
Mother 3, only child	13.7 (2)	NA	5.0 (13)	7	10	16
Mother 4, only child	12.7 (2)	13.0 (6)	26.5 (12)	30	21	32
Average C (pg/g TEQ)				23.5	26	39

Abbreviations: BF, breast-fed; C, concentration. Values in parentheses indicate the month after birth when sampling was performed.
[a]Data from Abraham et al. (*22*). [b]Concentration of TEQ in blood of infants. [c]Breast milk TEQ concentration. [d]Weeks of full breast-feeding. [e]Half-life model selected for model validation and further analysis. [f]Alternate half-life model in which half-life was 7 years at birth.

Even with the key uncertainties identified above, including the use of a simple, one-compartment PK model and the modeling of dioxin TEQs as though TEQ were a single compound, this approach appears to predict infant TEQ body burdens within the range observed and is adequately responsive to the different conditions of high and low exposure via breast-feeding.

This model validation exercise demonstrated the importance of half-life to predictions of infant TEQ body burden concentrations and the apparent validity of the short half-life for infants in contrast to the half-life on the order of years that appears to be valid for adults. At least in the context of this simple model, it would not be appropriate to assign half-lives on the order of years for infant body burden modeling. Besides this half-life, model predictions of infant body burden are most impacted by the dose of TEQs infants receive through breast milk or otherwise. The model responds linearly to changes in dose—if the dose taken in by the infant doubles, the infant body burden predictions double. Obviously, the initial concentration of TEQs in the infant is also affected by the mother's body burden. The remaining parameters are the infant physiologic parameters determining the size of the lipid reservoir into which the ingested dioxins deposit, the changing infant body weight and lipid fraction. The model responds in an inverse linear manner to these parameters—if the reservoir size is halved, the concentration doubles. There is realistically not a large range for these parameters and the average values selected below are probably sufficient for most assessment needs.

The dose is simply a picogram TEQ per day quantity taken in by the infant, which is determined externally; the model requires only the picogram TEQ per day input. It is a function of the amount of milk a child drinks, the lipid content of the mother's milk, the TEQ concentration in the milk, the fraction of ingested dioxin that is absorbed, and any other assumptions the user may make regarding the decline or rise in mother's milk concentration (or changes to lipid content of the milk) over time. We conducted several model runs to evaluate different nursing scenarios. We selected midrange values for all of the dose model parameters; only the time of nursing varied. We expected that this exercise would reasonably bound the exposures the majority infants in the United States would receive. Some mothers could have high TEQ body burdens because of an unusual or occupational exposure. To evaluate this possibility, we conducted a sensitivity test to evaluate the effect of doubling the mother's body burden, which resulted in not only a doubling of dose but also influenced the initial concentrations of TEQs in the infant.

Scenario Development and Evaluation

We used this modeling framework to evaluate five breast-feeding scenarios: formula-feeding only or breast-feeding for 6 weeks, 6 months, 1 year, or 2 years. These scenarios encompass current trends. In a comprehensive documentation of statistics for children born between 1990 and 1993, the Centers for Disease Control and Prevention (*24*) reported that 55% of all babies breast-fed, with about one-half breast-feeding longer than 5 months. The average duration of breast-feeding was 28.7 weeks. In a policy statement, the American Academy of Pediatrics (*25*) stated that exclusive breast-feeding is ideal nutrition and is sufficient to support optimal growth and development for 6 months after birth. They recommend that breast-feeding continue for at least 12 months, and thereafter for as long as mutually desired.

To model these scenarios, it was important to assign values to the mother's milk concentration regime over the breast-feeding period. This regime includes the assignment of an initial concentration and a scheme to model the expected decline over time. We assumed that the dioxin concentration in breast milk is 25 ppt TEQ lipid when lactation begins. This is the current average adult tissue concentration derived in the U.S. EPA's draft dioxin reassessment (*23*) from recent studies of dioxins in blood in background settings of the United States. By adopting this concentration as the initial concentration in breast milk, we assume that lipid concentrations of TEQs are equal in different lipid reservoirs and that a lipid-based blood concentration is equal to the lipid-based breast milk concentration, an assumption that is reasonably well recognized in the literature (*23*).

More importantly, however, the 25 ppt TEQ initial concentration in mother's milk can also be characterized as conservative because it is higher than is currently likely for the average U.S. woman of child-bearing age. The average adult concentration of 25 ppt TEQ lipid includes younger and older adults. It has been well established in the literature that dioxin exposures were higher during the middle decades of the 20th century than they are now (*6,23,26*) and that body burdens in older individuals are currently significantly higher than in younger individuals. It is likely that women of child-bearing age in the United States now have average body burdens < 25 ppt TEQ lipid, probably < 20 ppt TEQ lipid. However, it is also likely that there are populations with concentrations higher than this overall average. For example, concentrations of dioxin-like compounds in the blood of sport fishers and nonfishers in the Great Lakes region were higher, on average, than 25 ppt TEQ, and higher concentrations were found in sport fishers as compared to nonfishers (*27–29*).

The concentration of dioxin in breast milk is expected to change because lactation provides a significant avenue of depuration. Therefore, the scenarios require an assumption of the decline from the initial breast milk concentration of 25 ppt TEQ lipid. Lakind et al. (*4*) cited several references in which measurements of breast milk concentrations of lipophilic compounds (PCBs, DDE, DDT, PCDDs/PCDFs) were shown to decline during the course of lactation. They fit available data on TCDD to a curve, and their resulting relationship showed an 86% loss over 6 months. This is comparable to a modeling effort by Kreuzer et al. (*3*), who modeled a 70% decline in TCDD concentrations after 6 months. Their model was more mechanistic than that of LaKind et al. (*4*) and added the loss by breast milk to an overall female body burden model, which included inputs by food consumption and outputs by metabolic and nonmetabolic pathways. Patandin et al. (*2*), in their modeling of dioxin exposures from infancy to adulthood, cited data from Germany and England and concluded that breast milk concentrations of TCDD decline by 20% every 3 months. The data described in reports by Abraham et al. (*24–26*) suggested a TEQ decline of approximately 40% from early lactation to just under 1 year of breast-feeding.

Based on this information, we assumed that the initial 25 ppt TEQ lipid concentration in breast milk decreased linearly by 50% after 6 months, with a 50% decrease by the end of 12 months, and a total decline of 75% from initial concentrations. These concentration declines are in the middle of the range reported above. They translate to concentrations of 12.5 ppt TEQ lipid after 6 months and 6.3 ppt TEQ lipid after 1 year. For the 2-year breast-feeding scenario, we assumed that concentrations in breast milk remain at 6.3 ppt TEQ lipid from the end of the first until the end of the second year.

Table 1 shows key parameters for the dose calculation and for PK modeling for months during the first year of life and for key years thereafter. The dose parameters include infant body weights as well as doses of dioxin TEQ expressed in terms of picograms per day by either breast-feeding or background exposures. Breast-feeding doses drop from 800 pg TEQ/day (242 pg TEQ/kg-day on a body-weight basis) at birth to 200 pg TEQ/day (18 pg TEQ/kg-day) at 1 year. We assumed that the concentration in breast milk remains constant at 6.3 ppt TEQ lipid (dose to infant of 200 pg TEQ/day) from year 1 to year 2 during breast-feeding

for the 2-year nursing scenario. We assumed that the dose after breast-feeding equals background doses; the U.S. EPA (*27*) determined the background dose to be 54 pg TEQ/day (for ages 1–5 years), 59 pg/day (6–11 years of age), 64 pg TEQ/day (12–19 years of age), and 65 pg TEQ/day (> 19 years of age).

We used ModelMaker, Version 4.0 (ModelKinetix.com, Oxford, UK) to run the model and generate graphic results. We used Runge-Kutte numerical integration methods with a specified number of steps equaling 10,000 over a 70-year simulation (about 2.5 days/step).

The results from this exercise show the body burdens, expressed as body lipid concentrations, from birth up to 70 years of age (Figure 2) and then for a narrower time frame, from birth to 10 years of age (Figure 3). Other results for these five scenarios are shown in Table 4, including peak concentrations in the infant, time when the peak occurred, the area under the curve (AUC) corresponding to different times, and the ratio of the AUC for the breast-feeding scenarios and the AUC for formula feeding only. The AUC is defined as

$$\mathrm{AUC}(t) = \Sigma\, c(t), \qquad [4]$$

where AUC(t) is the area under the curve (parts per trillion-day) at time t and $c(t)$ is the lipid-based concentration in the infant each day (parts per trillion TEQ lipid). The AUC is a measure of accumulated exposure. For example, 1 year at a lipid-based concentration of 10 ppt would yield an AUC of 3,650 ppt-day (10 ppt × 365 days). A lifetime at an average body lipid concentration of 10 ppt would yield an AUC of 255,500 ppt-day (10 ppt × 70 years × 365 days/year). The AUC provides a parameter to compare accumulated exposure for different scenarios. For that reason, the ratios of the AUCs of the breast-feeding scenarios and the formula-only scenario are more important than the AUC values themselves; these ratios are shown in Table 4. For example, a ratio for a particular breast-feeding scenario of 6 indicates that the accumulated exposure for that scenario is 6 times that of the formula-feeding only scenario. The ratio can easily be translated to a corresponding measure of percent above or below the baseline scenario of formula-feeding only. For example, if the ratio is 6, this is equivalent to saying that the accumulated exposure for the breast-feeding scenario is 500% higher than the formula-only scenario [(6–1) × 100%]; if the ratio is 0.7, this is equivalent to saying that the accumulated exposure for the breast-feeding scenario is 30% lower than the formula-only scenario [–(0.7–1) × 100%].

The lipid concentrations are predicted to peak at approximately 44 ppt TEQ for the 6-month, 1-year, and 2-year scenarios (Table 4). These peaks uniformly occur at 9 weeks of age. For the 6-week breast-feeding scenario, the peak is 34 ppt TEQ lipid, which occurs at 6 weeks of age. The lipid concentrations decline after these peaks for the breast-feeding scenarios, but the decline is slower as the duration of breast-feeding increases. For the 2-year scenario, the lipid concentration stays near 40 ppt TEQ after 2 years of age (Figure 3). The 6-week scenario shows an increase in infant body lipid concentration to > 30 ppt TEQ, but then shows a rapid decline, so that it follows the formula-only scenario fairly well after 2 years of age. All four scenarios begin to merge near 10 years of age (Figure 2). The rise in concentrations seen in the later years results from the increase of percentage body fat and the subsequent increase in half-life as predicted by the elimination rate model that we used.

The AUC results in Table 4 show the accumulated exposure to be higher for each of the breast-feeding scenarios than for the formula-only scenario. This exceedance after 1 year is about a factor of 6 for breast-feeding for ≥ 6 months. For the first 10 years of life, the accumulated exposure is approximately 2 times higher for breast-feeding scenarios than for the formula-feeding only scenario. The ratios suggest that breast-feeding results in a lifetime exposure only 1.03–1.18 times higher than formula feeding, or from 3% to 18% higher than formula feeding only.

We conducted a sensitivity analysis to evaluate the effect of doubling the mother's body burden, which we assumed would double the dose to the infant as well as the initial body burden of the infant. We used the 6-month scenario for this evaluation and assumed that the dose to the infant would double over those 6 months and that the infant body burden at birth was 20 ppt TEQ instead of 10 ppt TEQ. Also, we included one run in which the initial infant's body burden was 20 ppt TEQ but the dose to the infant was the same as in the initial scenario. This second sensitivity run evaluated only the impact of the initial body burden.

The results of this sensitivity analysis are shown in Figure 4. As expected, the predicted infant body burden peak almost doubles, from 44 ppt TEQ to just under 90 ppt TEQ. The AUC doubles during the 6 months of breast-feeding. However, as expected, this gap narrows over time. After 10 years, the AUC for the elevated exposure is about 43% higher than the baseline 6-month scenario; after 70 years, the difference is only 9%. Figure 4 also shows that the initial body burden assumption has very little effect on modeling results. When only the initial body burden of the infant is increased from 10 to 20 ppt TEQ lipid, the peak concentration at 9 weeks increases slightly to 49 ppt TEQ with the higher initial body burden, but the AUC is only marginally different for the baseline

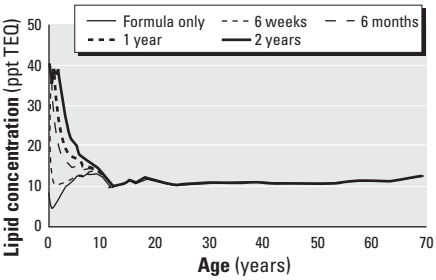

Figure 2. Demonstration of the model for evaluating impacts on lipid concentrations of infants resulting from various nursing scenarios during a lifetime.

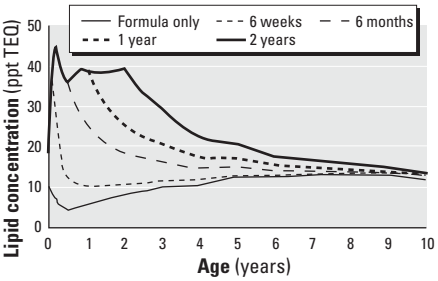

Figure 3. Demonstration of the model for evaluating impacts on lipid concentrations of infants resulting from various nursing scenarios during the first 10 years of life.

Table 4. Results of pharmacokinetic modeling for formula feeding and four breast-feeding scenarios.

Description of output	Formula	Breast-feeding scenarios			
		6 weeks	6 months	1 year	2 years
Peak concentration (pg/g lipid)	13.0	34.1	44.3	44.3	44.3
Peak (time after birth)	9 years	6 weeks	9 weeks	9 weeks	9 weeks
AUC after 1 year	2,168	5,989	12,129	13,645	13,645
AUC after 10 years	39,433	46,516	62,696	73,183	86,370
AUC after 70 years	275,419	282,654	299,304	310,210	324,202
$AUC_{BF}/AU_{formula}$					
1 year	—	2.8	5.6	6.3	6.3
10 years	—	1.2	1.6	1.9	2.2
70 years	—	1.03	1.09	1.13	1.18

BF, breast-feeding.

