Environmental chemicals in human milk: a review of levels, infant exposures and health, and guidance for future research

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Abstract

The aim of this review is to introduce the reader to various science and policy aspects of the topic of environmental chemicals in human milk. Although information on environmental chemicals in human milk has been available since the 1950s, it is only relatively recently that public awareness of the issue has grown. This review on environmental chemicals in human milk provides a resource summarizing what is currently known about levels and trends of environmental chemicals in human milk, potential infant exposures, and benefits of breast-feeding relative to the risks of exposures to environmental chemicals. The term “environmental chemicals,” as it pertains to human milk, refers to many classes of exogenous chemicals that may be detected in human milk. For example, pharmaceutical agents and alcohol are environmental chemicals that have been found in human milk. Other chemicals, such as heavy metals and volatile organic compounds, have also been detected in human milk. Most research on environmental chemicals in human milk has concentrated on persistent, bioaccumulative, and toxic (PBT) chemicals. In this review, a description of human milk is provided, including a brief review of endogenous substances in human milk. Determinants of levels of PBTs are discussed, as are models that have been developed to predict levels of PBTs in human milk and associated body burdens in breast-feeding infants. Methodologies for human milk sampling and analysis, and concepts for consideration in interpretation and communication of study results, as developed by the Technical Workshop on Human Milk Surveillance and Research for Environmental Chemicals in the United States are described. Studies which have compared the health risks and benefits associated with breast-feeding and formula-feeding are discussed.

Keywords: Human milk; Persistent bioaccumulative chemicals; Pharmaceuticals; Drugs; Models; Endogenous chemicals; Trends; Health effects; Technical Workshop on Human Milk Surveillance and Research for Environmental Chemicals in the United States

Introduction

The aim of this review is to introduce the reader to various science and policy aspects of the topic of environmental chemicals in human milk. Although information on environmental chemicals in human milk has been available since the 1950s, it is only relatively recently that public awareness of the issue has grown. This review on environmental chemicals in human milk provides a resource summarizing what is currently known about levels and trends of chemicals in human milk, potential infant exposures, and benefits of breast-feeding relative to the risks of exposures to those chemicals. In addition, methodologies for human milk sampling and analysis, and concepts for consideration in interpretation and communication of study results, as developed by the Technical Workshop on Human Milk Surveillance and Research for Environmental Chemicals in the United States, are described (proceedings in Journal of Toxicology and Environmental Health, vol. 65, no 22).
The term “environmental chemicals,” as it pertains to human milk, refers to many classes of exogenous chemicals that may be detected in human milk. For example, pharmaceutical agents and alcohol are environmental chemicals that have been found in human milk having originated from the mother’s voluntary exposures. Other chemicals, such as heavy metals and volatile organic compounds, have also been detected in human milk, principally from involuntary exposures. Most of the research on environmental chemicals in human milk has concentrated on a group of chemicals referred to as persistent, bioaccumulative, and toxic (PBT) chemicals. There are both practical and health-related reasons for concentrating on PBT chemicals. One practical reason is that these chemicals tend to be lipophilic (“fat-loving”) and persistent. Because human milk is rich in lipids, these chemicals have been reported in human milk in populations around the world, even in geographically remote regions. Thus, there is a relatively large database on these chemicals in human milk, which can be used to determine trends in chemicals over time and to examine potential associations between levels of chemicals and characteristics of the mother (e.g., diet, age, parity). The PBTs include several organochlorine pesticides, polychlorinated biphenyls (PCBs), dioxins and furans, and polybrominated diphenyl ethers (PBDEs). For detailed information on each of these PBTs, including information on manufacture, use, disposal, exposure, and health effects, the reader is referred to the toxicological profiles prepared by the Agency for Toxic Substances and Disease Control (ATSDR) (http://www.atsdr.cdc.gov/toxprofiles/tp17.html) and to the US EPA’s Priority PBT Profiles (http://www.epa.gov/opptintr/pbt). For additional information on dioxins and furans, the reader is referred to the US EPA’s Draft Dioxin Reassessment (USEPA, 2000).

In addition to PBTs, much is known about levels of pharmaceuticals in human milk and their potential to cause harm to the nursing infant. The American Academy of Pediatrics has published reviews on pharmaceuticals in human milk (AAP, 2001); fundamental information is summarized in this review.

In this review, we will first provide a description of human milk, including a brief review of endogenous substances found in human milk, and a description of the classes and concentrations of environmental chemicals (pharmaceuticals and PBTs) which have been reported in human milk. Next, determinants of levels of PBTs are discussed, as are models which have been developed to predict levels of PBTs in human milk and associated body burdens in breast-feeding infants. This is followed by a synopsis of a recent Workshop convened to develop guidelines for human milk sampling and analysis, and concepts for consideration in interpretation and communication of study results. Because of the toxicity of many of these chemicals, and the importance of breast-feeding to the health of the infant, research regarding the relative benefits and risks to the infant’s health associated with breast-feeding is summarized. The review concludes with a series of recommendations and research needs.

Composition of human milk

Human milk is a complex mixture of substances produced by the mother’s body (endogenous substances) and other substances introduced to the mother’s body (exogenous substances). Exogenous substances can be introduced by ingestion of food, drink, pharmaceutical agents, recreational drugs, and illicit drugs. Exogenous substances can also be introduced to the body by inhalation of chemicals (e.g., volatile chemicals used in the dry cleaning process or nicotine and other chemicals from cigarette smoke) and via dermal exposure (with the application of sunscreens, for example). For the purposes of this review, the description of exogenous chemicals in human milk will be limited to PBTs with a brief description of pharmaceuticals. However, it should be noted that other classes of environmental chemicals, including volatile chemicals and metals, have been detected in human milk (Jensen and Slorach, 1991).

Endogenous human milk constituents

The focus of attention on environmental chemicals in human milk can obscure the fact that human milk confers numerous and well-documented health benefits to the nursing infant. When considering the potential risks associated with environmental chemicals in human milk, it is equally important to consider the benefits associated with breast-feeding. In this way, a more balanced picture of risks and benefits can be given (LaKind et al., 2002). Thus, to convey the richness and complexity of human milk composition, in this section, a brief description of human milk is provided. If the reader wishes to explore this topic in greater detail, additional resources should be consulted (Diehl-Jones and Bols, 2000; Jensen, 1995; Lawrence and Lawrence, 1999; Schanler, 2001; Schreiber, 1997). LaKind et al. (2002) have summarized the main human milk constituents; that summary forms the basis for this section (the information on hormones in human milk is derived from Borgert et al., 2003).

Human milk contains hundreds of endogenous substances, many of which are critical for infant development. The composition of human milk changes over the course of lactation from birth to weaning, so that optimal nourishment coincides with the various stages of postnatal infant growth and development. The first milk produced by the new mother is called colostrum. In approximately 1–2 weeks postpartum, the mother’s mammary glands begin to produce mature milk. The transition to mature milk does not mean that the composition of milk remains constant from that time forward. Rather, the composition of milk changes throughout lactation. For example, it has been reported that as lactation duration increases, lipid levels in human milk...
increase (however, for some individuals, lipid levels decline over time (LaKind et al., 2000)), whereas levels of zinc and copper decline over the course of lactation (Casey et al., 1995). To add to the complexity, the composition of human milk also changes during an individual feeding. Such change is evident in the difference between foremilk (the first milk expressed during a feeding) to hindmilk (milk expressed later in a feeding), varying in composition by the types of lipid-soluble compounds that are present and in the percentage of lipids they contain (Hamosh et al., 1984; Jensen, 1995).

The main categories of human milk constituents are proteins, nonprotein nitrogen, carbohydrates, lipids, water-soluble vitamins, ionic constituents, trace minerals, and cells (Picciano, 2001). Human milk contains nutritive (e.g., lipids, carbohydrates, proteins, amino acids, minerals, and vitamins) and nonnutritive (e.g., enzymes, immunoglobulins, nucleic acids, hormones, growth factors, and cells, including macrophages, lymphocytes, and epithelial cells) constituents that both contribute to the infant’s well-being.

The principal constituent of human milk is water, in which all other constituents are dissolved or suspended (Lawrence and Lawrence, 1999). Following is a brief description of several of these important human milk constituents (LaKind et al., 2002).

Lipids
Lipids are the major energy-producing constituents in human milk (Picciano, 2001). Total fat in human milk varies from 30 to 50 g/l (equal to about 3–5% fat by weight). Lipids are not only the principal source of energy for the breast-feeding infant, but are critical for the synthesis and development of the infant and of the infant’s nervous system (Jensen, 1995; Picciano, 2001).

The amount of lipid in human milk is extremely variable, changing with: (i) the portion of a feeding (lipid content increases within the course of one feeding); (ii) the time postpartum (lipids appear to increase over the course of lactation from birth to weaning); (iii) different intervals between feedings; (iv) parity; (v) and infections (LaKind et al., 2002; Lawrence and Lawrence, 1999). Lipid levels may differ between the left and right breasts and at different times of the day (Lawrence and Lawrence, 1999). Because PBT chemicals are fat-soluble, the lipid fraction of human milk is important; variations in lipid levels will result in variations in concentrations of PBTs in samples of human milk. Thus, the concentrations of PBTs in human milk will be influenced by the time of sample collection (foremilk vs. hind milk and early vs. late in lactation).

Proteins
Proteins represent approximately 1% of human milk (Lawrence and Lawrence, 1999). Proteins in human milk provide: (i) amino acids necessary for growth; (ii) protective factors such as immunoglobulins; (iii) carriers for vitamins (e.g., folate) and hormones; and (iv) enzymatic and other biologic functions (Picciano, 2001).

Enhanced nutrient bioavailability
Human milk (in contrast to cow’s milk or infant formula) contains micronutrients in forms that permit ready absorption by the infant’s gastrointestinal tract. This absorption is essential for the nutrients to aid in growth and development.

Components which protect against illness
Because human infants are born with an immature immune system, they are at increased risk of infections. Human milk contains antibodies and other factors that assist the infant in warding off infections and parasites until such time as the immune system is fully functioning (LaKind et al., 2002) (see Hamosh, 2001; Lawrence and Lawrence, 1999, for detailed discussions of this topic).

Hormones
Human milk contains a variety of hormones (Britton and Kastin, 1991; Grosvenor et al., 1992; Hamosh, 2001; Koldovský, 1995), including pituitary, hypothalamic, pancreatic, thyroid, parathyroid, adrenal, gonadal, and gut hormones (Ebrahim, 1996; Grosvenor et al., 1992). Although there is a body of information regarding the function of hormones in the infant (Bernt and Walker, 1999; Koldovský, 1995) (e.g., the positive influence of the adrenal hormone cortisol on the maturation of the immature intestinal barrier), the exact function of many hormones in infants is not known (LaKind et al., 2002). Due to the large number and variety of hormones present in human milk, Ebrahim (1996) suggested that mammary glands be considered a major endocrine organ.

