

HUMAN MILK SURVEILLANCE AND RESEARCH OF ENVIRONMENTAL CHEMICALS: CONCEPTS FOR CONSIDERATION IN INTERPRETING AND PRESENTING STUDY RESULTS

Judy S. LaKind

LaKind Associates LLC, Catonsville, Maryland, USA

Nettie Birnbach

Professor Emeritus, College of Nursing, State University of New York
at Brooklyn, Boca Raton, Florida, USA

Christopher J. Borgert

Applied Pharmacology and Toxicology, Alachua, Florida, USA

Babasaheb R. Sonawane

National Center for Environmental Assessment, Office of Research
and Development, U.S. Environmental Protection Agency,
Washington, DC, USA

Mary Rose Tully

Human Milk Banking Association of North America, Chapel Hill,
North Carolina, USA

Linda Friedman

Rochester, New York, USA

This article describes issues related to the interpretation, presentation, and use of data from human milk surveillance and research studies. It is hoped that researchers conducting human milk studies in the future will consider these concepts when formulating study conclusions and presenting data. The key issues discussed are: (1) communication of information on human milk constituents to health care providers and the public; (2) complexities associated with assessing risks and benefits when comparing breast-feeding and

We thank the following organizations for generously providing support for the workshop: the Department of Health and Human Services, Health Resources and Services Administration; the U.S. Environmental Protection Agency; 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. We also thank the reviewers of this article for their suggestions.

The views expressed in this article are those of the authors and do not represent or reflect the views or policies of the U.S. Environmental Protection Agency. Mention of trade names of commercial products does not constitute endorsement of those products by the authors.

Address correspondence to Judy S. LaKind, PhD, LaKind Associates LLC, 106 Oakdale Avenue, Catonsville, MD 21228, USA. E-mail: lakindassoc@worldnet.att.net

formula-feeding; (3) use of human milk information for trends analysis and assessment of the efficacy of restrictions on use/release of chemicals in the environment; and (4) risk assessment and regulatory decision-making concepts regarding environmental chemicals in human milk. As researchers conduct surveillance and research involving human milk, it is of the utmost importance that the results of these studies are provided with information on risk and benefits that place the data in perspective, so that those involved in decision making regarding infant nutrition (e.g., expectant mothers, physicians, midwives, nurses, and lactation consultants) can appropriately interpret the research data.

Human milk is a rich and readily available fluid that can be easily collected over time with minimally invasive techniques. It is therefore of interest as a biomarker to those conducting research on population and/or individual exposures to environmental chemicals. Although data derived from such studies are valuable in assessing environmental exposure levels and potential risks, this information has public, as well as individual, health implications. Expectant mothers face a myriad of decisions regarding the care of their newborns. One of the most important early decisions is what is best for the infant in terms of nutrition: Is human milk or formula best for the infant? While the advantages to both mother and infant associated with breast-feeding are numerous and well documented, some are concerned about potential risks to the nursing infant from the presence of environmental chemicals in human milk. As researchers conduct surveillance and research regarding chemicals in human milk, it is of the utmost importance that the results of these studies are provided with information on risk and benefits that place the data in perspective, so that those involved in making decisions regarding infant nutrition (e.g., expectant mothers, physicians, midwives, nurses, and lactation consultants) can understand and appropriately interpret the data.

Milk is species specific, and human milk is thus best for human infants. Its benefits include optimal nutrition, as well as immunologic protection and an array of growth factors and other bioactive components. For these reasons, breast-feeding is the preferred choice for infant nutrition for many mothers and is recommended by researchers, individual health care practitioners, the World Health Organization, the U.S. Department of Health and Human Services, (U.S. DHHS), the American Academy of Pediatrics, the American Academy of Family Physicians, the American College of Obstetrics and Gynecology, the Academy of Breastfeeding Medicine, and other professional organizations concerned with infant nutrition. The World Health Assembly (WHA) recently adopted a resolution recommending exclusive breast-feeding for the first six months of an infant's life (WHA, 2001). The U.S. Food and Drug Administration (FDA) noted that "when it comes to nutrition, the best first food for babies is breast milk" (U.S. FDA, 1998). The American Academy of Pediatrics (AAP) "recommends breast milk as the preferred source of feeding for almost all babies for at least the first year of life" because "breast-feeding provides health, nutritional, immunologic, developmental, psychological, social, economic and environmental advan-

tages unmatched by other feeding options” and because “epidemiologic research shows that human milk and breast-feeding provide advantages with regard to general health, growth, and development, while significantly decreasing risk for a large number of acute and chronic diseases” (AAP, 1997). In addition to benefits to infant health, health benefits associated with breast-feeding have likewise been reported for mothers (AAP, 1997; U.S. DHHS, 2000).