6-month feeding scenario. The lack of meaningful impact of the initial infant body burden is also seen in Figure 3, which shows all of the evaluation scenarios. The infant body burden appears to quickly adjust to the dose: a high dose causes the infant body burden to increase quickly and a low dose, such as with formula feeding, causes the infant body burden to drop to a level supported by that dose. In short, the mother's body burden certainly affects the dose received by the child, and although the initial body burden of the infant is also affected (we presume), this does not appear to be critical to the infant's subsequent body burden in the first weeks and months of life.

Summary and Future Research Needs

In this paper, we evaluated infant exposure to dioxin-like compounds via consumption of breast milk. Limited measurements in the literature showed that breast-fed infants had higher body burdens compared to formula-fed infants by up to one order of magnitude. Levels in breast-fed infants ranged from near 10 ppt TEQ lipid to > 50 ppt TEQ lipid, with levels in infants in a region known to be affected by a nearby source of dioxin release (metals reclamation plant) > 100 ppt TEQ. In contrast, formula-fed infants were almost always < 10 ppt TEQ and, in some cases, < 5 ppt TEQ.

We used a simple, one-compartment PK model to translate the dose of dioxin TEQs received by the infant via breast-feeding to a body burden, expressed as a lipid concentration. The PK model, while simplistic in both structure and assignment of parameters, nonetheless appears to predict TEQ body burdens that are within the range of observed body burdens. In a limited model validation exercise, the model predicted an average infant body burden of 26 ppt TEQ lipid for six infants who had been breast-fed, whereas the average observed body burden for those six infants was 24 ppt TEQ.

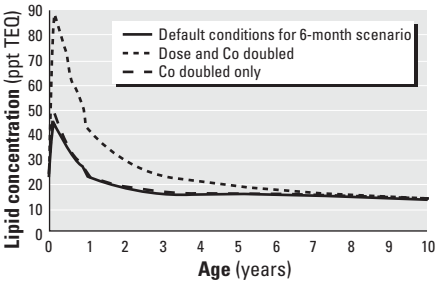

Figure 4. Sensitivity analysis showing how a doubling of dose affects the infant body burden for a 6-month breast-feeding scenario and how assuming a higher initial infant body burden affects the infant's body burden during the first 10 years of life. Co, initial TEQ concentration in infant.

We used this modeling framework to evaluate different breast-feeding regimes, including formula feeding only, and breast-feeding for periods of 6 weeks, 6 months, 1 year, and 2 years. First, we calculated temporally varying estimates of dose. Assuming a starting mother's milk concentration of 25 ppt TEQ lipid, we estimated infant doses to be 242 pg TEQ/kg-day at birth and 18 pg TEQ/kg-day after 1 year of breast-feeding. Using the PK model, we predicted that a peak infant concentration of 44 pg TEQ/g lipid would occur at 9 weeks of age. We found that the accumulated exposure to a child who had been breast-fed was significantly higher than a formula-fed only infant (where it was assumed that the infant dose via formula ingestion was similar to typical background exposures for young children). Specifically, ≥ 6 months of breast-feeding would result in accumulated exposure 6 times higher than a formula-fed infant during the first year of life, and this accumulated exposure would still be twice as high after 10 years. Over a lifetime, breast-feeding results in an accumulated exposure that is 3–18% higher than for a formula-fed infant, depending on the length of time of breast-feeding. Using a sensitivity analysis exercise, we demonstrated that the model is linearly responsive to dose received by the infant—doubling of the dose results in a doubling of infant impacts. This sensitivity exercise also showed that the model is relatively insensitive to the initial body burden of the infant. The infant's body burden adjusts very rapidly to the dose received: it declines quickly if the infant receives a low dose, such as from formula-feeding, and rises quickly if the infant has a much higher dose, such as from breast-feeding.

The model parameter of most uncertainty, and of significant impact to model results, is the overall dissipation rate assigned to TEQs. Empirical data in the literature has focused on the dissipation of TCDD in adults, with half-lives typically in the range of 7 years. Our assignment of this parameter for modeling infancy through adulthood was a hybrid of two approaches in the literature developed for PK modeling of TCDD. The model we used for infancy had half-lives < 1 year for this initial period in life, whereas the other model used for adulthood had half-lives from 6 to 20 years. Limited model validation suggested that the dissipation rate of TEQ in the infant was significantly higher (equivalently, the half-life was lower) than implied from data of TCDD in adults.

The U.S. EPA, in its draft reassessment of dioxin and related compounds (*23*), concluded that body burden is the most appropriate exposure matrix for evaluating the health consequence of exposure to dioxin-like compounds. Therefore, although the dose received by the infant via breast-feeding can be tens to even hundreds of times higher than the dose to an adult (on a body weight basis), the resulting body burden of the infant is within the range observed for adults. Specifically, even the peak body burden for the breast-feeding scenarios (44 ppt TEQ) is within a factor of 2 of the average adult body burden of 25 ppt TEQ. This elevation in infant body burden of dioxin-like compounds as a result of breast-feeding has been identified by several researchers in addition to the U.S. EPA (*2,3,4,19,22*); some of these studies have also concluded that the body burdens of breast-fed versus formula-fed infants have merged after a few years (*3,4*). However, the health consequence of this temporary elevation of infant body burdens is uncertain. The U.S. EPA (*23*), along with several others such as the American Academy of Pediatrics (*25*), concluded that the benefits of breast-feeding outweigh any potential risks associated with this practice, and they readily recommend breast-feeding over formula-feeding.

Future work on this PK model should focus on developing congener-specific half-lives that consider not only the differences in the absorption of these congeners in the body but, equally important, the metabolism of these congeners as a function of age. Additional data on infant impacts, such as infant blood TEQ concentrations to study the temporal change in infant body burden during the first weeks and months of life, would also be helpful in future validation of this and similar models.

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Pharmacokinetics of Toxic Chemicals in Breast Milk: Use of PBPK Models to Predict Infant Exposure

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Factors controlling the transfer of potentially toxic chemicals in the breast milk of nursing mothers include both chemical characteristics, such as lipophilicity, and physiologic changes during lactation. Physiologically based pharmacokinetic (PBPK) models can aid in the prediction of infant exposure via breast milk. Benefits of these quantitative models include the ability to account for changing maternal physiology and transfer kinetics, as well as the chemical-specific characteristics, in order to produce more accurate estimates of neonatal risk. A recently developed PBPK model for perchlorate and iodide kinetics in the lactating and neonatal rat demonstrates the utility of PBPK modeling in predicting maternal and neonatal distribution of these two compounds. This model incorporates time-dependent changes in physiologic characteristics and includes interactions between iodide and perchlorate that alter the distribution and kinetics of iodide. *Key words:* **breast milk, chemical exposure, lactation, PBPK modeling, pharmacokinetics.** *Environ Health Perspect* **110:A333–A337 (2002). [Online 13 May 2002]**
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Maternal milk has been recognized by public health officials as the most beneficial source of nourishment during infancy. The U.S. Department of Health and Human Services, through the Healthy People 2010 objectives, has set a target goal of early postpartum breast-feeding rates of 75% by the year 2010 (*1*). This emphasis on breast-feeding is motivated by the fact that breast milk provides the most complete form of nutrition for infants, imparts increased protection from diseases, and improves maternal health through the physiologic responses associated with lactation. However, potential risks associated with breast-feeding also need to be factored into the overall public health assessment when women are encouraged to breast-feed their newborn infants (*2*). For example, through the process of breast-feeding, it is possible for the mother to transfer to the suckling infant potentially toxic chemicals to which the mother has previously been exposed. Due to the rapid mental and physical changes that are taking place, neonates can be more susceptible to adverse effects resulting from chemical exposures (*2,3*).

Historically, the study of prescription drugs has provided a basis for understanding the governing principles behind transfer of chemicals through breast milk (*4*). These factors can be separated into two broad categories: maternal characteristics and chemical characteristics (*5,6*). Maternal characteristics include the degree of maternal exposure, physiology of the mother, maternal age, and parity (number of pregnancies). Chemical characteristics refer to aspects of the compound that affect its ability to be taken up in milk, such as the lipid solubility, degree of ionization, molecular weight, and ability to bind to maternal blood and/or milk components.

Maternal Factors and Physiologic Status

The most critical maternal factor in determining chemical dose to the infant is the extent and pattern of maternal chemical exposure. In the case of prescription drugs, dosage and frequency of ingestion are easily determined. For unintentional chemical exposures, whether they are environmental or occupational, the route and extent of exposure are often difficult to determine. It is necessary to recreate occupational, environmental, and even dietary influences to uncover possible sources of chemical exposure. Methylmercury (*6*) and polychlorinated biphenyls (PCBs) (*7,8*) are environmental contaminants that are concentrated in fish. In populations where fish is a large part of the diet, maternal consumption can determine the infant's exposure level to these toxins.

Maternal physiology, such as adipose tissue levels, age, parity, milk composition and volume, and breast-feeding patterns, also influence the amount of chemical passed to the infant (*9–11*). Lipophilic chemicals are partitioned into fatty tissue and can be stored there for long periods of time due to low blood flow in these tissues and limited tissue mass turnover. However, in the case of sudden weight loss, these chemicals can be released back into circulation, allowing them to be taken up into fat of the mammary gland. Maternal age and parity are also related to the transfer of chemicals in breast milk. Milk levels of dioxins would be likely to increase with maternal age, due to increases in extent of body fat, where the chemical accumulates. Conversely, milk levels of dioxins have been shown to decrease with increasing number of pregnancies (*12–14*).

Milk composition is quite variable, differing over the course of lactation as well as within individual breast-feeding sessions (*15,16*). Studies have shown human milk to contain high levels of protein (10%) in the first postpartum week, while lipid (fat) levels are relatively low (1%). However, the fat levels in mature milk increase (4%) and protein levels decrease (1%). Because the lowest relative lipid concentrations in milk occur during the first week after birth, when the milk is colostrum, transfer of highly lipophilic chemicals would be less likely to occur during early lactation. Conversely, because protein content is highest during this time, chemicals with high affinity for proteins may be more prone to be transported to the milk. Figure 1 shows the increase in fat content of human milk from a group of subjects over the course of lactation (*17*). Fat content increased significantly during the first 21 days of lactation, with a 40% increase in the first week, a constant level from 21 to 42 days, and a statistically insignificant increase to day 84, most likely due to decreased numbers of subjects in the study. Within feeding sessions, milk composition is also quite variable (*18*). For example, milk at the start of a feeding session contains less fat than milk at the end (1–2% vs. 4–6%). These changes in milk composition directly affect the amount of chemical transferred through milk due to possible interactions between milk components and the chemical of interest (*19*).

Chemical Characteristics

The aforementioned physical factors, together with chemical characteristics such as the polarity of the compound, determine chemical transfer in milk. Figure 2 shows the uptake of benzene (a lipophilic chemical) into milk versus the protein and triglyceride

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concentration of milk. The uptake of the organic chemical is directly related to milk fat content. However, there is no correlation between the amount of this hydrocarbon and the milk protein level. Nonpolar compounds are easily transported across lipid membranes and can be retained in milk fat due to their lipophilic characteristics (*21*). Ionic compounds are not expected to partition into milk in this manner. Some weak bases can preferentially enter the milk as a result of the pH gradient that exists between the blood (pH = 7.4) and milk (pH = 8), whereas other ionic compounds are transported into the milk via active uptake mechanisms (*22,23*).

Additional chemical-specific characteristics that help to determine the extent to which a compound will enter milk are molecular weight, maternal metabolism before transfer to the mammary gland, and protein binding in the plasma or mammary gland. In general, smaller compounds are transferred into mammary tissue more easily than those with high molecular weights (> 200 g/mol) (*24*). Some chemicals are metabolized within the mammary gland, resulting in lower levels of the original substance available for transfer to the infant (*25*). When chemicals are bound to protein in milk, they can accumulate, resulting in higher chemical concentrations. However, if protein binding takes place in the plasma, less chemical is available to enter the mammary gland, thereby reducing the milk concentration (*26,27*).

PBPK Modeling of the Transfer of Chemicals into Breast Milk

In addition to obtaining a qualitative understanding of the process by which infants are exposed to potentially toxic chemicals, it is important to quantitatively evaluate the risk of previous maternal exposure and predict possible infant doses that could result from inadvertent maternal exposures via occupation or environment. This was first accomplished with classical pharmacokinetic models; for example, Wilson et al. (*5*) used a three-compartment open model to describe the distribution and elimination of drugs in breast-feeding women. The infant dose was calculated by multiplying the maternal plasma drug concentration by the milk:plasma ratio (M:P) and the volume of ingested milk. However, Wilson et al. (*28*) drew attention to the significant uncertainty in this approach resulting from the fact that the concentrations of the drug in the mother's plasma and milk are time dependent and not always concurrent, which could lead to decreased accuracy in predicted infant exposure.

Recently, physiologically based pharmacokinetic (PBPK) models have been used to help quantify the transfer of a chemical to the infant during breast-feeding. These models of lactational transfer make it possible to account for time-dependent changes in maternal physiology and transfer kinetics, as well as chemical characteristics, in order to more accurately predict infant exposure. Shelly et al. (*29*) were one of the first research teams to employ PBPK modeling techniques in the development of a quantitative estimate of exposure to nursing infants from contaminated breast milk. These investigators used the model as a tool to describe the effect of the blood–air partition coefficient on the predicted distribution and potential delivered dose of inhaled volatile chemicals to infants via the breast milk. Although this work did not actually simulate laboratory data, it did provide the basis for estimating the impact of a chemical's lipid affinity on distribution to breast milk.

The use of PBPK modeling is also beneficial in reproducing changing exposure patterns (e.g., chronic vs. acute) and varied routes of exposure (e.g., inhalation vs. intravenous dosing). For example, Fisher et al. (*30*) developed a physiologic rat model for transfer of trichloroethylene from exposed dams to nursing neonates. Using this model, Fisher et al. (*30*) successfully described kinetic data for both TCE and its metabolite, trichloroacetic acid, in the dam and pup after both inhalation and intravenous exposures.