Vitamins and minerals
Human milk contains vitamins including: (i) vitamin A, which is required for vision; (ii) vitamin D, which aids in preventing vitamin D-deficiency hypocalcemia and rickets (although sunlight exposure is still needed); (iii) vitamin E, required for muscle integrity and resistance of erythrocytes to rupture; (iv) vitamin K, required for production of blood-clotting factors; (v) vitamin C, needed for collagen synthesis and for several enzyme and hormone systems; and (vi) vitamin B complex, which is necessary for several biochemical functions in the body (LaKind et al., 2002; Lawrence and Lawrence, 1999). Minerals in human milk include sodium, potassium, chloride, calcium, and magnesium (Jensen, 1995; LaKind et al., 2002; Schanler, 2001).

Nucleotides
Nucleotides are closely involved with cell function (LaKind et al., 2002). Nucleotides may augment iron absorption, modify lipid metabolism, affect the growth and development of the intestinal tract (Gill and Uauy,
1995), and impact the immunocompetence of the breast-fed baby (Carver et al., 1991).

Pharmaceuticals in human milk

The presence of a drug or chemical in milk involves the compound passing from maternal plasma across the mammary alveolar cell by any one of several mechanisms such as passive diffusion through the body of the alveolar cell, or by intercellular diffusion through spaces between the cells or ionophore diffusion using carrier molecules such as proteins (Schanker, 1962). The role of endogenous compounds in milk, such as lipids, proteins, and carbohydrates, in binding drugs or chemicals has not been completely clarified (Berlin, in press). Factors affecting the transfer of compounds into milk include: ionization (pK_a of the compound will determine differences between unionized drug in plasma and milk), lipid solubility, maternal plasma protein binding, and molecular weight. In general, small (less than 200 Da), unionized, lipid-soluble compounds will appear in milk relatively soon after maternal ingestion (within 1 h) and the plasma/milk ratio of the drug will be close to 1. For a large majority of drugs, the milk level is less than the simultaneous maternal plasma level. The exception will be weak bases for which the milk/plasma concentrations will be greater than 1. For most drugs, the percentage of the maternal dose that is transferred to milk is between 0.5% and 1.0%. There are some striking exceptions including certain beta blockers, where more than 5% of the maternal dose has been identified as passing into milk. The mechanism for these higher amounts is not currently known, but may involve facilitated transfer with endogenous milk compounds.

The American Academy of Pediatrics (AAP) has been very supportive of breast-feeding and for decades has been attempting to increase the number of breast-fed babies at hospital discharge as well as the duration of breast-feeding. To assist physicians caring for these infants, and to emphasize the need to permit maternal drug therapy, the AAP developed a Statement concerning the transfer of drugs and chemicals into milk utilizing published data in which drug concentrations were measured (AAP, 2001); the first Statement was published in 1983 with the third revision in 2001. The current Statement supports the safe use of drugs for maternal therapy in almost all cases. There have been very small numbers of reports of adverse reactions in the infant as a result of maternal drug ingestion (Anderson et al., 2003; Ito et al., 1993; Kacew, 1999). Drugs of abuse should not be used by the nursing mother. Mothers given radioactive isotopes should have their milk monitored for radioactivity; when radioactivity returns to background, nursing may resume. A small number of drugs, for which adverse infant reactions have occurred, will require frequent monitoring of the infant. Such monitoring may include obtaining serum levels of the drug in the infant. The literature cited in the AAP Statement supports placing most drugs in the category of “maternal medication usually compatible with breast-feeding.”

Exogenous substances (PBTs) in human milk: levels in the United States and temporal trends

Since the 1950s, researchers have been gathering information on levels of PBTs in human milk. This information has been derived from many countries and has been collected for different reasons. In certain cases, interest in PBTs in milk has stemmed from specific poisoning events; in other instances, research has been exploratory, as part of an effort to assess background levels of a chemical in the human milk of a sample population. In some investigations, the data have been collected using a standardized protocol (WHO, 2000) and the results of those studies can be compared to determine trends in levels of different PBTs over time or across countries. In many other instances, however, studies have been conducted with widely varying protocols, rendering interstudy comparison more difficult (LaKind and Berlin, 2002). Typically, results of human milk monitoring studies for PBTs are presented on a lipid basis, that is, amount of chemical per gram of lipid in human milk. This lipid adjustment, which normalizes the levels of PBTs to account for different lipid levels in milk within a mother and among mothers (Needham and Wang, 2002), improves interstudy comparability. Limitations inherent in comparing results across human milk monitoring studies have been described (LaKind and Berlin, 2002; LaKind et al., 2001; Sim and McNeil, 1992; Smith, 1999) and are expanded on in the Limitations of the database on environmental chemicals in human milk section. These limitations include: (i) differences in study design including use of pooled vs. individual samples; (ii) incomplete reporting of information on techniques for collecting human milk samples or characteristics of the mother; (iii) use of a participant sample that may not be representative of the general population; and (iv) timing of sampling of the milk (LaKind and Berlin, 2002).

In the following sections, information on levels and trends for four groups of PBTs is provided. These four groups are: organochlorine pesticides and metabolites; polychlorinated biphenyls; dioxins and furans; and polybrominated diphenyl ethers. Although the focus is on levels of PBTs in the United States, due to a scarcity of information on levels of PBTs in the United States, some international data will be described as well. Detailed compilations and reviews of levels of environmental chemicals in human milk should be consulted for additional information (Cone et al., 1983; European Commission Environment, 1999; Jensen and Slorach, 1991; LaKind et al., 2001; Solomon and Weiss, 2002; Sonawane, 1995; World Health Organization, 1989; World Wildlife Fund, 1999).
Organochlorine pesticides and metabolites

Organochlorine pesticides for which data on levels in human milk are available include chlordane, DDT compounds, dieldrin, heptachlor, hexachlorobenzene, and hexachlorocyclohexane (Berlin and Kacew, 1997). Although almost no recent human milk data on organochlorine pesticides are available for the United States (see Fig. 1), trend information for some of these chemicals for other countries is available. Levels and trends for the above chemicals are described in the following subsections.

Chlordane

As shown in Fig. 1, extremely limited data are available on levels of chlordane, or its stable metabolite oxychordane, in human milk in the United States. However, for other countries with restrictions on chlordane use, levels in human milk have declined substantially. For example, in Sweden, a decline in human milk levels of chlordane related to reductions in use of chlordane has been reported (Noreén and Meironyté, 2000).

DDT compounds

Levels of DDT compounds in human milk have declined substantially in countries where the use of these compounds has been restricted or banned for many years. In countries that have restricted the use of DDT compounds relatively recently, or still use these compounds for malaria control, human milk levels remain high. Smith (1999) showed that levels of DDT compounds in human milk from the United States and Canada declined from the 1970s to the 1990s.

Dieldrin

As shown in Fig. 1, essentially no current data are available on levels of dieldrin in human milk in the United States. However, for other countries with restrictions on dieldrin use, levels in human milk have decreased by as much as an order of magnitude in the years following restrictions (Solomon and Weiss, 2002).

Heptachlor and heptachlor epoxide

The stable metabolite of heptachlor, heptachlor epoxide, is the form of the pesticide most widely detected in human milk (Jensen and Slorach, 1991). The limited data on heptachlor epoxide in human milk from the United States are insufficient to determine whether levels have declined since the ban on the use of heptachlor.

Hexachlorobenzene

Extremely limited current data are available on levels of hexachlorobenzene (HCB) in human milk in the United States (Fig. 1). Other countries have reported significant declines in levels of HCB since the termination of use of HCB. These countries include Sweden and Norway. Data from Germany, Belgium, Canada, Denmark, the Netherlands, and Switzerland are also suggestive of declines in HCB levels in human milk (Solomon and Weiss, 2002).

Hexachlorocyclohexane

Extremely limited current data are available on levels of hexachlorocyclohexane (HCH) in human milk in the United States (Fig. 1). Other countries, including Germany, Sweden, and Japan, have reported steady decreases in HCH in human milk (Solomon and Weiss, 2002).

PCBs

The current information on PCB levels in human milk from women in the United States is sparse, as demonstrated by Fig. 2. Thus, despite the restrictions on uses of PCBs in the United States, it is difficult to discern whether levels in human milk have declined over time. However, in Sweden, where data on PCBs in human milk have been gathered for samples from 1972 to 1992, levels of PCBs in human milk have decreased (Fig. 3) (Noreén et al., 1996).

Dioxins and furans

Levels and trends of dioxins and furans in human milk were reviewed by LaKind et al. (2001). Emissions of dioxins and furans have been curtailed significantly over the last two decades, and a concomitant decline in levels of dioxins and furans has been observed. Dioxin/furan human milk data from several countries indicate a decline in levels over time (these countries include Austria, Belgium, Denmark, Finland, Germany, Hungary, Japan, Netherlands, Norway, Pakistan, Sweden, UK, Ukraine, Vietnam, and Yugoslavia) (Fig. 4 shows data for Germany, Norway, the
The data from Germany provide the most persuasive evidence for a decrease in human milk dioxin/furan levels over time (LaKind et al., 2001). Canadian human milk dioxin/furan data collected over the past 25 years by Health Canada showed the following decline in dioxin toxic equivalents (TEQs) (ppt, lipid basis) (although the values used for estimating toxic equivalents have been modified since the time of this publication, these values are internally consistent and demonstrate the overall decline): 1981–1982, 24.7 ppt; 1986–1987, 15.6 ppt; 1992, 14.5 ppt (Craan and Haines, 1998). Fig. 5 includes data on dioxins and furans in Canadian human milk; however, the decline suggested by the data reported by Craan and Haines (1998) is not obvious when shown with additional province-specific data (Liem et al., 1996). Data for the Western European countries also show an overall decline (LaKind et al., 2001). The data for the United States (Fig. 5) expose the limit of knowledge regarding “representative” levels of dioxins/furans in U.S. human milk and whether levels in the United States are decreasing (LaKind et al., 2001).

Summing up, for several countries with relatively large databases on dioxins and furans in human milk, the concentrations of these chemicals have apparently decreased over time. For countries without sufficient data (including the United States), an improved database (with greater number of samples collected over time from a broader geographic area with consistent study design) might demonstrate similar future reductions (LaKind et al., 2001).

**PBDEs**

The first published report of the presence of PBDEs (polybrominated diphenyl ethers, a class of flame retardants)
in human milk appeared in the late 1990s (Darnerud et al., 1998; Meironyte et al., 1998), although reports of the presence of these compounds in biotic tissue appeared in the early 1980s (Meironyte et al., 1999).

In a study that focused attention on the PBDEs, a team of researchers (Meironyte et al., 1999) analyzed pooled samples of breast milk which had been supplied by the Mother’s Milk Center in Stockholm. The pooled samples contained equal amounts of milk from each mother, and were collected from 1972 to 1997. Analysis of the samples revealed a continuous increase in the levels of PBDEs from 1972 to 1997, representing an approximate doubling of PBDE concentrations every 5 years (Norén and Meironyte, 2000). Levels appeared to have reached a plateau since that time.