Over the last 50 years, researchers have measured environmental chemicals in human milk. It has been noted that “despite a literature that is now almost 50 years old, there are very few instances in which morbidity has occurred in a nursing from a pollutant chemical in milk” (AAP, 1999). Nonetheless, some have questioned whether environmental chemicals in human milk adversely impact infant development and health. For example, the Natural Resources Defense Council (NRDC, 2002) stated that “any level of chemicals in breast milk is a potential health concern—for both mother and child.” To 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 (1) better understand the health status of breast-fed infants compared to infants on other forms of infant nutrition, and (2) improve our understanding of concentrations and exposures of environmental chemicals in both human milk and other sources of infant nutrition.

To understand under what conditions environmental chemicals in human milk might pose an unreasonable risk to the health and development of breast-fed infants, we must first understand the nature and the magnitude of exposures from breast-feeding. Few studies on environmental chemicals in human milk have been conducted in the United States. Thus, there is a serious lack of data and a growing need for a human milk sampling and analysis protocol and a well-coordinated surveillance program in this country.

This article describes issues related to the interpretation, presentation, and use of data from human milk surveillance and research studies. It is hoped that researchers conducting future human milk studies will consider this perspective when formulating conclusions and presenting data. The key issues discussed are communication of information on human milk constituents to the medical and health care provider communities and mothers, complexities associated with assessing risks and benefits when comparing breast-feeding and formula feeding, use of human milk information for trends analysis and assessment of the efficacy of restrictions on use/release of chemicals in the environment, and risk assessment and regulatory decision-making concepts in regard to environmental chemicals in human milk.

COMMUNICATING RESULTS OF HUMAN MILK STUDIES TO HEALTH CARE PROFESSIONALS AND THE PUBLIC

Scientifically designed and executed human milk surveillance and research studies will yield useful data that can be interpreted and communi-

cated to appropriate audiences. These findings must be made available to physicians, midwives, nurses, and other practitioners providing maternal and child care services, through professional, peer-reviewed publications, seminars, and continuing education programs. Ultimately, these findings must reach pregnant women or new mothers. Therefore, reliable information must be conveyed to the public through the popular press, the Internet, and public service announcements on television and radio, as well as written materials designed for the layperson. All factors germane to breast-feeding and human milk studies need to be clearly and concisely addressed, including an analysis of risks versus benefits of breast-feeding and formula feeding. With the availability of more sophisticated analysis capability, previously unrecognized chemicals (both exogenous and endogenous), as well as agents in products and foods, may be identified, and identified at lower levels than previously possible. In keeping with responsible reporting, it is important to ensure that outcomes of these studies are presented in a context that promotes understanding and informed decision making rather than alarm, since there are obvious consequences to the dissemination of such data.

A crucial component of good communication is keeping the audience and the desired message at the forefront. Several groups have grappled with improving the communication and understanding of the scientific information and its public health relevance. General guidelines for communicating science regarding nutrition and food safety were developed by an advisory group convened by the Harvard School of Public Health and the International Food Information Council Foundation (Harvard, 1998). The guidelines (excerpts are shown in Table 1) suggest methods for journalists, scientists, and other communicators to focus on the most critical information and provide "the necessary data, disclosures, and contextual qualifiers to help the

TABLE 1. Guidelines for Communication Information on Studies of Chemicals in Human Milk

For all parties:

1. Will your communication enhance public understanding of risks and benefits of breast-feeding and formula feeding?
2. Have you put the study findings into context?
3. Have the study or findings been peer reviewed?

For scientists:

1. Have you provided essential background information about the study in your written findings, or to journalists or others requesting it, in a language that can be understood?
2. Have you clarified the comparative risks and benefits?