An additional benefit of using PBPK modeling is the ability to use epidemiologic and animal data to predict human dose–response relationships. Human dosing studies during lactation are rarely available because of ethical issues. Therefore, in many cases, only epidemiologic and animal studies are available for use in risk assessment. It is possible to build a PBPK model based on known changes in physiology during lactation and chemical kinetics for exposures not associated with lactation. Thus, relatively few data are required to develop the chemical kinetic parameters unique to lactation (e.g., uptake in the mammary gland) and to validate dose–response relationships from effects associated with chemical exposures.

Byczkowski and Fisher (*31,32*) developed a PBPK model for the lactational transfer of tetrachloroethylene (PCE) in the rat. The authors then scaled the validated rat model up to the human and tested against data in nonlactating men and women exposed to PCE occupationally and after a single dose. Byczkowski and Fisher (*31,32*) used this model to estimate the extent of an accidental acute exposure of a lactating woman to PCE from maternal blood and milk PCE concentrations measured at approximately 3 and 26 hr postexposure. An equation obtained from the U.S. Environmental Protection Agency (EPA) (*33*) was used to link dose predictions from the PBPK model to cancer risk estimates resulting from PCE to predict the neonatal risk at doses that were not measured experimentally.

In the case of MeHg, two human data sets are available in which maternal and infant tissues were measured after ingestion of MeHg-contaminated food (*34,35*). Due to the nature of the studies, it was not possible to measure the amount ingested to determine administered dose. However, Byczkowski and Lipscomb (*36*) were able to develop a PBPK model for the lactating woman and nursing infant based on a previous model for the pregnant human (*37*). By accounting for the differences in physiology (*38*) and using the

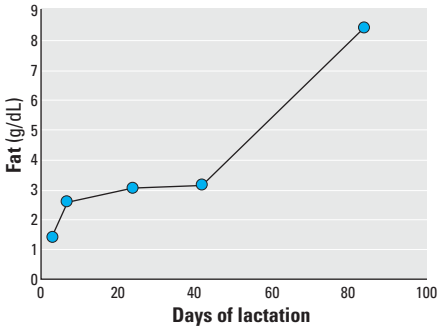

Figure 1. Changes in fat content of human milk during lactation in a group of mothers carrying their infants through normal pregnancy. Data from Bitman et al. (*17*).

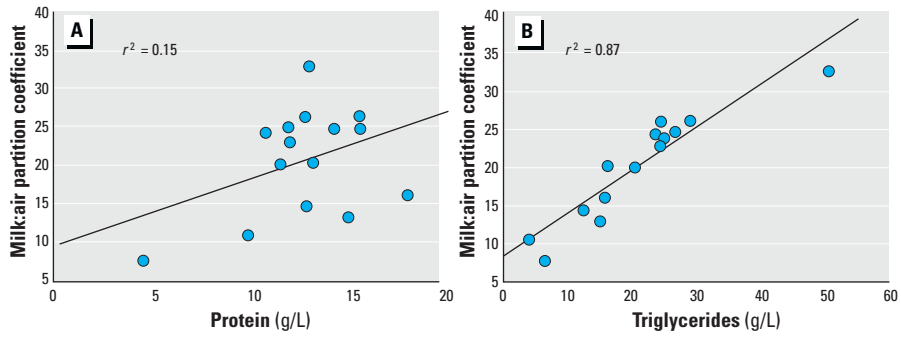

Figure 2. Effects of protein (*A*) and fat (triglyceride) (*B*) content on the human milk:air partition coefficient for benzene. Each point is one milk sample; all samples are from one human subject. Data from Greene et al. (*20*).

description of kinetics from the pregnant human model, Byczkowski and Lipscomb (*36*) used the lactation model to describe MeHg distribution from real-world exposures measured in maternal hair and milk, as well as infant blood, at both toxic and environmentally relevant doses. Additionally, they used the model to reconstruct the level and timing of MeHg exposure from tissue measurements taken after the episode.

Predicting transfer of inorganic chemicals via breast milk presents unique challenges that were not previously encountered in working with organic chemicals. Although the levels of organic compounds passed into the milk are based primarily on partitioning, both ionic compounds and metals are usually transferred into the mammary tissue via some type of transport process. Active transport can introduce higher concentrations into the milk than would be expected if only classical partitioning or binding were taken into consideration. For example, milk:plasma ratios > 1 have been reported for metals such as mercury (M:P = 3) (*39*) and cadmium (M:P = 2 to 6) (*40*) and for essential minerals such as iodide (M:P = 14–44) (*41*). Active transport mechanisms effectively concentrate necessary nutrients that are available in low concentrations from traditional food sources. However, when toxic chemicals are introduced in high levels through occupational or environmental exposure, they can have an adverse effect on postnatal development.

Manganese, for example, is an essential nutrient and a trace element. It is usually consumed in low levels by the mother and is therefore concentrated in milk in order to deliver the necessary levels to the infant (*42*). However, high levels of Mn can cause neurologic effects. Interestingly, maternal milk has been found to contain less Mn (~5 mg/L) than commercial soy-based formulas (several hundred milligrams per liter), suggesting that breast-feeding would result in a lower infant exposure to Mn (*43*).

PBPK Model for Perchlorate-Induced Inhibition of Thyroid Iodide Uptake

Perchlorate, the soluble anion of the solid rocket fuel ammonium perchlorate, is a thyroid iodide uptake inhibitor known to be present in the drinking water sources of several states (*44*). Because ClO_4^- has a similar size and shape to that of iodide, it is able to bind to sodium–iodide symporter (NIS) at the basolateral membrane of the thyroid epithelium, thereby reducing the amount of iodide available for hormone synthesis. The presence of NIS in the mammary gland also allows inhibition of iodide uptake, as well as the accumulation and transfer of the ClO_4^- anion, in the milk. Major health concerns

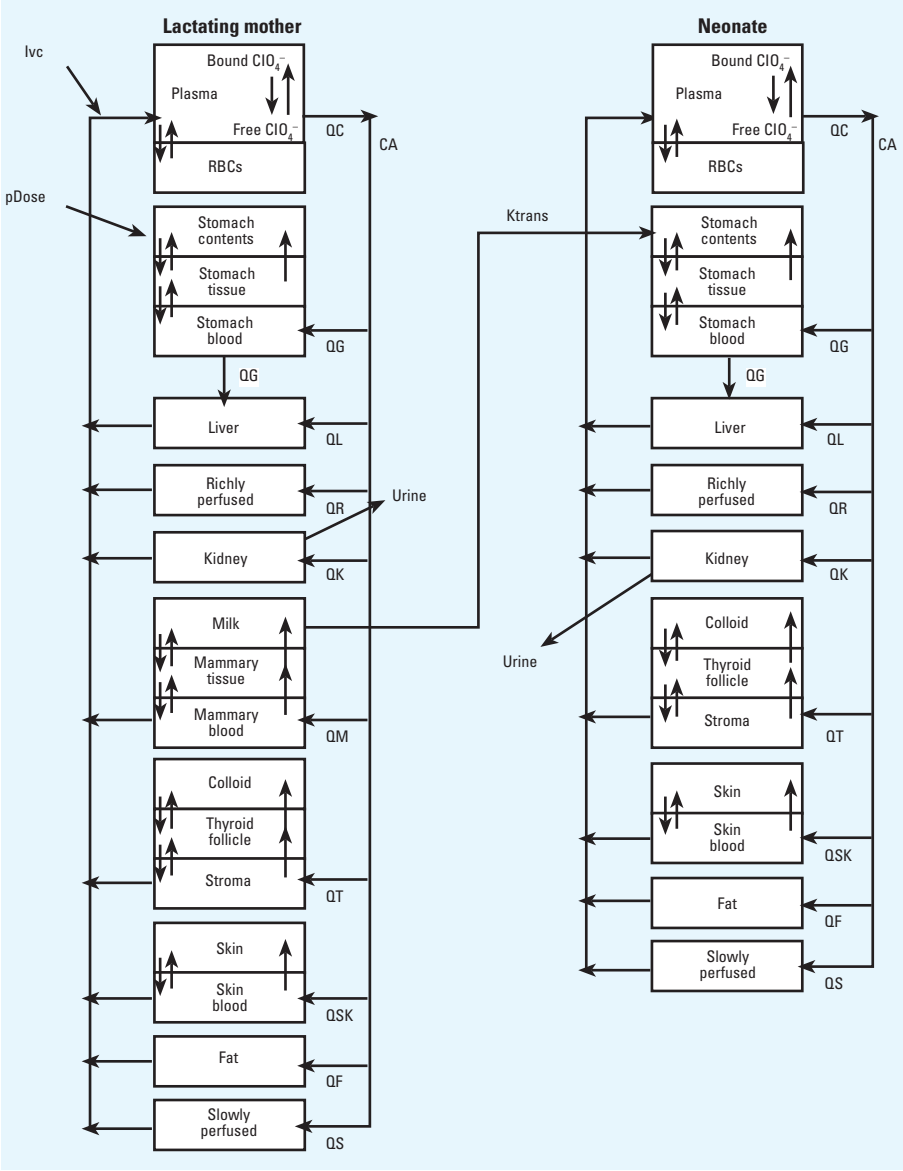

Figure 3. Model schematic for the lactational transfer of perchlorate and iodide from the mother to the neonate. Abbreviations: CA, arterial blood concentration; Ktrans, suckling rate; pDose, drinking water dose; QC, cardiac output; QF, blood flow total; RBCs, red blood cells.

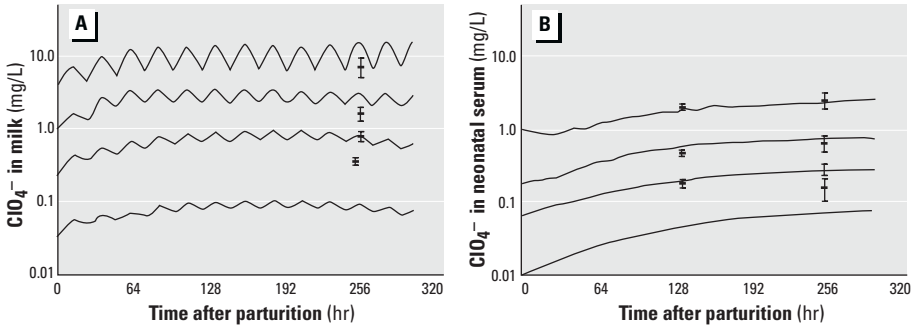

Figure 4. Perchlorate concentration in maternal milk (*A*) and male neonatal serum (*B*) after exposing lactating rats to 0.01, 0.1, 1.0, or 10.0 mg/kg/day ClO_4^- in drinking water. Solid lines indicate model prediction and cross-bars indicate mean ± SD of the data. Daily perchlorate dosing via maternal drinking water began during gestation and continued until the time of euthanization on either the 5th or 10th day of lactation. Data from Yu et al. (*48*).

from perchlorate exposure arise because thyroid hormones, which are synthesized from iodide, are necessary for normal physical and mental development during the period of rapid growth in late gestation and early infancy. Hypothyroidism and iodide deficiency are known to cause neurodevelopmental effects during this critical period (*3,45*). To quantify risk to the developing infant from maternal ClO_4^- exposure, we developed a PBPK model for perchlorate and iodide in the lactating and neonatal rat, focusing on the transfer of anions through milk and ClO_4^--induced inhibition of iodide in the thyroid as the measures of internal dose.

The perchlorate and iodide rat lactation models have compartments for the thyroid, stomach, skin, kidney, liver, fat, and plasma in the lactating dam and suckling neonate, and the mammary gland and milk in the dam. Tissues with active uptake include the mammary gland, milk, stomach, skin, and thyroid, and were described with multiple compartments and Michealis-Menten kinetics to simulate saturable transport. We obtained physiologic and kinetic parameters from the literature and from experiments. We obtained systemic clearance, milk transfer, and Michealis-Menten uptake parameters by fitting simulations to intralaboratory experimental data in the lactating and neonatal rat. The schematic of the lactation model for the rat and human is shown in Figure 3. A more complete description of the PBPK model for transfer of perchlorate in the lactating and neonatal rat has been published elsewhere (*46*).

The rat lactation model successfully describes the nonlinear behavior of ClO_4^- in the maternal thyroid and milk, as well as transfer to the neonate (maternal milk and neonatal serum; Figure 4). Iodide is also well described in the lactating and neonatal rat (maternal mammary gland and neonatal plasma; Figure 5). The model-predicted inhibition of iodide uptake in the maternal rat thyroid via exposure to ClO_4^- (shown against our measured data; Figure 6).

Although the primary concern is obviously the human effect, few data exist for human perchlorate exposure, and no quantitative ClO_4^- data in the lactating mother have been reported. Therefore, we first developed and validated PBPK models for both ClO_4^- and I^- in the rat and then extrapolated the models to the human by adjusting physiologic parameters. We scaled chemical-specific kinetic parameters allometrically from the rat lactation model, except for those parameters for which species differences are known to exist. We calculated kinetic parameters with significant species differences (e.g., follicular uptake and colloidal storage of iodide in the thyroid, ClO_4^- binding to plasma proteins) between the lactating human and the lactating rat using the ratio of male rat:human parameters derived from available data and the concurrently developed male rat and nonpregnant human models (data not shown).

We then validated the human model against available radioiodide data in lactating women and nursing infants. Figure 7 shows model-predicted iodide in human milk after a single intravenous dose of radioiodide ($^{131}I^-$) to the mother using the data of Dydek and Blue (*47*). Because only iodide data were available for model validation, we based extrapolation to human perchlorate kinetics on the assumption that if the model is able to describe both anions in the rat and is successfully extrapolated to human iodide exposure, then the model should also produce a reasonable estimate of predicted ClO_4^- kinetics in the human.