In North Rhine-Westphalia, Germany, human milk samples collected in 1992 and 2000 were analyzed for PBDEs (Fürst, 2001). Although the number of analyses was limited, the data suggested that levels of PBDEs for the 2 years were similar, in contrast to the results found in Sweden. Analysis of the samples revealed a continuous increase in the levels of PBDEs from 1972 to 1997, representing an approximate doubling of PBDE concentrations every 5 years (Norén and Meironyte, 2000). Levels appeared to have reached a plateau since that time.

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Ryan and Patry (2000) found that levels of PBDEs in Canadian human milk in 1992 were comparable to levels reported in Europe for milk collected at approximately the same time. Ryan and Patry (2000) also presented data on additional Canadian human milk samples analyzed for six congeners of PBDEs and noted a wide regional variation in the sum of the six PBDEs (e.g., 2.57 μg/g milk lipid in Ontario and 19.08 μg/g milk lipid in the Maritimes). Additional human milk samples from a milk bank in Vancouver collected in 2001–2002 showed an order of magnitude increase in levels of PBDEs in the previous 10 years (Ryan et al., 2002).

Limited data on PBDEs in human milk from women residing in the United States are available. One study looked at a pooled sample of breast milk taken from women living in Austin, TX and Denver, CO (Pärke et al., 2001). The level of total PBDEs was reported to be approximately 40 times higher in U.S. human milk than the levels reported for Sweden. The authors recognize that the results from this one pooled sample are not necessarily representative of the U.S. population as a whole, but note that the results point to a need for further study.

**Limitations of the database on environmental chemicals in human milk**

Past human milk monitoring studies have provided valuable biomonitoring data and have contributed to an understanding of infant exposures during breast-feeding. Many of today’s desired uses of the data on environmental chemicals in human milk may not have been foreseen at the time the research was conducted. Nonetheless, one use of the database is to examine trends in concentrations of environmental chemicals temporally and geographically. In addition, many have looked for associations between levels of specific environmental chemicals in human milk and lifestyle or other attributes to determine exposure pathways and other factors that might be related to body burdens. For these types of assessments, limitations in study design have been noted (LaKind and Berlin, 2002; LaKind et al., 2001; Sim and McNeil, 1992). The following discussion is drawn from LaKind and Berlin (2002).

The key limitations include protocols for sampling and analysis, incomplete reporting of data, nonrepresentative populations included for study, timing of sampling of human milk, and types of chemicals evaluated. Each of these is discussed briefly below.

**Sampling and analysis protocols**

Because the composition of human milk changes within a feeding and over the course of the day, differences in the way human milk samples are collected can impact on the usefulness of the results. For example, some studies report analytical results for each individual human milk sample provided. Either for convenience, or due to the cost of analysis and the volume of the milk sample required for analysis, other researchers have found it necessary to collect human milk from two or more mothers and combine, or pool, them before analysis. If equal volumes of human milk from the contributing women are pooled, the result is an average chemical concentration for the population of participants. However, pooling of samples results in loss of information on ranges of concentrations; further, it is not possible to examine associations between lifestyle and other factors and levels of environmental chemicals in human milk when samples have been pooled (LaKind and Berlin, 2002).
Incomplete collection or reporting of information

Certain types of information can assist in the interpretation of data collected in human milk monitoring studies. However, for many human milk studies, this information was either not gathered, or it was not included in the published results. Information useful to the interpretation of study results includes the methods used to collect the human milk samples (e.g., manual or with a pump), the timing of sample collection (e.g., early or later in the course of lactation), and demographic and lifestyle information (e.g., smoking status of the mother or other family members, the age of the mother, parity, dietary information, potential for occupational exposures) (LaKind and Berlin, 2002). Further, few studies provide information on whether the infant diet is being supplemented with formula or other sources of nutrition, which would likely be associated with a decrease in the volume of human milk consumed, thus influencing the infant’s exposure to environmental chemicals in human milk.

Nonrepresentative sampling

Some large-scale studies of human milk monitoring have been conducted (e.g., Rogan et al., 1986a, 1986b). However, most studies have focused on relatively small populations of women from limited geographical areas (LaKind and Berlin, 2002).

Timing of sampling

The concentrations of certain environmental chemicals in human milk (e.g., some PBT chemicals) decrease over the course of lactation (Fürst et al., 1989; LaKind et al., 2001). Therefore, relatively uniform timing of sampling would improve interstudy comparability. Past human milk monitoring studies have not been consistent with timing of sample collection. Time postpartum for sample collection has ranged from 1 to 3 weeks (Mussalo-Rauhamaa et al., 1988) to as late as 1–3 months postpartum (Iida et al., 1999). As noted previously, not all research is performed with the purpose of interstudy comparability. However, these differences in time of sample collection limit our ability to use the data to explore trends and determinants of levels in human milk, or to reach conclusions about infant exposures (LaKind and Berlin, 2002).

Number and types of chemicals monitored

Most studies on environmental chemicals in human milk have examined chlorinated organic chemicals such as dioxins, furans, PCBs, and chlorinated organic pesticides (see, e.g., the review of data in Berlin and Kacew, 1997; Jensen and Slorach, 1991). Thus, there is substantially less information on other classes of environmental chemicals, such as PBDEs and volatile organic chemicals (LaKind and Berlin, 2002; Schreiber, 1997).

Estimating PBT levels in human milk and infants: determinants and models

Human milk monitoring for environmental chemicals can provide information on levels of PBTs in mother’s milk and on doses to the breast-feeding infant. Another method for estimating PBT levels in milk or doses to the infant is through the development of models. These can be especially useful in the estimation of infant body burdens because it is not feasible to conduct biomonitoring (e.g., taking blood or adipose tissue samples) with infants. In this section, factors that influence the levels of PBTs in mother’s milk are described. Next, models that have been developed to predict concentrations of PBTs in mother’s milk and the breast-feeding infant are briefly reviewed. Readers are encouraged to consult the cited articles for model details.

Determinants of levels of PBTs in human milk

Several factors are thought to influence the level of PBTs in human milk. These potential determinants, discussed in the following subsections, include duration of lactation, number of previously breast-fed children, age, weight (including weight loss and body mass index), diet, and lifestyle (Jensen and Slorach, 1991). Because PBTs partition into the lipid fraction of human milk, the amount of lipids in the milk will impact total PBTs found in the milk. However, most results of human milk monitoring studies are presented on a lipid-normalized basis, accounting for variations in lipid levels in human milk. Therefore, this factor will not be discussed further.

Influence of lactation on PBTs in human milk

Depuration, or elimination kinetics, describes the reduction in a mother’s body burden of one or more chemicals, including PBTs, by breast-feeding. As the mother’s body burdens decline, so do the levels of many of the chemicals in the mother’s milk. Depuration of chemicals via lactation is a necessary, but inadequately characterized, parameter in evaluating infant exposure to chemicals in human milk (LaKind et al., 2000). Both the actual rates of depuration for individual chemicals, as well as factors that may influence those rates, are poorly understood. Factors which could conceivably influence depuration include the initial concentration of the chemical in the mother’s milk, the mother’s age, parity, the volume of milk consumed by infant, supplementation with formula or solid foods, and properties of the individual chemicals (LaKind et al., 2001).

In terms of estimating infant doses of PBTs via breast-feeding, understanding rates of depuration is essential. Without robust information on the kinetics of this process, daily infant doses to PBTs in human milk and overall infant body burdens will be inaccurately estimated.
The scientific literature on depuration of PBTs via lactation has been reviewed by LaKind et al. (2001). It should be noted that many of the studies, which provide information on depuration, were not designed specifically to explore this process. Thus, not all of the studies yielding information on depuration are well-suited for the development of a database on depuration kinetics. For example, for the studies on dioxins and furans in human milk, Table 1 shows the parameters for which minimal to no information was available; this limits our ability to quantify depuration rates and to understand processes associated with depuration (LaKind et al., 2001).

Space does not allow for elaboration of specifics on individual depuration studies in this review; the reader is referred to LaKind et al. (2001) and the citations within for detailed information. A review of studies on changes in concentrations of PBTs in human milk over the course of lactation makes apparent that the extant data are not adequate for deriving depuration rates for PBTs or to make generalizations about the determinants of elimination kinetics (LaKind et al., 2001).

**Influence of age/parity on PBTs in human milk**

PBTs accumulate in the lipids of humans, and neither urinary nor fecal excretion is a significant route of elimination. Thus, as the age of the individual increases, the levels of PBTs in the lipids increase, as well. The positive relationship between levels of PBTs in milk and the mother’s age was found by Albers et al. (1996) in a survey of human milk from approximately 320 women. Others have reported this association, as well (Bates et al., 1994; Dillon et al., 1981; Fitzgerald et al., 2001; Hong et al., 1994; Mussalo-Rauhamaa et al., 1988; Pluim et al., 1993; Rogan et al., 1986a; Gladen et al., 1999). Jensen and Slorach (1991) note that not all studies have found this association (e.g., Mes et al., 1993), and that these inconsistencies might be ascribed to differences in the mothers’ exposures, confounders such as parity, and the narrow age interval of the mothers participating in studies on human milk.

Breast-feeding is a major route of elimination of PBTs. With increasing parity (and with associated lactations), it is expected that the body burdens of PBTs in the mother would decline. This was found to be the case in a study of approximately 320 women, where the cumulative length of former lactations was negatively associated with concentrations of four PBTs (Albers et al., 1996). Others reported lower levels of PBTs in milk associated with previous lactations as well (Dillon et al., 1981; Fitzgerald et al., 2001; Fürst et al., 1989; Hong et al., 1994; Kostyniak et al., 1999; Mes et al., 1993; Newsome et al., 1995; Pluim et al., 1993; Rogan et al., 1986a; Vaz et al., 1993). In contrast, Czaja et al. (1997, 2001) found that increased parity (with lactations) was not associated with lower levels of PBTs in milk and postulated that this was due, in part, to the greater age of the multiparas, as well as to continued supplementation of body burden by diet.

**Influence of diet, body weight, and weight change on PBTs in human milk**

In a study of three mothers, Ramos et al. (1997) found that the mother with the highest animal fat in her diet had the highest levels of PCBs; this same mother experienced the greatest pregnancy weight gain of the three. The mother with the lowest amount of animal fat in her diet and the smallest weight gain also had the lowest amount of PCBs in her milk. Others have also reported positive associations between fatty foods and levels of certain PBTs in human milk (Campoy et al., 2001; Pluim et al., 1993). Levels of DDT compounds in human milk have been positively associated with the amount of fish, chicken, fruits, milk, and potatoes consumed weekly (Schinas et al., 2000).