For journalists:

1. Is your story accurate and balanced?
 2. Have you applied a healthy skepticism in your reporting?
 3. Does your story provide practical advice for expectant mothers and those involved in counseling on infant nutrition?
-

Note. Adapted from Harvard (1998).

TABLE 2. Questions the Public Might Ask to Evaluate Science Information When Making Informed Health Decisions

-
1. What is the message?
 2. Is the source reliable?
 3. How strong is the evidence overall?
 4. Does this information matter?
 5. What do the numbers mean?
 6. How does this risk compare to other risks?
 7. What actions can be taken to reduce risk?
 8. What are the trade-offs?
 9. What else do I need to know?
 10. Where can I get more information?
-

Note. From *Health InSight* (1999).

public evaluate a study's relevance and importance" (Harvard, 1998). These suggestions are relevant to the communication of information on chemicals in human milk; Table 1 includes guidelines adapted from Harvard (1998) for use in communicating information on human milk studies. Similarly, Harvard's Center for Risk Analysis chaired a diverse steering committee and multistakeholder advisory group that developed questions (Table 2) the public might ask to evaluate science information when making informed health decisions (*Health InSight*, 1999). The sets of questions developed by these two groups provide researchers with clear guidelines for the communication of their scientific studies.

A key feature of effective communication is imparting clear, understandable messages so that readers can weigh the various perspectives needed to inform personal decisions. According to the U.S. Department of Health and Human Services *Blueprint for Action on Breastfeeding* (2000), mothers who breast-feed need current, culturally relevant breast-feeding information provided by trained health care professionals. Those professionals need ongoing education on such topics as breast-feeding counseling and lactation management, among others. A carefully executed educational program can demonstrate that the benefits of breast-feeding outweigh the risks, or define certain situations (such as poisonings or unusual occupational exposures) that may preclude breast-feeding. Both the benefits of breast-feeding that accrue to the mother and infant and information regarding potential deficiencies in formula need to be delineated (AAP, 1997). One method for achieving this is to ensure that the data from human milk surveillance and research studies be made widely available, with scientifically sound interpretations, in both the peer-reviewed literature and more publicly accessible venues.

Ideally, expectant mothers need to be apprised of all the advantages of breast-feeding, as well as the potential consequences of not breast-feeding early in their pregnancy. They also need information about avoiding certain

chemicals while breast-feeding, as well as practical dietary implications of such avoidance. The task of providing this information is frequently assigned to the nursing staff in prenatal clinics and obstetrical offices. On postpartum hospital units, it is the nurse or lactation consultant who assists in putting the infant to breast and instructing the mother on breast-feeding strategies. Clearly, the knowledge base and attitudes of childbirth educators, nursing personnel, and lactation consultants are critical components in the encouragement of breast-feeding. Any education program that is adopted must be targeted to all health care providers involved in the various phases of child-bearing, childbirthing, and child rearing to ensure that women and their partners receive the unbiased information needed to make an educated decision. Appropriate utilization of the data derived from reliable human milk surveillance and research may help the United States reach its *Healthy People 2010* goal to increase breast-feeding rates to 75% at birth, 50% at 6 mo, and 25% at 1 yr, by 2010.

COMPLEXITIES INHERENT IN COMPARING RISKS AND BENEFITS OF HUMAN MILK AND FORMULA

Risk is a term that describes potential safety or harm, and in the context of chemicals, understanding risk requires an understanding not only of the toxicity of a chemical, but the extent to which humans are exposed to those chemicals. To address the potential concerns of the health care community and expectant mothers regarding infant exposure to chemicals in human milk, and to delineate data gaps that will need to be addressed by future human milk studies, an understanding of what is known about environmental and endogenous chemicals in human milk is needed. Further, since no activity is without risk, the risks associated with *not* breast-feeding (i.e., with the use of infant formulas or cow's milk) also need to be described. It is not the intent of this section to provide an exhaustive review of chemicals in human milk, but rather to provide sufficient information such that (1) the complexities underlying the comparative risk analysis of breast-feeding and formula feeding become clear, and (2) the importance of providing context to the results of human milk surveillance and research monitoring studies is apparent. In general, we hope to encourage those conducting human milk monitoring studies to contemplate critical questions, including: How does one compare the many health benefits associated with components of human milk, which are crucial to the growth and healthy development of the infant, with potential risks from exposure to other chemicals in human milk? How does one compare potential risks from exposure to chemicals in human milk to the risks associated with chemicals in infant formulas (including risk associated with the water used to prepare formulas)? We provide here a synopsis of important endogenous substances in human milk and a review of classes of previously investigated exogenous chemicals found in human milk (for an in-depth treatment of this subject, see Lawrence

& Lawrence, 1999, and Jensen, 1995). This information is included to provide understanding of the complexity of human milk, which underlies the complexities associated with assessing risks and benefits from various sources of infant nutrition.