Summary

The advantage of using PBPK models for predicting perchlorate kinetics and iodide inhibition, as well as for other chemicals, is increased confidence in predicted kinetics under different exposure scenarios and in different species. Changes in physiology through most life processes (e.g., lactation), as well as mechanistic knowledge (e.g., binding or transport processes), can be incorporated quantitatively into the calculation of chemical kinetics. As a result, using these models, we are able to integrate data from a variety of sources, both animal and human, to improve both the accuracy and reliability of the resulting risk assessment.

In the case of perchlorate and iodide, we incorporated kinetic, mechanistic, chemical, and physiologic information into the model to quantify thyroidal inhibition of iodide uptake in the mother and chemical dose to the neonate in the absence of human data. In the case of MeHg, Byczkowski and Lipscomb (*36*) used a PBPK model to reconstruct maternal exposures associated with infant toxicity. Modeling of lactational transfer of lipophilic chemicals has also been used to predict exposures to nursing infants compared to maternal exposure as a function of chemical properties (*28*). These examples demonstrate the potential value of PBPK modeling for predicting the risk associated with breastfeeding from a quantitative perspective.

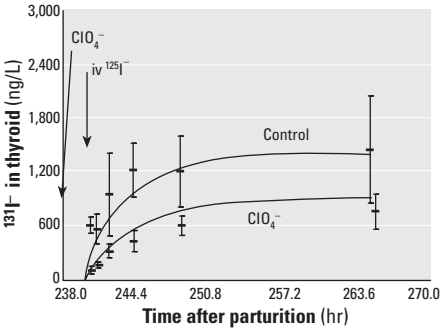

Figure 6. $^{131}I^-$ concentration in maternal thyroid of rats after an intravenous (iv) dose of 1.87 ng/kg $^{125}I^-$ to the dam, with or without an iv dose of 1.0 mg/kg ClO_4^- 2 hr later. Solid lines indicate model prediction and cross-bars indicate mean ± SD of the data. The iv doses of $^{131}I^-$ and ClO_4^- were given on the 10th day of lactation. Data from Mahle et al. (*49*).

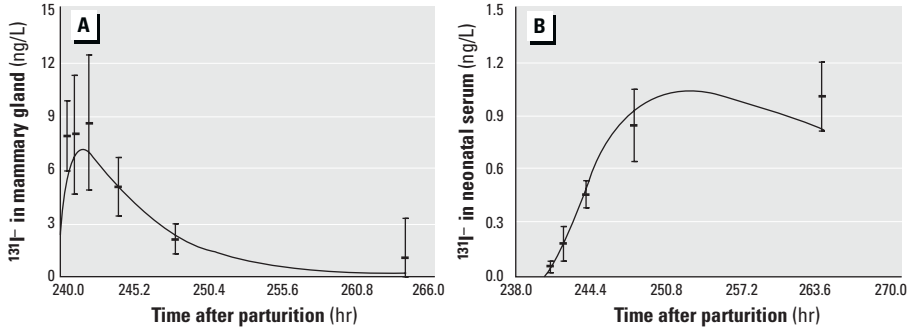

Figure 5. $^{131}I^-$ concentration in maternal mammary gland (*A*) and male neonatal serum (*B*) after exposing lactating rats to 2.19 ng/kg $^{125}I^-$ via intravenous injection. Solid lines indicate model prediction and cross-bars indicate mean ± SD of the data. Daily perchlorate dosing began via maternal drinking water during gestation and continued until the time of euthanization on either the 5th or 10th day of lactation. Data from Mahle et al. (*49*).

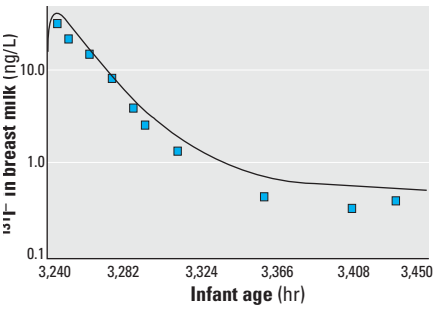

Figure 7. $^{131}I^-$ concentration in human milk of one mother after an oral dose of 77.4 ng $^{131}I^-$. Data from Dydek and Blue (*47*). Solid lines indicate model prediction and points indicate individual data points. The single intravenous dose of $^{131}I^-$ was given at 3,240 hr (fourth month of lactation).

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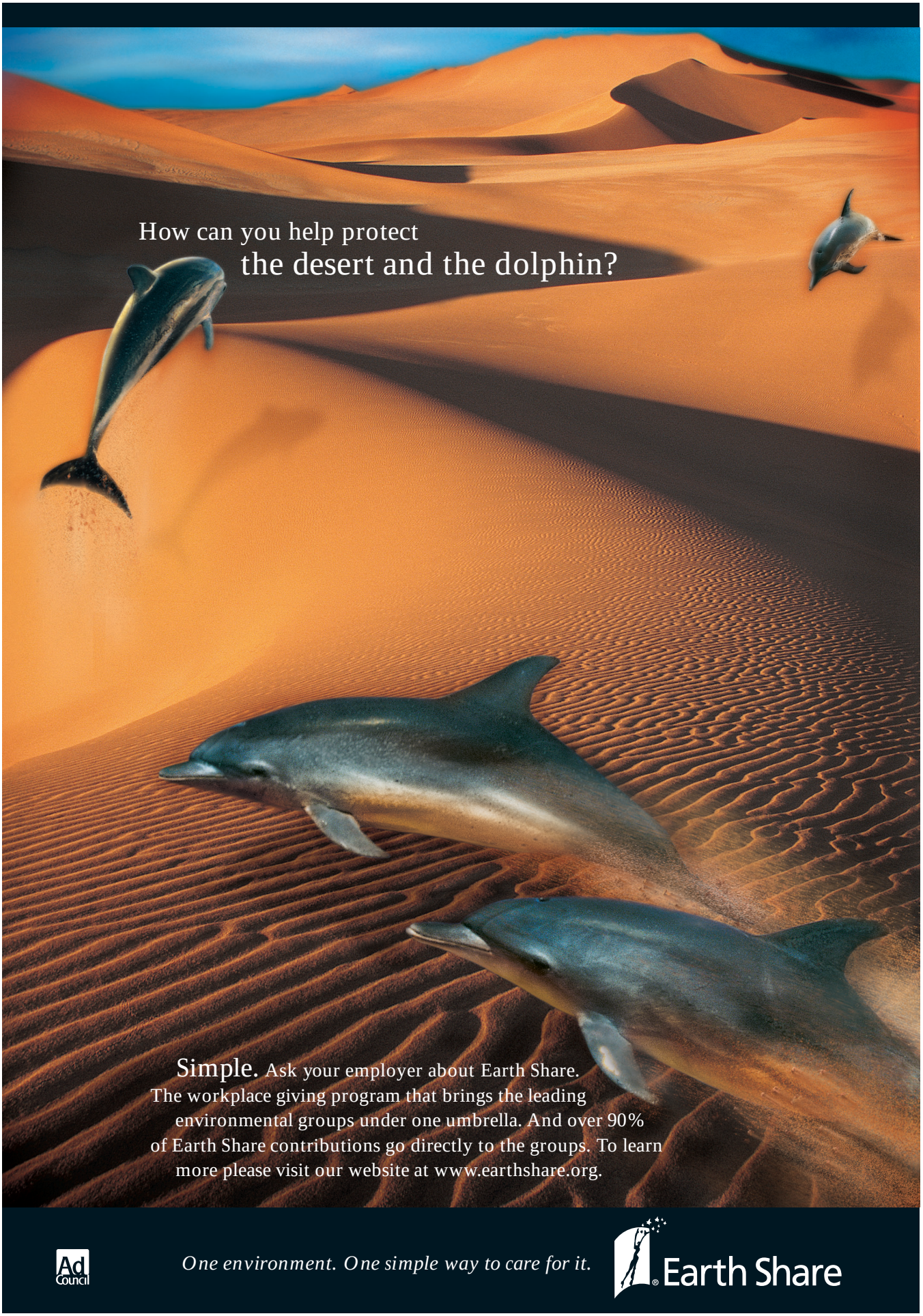
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Chemical Contaminants in Breast Milk: Time Trends and Regional Variability

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Research on environmentally related chemical contaminants in breast milk spans several decades and dozens of countries. The ability to use this research as an environmental indicator is limited because of a lack of consistent protocols. Data on xenobiotics in breast milk are influenced by choices in sample selection, sample pooling, analysis, and reporting. In addition, most studies have focused only on a small panel of persistent organic pollutants, despite indications that a wide range of additional chemical contaminants may also enter breast milk. Despite these limitations, however, it is possible to draw some generalizations. In this paper we review available data on levels of organochlorine pesticides, polychlorinated biphenyls (PCBs), polychlorinated dibenzodioxins (PCDDs), polybrominated diphenyl ethers (PBDEs), metals, and solvents in breast milk. Examples drawn from around the world illustrate the available data and the patterns that have appeared in various areas over time. Over the past few decades, levels of the organochlorine pesticides, PCBs, and dioxins have declined in breast milk in countries where these chemicals have been banned or otherwise regulated. In contrast, the levels of PBDEs are rising. Regional differences in levels of xenobiotics in breast milk are related to historical and current local use patterns. Diet is a major factor that influences breast milk levels of persistent organic pollutants, with patterns in fish consumption playing a particularly significant role. Improved global breast milk monitoring programs would allow for more consistent data on trends over time, detection of new xenobiotics in breast milk, and identification of disproportionately exposed populations. *Key words:* breast-feeding, breast milk, chemical contaminants, dioxins, pesticides, pollutants, polychlorinated biphenyls.
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http://ehpnet1.niehs.nih.gov/docs/2002/110pA339-A347solomon/abstract.html

Many nonpharmaceutical chemical contaminants, particularly those that are lipophilic and of relatively low molecular weight, can accumulate in breast milk. The potential health effects of these contaminants, also known as xenobiotics, on both mother and child is of great concern, making it important to carefully monitor contaminant levels and trends. Although some countries, most notably Sweden and Germany, have ongoing breast milk monitoring programs in place, data from the rest of the world are spotty. Few data exist for the United States and for most developing countries, particularly over the past two decades. Many of the studies that have been conducted are small and not necessarily representative of the larger population of the country where sampling was done. Almost all of the studies on xenobiotics in breast milk have focused on the same chemicals: organochlorine pesticides, polychlorinated biphenyls (PCBs), and dioxins. Few data are available on metals, solvents, and other chemicals. The fact that most studies have focused on the same panel of persistent organic pollutants (POPs) is problematic because it limits the ability to detect new or rising trends in contaminants and thereby may impede effective public health responses.

Efforts to compare levels of specific environmental contaminants across time and place are limited by other obstacles. There has historically been no standardized method for conducting breast milk monitoring studies, with the partial exception of those studies coordinated by the World Health Organization (WHO) (*1*). A range of issues including donor selection, the timing of sample collection, the use of preservatives in archived samples, and different methods for estimating population averages (pooled vs. single sample detection) can all significantly affect the results of a study and have made comparisons difficult (*2,3*). Studies may also differ in their data reporting or in their measurement variables. This is problematic because the quantity and presence of different congeners, metabolites, and impurities reflect different exposure scenarios and different stages in metabolism. Some studies report levels only for a subset of chemicals, so it is difficult to determine if gaps are a result of analytic limitations or if the data truly reflect different types of exposure.

The data that do exist suggest that bans and restrictions in recent decades on the use of many of the POPs have led to a decline in levels of these chemicals in breast milk (*3–6*). Conversely, there are other chemicals that have only recently been tested in breast milk whose levels may be increasing. The polybrominated diphenyl ethers (PBDEs), currently used as flame retardants, are the only set of chemicals known to be on the rise in breast milk (*7*); nothing can be said about the many chemicals not included in test panels.

All investigations of contaminants in breast milk must be sensitive to the overriding benefits of breast-feeding. The advantages of breast-feeding have been documented in the neonatal period and extend throughout childhood and into adulthood (*8*). There are also clear health benefits to the mother (*9*). Breast-feeding confers nutritional, immunologic, neurologic, and emotional advantages that have been well documented (*10*). Although the weight of the scientific evidence to date indicates that the advantages of breast-feeding outweigh any risks from contaminants in breast milk, it is important to identify contaminant trends, locate disproportionately exposed populations, and take public health measures to decrease and eliminate xenobiotics from breast milk. A review of data on levels of contaminants in breast milk from women around the world can provide useful information for guiding exposure reduction efforts and for demonstrating the utility of more consistent, routine, breast milk monitoring for a broader spectrum of chemical contaminants.

Study Design and Data Comparability

Numerous methodologic discrepancies in study design, sample analysis, and reporting make interpretation of the literature on contaminants in breast milk challenging.

Many of the studies are limited by small sample sizes. This problem is compounded by the common practice of pooling samples from study populations so that only an average is available, and variability within the group is not examined. Many studies include data from women of various ages, parity, and duration of breast-feeding. Because levels of many contaminants are associated with age, parity, and duration of lactation, the mixing of breast milk samples from women with these various characteristics makes it more difficult to identify differences related to actual exposure conditions. The selection of study participants may also bias study results. Some studies may have selected women participants based on potentially high exposure to the chemical of interest so

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that the reported values may not represent the general population of the region.

Perhaps the most critical methodologic challenge relates to chemical analysis. Analytic methods have varied widely. For example, it is difficult to compare studies of PCBs in breast milk because of differences in the number of PCB congeners measured, differences in the analytic method used, and differences in reporting the results (*11*). This issue can also be seen with the choice of dioxin congeners measured. In studies of dioxin levels in breast milk, the congener 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) is almost always measured. However, different researchers may measure different assortments of the remaining dioxins and furans. For coordinated studies, all 17 congeners must be measured so that data are comparable (*1,12*). Measurement issues are also evident with organochlorine pesticides that may have different metabolites measured in different studies. For example, numerous forms of the pesticide chlordane can be found in breast milk (oxychlordane, *trans*-nonachlor, *cis*-nonachlor, etc.). The quantity and presence of these different metabolites and impurities reflect different exposure scenarios and stages in metabolism. Depending on the study, there may only be levels reported for certain forms of the chemical. It is difficult to determine if these gaps are a result of analytic limitations or if the data truly reflect different types of exposure.