A positive association between levels of PBTs in human milk and fish consumption has been reported (Albers et al., 1996). Ohta et al. (2002) found a strong positive relationship between levels of PBDEs in human milk and consumption of fish and shellfish. However, other studies examining this factor did not find such a correlation (Campoy et al., 2001; Mes et al., 1993; Mussalo-Rauhamaa et al., 1988) or reported mixed results, depending upon the PBT (Newsome et al., 1995; Rogan et al., 1986a). The correlation between consumption of fish and increased levels of PBTs in human

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**Table 1**

Synopsis of study data provided on parameters potentially influencing depuration of dioxins and furans

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of women</th>
<th>Study duration (postpartum)</th>
<th>Breastmilk sampling method</th>
<th>Donor age (years)</th>
<th>Parity</th>
<th>Supplementation information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fürst et al. (51)</td>
<td>1</td>
<td>1–60 weeks</td>
<td>NP</td>
<td>NP</td>
<td>2</td>
<td>NP</td>
</tr>
<tr>
<td>Jödicke et al. (52)</td>
<td>1</td>
<td>13–16 weeks</td>
<td>NP</td>
<td>28</td>
<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>Hori et al. (53)</td>
<td>1</td>
<td>4–26 weeks</td>
<td>NP</td>
<td>NP</td>
<td>1</td>
<td>NP</td>
</tr>
<tr>
<td>Schecter et al. (54)</td>
<td>1</td>
<td>pre- and 2 years</td>
<td>NP</td>
<td>36</td>
<td>3</td>
<td>NP</td>
</tr>
<tr>
<td>Abraham et al. (55)</td>
<td>1</td>
<td>1 and 5 months</td>
<td>Emptying whole breast</td>
<td>NP</td>
<td>NP</td>
<td>supplemented at 5 months</td>
</tr>
</tbody>
</table>

NP, not provided.


a Mother breast-fed one child for 16 months and then breast-fed twins for 2 years.
milk appears more consistent when consumption is of locally caught fish with high levels of contamination. Populations consuming large quantities of locally caught fish include sports fishermen, commercial fishermen, and native populations (Dewailly et al., 1994); these populations may be more highly exposed to PBTs, with resultant higher levels in their milk. For example, an indigenous population in Canada (Inuit women), whose diet was largely composed of local fish and sea mammals, had significantly higher levels of PBTs in milk than a control population (Dewailly et al., 1994). In another study, decreases in the levels of PBTs in milk have been linked to a decline in consumption of local fish (Fitzgerald et al., 2001). A positive association between PBTs in human milk and consumption of Lake Ontario fish has also been reported (Kostyniak et al., 1999).

A positive relationship between consumption of vegetables and the presence of pesticides in human milk has been observed (Campoy et al., 2001). Levels of γ-HCH in human milk from Greece were higher in women who consumed greater portions of fresh vegetables (Schinas et al., 2000).

Short-term changes in diet during lactation (e.g., low fat/high carbohydrate/low dioxin diet and high fat/low carbohydrate/low dioxin diet) did not appear to influence the levels of dioxins in the milk of 34 women (based on a 5-day diet in the fourth week postpartum) (Pluim et al., 1994a).

Bates et al. (1994) did not find an association between certain PBTs in human milk and the body mass index (BMI) of the mother (one exception was a positive association between BMI and 1,2,3,7,8-pentachlorodibenzofuran). Pluim et al. (1993) also reported no correlation between PBTs in human milk and BMI.

Vaz et al. (1993) observed increases in levels of PBTs in the milk of a woman who fasted during lactation (losing 10 kg). This association may have been due to mobilization of PBTs in adipose tissues during fasting, leading to increased levels in milk (Jandacek and Tso, 2001; Vaz et al., 1993). In contrast, Lovelady et al. (1999) found that moderate weight loss (average weight loss of 4.1 kg) in breast-feeding women did not result in increased levels of PBTs in their milk. Mussalo-Rauhamaa et al. (1988), in a study of 165 women living in Finland, did not observe a relation between PBTs in human milk and weight loss.

**Influence of lifestyle and demographics on PBTs in human milk**

A positive association between cigarette smoking by the mother and levels of PBTs (DDE and PCBs) in milk has been described (Dillon et al., 1981; Hong et al., 1994; Rogan et al., 1986a). Others did not find this association for PBTs (Bates et al., 1994; Mussalo-Rauhamaa et al., 1988; Pluim et al., 1993).

Conflicting results related to place of residence have been published. Dillon et al. (1981) observed that mothers who live in urban areas have higher levels of certain PBTs (PCBs and DDT compounds) in their milk as compared to those living in rural areas. However, Bates et al. (1994) did not report such an association. No differences in levels of PBTs in human milk were observed among Finnish women living in plywood industry regions (which could have higher levels of heptachlor and heptachlor epoxide), women working in the plywood industry, or other women (Mussalo-Rauhamaa et al., 1988). Women living near a PCB-contaminated waste site did not have higher levels of PCBs than other populations (Korrick and Altshul, 1998).

Koopman-Esseboom et al. (1994a) concluded that women living in an industrialized part of the Netherlands had higher levels of dioxins and PCBs in their milk than women living in semiurban areas.

A positive association between regular alcohol consumption and levels of PCBs in human milk has been reported (Rogan et al., 1986a), although this was not observed by Hong et al. (1994). A few instances of higher human milk levels of PCBs associated with occupational exposures have been reported (Korrick and Altshul, 1998; Yakushiji et al., 1978).

**Summary**

For most of the potential determinants of levels of PBTs in human milk described above, the literature is not entirely consistent. However, in reviewing the literature, there appears to be sufficient information to support the following: (i) levels of most PBTs in human milk appear to decline over the course of lactation; (ii) most women appear to have lower levels of PBTs in milk with each successive lactation; (iii) levels of PBTs in human milk increase with the age of the mother; and (iv) consumption of large amounts of fish and marine mammals caught locally from polluted waters is associated with higher levels of some PBTs in human milk.

**Models for estimating PBT levels in human milk and the infant**

Early attempts to estimate infant exposure to PBTs in human milk used point estimates of dose; that is, levels of PBTs in human milk were combined with the daily volume of milk consumed by an infant and the infant’s body weight to derive a traditional dose in units of mg PBT per kg body weight per day. However, it has been recognized that the values for exposure parameters related to PBTs in human milk are not static, but are in fact time-dependent. It has also been recognized that body burden may be a more useful metric of infant exposure, rather than dose. Thus, models have been developed which estimate infant body burdens of PBTs using time-dependent variables. The types of variables incorporated into these models include volume of milk consumed by the infant, depuration rate, half-life of the chemical in the infant, infant body weight, duration of breast-feeding, absorption of the chemical by the infant, infant lipid fraction, and percentage of lipid in the mother’s milk. Some of these variables have been fairly well-charac-
ized (e.g., infant body weight); others have not (e.g., half-life of PBTs in the infant). Although very few data on levels of PBTs in infants are available, some researchers have used these data to validate their models. Several of these models, most of which are time-dependent, first-order, single-compartment models used to characterize infant body burdens of PBTs from breast-feeding, are described below. More complex physiologically based pharmacokinetic models describing infant exposures to chemicals in breast milk have been developed (Clewell and Gearhart, 2002), but have not, to date, been applied to the PBT chemicals that are the focus of this paper.

Smith (1987) developed mathematical formulations to estimate mothers’ body burdens and infant doses to dioxins and furans (as well as infant body burdens) for mothers residing near waste incineration plants. One of these formulations assumes no maternal depuration of dioxins and furans over the course of lactation. Smith (1987) also assumed that the half-lives for these chemicals are the same for adults and infants, and used first-order kinetics to describe the decrease in body burden as a function of half-life.

Smith also developed models for estimating the infant body burden of dioxin equivalents from breast-feeding at a given age and for cumulative exposure dose with or without consideration of depuration during lactation. Smith (1987) found that a baby breast-fed for 12 months would have a resultant body burden of dioxin equivalents only slightly higher than the mother’s body burden and that added lifetime exposure doses to the infant from human milk are small. In general, Smith (1987) noted that if the model is valid, then the results indicate that emissions from modern municipal waste incineration plants make a small contribution to levels of dioxins and furans in human milk.

Sullivan et al. (1991) developed and validated a model (modified from the model by Smith, 1987) to estimate levels of dioxins in infant fat before and after breast-feeding and the dose to the infant during breast-feeding. Sullivan et al. (1991) also presented an equation describing the change in concentration of the chemical in maternal fat during the period of breast-feeding for estimating the concentrations in infant fat, and for estimating concentrations of the chemical in the fat of the infant post-breast-feeding. The model was tested by using data from a study on dioxin exposures to rhesus monkeys and their infants. Sullivan et al. (1991) used a reduced infant half-life (as compared to adult half-life) for dioxin in their model, based on results from the rhesus monkey study which showed a good correlation between actual vs. modeled fat dioxin levels in rhesus monkeys.

Ayotte et al. (1996) modeled infant body burdens (liver and adipose tissue) of dioxins, furans, and PCBs from breast-feeding using a toxicokinetic model and drawing on PBT levels in human milk fat from an Inuit population in the Arctic to estimate the impact on body burdens of the breastfed children from birth to 75 years of age. Maternal depuration via lactation was not considered in the model. The model suggests that one’s body burden of dioxin-like compounds resulting from breast-feeding is influenced over the course of one’s lifetime, but that the effect of having been breast-fed is minimal after 20 years.

Kreuzer et al. (1997) developed a physiologically based, one-compartment, toxicokinetic model for dioxin (specifically 2,3,7,8-tetrachlorodibenzo-p-dioxin, or TCDD) in humans, with a focus on infant uptake of TCDD via breast-feeding. The TCDD model can be used to simulate body burdens (including lipids of adipose tissue, liver, feces, blood, and human milk) of TCDD during the entire lifetime, considering developmental changes in physiological and biochemical parameters, as well as changes in diet. The model incorporates information on age- and gender-related changes in body, liver, adipose, and muscle tissue volume, and food consumption. Age-dependent variables in the model include physiological parameters, food intake, TCDD elimination by metabolism, and fecal excretion. The authors assumed that the mother’s lipid levels of TCDD were equal to the newborn’s lipid TCDD levels and the TCDD levels in the mother’s breast milk lipid at the start of nursing. Kreuzer et al. (1997) also included depuration in their model and reported a good correlation between modeled and published values of TCDD in mother’s milk by assuming an approximately 70% decline in the levels of TCDD in milk after 6 months of daily nursing.

The model predicts that TCDD levels in the lipids of exclusively breast-fed infants will rapidly increase to a level higher than formula-fed infants; this is followed by a post-weaning decrease. At about 7 years of age, the model predicts that lipid levels of TCDD in breast-fed and formula-fed infants will reach the same concentration. The model results for infant body burdens were confirmed by measured dioxin levels from the adipose tissue, blood, and feces of infants (with the adipose tissue data derived from three stillborn infants and 17 infants who died from sudden infant death syndrome). In general, Kreuzer et al. (1997) found that levels of TCDD in adipose tissue were lower for the breast-fed infants than for the adults and that the body burden of TCDD reached after 6 months of breast-feeding does not lead to an increased lifetime body burden. There is an initial decline in TCDD concentrations in the infant after birth due to a dilution effect; that is, the fast growth of the infant leads to dilution of TCDD in the body. An important finding of the authors is that the value of the half-life for TCDD elimination changes over the course of a human lifetime; the half-life of non-metabolic elimination (principally by fecal elimination) of TCDD was estimated by the authors to be 0.42 years in the newborn, increasing to 9.5 years in a 40-year-old adult.