What Is Human Milk?

Human milk is a complex fluid comprised of hundreds of endogenous and exogenous substances. Many of these substances are crucial to the development of the maturing infant; others are less desirable. The composition of human milk evolves as the infant ages to provide optimal postnatal growth for the human newborn and is programmed to continue the development that started in utero. The concentrations of various biochemical constituents change over the course of lactation (from birth to weaning). The transition from the production of colostrum, the first milk produced by the mammary glands, to mature milk takes 1 to 2 wk. However, the composition of milk continually changes throughout the entire period of lactation, in some cases adapting to the infant's changing nutritional needs as well as the environmental pathogens to which the mother is exposed. The composition also varies throughout the course of an individual feeding (fore-milk to hind-milk), with the largest variation in the percentage of lipids and in those compounds that are lipid-soluble (Hamosh et al., 1984; Jensen, 1995).

The provenance of the constituents that make up human milk can be categorized into three major groups: endogenous substances, exogenous substances from voluntary exposures, and exogenous substances from involuntary exposures. The endogenous substances include lipids, proteins, carbohydrates, enzymes, immunoglobulins, minerals, vitamins, cytokines, hormones, and other bioactive components. The exogenous substances that are present via voluntary exposures include medications, recreational compounds, and illicit drugs; those that are present through involuntary exposures include environmental chemicals, such as pesticides, that may be present in water, air, soil, and food.

Endogenous Substances Human milk contains components that contribute to the well-being of the infant. Nutrients include lipids, carbohydrates, proteins, amino acids, minerals, and vitamins. Nonnutritive components include enzymes, immunoglobulins, nucleic acids, hormones, growth factors, and cells, including macrophages, lymphocytes, neutrophils, and epithelial cells. Provided here is a brief overview of some of the important human milk components, including those that are generally not found in infant formula. [For a comprehensive description of the composition of human milk, see Jensen (1995).] The main constituent of human milk—water—is not discussed here, but it is important to note that all other constituents are dissolved or suspended in water (Lawrence & Lawrence, 1999).

Lipids Lipids, which make up 3 to 5% of human milk, are the major source of kilocalories and are crucial for the growth and development of the infant and of the infant's nervous system (Jensen et al., 1995). The impor-

tance of this becomes evident when considering that the human brain more than doubles in size during the first year of life.

The amount of lipid in human milk is extremely variable and influenced by many factors. For example, lipids increase within the course of one feeding, over the course of lactation from birth to weaning, with shorter intervals between feedings, and decrease with parity (number of children) and infections. Lipid levels may even differ between breasts and at different times of the day. One practical consequence of this variability is that the concentration of chemicals that are fat soluble (for example, certain environmental chemicals) will vary as a function of the lipid content of the sampled human milk. Thus, one can expect that these concentrations will depend on such factors as when during the feeding the milk sample was collected.

The nutritional state of the mother and the composition of her diet are also factors in the lipid biochemistry of her milk. If the mother is weight stable, the lipid profile in her milk reflects the types of fats in her diet. If she is losing weight, her fat stores serve as a source of the milk lipids. One of the lipid components that does not vary, even with manipulation of the mother's diet, is cholesterol. Cholesterol, synthesized in the mammary gland, is an essential component of cell membranes (Potter & Nestel, 1976) and is required for the cells to function, grow, and replicate (Lawrence & Lawrence, 1999). In contrast, the human milk level of docosahexaenoic acid (DHA), an omega-3 fatty acid that plays a role in nerve, brain tissue, and retinal development, is always present but the level can be influenced by the mother's diet (Birch et al., 1998). At present, infant formulas contain no cholesterol, while DHA has recently been approved by the Food and Drug Administration for addition to formula.