There are also distinct differences in the way breast milk monitoring data are reported. Some studies do not present information on the base population sampled, including occupational exposures, ages, parity, and other relevant variables. Furthermore, the conventions for reporting results have changed over time. For example, unlike many other chemicals whose toxicity is expressed in terms of a measured concentration, toxicity of dioxins and furans is conventionally expressed in terms of toxic equivalencies (TEQs) (*13*). The most common is WHO's International TEQ, or I-TEQ (*13*). But some studies use other toxic equivalency calculation schemes. In such cases, it is difficult to compare these with studies using I-TEQs.

Most methodologic problems stem from the lack of a standardized protocol for conducting breast milk monitoring programs. Many scientists have called for the adoption of a consistent method based on the WHO protocol, which addresses some (but not all) of the challenges described above (*3,12,14*).

Review of Available Data by Chemical

Despite the difficulties in generalizing across studies, there are some consistent predictors of levels of contaminants in breast milk (*4*). Levels of POPs are influenced by global and local use patterns of the chemical and by diet, maternal age, parity, and duration of lactation (*15*). Heavier local or regional use of POPs is consistently associated with elevated local or regional levels of residues in breast milk samples (*16,17*). However, the absence of local use does not mean that no contamination is detectable. Long-range transport and diet has resulted in detectable breast milk residues in countries where these chemicals were never used (*18*).

It is perilous to extrapolate from observed levels of contaminants in breast milk around the world to predict potential health effects or to declare specific levels safe. Although some regulatory agencies have set benchmark levels for some contaminants in breast milk, these benchmarks may not be completely reliable. Different international and national agencies may set different benchmark levels. In addition, some scientists have questioned whether current benchmark levels adequately protect the developing neonate from some of the more newly recognized health effects of organochlorine contaminants, such as endocrine-disrupting effects (*4*). In general, however, the levels of the organochlorine pesticides in countries where these chemicals have been banned have dropped well below all current benchmark levels. Commonly detected levels of dioxins and polychlorinated biphenyls, on the other hand, are above most regulatory benchmarks (*19*).

In the absence of poisoning incidents or local exposure, dietary exposure has been shown to be an important predictor of levels of many POPs in breast milk. In Germany, Schade and Heinzow (*20*) showed that women who ate a healthy diet (low meat consumption and high vegetable and fruit intake) for at least 3 years had much lower levels of hexachlorobenzene (HCB) and hexachlorohexane (HCH) in their breast milk compared to women who ate more than 700 g of meat per week. Dioxin exposure has also been shown to be strongly correlated with diet (*21*). Vegetarian mothers have been shown to have lower levels of dioxin in their milk compared to women who eat a diet rich in meat (*22*).

In general, bans on the production or use of POPs have been associated with decreasing residues of these chemicals in breast milk samples over the subsequent decades (*5*). Although levels have not declined to zero, there is evidence of downward trends. Conversely, continued use of POPs is associated with time-related increases in breast milk contamination. The following sections review some of the data on specific chemicals to illustrate time trends and regional differences in breast milk levels of common contaminants.

Chlordane. Chlordane, a mixture of more than 26 compounds, is an organochlorine cyclodiene pesticide. Chlordane has been used as an agricultural pesticide, on home lawns and gardens, and against termites. Chlordane has been banned in at least 47 countries and severely restricted in an additional 14 (*23*). Like most POPs, the breakdown of chlordane once it has attached to soil particles or sediment is very slow; in some cases, it has been found in soil up to 20 years after initial treatment (*24*). Chlordane is rapidly metabolized in organisms into oxychlordane and γ-chlordane or into impurities such as *trans*-nonachlor or *cis*-nonachlor. It is these breakdown products that persist in the tissue of fish, birds, and mammals and that are found in breast milk (*25*).

Studies examining chlordane metabolites in breast milk have been conducted in at least 14 countries, including Australia, Canada, Israel, Japan, Kazakhstan, Mexico, Russia, Spain, Thailand, the United States, and Scandinavian countries (*18,24–28*). Data from areas where chlordane was used show significant variability of levels associated with use patterns. For example, in the 1970s in the United States, lactating women in the southern states had an average of 113 ng/g lipid (range 108–118 ng/g) of chlordane in their milk compared to 79 ng/g (range 76–82 ng/g) among women living in other regions, probably due to agricultural use and more intensive home termite control (*24*). Similarly, in Japan in the 1980s, women living in homes where chlordane was used for termite control had breast milk chlordane levels 4.4 times higher than women whose households used no form of chlordane (*27*).

Chlordane residues, however, have not been confined to regions where the chemical was used. For example, chlordane was detected in the breast milk of women in Finland in the mid-1980s, even though the chemical was never used in Finland and was heavily restricted in neighboring countries. Exposure has been attributed to bioaccumulation in Baltic fish (*18*).

Despite the persistence of chlordane in the environment, data from Sweden demonstrate a declining trend in average breast milk residues of chlordane metabolites in the decades since the chemical was banned in most European countries (*28,29*). The peak concentrations of chlordane reported in the 1970s in Sweden were 4- to 5-fold lower than the contemporaneous average concentrations found in the United States (*25*).

Dieldrin and aldrin. Dieldrin and aldrin are closely related organochlorine insecticides that are extremely persistent in the environment. Both pesticides have been used in agriculture, and dieldrin was also used for vector control, for veterinary purposes, and for termite control (*30*). In both plants and animals, aldrin quickly converts to dieldrin.

Once present in soil or water, dieldrin breaks down very slowly, does not easily evaporate into the air, and binds to soil particles. Plants take up aldrin and dieldrin residues directly from the soil. In animals, including humans, dieldrin is stored in the fat and leaves the body very slowly (*31*). Dieldrin and aldrin are the most widely banned and restricted class of pesticides in the world (*32*). As of 1995, aldrin and dieldrin had been banned or severely restricted in more than 70 countries (*23*).

Studies evaluating residues of aldrin and dieldrin in breast milk have been conducted in at least 28 countries, including Brazil, France, Great Britain, Greece, Italy, Kenya, Saudi Arabia, Ukraine, and Vietnam. Dieldrin has been found in > 99% of breast milk samples tested in most countries (*33*). Because dieldrin is lipophilic and breast milk contains a much greater lipid concentration than blood, the level of dieldrin in a woman's milk is generally about six times higher than the level in her blood.

When dieldrin and aldrin first came into widespread international use, detection prevalence in breast milk rose dramatically. As countries have restricted and banned the use of both chemicals, the prevalence of detection has remained high, but levels detected in breast milk have dropped significantly (*25,28,34*). Some countries have seen a 10-fold decrease in the level of detectable dieldrin in the years following restrictions. Data from Sweden show a clear decrease in average levels of dieldrin detected in breast milk over several decades (Figure 1) (*28*). Data from Canada, Denmark, Germany, and Japan also show apparent decreases over time (*25,35,36*). Insufficient studies have been conducted in the United States, making it impossible to reliably document changes in dieldrin residues over time. The few data available suggest that the ban in the United States may have resulted in similar decreases (*25,35*).

In some countries with ongoing dieldrin use, breast-milk levels relate closely to local use patterns (*16,37*). In areas where dieldrin is used more heavily, levels in breast milk are often significantly higher. Studies in European countries and in the United States when dieldrin was still in use showed significantly higher concentrations of dieldrin in breast milk in southern areas than in northern areas. This has been attributed to higher agricultural pesticide use in the southern areas (*25*). Kenya still uses dieldrin in agriculture, and breast milk of women living in areas with intensive agricultural production has much higher levels of dieldrin than breast milk from women in nonagricultural areas. Figure 2 shows the differences in average dieldrin levels in breast milk during the 1980s around Kenya; the agricultural areas of Loitokitok had the highest levels (*16,17*). The dieldrin concentrations in Loitokitok are extremely high compared to benchmarks. For example, the U.S. Food and Drug Administration established an action level (the level at which it will consider removing a product from the market) for dieldrin residue in cow's milk of 7.5 ng/g lipid (*15*). The Kenyan study showed concentrations more than 300 times this level in breast milk. However, it is important to note that this benchmark has not been established as a true safety level for dieldrin. It differs from other benchmarks established by Codex Alimentarius and the WHO (*33*). There have been no studies that we are aware of evaluating exposures to dieldrin and adverse health effects in breast-fed children.

DDT. DDT (dichlorodiphenyltrichloroethane) is a commercial organochlorine insecticide that has been widely used on agricultural crops as well as for vector control (*38*). DDT and its by-products can persist in soil and sediments for more than 15 years and are known to bioaccumulate in animal tissues. As of 1995, DDT had been banned for all uses in 49 countries and restricted to vector control in 23 (*23*).

The half-life of DDT in humans is approximately 4 years. DDT's major metabolite, dichlorodiphenylchloroethane (DDE), has a half-life of approximately 6 years (*28*). The relative proportion of DDT and DDE detected in human tissues can be an indication of the length of time since exposure. In areas where DDT exposure is recent, the DDE/DDT ratio is low, whereas in areas where substantial time has passed since use, the DDE/DDT value is higher. Because DDE is attracted to fat, levels in breast milk are often six to seven times higher in a mother's milk than in her blood (*39*).

Although DDT residues in breast milk have been measured in more than 60 countries, only a few nations have comprehensive trend data where multiple studies have been done over time, using large study populations and consistent methods. After the restriction and ban of DDT in some nations, average breast-milk levels decreased substantially. Smith (*5*) analyzed trend data from around the world and found that the average levels of DDT in breast milk in most countries declined in direct correlation with the length of time since DDT restriction. DDT levels in breast milk in Sweden continuously declined from 1967 through 1997 (Figure 3) (*28*). The use of DDT was severely restricted in Sweden in 1970 and completely banned in 1975. Germany has also witnessed a rapid decline in average concentrations of DDT in breast milk. Between 1969 and 1995, detectable residue levels decreased by 81%. DDT was banned in Germany in 1972 (*20,22,25,36,40,41*). Other countries where studies have revealed a downward trend include Canada, Denmark, Norway, Switzerland, Turkey, Yugoslavia, the Czech Republic, Great Britain, Hong Kong, Israel, India, and Japan (*18,25,40,42,43*).

The difference between areas that currently apply DDT and those that have only the residue of past exposures is particularly evident in data from Zimbabwe and Mexico. DDT was banned for agricultural use in Zimbabwe in 1982 (*44*), but national averages for DDT in breast milk still show moderately high levels (~6,000 ng/g DDT in lipid). Exposure is generally in the form of DDE, indicating that exposure to DDT was not recent. However, the Kariba region of Zimbabwe, the only region that still actively uses DDT for malaria control, shows much higher levels of total DDT residues (> 25,000 ng/g DDT in lipid) (*44*). In 1984, WHO established an acceptable daily intake (ADI) level for consumption of DDT in milk. This value of 20 µg/kg/day can be converted into an acceptable level of 5,000–6,000 ng/g DDT in lipid (*5*). The levels of DDT in some regions of Zimbabwe are above that level.

In Mexico, DDT use has been partially restricted since 1972 and more stringently restricted since 1990. Since that time, overall

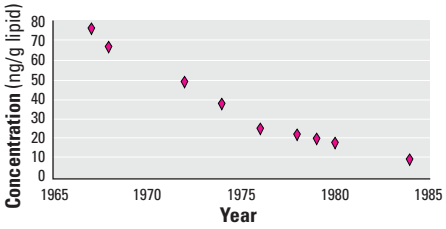

Figure 1. Dieldrin in breast milk in Sweden.

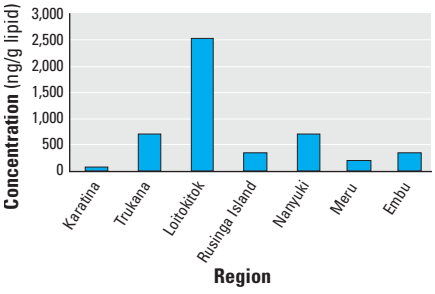

Figure 2. Dieldrin in breast milk in Kenya, 1983–1985.

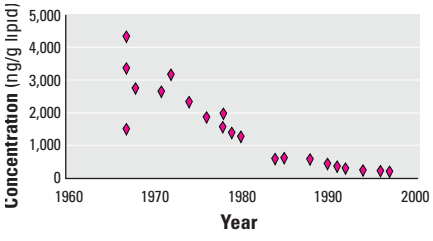

Figure 3. DDT in breast milk in Sweden.

average DDT levels in breast milk appear to have declined (*45–48*). Despite this downward trend, regional data give cause for concern in those parts of Mexico where DDT continues to be used for malaria control. In the suburban area near Veracruz City, for example, DDT is sprayed at least every 6 months on indoor surfaces and dwellings. Women from suburban areas of Veracruz have higher levels of DDT in their breast milk (average of 10,000 ng/g lipid) than do urban or rural residents of the same area (2,600 and 8,000 ng/g lipid, respectively). In addition, the ratio of DDE/DDT is lower in suburban women, suggesting that these women's residue levels stem from recent, direct exposure. In contrast, the women from the urban and rural areas have high DDE/DDT ratios, suggesting that their breast-milk levels have risen from historical exposures or from exposures through food (*49*).

The average levels of DDT in breast milk have varied considerably among nations. Figure 4 shows the wide range of levels of DDT found in breast milk in different countries between 1974 and 1976. It was during this time that many industrialized nations banned or began to restrict the use of DDT. At about the same time, use of DDT in developing nations was peaking (*18,25,28, 34,42,43,45,50–55*). Figure 4 reflects data from studies with different designs (as discussed previously). For some of the countries included in the figure, multiple studies may have been conducted in the same time period. Where multiple studies were conducted, the study with the largest study population was included in the figure (*25,28,34*). Some of the studies were included because no other data for that country exist. This graph illustrates the wide variation that may exist between regions worldwide.