LaKind et al. (2000) developed a first-order, single-compartment model to characterize incremental distributions of body burdens of TCDD and DDE in breast-fed infants, where the exposure was attributed to presence of TCDD and DDE in human milk in North America. The
model included the known variability in the relevant exposure parameters and incorporated the time-dependent nature of some of the variables. The output from the model is a distribution of potential infant body burdens of TCDD and DDE (per kilogram body weight of the infant). The model parameters considered included toxicokinetics of the chemicals in the infant (e.g., half-life due to nonmetabolic elimination), lipid content of milk longitudinally, time-dependent concentration of chemicals in the mother’s milk (depuration), volume of milk ingested, infant growth, and chemical absorption in the infant GI tract. The model equation was solved probabilistically to determine dose distributions. LaKind et al. (2000) assumed that chemicals depurate exponentially with time, using a value of 50% reduction in the initial breast milk concentration of TCDD and DDE after 6 months of nursing, with additional runs performed using values of 30% and 70% depuration over 6 months of lactation. Initial concentrations of TCDD and DDE in the mother’s milk were based on data from human milk studies in Canada. The shorter infant half-life for TCDD described by Kreuzer et al. (1997) was used in the analysis of LaKind et al. (2002).

The model by LaKind et al. (2000) predicts that the incremental TCDD/DDE body burden within breast-fed infants is expected to rise rapidly from birth to 3 months of age. Even for infants breast-fed for the first 12 months of life, body burdens are expected to peak at the age of approximately 5–6 months. In addition, sharp decreases in body burden occur immediately following weaning. By 2 years postpartum, the model indicated a substantial decrease in incremental body burdens of TCDD and DDE in infants.

Lorber and Phillips (2002) developed and validated a pharmacokinetic model to estimate the impact of breast-feeding on an infant’s body burden of dioxin TEQs. Their model is a one-compartment, first-order, non-steady-state model. The authors assumed that a dioxin TEQ behaves as a single compound, with no congener-specific differences in elimination rates or other parameters. They adopted a shorter half-life for dioxins in infants, as proposed by Kreuzer et al. (1997). The authors applied their model to five scenarios: formula-feeding only, and breast-feeding durations of 6 weeks, 6 months, 1 year, and 2 years. They assigned an initial concentration of dioxin TEQs in human milk of 25 ppt and modeled the levels in human milk over time with a linear decline. Lorber and Phillips (2002) validated their model with data from a study of dioxins, furans, and PCBs measured in the blood of infants and the milk of their mothers (Abraham et al., 1998). One aspect of the model validation was to determine whether the use of a reduced half-life in infants for dioxin TEQs corresponded to the model validation was to determine whether the use of a reduced half-life in infants for dioxin TEQs corresponded to the model validation was to determine whether the use of a reduced half-life in infants for dioxin TEQs corresponded to the model validation was to determine whether the use of a reduced half-life in infants for dioxin TEQs corresponded to the model validation was to determine whether the use of a reduced half-life in infants for dioxin TEQs corresponded to the model validation was to determine whether the use of a reduced half-life in infants for dioxin TEQs corresponded to the model validation was to determine whether the use of a reduced half-life in infants for dioxin TEQs corresponded to the model validation was to determine whether the use of a reduced half-life in infants for dioxin TEQs corresponded to the model validation was to determine whether the use of a reduced half-life in infants for dioxin TEQs corresponded to the model validation was to determine whether the use of a reduced half-life in infants for dioxin TEQs corresponded to the model validation was to determine whether the use of a reduced half-life in infants for dioxin TEQs corresponded to the model validation was to determine whether the use of a reduced half-life in infants for dioxin TEQs corresponded to

In general, Lorber and Phillips (2002) found their model capable of predicting infant dioxin TEQ body burdens and responsive to different conditions of exposure during breast-feeding. The model predicts that accumulated exposures of dioxins in breast-fed infants would be significantly higher than accumulations in formula-fed infants, and that this higher accumulation would persist into childhood (see, e.g., Fig. 6, which shows the variation in an individual’s lifetime body burden of dioxin TEQs as a function of different breast-feeding/formula-feeding scenarios). Lorber and Phillips (2002) note that although the doses of dioxin TEQs to the infant from breast-feeding could be one to two orders of magnitude higher on a body weight basis than the dose to an adult, the resulting infant body burden is within the range observed for adults.

Methodologies for surveillance and research on environmental chemicals in human milk

As evidenced by the previous sections of this review, investigators from numerous countries have conducted surveillance and research on human milk. Many of these studies have been conducted using methodologies that differ in minor or more substantive ways from each other. Differences in study design and reporting of results can adversely impact one’s ability to discern temporal and geographic trends in environmental chemicals in human milk, and to understand relationships between levels of chemicals in human milk and factors potentially influencing those levels. These differences, described previously in this review and by LaKind and Berlin (2002), LaKind et al. (2001), and Sim and McNeil (1992), include sampling and analytical methods, incomplete reporting, nonrepresentative sampling, timing of sampling, and types of chemicals studied. Guidance for conducting human milk surveillance and research addressing these limitations would advance the science of biomonitoring and assist in improving interpretations of future studies of environmental chemicals in human milk.

It has been noted that “...[c]arefully planned and executed programs of human milk sampling and analysis...
would provide the information necessary to assess infant exposures during nursing and to provide consistent and scientifically sound information on benefits and risks of breast-feeding.\(^1\) LaKind and Berlin, 2002; LaKind et al., 2001. Human milk monitoring is relatively noninvasive, allows for the collection of large volumes of human fluid, and has a high fat content. Human milk is therefore an excellent matrix for examining biomarkers of exposure for both the mother and infant. There have been calls for increased human milk surveillance and research in the United States (Hooper and MacDonald, 2000; LaKind et al., 2001). The goals of these types of programs include: (i) acquiring information about women from different geographic regions and socioeconomic and demographic backgrounds; (ii) analyzing a larger number of environmental chemicals in human milk; (iii) obtaining data on concentrations of chemicals in human milk over the course of lactation so that the changes over time can be quantified; (iv) assessing temporal and geographic trend in levels of environmental chemicals in human milk; (v) making the results of these studies available in both the peer-reviewed literature and publicly accessible venues, with interpretation; and (vi) using the data on environmental chemicals in human milk as the basis for comparing relative risks and benefits of breast-feeding and formula-feeding (LaKind and Berlin, 2002; LaKind et al., 2001).

The Technical Workshop on Human Milk Surveillance and Research on Environmental Chemicals in the United States

Interstudy comparability of human milk studies on environmental chemicals in the United States and elsewhere could be improved with the development and use of harmonized guidelines for study design and interpretation. Although one set of guidelines has been developed by the World Health Organization (2000), certain features of the WHO guidelines do not address the limitations described above (e.g., the WHO guidelines suggest pooling of milk samples). Therefore, a Workshop (the Technical Workshop on Human Milk Surveillance and Research on Environmental Chemicals in the United States) was convened to develop state-of-the-science guidelines describing the various aspects of human milk surveillance and research programs (LaKind and Berlin, 2002).\(^1\) An Expert Panel (representing academia, industry, nonprofit organizations, and the federal government) drawn from the fields of pediatrics, family medicine, nursing, lactation, human milk sampling, analytical chemistry, epidemiology, pharmacology, toxicology, nutrition, and risk evaluation and communication participated in the Workshop, held at the Milton S. Hershey Medical Center, Pennsylvania State University College of Medicine (15–17 February 2002). The Panel was charged with describing the components of well-conducted human milk surveillance and research studies, including the following topics (LaKind and Berlin, 2002): guidelines for participant selection, guidelines for human milk sampling, questionnaire development guidelines, guidelines for chemical selection, analytical guidelines, and guidelines for uses and interpretation of information on environmental chemicals in human milk. The results of the deliberations of the Panel have been published (Journal of Toxicology and Environmental Health, vol. 65, no. 22) and are summarized briefly in the following sections. For more detailed information on each of these topics, the reader is referred to the original citations.

Selection of participants in human milk surveillance and research

A necessary and important first step in human milk surveillance and research studies is the careful selection of study participants. The basis for participant selection depends on the goals of the study. For example, for a study intended to provide data for estimating temporal or geographic trends, the selection of subjects requires consideration regarding how to achieve a representative sample population.

Guidelines for participant selection have been put forth by the WHO, which has coordinated three rounds of international studies on concentrations of PCBs, PCDDs, and PCDFs in human milk (WHO, 2000). The guidelines include: (i) donors should be primiparous; (ii) both mother and child should be apparently healthy, and the pregnancy should have been normal; (iii) the mother should be breast-feeding only one child (i.e., no twins); (iv) mothers who have resided outside the area for more than 6 months in the last 5 years should be excluded; and (v) only mothers exclusively breast-feeding should be included. Because the WHO guidelines were designed and are maintained for the express purpose of surveillance of dioxin-like compounds in human milk and for assessment of temporal trends, certain aspects of the guidelines may not be appropriate for a comprehensive human milk research program in the United States or for other chemicals (Groer et al., 2002). For example, the WHO guidelines were developed for monitoring of dioxin-like compounds, which are persistent and lipophilic; these may not be relevant to a study of other types of chemicals with different physicochemical properties. For research on chemicals with short half-lives in the human body but to which women may be exposed on a regular basis (e.g., chemicals in personal care products or in a workplace environment), a 5-year residency requirement may not be necessary.

\(^1\) Workshop support was provided by the US Environmental Protection Agency; the Department of Health and Human Services, Health Resources and Services Administration; the National Institute of Child Health and Human Development, National Institutes of Health; the Brominated Flame Retardant Industry Panel of the American Chemistry Council; the Nurses Leadership Council; Penn State University College of Medicine; the Public Health Policy Advisory Board; and the Research Foundation for Health and Environmental Effects.
Groer et al. (2002) describe key factors for consideration in participant selection, including: (i) consideration of maternal factors which may influence environmental chemical mobilization from lipid reserves, such as dietary changes, weight changes, and interactions with drugs; (ii) evaluation of populations for which there may be special concerns (e.g., certain ethnic and cultural groups, or low income populations); and (iii) the involvement of participants who would be willing to remain involved in the study for longer periods of time, so that a proportion of the mother–infant pairs can be studied longitudinally.

Investigators can identify potential participants with the use of U.S. birth certificates, which, as of 2003, will include a new question regarding whether the mother is planning to breast-feed. Participants may also be identified from ZIP codes or federal Woman, Infants, and Children (WIC) data. Finally, researchers may want to consider the La Leche League International (LLLI) for identifying participants since mothers who affiliate with LLLI are a potential source of women who exclusively breast-feed for long periods of time.

Guidelines for human milk sampling

Human milk surveillance is typically performed to monitor temporal changes in concentrations of environmental chemicals or to compare concentrations of environmental chemicals among different populations. Research goals are varied. However, in either case, to make valid interstudy comparisons, human milk sampling methods should be consistent across studies (Lovelady et al., 2002). Lovelady et al. (2002) provide fundamental guidance and describe key issues related to the human milk collection process that should be considered by investigators. These are summarized briefly here (with additional guidance provided by Needham and Wang, 2002, where indicated).