Heptachlor. Heptachlor is an organochlorine cyclodiene pesticide that has been used to control termites and as an insecticide on seed grains and food crops. Heptachlor epoxide, the main metabolite of heptachlor, is extremely persistent in soil. In some cases, trace amounts of heptachlor epoxide have been found in soil 14–16 years after application (*56*). Plants can draw heptachlor epoxide directly from the soil, and the chemical bioaccumulates in animals. Heptachlor has been banned or restricted in more than 60 countries (*23,57*). However, some of these countries still permit its use for termite and other pest control, and many developing nations still use heptachlor for agricultural purposes (*58*). Despite the imposition of a ban on use in the United States in 1988, U.S. customs data showed that heptachlor was exported in large quantities through 1994 (*59*).

Judging from available data, heptachlor epoxide residue levels in breast milk appear to be decreasing. However, in the time frame for which data are available, the incidence of contamination increased. Early studies often detected heptachlor and heptachlor epoxide in < 10% of samples tested, whereas later studies approached 100% detection with similar analytic methods. As countries have restricted and banned heptachlor, levels detected in breast milk have dropped, often by more than 10-fold (*25*).

In Alberta, Canada, between 1966 and 1978, the average levels of heptachlor epoxide increased from an average of 2 ng/g lipid to 29 ng/g lipid (*35*). More striking, however, was the increase in the incidence of detection. From 1966 to 1970, only 5% of collected samples contained detectable levels of heptachlor epoxide. In a 1977–1978 study, the detection incidence had increased to 94% of collected samples (*35*). The use of heptachlor in Canada was discontinued in 1985 (*57*). The limited data available suggest that levels in breast milk have probably begun to decrease.

Regional differences have also been reported. In the United States, levels in the Southeast were nearly double the levels in the rest of the country during the period when heptachlor was still used (*24*). When heptachlor was still used in Belgium, women in the north had breast milk levels 4-fold higher than women in the south, probably related to agricultural use patterns (*25*). In Spain, a more than a 2-fold difference in heptachlor epoxide levels was found between rural and urban populations, probably due to agricultural use in rural areas (*25*).

Hexachlorobenzene. HCB is a persistent organochlorine chemical that is both a pesticide and an industrial by-product. Its main use is as a fungicide on seed grains (*25*). HCB is formed as an industrial by-product in chlorination processes, such as wastewater treatment (*60*). It also forms as a by-product in the manufacturing and production of the wood preservative pentachlorophenol, of chlorinated solvents such as perchloroethylene and carbon tetrachloride, and of various pesticides (*25,60*). HCB binds strongly to soil particles as well as to sediment and builds up in plants when it is present in soil (*61*).

Poisoning incidents in Europe and the United States involving HCB have illustrated the importance of diet as an exposure pathway for breast milk contamination. In an industrial area of Louisiana, cattle were quarantined because of high levels of HCB in their milk and fat. The source of the contamination was thought to be the area where the cattle grazed, which had been contaminated by the disposal of HCB wastes (*60*). The most notorious example of breast milk contamination by HCB occurred in Turkey in the 1950s. HCB-treated seed wheat intended for agriculture was used for food. Between 1955 and 1959, about 500 people were fatally poisoned by eating bread made with the contaminated seed. More than 4,000 people became ill as a result of the exposure. In some villages, almost all breast-feeding children under the age of 2 years whose mothers had eaten tainted bread died. Locally, this condition was called *pembe yara*. In one mother's breast milk during the incident, the HCB level was 20,000 ng/g in lipid, approximately 2,000 times the average levels of contamination found in breast milk samples around the world (*25,60*). Follow-up studies 20–30 years after the poisoning found average HCB levels in breast milk still more than 7 times the average for unexposed women in that part of the world (*62,63*) and 150 times the level allowed in cow's milk (*64*).

Studies evaluating HCB in breast milk have been conducted in at least 34 countries. Historically, women in areas with less industrialization have had significantly lower levels of HCB in their breast milk. For instance, average HCB levels detected in breast milk in Kenya in the mid-1980s were just 1% of average levels found in Sweden and Germany at a similar time (*17*). HCB levels in breast milk have declined in some industrialized countries over the past two decades, probably as a result of changes in fungicide use and procedural improvements in industry that have led to a reduction in the generation of HCB

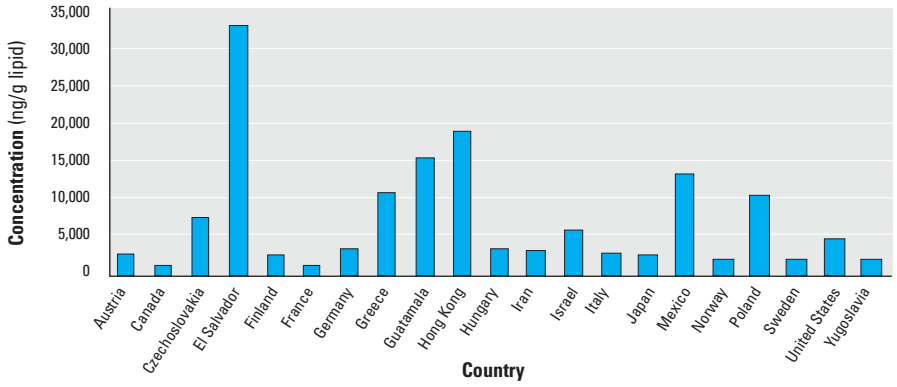

Figure 4. DDT in breast milk around the world, 1974–1976.

by-products (*25,28,36*). In Czechoslovakia, higher levels of HCB in breast milk were found in industrial areas. These areas (Prague and Kladno) were home to a variety of industries that emitted HCB (*65*). A study in 1992 found that HCB levels in the breast milk of women living in the Kola Peninsula of Russia were twice as high as in Norway and the Netherlands (*66*). This area also has much higher levels of industrial pollution than other parts of Europe.

Sweden has witnessed a clear decline in the levels of HCB detected in breast milk (Figure 5). In 1980, Sweden stopped using HCB as a fungicide. In addition, HCB production as an industrial by-product decreased with improvements in industrial technologies (*28*). Norway experienced a similar decrease, with levels of HCB in breast milk dropping by 65% between the mid-1970s and early 1990s (*67*). Studies conducted in Germany, Belgium, Canada, Denmark, the Netherlands, and Switzerland suggest a decline in the HCB levels found in breast milk, with a decline of more than 85% in Germany (*25*).

Hexachlorocyclohexane. HCH is an insecticide made up of a mixture of eight isomers. Different isomer forms have different levels of persistence and bioaccumulate in breast milk differently. The γ-isomer of HCH, also known as lindane, is widely used as an insecticide directly applied to the body and scalp to treat head and body lice. The β-isomer of HCH is the most persistent and bioaccumulative form. The α- and γ-isomers of HCH are converted into the β-isomer in organisms. As a result of this conversion, as much as 90% of HCH detected in human tissues and breast milk is β-HCH (*25*). HCH is banned or severely restricted in more than 60 countries. Lindane is specifically banned or restricted in 46 countries (*23*), but its use is often permitted for special uses by exemption. For instance, in the United States, mixed HCH has been banned as an insecticide, but lindane is still allowed as a pharmaceutical for topical application against head lice and scabies, and as a seed treatment.

Studies evaluating HCH contamination of breast milk have been conducted in 41 countries (*25*). In general, countries that have monitored breast milk for HCH residues over time have witnessed a steady decrease. Clear downward trends have been reported in the North Rhine Westphalia region of Germany and in Stockholm, Sweden, between 1974 and 1984 (Figure 6) (*28,36*). Since Japan banned HCH in the 1970s, levels of the pesticide in breast milk have decreased (Figure 7) (*25,55*).

HCH levels in breast milk are extremely variable and often reflect differences in regional use and exposure patterns. Unusually high levels of HCH in breast milk have been associated with areas of high use. In China and Japan, HCH was commonly used as an insecticide in rice fields, and levels as high as 6,500 ng/g of HCH in lipid have been measured in these countries (*25*). A 1982 study in Norway, a decade after HCH was banned in that country, found higher levels of the β-isomer of HCH in women who had immigrated from developing countries. Immigrant women had an average level of 433 ng/g β-HCH in their lipid, whereas native Norwegian women had an average of 80 ng/g. The difference was attributed to the likelihood of higher exposures in developing countries (*68*).

Dioxins and furans. Dioxins and furans are two closely related groups of chemical by-products that are produced throughout the world. The dioxin and furan congeners thought to be most toxic to humans are the 7 dioxins and 10 furans known as the 2,3,7,8-congeners. Most studies measuring human exposure to dioxins and furans focus on this group. In breast milk monitoring studies, the term "dioxin" refers to this group of 17 congeners.

Dioxins and furans are listed by several governmental and international agencies as known causes of cancer in humans. Studies have also linked dioxins and furans to reproductive problems, abnormalities in fetal development, immune alterations, and disruption of hormones (*19*). Unlike other contaminants discussed in this paper where little research into the health effects of low-level exposure is available, there has been considerable work showing effects of dioxin exposure at low levels near the range detected in breast milk (*13*). Dietary exposure makes up more than 90% of human dioxin intake (*21*). Because dioxins and furans are so persistent, lactation is one of the main routes of excretion.

Dioxins and furans have been measured in the breast milk of women from at least 35 countries, including Albania, Cambodia, Croatia, Estonia, the Faeroe Islands, India, Jordan, New Zealand, Pakistan, South Africa, Thailand, Vietnam, most European countries, and the United States (*12,13,28,69–79*). The general time trend in many countries seems to be toward a slight decrease of dioxin levels in breast milk over the past decade (*3*). In some countries, the decrease has been quite dramatic, with levels reduced by as much as 50% (*69*).

Coordinated WHO studies in Europe from 1986 to 1993 showed an average decrease in dioxin levels of approximately 35%, with consistently higher levels in industrial areas (*70*) (Table 1). Extensive data from Sweden (Figure 8) shows a downward trend in average breast milk levels over 25 years, with a relatively steep decline from the 1970s to the mid-1980s and evidence of a plateau since the mid-1980s(*28,74*). In many other countries, it has been difficult to make a national assessment of whether levels are going down because of regional variations. For instance, in Croatia, average breast milk levels of dioxin in Krk decreased between 1986 and 1988, while in Zagreb, they increased (*12,14*). Similarly, findings in Finland and Kazakhstan showed different trends for different regions (*12,14,79–81*). It is clear that regional variation is important, and different exposure scenarios may have resulted in extremely different levels.

More subtle regional variations have been identified in some studies. For example, in Finland, significant differences in the congener composition of dioxins in breast milk emerged in different regions of the country. The researchers eventually traced the differences to the types of fish consumed in these regions (*82*). Different species of fish were contaminated with different congener combinations. Similarly, the specific dioxin congeners associated with Agent Orange have been identified in some subpopulations. In Vietnam, concentrations of certain dioxin congeners in breast milk were especially high after intensive aerial spraying of Agent Orange during the Vietnam War (*83*).

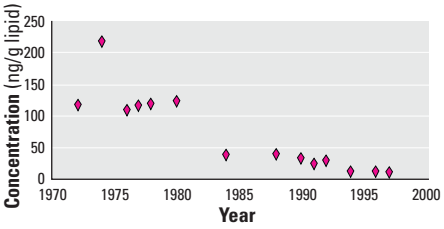

Figure 5. HCB in breast milk in Sweden.

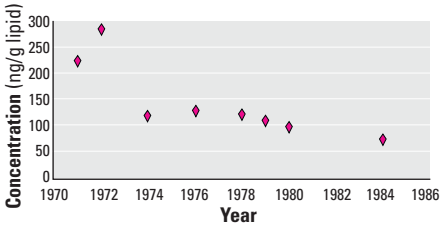

Figure 6. β-HCH in breast milk in Stockholm, Sweden.

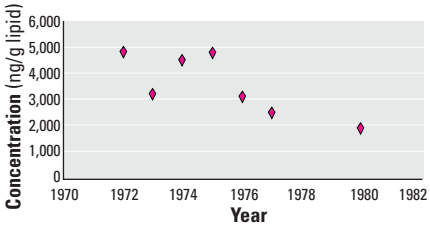

Figure 7. β-HCH in breast milk in Japan.

Especially high levels of dioxin in breast milk as a result of Agent Orange exposure have also been an issue in Kazakhstan (*80*). In Kazakhstan, women in one geographic region have some of the highest levels in the world of 2,3,7,8-TCDD in their breast milk: Levels in primiparous women in the most exposed area average 53.4 pg/g fat, 10 times higher than U.S. levels. The levels are most likely related to the use of Agent Orange to control weeds in the rice fields. The dioxin contaminants ran off into the lake and accumulated in fish, the dietary staple in the region.

Polychlorinated biphenyls. PCBs generally occur as a mixture of several of 209 individual congeners. These persistent chemicals were widely used as flame retardants, in surface coatings, and in electrical equipment such as transformers. The most serious effects of PCBs are on the brain. Low-level PCB exposures, particularly before birth, have been linked to lower IQ, hyperactivity, shortened attention span, and delayed acquisition of reading skills (*84,85*). PCBs interfere with thyroid hormone, and some researchers believe that this mechanism may explain some of the neurologic effects of PCBs (*86*). Thyroid hormone is essential for normal growth and development of the brain before birth and throughout infancy (*87*).

PCBs occur as environmental contaminants around the world. Researchers report that almost all samples of human blood, fat, or breast milk show some detectable level of PCBs (*88*). Many studies evaluating PCB levels in women have found concentrations in breast milk that are 4–10 times higher than in blood. However, some studies indicate that prenatal exposure (via transplacental transfer) of PCBs that may be more significant to the later health of the child (*11,89*).

PCBs have been measured in breast milk of women from at least 35 countries, including most of Europe, Greenland, Lithuania, Nigeria, the United States, and Zaire (*25,28,65,66,69*). Because of the challenges presented by the data measuring PCBs in breast milk, it is difficult to assess trends. Some researchers have speculated that, over the last 25 years, levels may have decreased slightly (*88*). However, that conclusion is hardly definitive, and the question will most likely remain unanswered until data standardization issues are addressed. In Sweden, where data have been collected following fairly consistent methods over time, evidence of a downward trend has emerged (Figure 9) (*28*).