A key principle of human milk sampling is that the process should not be an undue burden to the mother nor should it compromise the infant’s nutritional status (Lovelady et al., 2002). Longitudinal sampling of human milk should be conducted, where possible, to estimate infant exposure to environmental chemicals from human milk. Human milk samples should be collected from individual women and analyzed individually, rather than pooling samples from more than one woman before analysis. This allows for (i) determining potential associations between characteristics of the mother (e.g., lifestyle factors, demographics) and levels of chemicals in her milk, and (ii) estimation of the ranges of concentrations of chemicals in milk. Utilization of human milk samples obtained from milk banks is discouraged for the following reasons: (i) women donating milk to a bank may not be representative of the population (e.g., they may be “super-producers” of milk and therefore have a lower burden of environmental chemicals in their milk due to depuration); (ii) because women donate milk at different stages of lactation, researchers will not be able to compare results across women due to depuration; (iii) information on participants needed to understand factors affecting levels of chemicals in the milk is not collected at milk banks (e.g., lifestyle factors, demographics), limiting interpretation of the data; and (iv) milk bank methods for collecting human milk (including the storage containers used) are not standardized (Lovelady et al., 2002).

The first milk sample should be collected after lactation has been established, approximately 2 weeks to 1 month postpartum. If an electric breast pump is used, the research should include an individual trained to deliver, demonstrate, and retrieve the electric pump (Lovelady et al., 2002). Breast pumps must be free of contamination (Needham and Wang, 2002). Lovelady et al. (2002) and Needham and Wang (2002) provide additional detailed information in collection, storage, and preparation of samples.

Guidance on the development of participant questionnaires

Collection and analysis of human milk samples for environmental chemicals is a time-consuming and expensive process. To ensure that the data obtained as part of any human milk sampling and analysis program are valid and interpretable, information on participants is collected (see Bates et al. for additional information on informed consent issues). This information is designed to: (i) ensure eligibility for study participation; (ii) confirm eligibility for pooling of milk samples; (iii) determine comparability of results with results of other human milk studies; (iv) explain atypical results; (v) identify factors influencing concentrations of environmental chemicals; and (vi) identify potential confounding factors for elevated levels (Bates et al., 2002). It is essential that the questionnaire process maximize the amount of information that can be gained from such an endeavor and that participants remain fully informed of the study’s goals and results. Bates et al. (2002) discussed the following features of a well-designed questionnaire:

(i) Although questionnaires may be either self-administered or interviewer-administered, interviewer-administered questionnaires are preferred (Armstrong et al., 1992) because this process is more amenable to collecting information on complex questions, ensures completeness and consistency of answers, and allows for follow-up questions to be asked.

(ii) A study might require more than one questionnaire, for example, a screening questionnaire to determine whether potential participants fit the selection criteria, and a more detailed questionnaire for the study itself.

(iii) The wording of questions should be clear and directed to the participant. Questions should be ordered logically, with the most sensitive topics appearing later in the questionnaire.

(iv) For ease of analysis and collection of comparable data, questions with open-ended responses should be kept to a minimum.
(v) Questionnaires developed by the investigator should be pilot-tested to determine whether the questions are clear and unambiguous.

Bates et al. (2002) conclude that “...in regard to questionnaire design, ... there is no one way to carry out a human milk study. The final design will depend particularly on the study objectives and the target population.” Questionnaires from past human milk monitoring studies can be reviewed for ideas and may be used in future studies with permission from the questionnaire authors. However, investigators should approach previously used questionnaires with caution, as they may not be best suited for the study at hand.

**Guidance on chemical selection**

Efforts to assess levels of environmental chemicals in human milk have focused principally on a relatively small number of chemicals; most of these are persistent, chlorinated organic compounds. However, human milk may contain other environmental chemicals, for example, from occupational exposures or exposures to personal care products, which have been the subject of limited to no study (Berlin and Kacew, 1997). Because cost is a consideration in any study on environmental chemicals in human milk, the question of how to prioritize environmental chemicals for future study is an important one. Berlin et al. (2002a, 2002b) have developed several criteria which are designed to assist investigators in thinking more broadly about the types of chemicals that require research.

The general concept put forth is that additional consideration needs to be given to those “...chemicals with past widespread use or production and that may remain in humans because of their long biological half life, and ... chemicals with shorter half lives but that, due to their frequent use, may result in frequent exposures to pregnant and lactating women and their infants” (Berlin et al., 2002a). In selecting chemicals for study, issues regarding practicality must be considered; these include the availability of analytical methods, volume of milk sample required, stability of the chemical in milk, and analytical cost (Berlin et al., 2002a).

Berlin et al. (2002a) list the following criteria for selection of environmental chemicals for investigation: (i) lipid solubility and environmental persistence; (ii) extensive exposure as a result of production, release, or significant contact; (iii) known or suspected toxicity in a biological system; (iv) historical interest, trend information; (v) chemicals of emerging concern; and (vi) medicinal or occupational use.

Berlin et al. (2002a) also enumerated specific chemicals which should be considered for future human milk surveillance and research studies. Berlin et al. (2002a) note that the list is not static, but rather will need to be modified as new information on chemical toxicity/exposure is acquired and new chemicals are introduced into the environment.

**Guidance on analytical issues**

Once human milk samples have been collected as part of a human milk surveillance study or research program, they are sent to a laboratory for chemical analysis. The Expert Panel addressed issues related to the analytical component of human milk studies; these are described by Needham et al. (2002) and summarized here. This discussion is limited to general considerations for the analytical component of human milk studies. For information on analytical issues/methods related to specific chemicals, the reader should consult Needham et al. (2002) and Needham and Wang (2002). For information on specific analytical methods, both Thoma et al. (1977) and Vaz (1991) are useful.

There is no one single analytical method that must be used; rather, the method best suited for any given study depends on the chemical/physical properties of the environmental chemicals to be measured, the concentration ranges of those chemicals, the availability of laboratory equipment, time required for analysis, and cost. Additional general requirements for analytical methods described by Needham et al. (2002) include “…defining and demonstrating a number of essential criteria including the following 6 terms: accuracy, precision, specificity, linearity and range, limit of detection, and ruggedness/robustness.” A laboratory must demonstrate its ability to achieve reliable results by successfully participating in interlaboratory studies or by analyzing reference samples of human milk and obtaining satisfactory results (Needham et al., 2002).

In addition to the above requirements, Needham et al. (2002) discussed the importance of ensuring that the quality of the method be maintained (Taylor, 1987) by instituting a quality assurance/quality control (QA/QC) program. A QA/QC program includes such items as: verified chemical standards, calibration of laboratory equipment, the use of labeled internal standards, trained analysts, analysis of laboratory blanks to assess contamination within the laboratory, analysis of field blanks to evaluate potential contamination during the sampling/shipping process, and participation in proficiency testing studies such as the World Health Organization studies (Needham et al., 2002; Yrjänheikki, 1989). Needham et al. (2002) also note the importance of ensuring that the analytes are stable in the stored milk over time, including milk samples which have been subjected to freeze–thaw cycles.

**Guidance on interpretation and communication of results of studies on environmental chemicals in human milk**

Information on levels of environmental chemicals in human milk serves several purposes, including assessing temporal and geographic trends in body burdens of those chemicals, estimating infant exposures via lactation, and anticipating which chemicals might be of emerging concern. However, the collection of, and reporting on, information on environmental chemicals in human milk can have health
Risks and benefits: breast-feeding and formula feeding

The presence of persistent, bioaccumulative compounds in human milk means that infants who breast-feed are exposed to those chemicals via nursing. However, as described earlier in this review, human milk also confers numerous health benefits to the infant. In contrast, formula has not been shown to contain persistent, bioaccumulative compounds, but is lacking in many of the human milk constituents that afford health benefits. Furthermore, both human milk and formula contain other environmental chemicals (e.g., those in the water used to make formula, and non-persistent compounds in human milk) which complicate any assessment of health risks and benefits. Despite this complex picture, comparisons of infants who are breast-fed as compared to those who are formula-fed have generally shown that breast-fed infants have health advantages over formula-fed infants. In addition, studies of infants exposed to environmental chemicals in human milk have, for the most part, not shown adverse health effects to the nursing infant.

Studies of health risks and benefits associated with environmental chemicals in human milk are of two types: evaluations using a risk assessment approach, and studies of cohorts of mother–infant pairs where concentrations of specific chemicals have been measured in the mothers’ milk. These studies are reviewed in the following sections. Both of these types of studies have strengths and limitations. Their strengths include: (i) the use of standard risk assessment practices to merge information on measured levels of various PBTs in human milk with known toxicological effects to quantify health risk; (ii) the consideration of both potential risks and known benefits; and (iii) the evaluation of potential health impacts and benefits using relatively large populations. Potential questions arise from these studies, as well, including: (i) Are the study populations representative of the area of interest in terms of geography, socioeconomics, occupation, and other factors influencing PBTs in human milk, breast-feeding practices, and infant health outcomes? (ii) Can the potential for health effects from environmental chemicals other than PBTs be evaluated from these study results? (iii) Are the risk assessment assumptions utilized valid for current populations in the area of interest? (iv) Are the effects noted in studies of human populations both statistically and clinically signifi-
Risk–benefit assessments of formula- and breast-feeding

Three studies on the potential for risk of adverse health effects to infants from exposure to organochlorine compounds via breast-feeding as compared to the benefits of breast-feeding are described in this section.

Rogan et al. (1991) combined cancer risk assessment methods with information on lifetime exposures to several PBTs (dieldrin, oxychlordane, heptachlor epoxide, DDE, PCBs, and TCDD) to derive estimates of cancer risk (which Rogan et al. equated with excess mortality) associated with breast-feeding. This risk was compared with risk of infant mortality associated with not breast-feeding. Because insufficient data were available to estimate cancer potencies specifically from exposure to PBTs via breast-feeding, data from lifetime animal studies were used and potencies were derived based on lifetime average dose. Assessment of postneonatal mortality was estimated from a study on the effects of breast-feeding on mortality in developed countries. Rogan et al. (1991) estimated the upper bound increase in cancer risk associated with excess lifetime exposure to the six PBTs in human milk (listed above) to be 12–80 excess cancers per 100,000 infants. However, the risk of postneonatal mortality associated with not breast-feeding was estimated to be 256 per 100,000 infants. Rogan et al. (1991) concluded that “... on the basis of lifetime cancer risk alone, there is not sufficient evidence to advise against breast feeding on the basis of the commonly observed range of contaminant concentrations.” Rogan et al. (1991) also used their risk estimates to determine an estimated loss of life expectancy from exposure to the six PBTs in breast milk of less than 3 days, as compared to the decrease in life expectancy in infants not breast-fed of about 70 days. Thus, no advantage was found in not breast-feeding, and the results suggested that not breast-feeding may be a disadvantage.