Many researchers have investigated the role of diet in the level of PCBs present in breast milk. In the United States, fish consumption in the Great Lakes area has been associated with a higher body burden of PCBs (*90*). In Canada, Inuit and fishing populations have higher levels of PCBs in breast milk than do urban populations. Figure 10 shows the difference in some PCB congeners in breast milk levels of Inuit and Caucasian women in Quebec, Canada, in 1989 and 1990 (*69*). Inuit women, whose diet includes fish and marine mammals, had much higher breast milk levels than urban, Caucasian women. Fish and marine mammal consumption are not the only dietary exposures of concern. In the Czech Republic, the use of a PCB-containing paint in grain silos led to breast milk levels higher than those found in neighboring regions and countries (*65*).

Polybrominated diphenyl ethers. PBDEs are a class of widely used flame retardants. They are added to the plastic material in televisions and computers and are also found in construction materials, furniture, and textiles (*7*). Unlike the PCBs and many of the organochlorine pesticides, the PBDEs are still widely used throughout the world. The production and use of PBDEs have steadily increased since the 1970s. PBDEs can enter the environment during the production and disposal of materials containing PBDE flame retardants, as well as during the lifetime of PBDE-containing products. PBDEs are not chemically bound to plastics, so they can evaporate into indoor air or the outdoor environment (*91*). Once released, PBDEs can build up in the environment and in living organisms, binding strongly to sediment and building up in fish and other aquatic organisms (*7*).

The similarity of the PBDEs to dioxins and PCBs has been a concern because their negative effects on health may prove to be similar (*92*). In particular, scientists have found indications that the PBDEs may affect hormone function and may be toxic to the developing brain (*93*). The PBDEs have been associated with non-Hodgkin lymphoma in humans, a variety of cancers in rodents, and disruptions of thyroid hormone balance (*92*). No restrictions have been placed on the production and use of PBDEs, but the Swedish government has announced an intention to ban PBDEs in products sold in Sweden, based partly on the detection of these chemicals in breast milk (*28,92*).

Only a few studies have sought to measure PBDEs in breast milk. Extensive data from Sweden and some limited data from Germany have been collected. In the Swedish study, archived samples collected between 1972 and 1997 were analyzed for the presence of PBDEs to get an overall summed total of PBDEs in milk (*7,28*). An average for each time period was calculated (Figure 11). The data from Sweden show a logarithmic increase in the quantity of PBDEs detected in women's breast milk.

Toxic metals. A number of potentially toxic metals have been reported in breast milk, including lead, mercury, cadmium, and arsenic. Unlike the POPs, metals do not bind to fat and so do not usually accumulate to higher concentrations in breast milk than in blood (*94*). As a result, infants are likely to be exposed to higher levels before birth than during breast-feeding. Nonetheless, metals in breast milk are important as an additional pathway of exposure and as an indicator of likely prenatal exposures.

Metals have been detected in breast milk around the world. Twenty-six countries have conducted studies detecting toxic metals, including Bulgaria, Guatemala, Hungary, Iraq, Malaysia, the Philippines, Rumania, and the United States. A WHO study on trace elements in breast milk showed that levels of mercury are extremely variable around the world. Among women who eat a lot of fish, for example, levels of mercury in breast milk may exceed levels in unexposed women by 100-fold (*95*). Peak measured levels of lead and cadmium worldwide exceed the median by 10-fold, whereas the measured range for arsenic levels is low and very narrow (*22*).

Several studies have found higher blood lead levels in formula-fed infants than in breast-fed infants (*96*). This may be a result of contaminated formula cans or formula prepared using tap water with high lead levels. Lead levels in blood and breast milk correlate closely with areas where lead is still used in gasoline, with the highest levels in areas with heavy traffic. In addition, mothers in countries where lead is still used in gasoline, and mothers living near lead smelters have higher

Table 1. Dioxins in breast milk in the European Union.

	1988	1993	Change
Rural	28.2	17.7	37% decrease
Urban	29.5	19.2	35% decrease
Industrial	35.9	24	33% decrease

Data shown are average concentrations (pg I-TEQ/g fat).

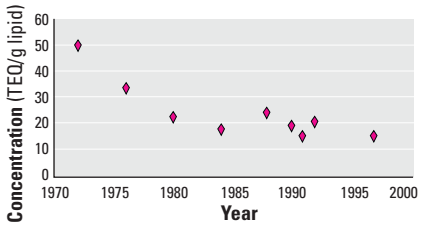

Figure 8. Dioxins in breast milk in Sweden.

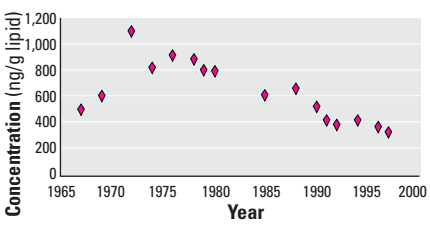

Figure 9. PCBs in breast milk in Sweden.

levels of lead in their breast milk due to community contamination (Figure 12) (*97*).

Much of the lead in breast milk does not come from the mothers' exposures during lactation. Instead, it comes from lead stored in the bones. Calcium extraction from bone is greatest during lactation, and, as a result, lead stored in the mother's bones also enters the blood and breast milk during pregnancy and lactation, posing an exposure risk to the fetus (*98*). Fortunately, sufficient calcium intake during pregnancy and lactation reduces the extraction of lead from bone (*99*). Thus women can significantly reduce their child's exposure to lead by getting adequate calcium during pregnancy and lactation.

Breast milk levels of mercury are usually lower than levels of lead. Mercury does not accumulate in breast milk; in fact, the levels in the mother's blood are generally about three times higher than the levels in milk (*97*). Therefore, prenatal exposure is generally more important than lactational exposure to mercury. Two major forms of mercury can enter breast milk. The most hazardous, methylmercury, does not enter breast milk at high rates because it is attached to red blood cells. But what little does get into breast milk is easily absorbed in the intestine of a nursing infant. The second form, inorganic mercury, enters breast milk easily but is not well absorbed in the infant's gastrointestinal system (*100*).

In the past, mercury has been responsible for mass poisonings in Minamata, Japan, and in Iraq. In both cases, food contaminated with methylmercury led to illness and death. Some of those affected were breast-feeding children whose mothers had eaten the contaminated food. However, in both of these scenarios, the levels of mercury were far higher than those reported in fish-eating populations today (*95*).

Cadmium levels in breast milk are significantly associated with cigarette smoking. One German study showed a direct relationship between the number of cigarettes a mother smokes per day and the level of cadmium in her breast milk (*101*). However, some studies indicate that an infant's exposure to cadmium from soy infant formula is about 20 times higher than the levels generally found in breast milk (*102*).

Solvents. Organic solvents are ubiquitous in both industrial and household settings. These chemicals are present in paints, varnishes, thinners, dry-cleaning fluids, some glues, degreasers, and gasoline. Solvents include a wide variety of chemicals with varying properties, defined more by their use than by their chemistry or toxicity. In general, organic solvents are highly volatile and readily absorbed through the skin. These chemicals are also common water contaminants. As a result of their widespread presence in the environment, solvents are found in human urine, exhaled breath, blood, and fat (*103*). Because solvents are relatively short-lived in the body, detection implies recent exposure.

Numerous organic solvents have been detected in breast milk, including benzene, chloroform, methylene chloride, styrene, perchloroethylene, toluene, trichloroethylene, 1,1,1-trichloroethane, and xylene (*104*). Breast milk levels of these compounds may be higher than blood levels in part because breast tissue does not eliminate solvents as quickly as does blood (*104*). Perchloroethylene, in particular, is known to concentrate in breast milk to levels about three times higher than levels in blood (*105*). That said, much of the research on this group of chemicals has been preliminary and is of two types: theoretical models estimating which solvents may get into breast milk, and small monitoring studies (*106*). The short-lived nature of solvents makes sampling difficult because samples need to be collected and transported in a specialized way and analyzed quickly so they do not evaporate away between the time of collection and the time of analysis. Most countries have not conducted studies of solvents in breast milk and have gathered no data representative of the general population. Due to limited data, it is possible only to conclude that some solvents get into breast milk; no information relevant to the levels of exposure, geographic differences, or time trends are available.

In one case report, a lactating mother who visited her husband daily at a dry cleaning firm had high levels of perchloroethylene in her milk (*107*). This case does not reflect normal population-level exposure to perchloroethylene; however, it is an important indicator of the potential for exposure to the nursing infant. A modeling study predicted elevated levels of perchloroethylene in the breast milk of women living in apartments in buildings containing dry cleaning businesses (*108*). In another modeling study, three solvents (perchloroethylene, bromochloroethane, and 1,4-dioxane) were estimated to accumulate in breast milk in excess of the U.S. Environmental Protection Agency's (EPA) health advisory level for drinking water if the mother was exposed at the legally allowable workplace limit (*105*). In addition, predicted breast milk levels of carbon tetrachloride and trichloroethylene were extremely close to the U.S. EPA health advisory level. These estimates are likely to underestimate potential risk to breast-feeding children of mothers exposed to solvents in the workplace because the U.S. EPA risk values used were for noncancer health effects in adults, whereas several of the solvents evaluated are carcinogens and the exposure is to neonates.

Solvents are an avoidable source of potential chemical exposures. Although little information has been gathered about these chemicals in breast milk, we do know that many solvents can enter the mother's body and then transfer into her milk. Because use of these chemicals is so widespread, the subject merits further research.

Summary

Although monitoring of environmental xenobiotics in breast milk has been relatively limited, the available data do provide some useful information about patterns of pollution over time and determinants of exposure. Many of the persistent organic pollutants have significantly decreased in countries that have placed bans on production and use. Exposure varies significantly based on local chemical use and on dietary habits in the population under study. International efforts to eliminate persistent organic pollutants may help address some of the areas where levels remain high.

Breast milk contamination is an important indicator of potential future public health and environmental problems. Increasing levels of the brominated diphenyl ethers and recent reported detections of other chemicals

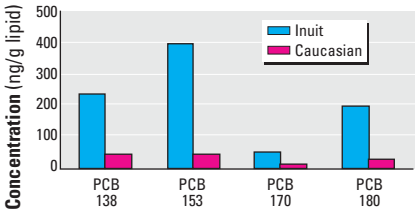

Figure 10. Specific PCB congeners in breast milk in Canada (1989–1990). Data from Dewailly et al. (*69*).

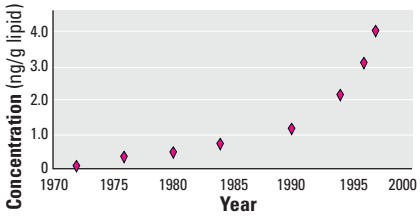

Figure 11. PBDEs in breast milk in Sweden.

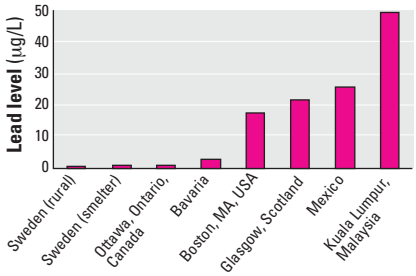

Figure 12. Lead in breast milk by location.

such as naphthalenes and various cosmetic products including musk xylenes, nitro musks, polycyclic musks, octyl methoxycinnamate, and benzophenone-3 (*74,109–111*) create a compelling reason to research the health effects of these chemicals, increase monitoring efforts, and design health-based strategies for reducing or eliminating exposure.

It is critical to move beyond studies of the same small group of chemicals in a few subjects in limited geographic areas using inconsistent protocols to a more systematic international breast milk monitoring program (*3,112*). Such a program would use a consistent protocol to monitor for an expanded range of suspected contaminants. The results would be useful to guide research and public health interventions worldwide. It is only with more information from many women and in many locations that we will be able to track trends, identify potential hazards, and protect future generations.

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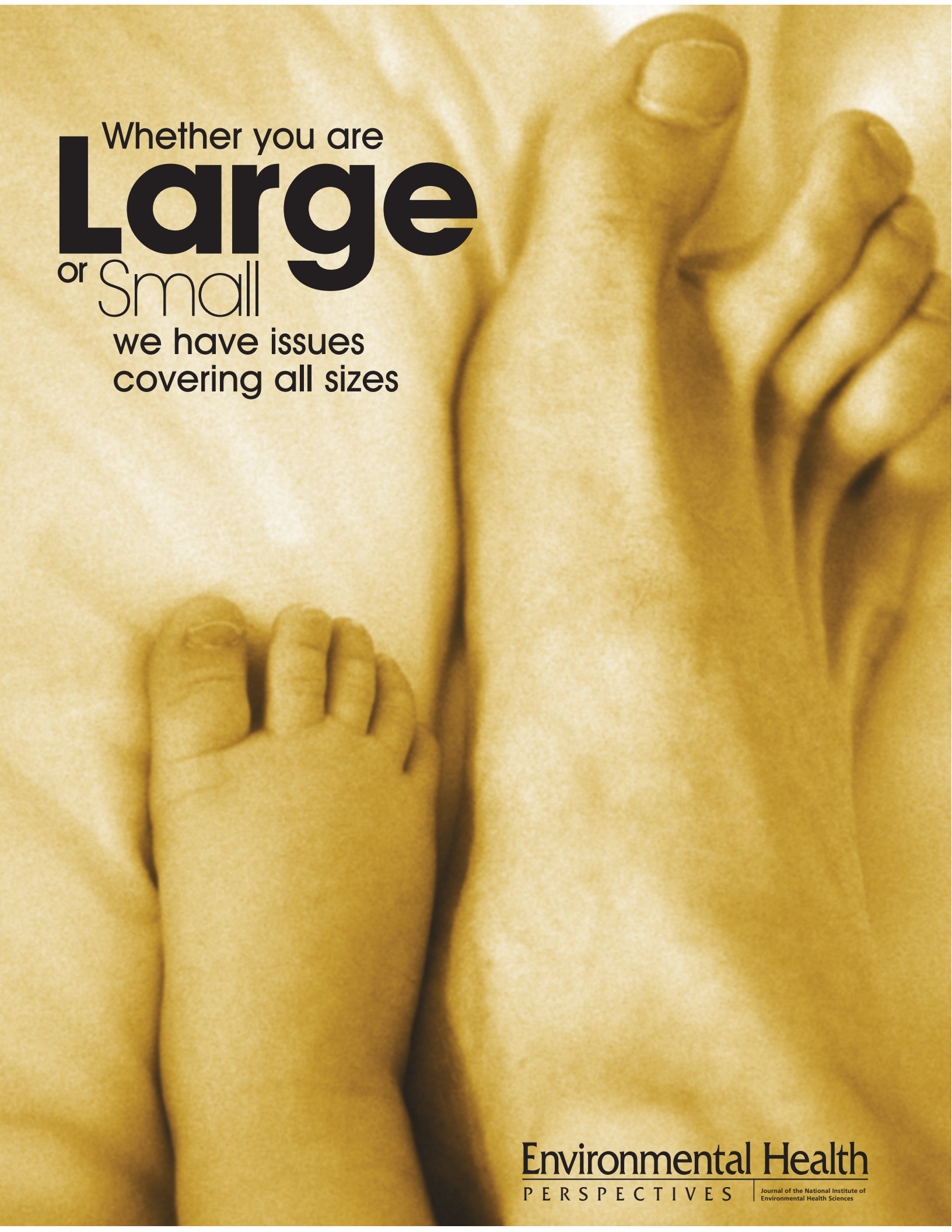

Environmental Health
PERSPECTIVES
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Global Perspectives in Breast Milk Contamination: Infectious and Toxic Hazards

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Breast milk is the natural and optimal food for infants. In addition to meeting nutritional needs, breast milk provides numerous immunologic, developmental, psychologic, economic, and practical advantages. It is postulated that breast-feeding may also be related to the prevention of some adult health problems such as diabetes and coronary heart disease. Malnutrition among infants and young children, which remains one of the most severe global public health problems, is among the main reasons that the World Health Organization (WHO) so strongly supports breast-feeding. However, WHO recognizes the growing concern expressed by scientists, health professionals, environmentalists, and mothers about the potential risks posed by the presence of toxicants and infectious agents in breast milk. In this paper we review the main infectious hazards (tuberculosis, hepatitis B, and human immunodeficiency virus) and selected chemical hazards (tobacco, persistent contaminants) and the activities undertaken by WHO. We conclude that in cases where there is a high degree of pollution from chemical sources occurring simultaneously in a bacterially contaminated environment, the choice is not simply between polluted breast milk and risk-free substitutes. Rather, informed choice is based on assessing the known and unknown risks of artificial feeding versus the unknown, but potential, risks of chemical contamination of breast milk. Clearly, the possible toxicity of compounds requires further investigation. Of much greater importance, however, are effective measures to protect the environment for the entire population by controlling the use of these toxic products. Current scientific evidence does not support altering WHO's global public health recommendation of exclusive breast-feeding for 6 months followed by safe and appropriate complementary foods, with continued breast-feeding, up to 2 years of age or beyond. *Key words:* **breast milk, chemicals, dioxins, infectious agents, hepatitis B, HIV, human immunodeficiency virus, pollutants, tuberculosis.** *Environ Health Perspect* **110:A349–A351 (2002). [Online 13 May 2002]**
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Breast milk is the natural and optimal food for infants. In addition to meeting nutritional needs, breast milk provides numerous immunologic, developmental, psychologic, economic, and practical advantages (*1*). Appropriate feeding practices are essential for the growth, development, health, nutrition, and survival of infants and children everywhere (*2*). It has been postulated that breast-feeding may also be related to the prevention of some chronic diseases (e.g., diabetes, obesity) (*3,4*). Malnutrition among infants and young children, which remains one of the most severe global public health problems, is among the main reasons that the World Health Organization (WHO) so strongly supports breast-feeding. Malnutrition is responsible, directly or indirectly, for fully 60% of the 10.9 million deaths annually among children under 5 years of age (*5*).

To protect breast-feeding from commercial influences, in 1981 WHO adopted the International Code of Marketing of Breast-milk Substitutes, which is now being implemented worldwide. Together with the United Nations Children's Fund (UNICEF), in 1991 it launched the Baby-friendly Hospital Initiative so that maternity services can effectively protect, promote, and support breast-feeding. In a recent recommendation, WHO urged its member states to strengthen activities "to protect, promote and support exclusive breast-feeding for 6 months as a global public health recommendation, and to provide safe and appropriate complementary foods, with continued breast-feeding for up to 2 years of age or beyond" (*6*).

WHO recognizes the growing concern expressed by scientists, health professionals, environmentalists, and mothers about the potential risks posed by the presence of toxicants and infectious agents in breast milk. WHO programs dealing with chemical safety, food safety, reproductive health and research, human immunodeficiency virus (HIV)/AIDS, nutrition, vaccines and immunization, communicable diseases, and child and adolescent health and development currently address these issues. A number of studies are promoted, guidelines are issued, and recommendations made on matters related to potential infectious and toxic risks.

For example, WHO has prepared guidance on breast-feeding and hepatitis B, tuberculosis, and HIV transmission, which are among the main global infectious disease threats to human health. In addition, a number of studies have been promoted and recommendations made concerning selected environmental pollutants; additional information is available on the WHO Homepage on the Internet (*7*). A brief overview follows.

Main Infectious Hazards

In all cases of maternal tuberculosis, mothers should be treated with an appropriate therapy such as the standard short-course regime with isoniazid, rifampicin, pyrazinamid, and ethambutol (which are safe during pregnancy and breast-feeding); infants should not be separated from their mothers, and breast-feeding should be encouraged (*8*). Additional recommendations depend on the timing of diagnosis. When maternal tuberculosis is diagnosed > 2 months before delivery, and if the sputum smear is negative just before delivery, the infant should be immunized with BCG (*Mycobacterium bovis* Bacillus Calmette-Guerin) as soon as possible, but preventive chemotherapy should not be given. However, if the smear is positive, the infant should receive isoniazid for 6 months and be immunized with BCG after stopping isoniazid. When maternal tuberculosis is diagnosed 2 months before or after delivery, the infant should receive isoniazid for 6 months and be immunized with BCG after stopping isoniazid. When maternal tuberculosis is diagnosed > 2 months after delivery, the infant should receive isoniazid for 6 months and be immunized with BCG if it was not given at birth (*9*).

Hepatitis B virus infection (HBV) is of major public health importance: there are > 350 million chronic carriers, and complications kill about 1 million people annually. In highly endemic areas (Southeast Asia and sub-Saharan Africa), transmission occurs mainly perinatally or through close contact between children. In areas of low endemicity (including Western Europe and North America), perinatal transmission is less common (*10*). Even though the HBV antigen has been detected in breast milk, there is no evidence that breast-feeding increases the

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risk of mother-to-child transmission (*11,12*). The risk associated with breast-feeding is negligible compared to the high risk of exposure to maternal blood and body fluids at birth. Some concern exists about breast pathology (cracked or bleeding nipples, lesions with exudates) that could expose the infant to infectious doses of HBV. Immunization can prevent development of the persistent carrier state in 70–90% of infants of carrier mothers, and protection can increase to 85–90% when hepatitis B immunoglobulin (HBIg) is administered within 24 hr of birth together with the first dose of vaccine (*13*). WHO recommends that all infants receive hepatitis B vaccine as part of routine childhood immunization, the first dose to be given within 48 hr of birth when feasible. Breast-feeding remains the recommended method of feeding (*14*).

It has been estimated that 800,000 children younger than 15 years of age were newly infected in 2001 and that > 90% were due to mother-to-child transmission (MTCT) (*15*). Breast-feeding is associated with an increased risk of transmission, depending on duration and other risk factors. In untreated women who continue breast-feeding after the first year, the absolute additional risk of transmission is 10–20% (*16,17*). This risk must be balanced against the increased risk of morbidity and mortality due to malnutrition and diarrheal or other infectious diseases associated with replacement feeding (*2*). In addition, evidence from one study suggests that exclusive breast-feeding in the first 3 months of life may carry a lower risk of HIV transmission than partial breast-feeding (*18*). A three-pronged strategy is recommended by United Nations agencies for the prevention of MTCT, which includes the primary prevention of HIV infection among expectant parents, the prevention of unwanted pregnancies in HIV-infected women, and the prevention of viral transmission with antiretroviral regimens, improved obstetric care, and safer feeding practices. Interventions such as long and complex courses of zidovudine, cesarean section, and avoidance of breast-feeding have shown to reduce HIV transmission from mother to child (*19*). However, these measures are not always practical or safe in resource-limited settings.

A technical consultation on the prevention of MTCT convened by WHO/UNICEF/UNAIDS (Joint United Nations Programme on HIV/AIDS) in October 2000 (*20*) made the following recommendations: only when replacement feeding is acceptable, feasible, affordable, sustainable, and safe is avoidance of all breast-feeding by HIV-infected mothers recommended; otherwise, exclusive breast-feeding is recommended during the first months of life. Mothers should be advised to discontinue breast-feeding as soon as possible, taking into consideration local circumstances, the situation of the mother, and the risks associated with replacement feeding. For women who are HIV negative or whose status is unknown, exclusive breast-feeding for 6 months, with adequate complementary feeding and continued breast-feeding thereafter, should be encouraged.

Selected Chemical Hazards

A number of drugs, industrial chemicals, and environmental contaminants can be present in breast milk. Reports on the potential effects resulting from exposure to toxic substances in breast milk are found in the medical literature and in statements by scientific bodies. For example, antianxiety drugs, antidepressants, neuroleptics, nicotine, and silicones have been considered recently by the American Academy of Pediatrics (*21*).

Smoking represents a special hazard. It increases the exposure of mothers and infants to many chemical compounds, including pesticide residues and known carcinogens. It is associated with increased levels of chemical contaminants in milk as well as reduced duration of breast-feeding and increased levels of infant distress ("colic"). Women who smoke should be encouraged to breast-feed and to eliminate, or at least reduce, cigarette smoking during pregnancy and lactation.

In the last decade, major concern has been expressed and there has been some debate about the presence of environmental contaminants such as heavy metals (e.g., mercury, lead), pesticides, and persistent organic pollutants in breast milk and their potential effects on the health and development of infants. In some instances, mothers with known or suspected high levels of contaminants in breast milk due to acute or chronic exposure have been advised to reduce or interrupt breast-feeding. For example, workers exposed to polychlorinated biphenyls (PCBs), women consuming high fish diets in highly polluted areas, women affected by the Yusho incident in Japan who ingested rice oil contaminated with PCBs and furans, and women affected by the Yu-cheng incident in Taiwan where cooking oil was contaminated by PCBs and other polychlorinated compounds, have been advised to reduce or interrupt breast-feeding. Exposure to PCBs and dioxins has been associated with a greater susceptibility to infectious diseases in infants (e.g., middle-ear infections, chickenpox) and a lower prevalence of allergic reactions.

WHO's Regional Office for Europe (WHO/EURO) coordinated two studies (1987–1989 and 1991–1993), in collaboration with other organizations, to evaluate the levels of dioxins in mother's milk (as a surrogate measure for body burden). A third study is in progress. These studies aimed to assess the possible health risks, especially in infants, and to control and prevent environmental exposure to those contaminants. The studies included the consideration of polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), dioxin-like PCBs, and other PCBs. In March 1994, the Bilthoven Division of WHO/EURO organized a consultation to review the available results of the first two studies and concluded that *a*) levels of PCDDs and PCDFs were not increasing, although the situation for PCBs was unclear (noncomparable analytic methods had been used); *b*) primary preventive measures to limit environmental pollution were the most effective way to limit exposures; and *c*) breast-feeding should be encouraged and promoted due to its multiple benefits for the overall health and development of infants.

Based on available evidence, the WHO/EURO consultation noted that infant exposure through breast milk was considerably less important than exposure *in utero*. Risk management should thus aim to limit intake of contaminated food by the mother rather than restrict breast-feeding.

In 1998, the Global Environment Monitoring System, Food Contamination Monitoring and Assessment Programme assessed the risk of selected organochlorine contaminants in breast milk. Data were reviewed on breast-milk levels of DDT complex, hexachlorobenzene (HCB), γ-hexachlorocyclohexane (γ-HCH; lindane), isomeric mixtures of HCH (aldrin and dieldrin) and PCBs. The reported levels of residues in human milk of the HCH isomers aldrin and dieldrin were close to reference intake values (few reported higher values). DDT was reported in higher concentrations in developing countries, and HCB levels were high in industrialized countries. The levels of PCBs in breast milk raised greatest concern. In industrialized countries, concentrations exceed the reference intake of 1 μg/kg of body weight; however, levels over time were stable or only slowly decreased.

The overall conclusions from this assessment were that *a*) responsible authorities should consider incorporating into national risk assessment procedures mechanisms to assess potential health risks posed by breast-milk contaminants; *b*) decision making for any contemplated intervention should include a quantitative estimate of risk-based reference intakes for breast-milk contamination and take into account the well-established benefits of breast-feeding as well as socioeconomic factors; and *c*) under most circumstances authorities can and should reassure mothers that breast milk is by far the best food for their babies.

Conclusion

In cases where there is a high degree of pollution from chemical sources occurring simultaneously in a bacterially contaminated environment, the choice is not simply between polluted breast milk and risk-free substitutes. Rather, informed choice is based on assessing the known and unknown risks of artificial feeding versus the unknown, but potential, risks of chemical contamination of breast milk. Clearly, the possible toxicity of compounds requires further investigation. Of much greater importance, however, are effective measures to protect the environment for the entire population by controlling the use of these toxic products.

The subtle effects observed in studies are associated more with transplacental exposure rather than with exposure through breast-feeding. Current scientific evidence does not support altering WHO's recommendation for exclusive breast-feeding for 6 months as a global public health recommendation and the provision of safe and appropriate complementary foods, with continued breast-feeding for up to 2 years of age or beyond.

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