Ayotte et al. (1996) evaluated human health risks to Inuit infants, a population highly exposed to dioxin-like compounds. The Inuit population residing in the Arctic is exposed to high levels of PBTs such as dioxins, furans, and PCBs due to their traditional diet of large amounts of fat from sea mammals. Ayotte et al. (1996) modeled body burdens of dioxin-like compounds in breast-fed Inuit infants, and found that breast-feeding influences body burdens of these compounds until about 20 years of age. Modeled infant adipose tissue and liver concentrations of dioxin-like compounds were compared to levels which produced adverse effects in laboratory animals, with the assumption that laboratory animals and humans would respond similarly. The authors concluded that “… the body burden of dioxin-like compounds in Inuit may be high enough to induce adverse effects on male and female reproductive systems.” However, they further noted that it is not possible to draw confident conclusions regarding the potential for these adverse effects to actually occur in Inuit infants due to differences in sensitivity between humans and laboratory animals, differences in the durations and magnitude of exposure between humans and laboratory animals, and potential interactions among the different environmental chemicals in the human milk mixture.

Hoover (1999) used probabilistic techniques (Monte Carlo simulation) to derive exposure estimates of organochlorine compounds to Canadian breast-fed infants. These exposure estimates were used to assess potential noncancer health risks by comparing exposure with published tolerable daily intakes. Hoover (1999) estimated both the percentage of the breast-feeding population exceeding tolerable daily intakes, as well as hazard quotients associated with those exposures. Excess cancer risks were derived using standard risk assessment methods; these were compared to the mortality risks associated with not breast-feeding as computed by Rogan et al. (1991). In addition, a qualitative comparison was made between the beneficial effects of breast-feeding as compared to the potential health effects of organochlorine chemicals in human milk.

Hoover (1999) calculated the percentage of the Canadian population of breast-fed infants expected to exceed guidance values (reference doses, Acceptable Daily Intakes, or Tolerable Daily Intakes) and found that for most of the chemicals evaluated, less than 5% of the population exceeded any guidance value. The exceptions were DDE, dieldrin, heptachlor epoxide, PCBs, TCDD, and total dioxin equivalents. Hazard quotients, the ratio of predicted exposure to a guidance value, were also estimated (Hoover, 1999). Hazard quotients below 1 indicate that adverse health effects are not expected. Most of the values for mean exposures were below 1 with the exception of DDE, heptachlor epoxide, PCBs, and dioxins and furans; in some cases, these exceedances were found only when exposures were compared to one of the reference values.

Hoover (1999) also evaluated cancer risk to infants from breast-feeding for the first year of life. Estimated cancer risks were below or close to $1 \times 10^{-5}$ for most of the chemicals assessed, with the exception of PCBs, TCDD, and total PCDDs/PCDFs. Hoover (1999) noted that the 95th percentile risk for all chemicals of $4 \times 10^{-4}$ is a highly conservative estimate, and that this estimate of 95th percentile risk is a factor of 6 below the risk of not breast-feeding (Rogan et al., 1991, estimated risk from not breast-feeding to be $25.6 \times 10^{-4}$). Hoover (1999) noted that the “predicted cancer risks of PCBs and PCDDs/PCDFs are theoretical, whereas the evidence for the mortality risks of not breast-feeding is stronger.” Thus, the research showed that the benefits of breast-feeding for the Canadian study population outweighed the estimated cancer risks and it was concluded that the benefit of decreased mortality was greater than the potential cancer risk for PCBs and PCDDs/PCDFs.
Finally, Hoover (1999) performed a qualitative comparison of the documented benefits of breast-feeding with the potential health risks associated with exposure to organochlorines, and stated that “[e]ven for health endpoints that could be adversely affected by exposure to organochlorines, such as neurodevelopmental, the benefits of breast milk appear stronger.”

Complexities inherent in comparing risks and benefits of human milk and formula

Because no activity is without risk, risks associated with not breast-feeding (i.e., using infant formulas or cow’s milk) should be described when information on studies of environmental chemicals is disseminated. LaKind et al. (2002) provide several questions that investigators are encouraged to consider: (i) How can the known health benefits associated with breast-feeding be compared with potential risks from exposure to environmental chemicals in human milk? (ii) How can potential risks from exposure to environmental chemicals in human milk be compared to the potential risks associated with chemicals in infant formulas (including risk associated with the water used to prepare formulas)? (iii) How can the psychosocial benefits accrued from breast-feeding be factored into a risk analysis? (iv) Is the exposure via nursing/formula-feeding the only source of exposure to an environmental chemical, or are other sources of exposure occurring simultaneously? (v) In a risk evaluation, how does one account for differences in developmental maturity between full-term newborns and premature infants?

Mother–infant cohort studies

Four large cohorts of mother–infant pairs have been followed to explore the potential health effects of pre- and postnatal exposure to environmental chemicals, with postnatal exposure occurring via breast-feeding (an additional large mother–infant cohort study is underway in Germany, but results of the study have not yet been published). Studies related to these cohorts (the North Carolina, Michigan, Dutch, and German cohorts) are summarized here. Although potential infant health effects associated with both prenatal and postnatal exposures were considered, only postnatal (i.e., breast-feeding) exposures are described in this section.

In addition to these four large cohorts, a smaller cohort of infants (N = 36) was studied for effects of postnatal exposure to PCDDs, PCDFs, and coplanar PCBs on infant immune system and thyroid hormone status (Nagayama et al., 1998a, 1998b). Blood samples from 1-year-old Japanese infants were analyzed for serum levels of T3, T4, TSH (thyroid stimulating hormone), TBG (thyroxine binding globulin), and lymphocyte subsets. Levels of PCDDs, PCDFs, and coplanar PCBs (expressed at toxic equivalents, or TEQs) in mothers’ milk at 3 months postpartum were 27.1 ppt (mean, lipid basis), 15.2 ppt (minimum, lipid basis), and 48.5 ppt (maximum, lipid basis). Nagayama et al. (1998a) reported that infants exposed to higher levels of dioxin TEQs via breast-feeding had lower levels of serum T3 and T4, but no correlation was seen with TSH and TBG. In addition, Nagayama et al. (1998b) found that dioxin TEQs in breast milk were positively associated with infant levels of CD4+ (helper/inducer T cells) lymphocytes and negatively associated with CD8+ (suppressor/cytotoxic T cells) lymphocytes. The authors did not present information on whether one would anticipate an observable adverse health effect in the infants based on these changes or whether the levels of lymphocytes and thyroid hormones in the breast-fed infants were within clinically normal ranges.

A small-scale study was conducted in Amsterdam, with recruitment of between 35 and 38 mother–infant pairs from 1990 to 1991 (Pluim et al., 1994b, 1996). Levels of dioxins in the mothers’ milk were determined from samples collected 3 weeks postpartum. Blood was collected from the infants at 1 and 11 weeks of age and analyzed for leukocytes, platelets, differential, activities of γ-glutamyl transferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and plasma levels of cholesterol and total and conjugated bilirubin. The authors estimated cumulative intake of dioxins from breast-feeding for the 11-week-old infants and found a significant positive association between the infants’ cumulative intake and ALT and AST plasma activities. A significant negative relation was reported between cumulative dioxin intake and number of platelets. The authors interpreted their findings as suggestive of liver effects to the newborn from postnatal exposure to dioxins. The authors further noted that the clinical significance of the findings was unclear because AST and ALT activities were in the normal range for all but three infants (Pluim et al., 1994b). The infants were also assessed up to about 6 months of age for body weight, length, head circumference, Quetelet index, liver size, and neurological development (Pluim et al., 1996). No relationship was found between dioxin exposure from breast-feeding and growth or neurological status in the first 6 months of life.

The North Carolina Breast Milk and Formula Project

The North Carolina Breast Milk and Formula Project (Project) was a study designed to examine the potential adverse health effects to infants from exposure to DDE and PCBs in human milk (Rogan and Gladen, 1985, 1991; Rogan et al., 1986a, 1986b, 1987; Gladen et al., 1988). The Project recruited a nonrandom cohort of 865 infants from 1978 to 1982 (Rogan and Gladen, 1985), with infants and mothers drawn from Greenville, Durham, and Raleigh, NC. The following were sampled: maternal blood, cord blood, and placenta, and colostrum, early milk, or formula for each infant, depending on their source of nutrition. The median concentrations (lipid basis) of DDE and PCBs in milk at time of birth were 2.43 and 1.77 ppm, respectively; the maximum DDE and PCB levels were 25.4 and 16 ppm, respectively; the 95th percentile for DDE and PCBs were 6.72 and 3.91 ppm, respectively (Rogan et al., 1986a, 1986b, 1987; Gladen et al., 1988).
Children were monitored clinically and developmentally until 5 years of age and then at puberty (Gladen et al., 2000). Newborns were evaluated with the Brazelton Neonatal Behavioral Assessment Scales (Rogan et al., 1986b). Medical histories for each child in the Project were taken at every visit and duration of breast-feeding was recorded (Rogan et al., 1987). Illnesses, including upper respiratory illness, otitis media, gastroenteritis, eczema, asthma, allergies, and lower respiratory infections were not associated with PCBs or DDE in human milk. At 6 and 12 months, children in the Project were evaluated using the Bayley Scales of Infant Development (Mental Development Index, or MDI, and Psychomotor Development Index, or PDI) (Gladen et al., 1988). No adverse effects were related to breast-feeding. Another evaluation with Bayley Scales of Infant Development occurred at 18 and 24 months of age; Rogan and Gladen (1991) reported no adverse effects from DDE or PCBs in human milk. An examination of 594 of the children at puberty (from 10 to 15 years of age) revealed no effects from breast-feeding on height, weight, or stage of pubertal development (Gladen et al., 2000).

The relationship between levels of DDE in human milk and reduced lactation duration or failure to lactate was explored, with the hypothesis that DDE exerts an estrogenic effect on the mother (Rogan and Gladen, 1985). The definition of lactational failure and reasons for weaning were (Rogan et al., 1987, p. 1296): “...at most one month mostly breast-fed and two months until final weaning,” where the causes included insufficient milk, poor weight gain, the baby was allergic to milk, the baby had difficulty breast-feeding, or the baby became ill. Rogan et al. (1987) found that children whose mother’s milk had higher levels of DDE were breast-fed for shorter periods of time.

The Michigan cohort

The Michigan cohort, recruited in the early 1980s, consisted of 242 infants of women who consumed moderate amounts of fish from Lake Michigan (at least 11.8 kg fish over a 6-year period) and 71 infants of mothers who did not consume fish from Lake Michigan (Jacobson et al., 1984). The nonrandom cohort (which overrepresented mothers who had consumed relatively large amounts of Lake Michigan fish contaminated with PCBs) participated in a longitudinal study on the effects of both in utero and postnatal PCB exposures (Jacobson, 2000). Infant exposure was assessed by the mother’s report of contaminated fish consumption, by the PCB levels in infant cord serum (81 samples), and by PCB levels in the mother’s milk (67 samples). To determine the amount each infant breast-fed (ranging from exclusively bottle-fed to exclusively breast-fed), information on their feeding patterns was obtained at 2, 4, 5 and 7 months postpartum (Jacobson et al., 1985).

One hundred twenty-three infants in the cohort were administered Fagan’s test of visual recognition memory at 7 months. Deficits in infants’ visual recognition were not predicted by postnatal exposure via breast-feeding (Jacobson et al., 1985). Two hundred thirty-six of the infants were evaluated at 4 years of age (Jacobson et al., 1990). Activity was found to be affected by exposure to PCBs via lactation. However, the authors noted that “effects on activity are negligible unless the infant has breast fed for at least 1 year” and that the effect “was relatively subtle, and its clinical significance is uncertain” (Jacobson et al., 1990). No association was found between exposure to PCBs via breast-feeding and IQ deficits in the children at infancy, or at ages 4 and 11 (Jacobson, 2000).

The Dutch PCB/Dioxin Study

A cohort of mother–infant pairs was recruited from 1990 to 1992 to participate in a prospective longitudinal study to assess health effects of PCBs and dioxins both in utero and from breast-feeding; the study was called the Dutch PCB/Dioxin Study (Koopman-Esseboom et al., 1993, 1994b). Two hundred five women participated, with approximately half the cohort breast-feeding their infants and the other half using formula (Koopman-Esseboom et al., 1993). Blood samples of mothers in the last month of pregnancy and of the umbilical cords were taken and analyzed for PCBs. Human milk samples (collected 2 weeks postpartum) were collected and analyzed for PCBS, dioxins, and furans. The authors examined maternal and infant thyroid hormone status for 78 of the mother–infant pairs (Koopman-Esseboom et al., 1994b). The authors reported that higher dioxin and PCB TEQs in human milk were associated with higher infant plasma TSH levels in the second week and third month after birth and lower plasma free thyroxine and total thyroxine levels in the second week after birth. However, the authors further observed that the higher thyroid hormone levels could be due to either in utero or lactational exposure, and that these thyroid levels were in the normal range (Koopman-Esseboom et al., 1994b).

Four hundred eighteen infants were also assessed for neurological optimality using the Prechtl neurological examination (a comprehensive, age-adequate neurological examination including assessments of reflexes and muscle tone) between the 10th and 21st days postpartum (Huisman et al., 1995a). The authors found that higher concentrations of PCBS, dioxins, and furans in human milk were associated with reduced neonatal neurological optimality and that increased concentrations of planar PCBS in human milk were associated with higher incidences of hypotonia or decreased muscle tone (Huisman et al., 1995a). According to Huisman et al. (1995a), because of the “very minor character of the deviations,” the authors did not advise against breast-feeding. In a follow-up neurological examination of these same 418 children at 18 months of age, Huisman et al. (1995b) could not detect any effect of lactational exposure to PCBS and dioxins. In fact, the
authors found a “beneficial effect of breast-feeding on fluency of movements.”

Infants were also evaluated at 3, 7, and 18 months of age for mental and psychomotor development with the Bayley Scales of Infant Development (Koopman-Esseboom et al., 1996). At 3 and 7 months, no influence of perinatal exposure to dioxins or PCBs on mental outcome was found. At 7 months, the authors found a negative association between breast-feeding and psychomotor outcome (i.e., infant exposures to PCBs and dioxin via breast-feeding had an adverse effect on psychomotor outcome), but breast-fed infants' scores were not significantly different from formula-fed infants. At 18 months, no relationship was found between perinatal dioxin or PCB exposure and mental or psychomotor scores.

At 42 months of age, Weisglas-Kuperus et al. (2000) found a positive association between perinatal exposure to PCBs and dioxins and increased susceptibility to infectious diseases (and possibly a lower occurrence of allergies). In addition, Weisglas-Kuperus et al. (2000) found that the breast-fed children did better than formula-fed children in both neurological and cognitive outcomes. Lactational PCB and dioxin exposures did not adversely affect the growth rate of the breast-fed children (Patandin et al., 1998). In addition, at 42 months, Patandin et al. (1999) did not find an association between lactational exposure to PCBs and dioxins and cognitive abilities.

The German cohort

One hundred seventy-one healthy mother–infant pairs participated in a study in Germany to evaluate the potential effects of pre- and postnatal exposures to PCBs on mental and motor development of the infants (Walkowiak et al., 2001). Mothers were recruited between 1993 and 1995. PCBs were measured in infant cord blood, in infant serum at 42 months of age, and in the milk from 126 mothers. The authors used the HOME score to evaluate the home environment of the infants at 18 months of age. Infants were tested with the Bayley Scales of Infant Development (both mental and motor) at ages 7, 18, and 30 months and with the Kaufman Assessment Battery for Children at 42 months. The authors reported a negative association between PCB levels in human milk and Kaufman scores at 42 months but not with Bayley scores at 30 months.

Risk assessment and regulatory decision-making

According to LaKind et al. (2002), the purpose of assessing risks of environmental chemicals in human milk should be to assist physicians and public health care providers in: (i) understanding when it is necessary to analyze a patient’s human milk for environmental chemicals; (ii) counseling mothers whose milk does not pose health risks about the benefits of breast-feeding; (iii) giving guidance to mothers whose milk contains a level of environmental chemical that could be detrimental to their nursing infant; and (iv) recommending the proper nutrition source for the infant.

To achieve these goals, risk assessments associated with environmental chemicals in human milk must reflect the fact that scientific accuracy is of greater importance than conservatism because the consequences of overestimating risks may actually pose a health risk with concerned mothers denying themselves or their infants health benefits by not breast-feeding (LaKind et al., 2002). Thus, risk assessments of environmental chemicals in human milk need to be based on an acceptable level of accuracy predicated on scientific evaluation rather than purely reflecting use of the Precautionary Principle (LaKind et al., 2002). Similarly, it must be acknowledged that since infants derive health benefits from feeding regardless of whether they are breast-fed or formula-fed, it is difficult to compare any potential health risks from infant nutritional sources using the current risk assessment methodologies for environmental chemicals. In addition, acceptable daily intakes, reference doses, and cancer slope factors do not necessarily provide a useful tool for making public health decisions because these are usually based on chronic toxicity hazards, which are not necessarily germane to infant exposure patterns from human milk (LaKind et al., 2002). It is also important to consider factors that could underestimate risk [e.g., the potential for neonates to be more (or less) sensitive to the effects of chemicals than adults and the fact that many types of animal toxicity tests employ young adult animals rather than neonates] (Hoover, 1999; LaKind et al., 2002).

Summary

Many professional organizations and individuals with expertise in child health and lactation have examined the literature on the subject of breast-feeding in general, and of environmental chemicals in human milk, and continue to recommend breast-feeding despite the presence of environmental chemicals in human milk (Frank and Newman, 1993; GBPSR, 1999; Kacew, 1994; Schreiber, 2001). In general, LaKind et al. (2002) synopsized the benefits of breast-feeding (as described originally by Lawrence and Lawrence, 1999, and the AAP, 1997) as: “nutritional benefits for normal growth and development ...; psychological and cognitive benefits, including more rapid development of visual acuity, detectable improvements in educational achievement, and improved scores on developmental scales; improved efficiency of digestion and absorption because of the greater bioavailability of essential nutrients in human milk as compared to infant formula; protection against infections of the upper and lower respiratory system and middle ear, due to the presence of defense agents in human milk; significantly reduced risk of ulcerative colitis, bacteremia, bacterial meningitis, urinary tract infections, lymphoma, allergic diseases, and necrotizing enterocolitis, and as an adult, Crohn’s disease.”
Conclusions, research needs, and recommendations

The aim of this review is to introduce the reader to various science and policy aspects of the topic of environmental chemicals in human milk. Issues related to components of human milk (both endogenous and exogenous), concentrations and temporal/geographic trends of environmental chemicals in human milk, modeling of infant body burdens of environmental chemicals from lactational exposure, and analyses of health benefits and risks associated with environmental chemicals in human milk were described. In addition, methodologies for conducting surveillance and research on environmental chemicals in human milk, which were the subject of discussion by an Expert Panel at the Technical Workshop on Human Milk Surveillance and Research for Environmental Chemicals in the United States, were summarized. The issue of environmental chemicals in human milk has experienced increased visibility, and the need to augment our understanding of levels of these chemicals in the milk of women residing in the United States has been articulated (LaKind et al., 2001; Landrigan et al., 2002).

Although the health benefits to the infant from breast-feeding have been documented, health care practitioners and expecting and new mothers still might remain uncertain as to whether breast-feeding is preferable to formula feeding. Because of these uncertainties, LaKind et al. (2002) noted that “[t]o the extent that a new mother might choose not to breast-feed because of fear of environmental chemicals, it is critical that studies be conducted to (i) better understand the health status of breast-fed infants compared to infants on other forms of infant nutrition, and (ii) improve our understanding of concentrations and exposures of environmental chemicals in both human milk and other sources of infant nutrition.”

The need for a program of human milk surveillance, as well as related research on environmental chemicals in human milk, was outlined by the Workshop’s Expert Panel. The Panel developed a series of conclusions and recommendations for environmental chemicals in human milk; these are summarized here (Berlin et al., 2002b):

(i) Studies on environmental chemicals in human milk should not adversely affect the participating mother’s decision to breast-feed. Using minimally invasive methods for collection of milk and of information from any study participant, as well as providing information on the study to the participant, should reduce the possibility of disrupting breast-feeding or negatively affecting the decision to breast-feed.

(ii) Although the scientific and public health value of studies on environmental chemicals in human milk is important, it is equally important to recall that “… the mere presence of an environmental chemical in human milk does not necessarily indicate that a health risk exists for breast-fed infants. The accumulated data overwhelmingly supports the positive health value of breast-feeding infants” (Berlin et al., 2002b).

An outcome of the Technical Workshop on Human Milk Surveillance and Research for Environmental Chemicals in the United States was an enumeration of research needs. Despite the fact that the benefits for both mother and infant associated with breast-feeding are well recognized, concerns have been expressed regarding environmental chemicals in human milk. Because it is not currently possible to completely address these concerns (because of a dearth of information on levels of environmental chemicals in human milk in the United States and on the potential adverse health effects, if any, of environmental chemicals in human milk), the Panel recommended several components of a research agenda to address these uncertainties, including the following (Berlin et al., 2002b):

1. Determining the concentrations of environmental chemicals in human milk and infant formula in the United States, with particular attention given to disproportionately exposed populations.
2. Identifying biomarkers of exposure, susceptibility, and effects in humans to predict potential health effects associated with environmental chemicals to breast-fed and formula-fed infants, and others.
3. Developing methods to analyze the risk/benefit ratio for breast-feeding vs. formula feeding.
4. Developing strategies for dissemination of research findings, through education and other means (e.g., creation of an internet-accessible database) to health care providers and the public, including communicating the known benefits of breast-feeding as well as the potential health risks of environmental chemicals found in human milk and infant formulas.
5. Supporting, organizing, and coordinating research and service efforts to protect infants from unacceptable exposures to environmental chemicals in human milk and infant formula.

References


Hoover, K., MacDonald, T.A., 2000. The PBDEs: an emerging environ-


United States Environmental Protection Agency (USEPA), 2000. Draft Dioxin Reassessment. Draft Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds. September. EPA/600/P-00/001B. Available at: [http://cfpub.epa.gov/ncea/cfm/part1and2.cfm?ArtType=default].