Proteins Proteins make up approximately 1% of human milk (Champe & Harvey, 1994). Amino acids, the building blocks of proteins, are present in varying concentrations in milk from different animal species. For example, human milk is rich in the amino acid taurine (2-aminoethanesulfonic acid), whereas cow's milk has virtually no taurine (Lawrence & Lawrence, 1999). This particular amino acid plays an important role in digestion, in the function of the nervous system, and in the development of the retina in the eye (Gaul, 1989). Although formula manufacturers are now beginning to add to taurine to some of their products, it is only one of the many species-specific components of human milk.

Enhanced nutrient bioavailability For a nutrient to aid in growth and development, its biochemical constituents must be absorbable in the gastrointestinal tract, and after passing through the liver must be usable by the tissue. Many human milk micronutrients are present in particular molecular species that permit a more efficient absorption than the species present in cow's milk or formula preparations. For example, 49% of the iron in human milk is absorbed by the gastrointestinal tract of the infant, whereas only 4% of the iron in iron-fortified formula is absorbed (Lawrence & Lawrence, 1999).

Components that protect against illness Human infants are born with an immature immune system, leaving them vulnerable to infection. It has

been known for over 100 years that human milk contains antibodies and other factors that help the infant fight off various infections and parasites until the immune system is fully functioning (see Lawrence & Lawrence, 1999, for an extensive review). Breast-fed infants have a lower incidence of acute infections such as respiratory infections, otitis media (ear infections), and gastrointestinal infections (Hamosh, 2001). In addition, breast-feeding reduces infections by decreasing exposure to pathogens that may be present in foods or formula contaminated during handling or storage. There are also several components of human milk, not all specifically identified, that reduce the incidence of certain chronic diseases and decrease the incidence of allergy. Breast-fed infants also have a lower incidence and reduced severity of allergic symptoms including eczema and asthma (Burr et al., 1993; Gruskay, 1982). Breast-feeding appears to be protective against the development of Hodgkin's disease, lymphoma, and childhood acute leukemia (Davis et al., 1988; Shu et al., 1999).

Much of the lipid in human milk is found in milk fat droplets, which are surrounded by a membrane containing glycoproteins that provide protection against various infections. These contain (1) mucin, which prevents diarrhea-causing bacteria such as *Escherichia coli* from binding to cells in the digestive system, (2) lactoferrin, which is bactericidal and antiviral (Hamosh, 2001; van der Strate et al., 2001), (3) various oligosaccharides, which inhibit the binding of several disease-producing bacteria, and (4) glycosaminoglycans, which are involved in preventing viral infections such as HIV (Peterson et al., 1998).

Colostrum, the milk secreted during the first few days postpartum, contains a high concentration of secretory immunoglobulin A (sIgA), which is very stable at low pH and resistant to digestion by the enzymes of the infant's gastrointestinal tract. The sIgA protects the infant's intestinal mucosa from bacteria and viruses. In addition to sIgA, other human milk components inhibit the growth and reproduction of viruses that cause gastrointestinal problems including diarrhea. During the first 1 to 2 yr of life, these immunoglobulins are absorbed intact by the infant and distributed throughout the infant's body. At about 2 yr of age, intestinal closure occurs, preventing intestinal absorption of such large molecules.

Human milk also contains maternal antibodies. These include antibodies against bacteria and viruses to which the mother has been exposed, as well as diseases she has been vaccinated against, such as polio, influenza, and rhinovirus.

Hormones Hormones reported in human milk include both nonpeptide hormones such as thyroxine (T_4) and hormonally active peptides such as prolactin and somatostatin (Koldovsky, 1995; Koldovsky & Strbak, 1995). The concentration of many of these substances in human milk changes as the infant matures. While much is known about the function of endogenously produced hormones in the infant (Koldovsky, 1995; Bernt & Walker, 1999), such as the positive influence of cortisol, an adrenal hormone, on the maturation of the immature intestinal barrier, in many cases the exact function of milk-borne hormones in the infant is unknown.

Vitamins and minerals Human milk contains several vitamins, including vitamin A (required for vision), vitamin-D (which helps to prevent vitamin-D-deficiency hypocalcemia and rickets, although not in sufficient quantity to prevent rickets without sunlight exposure), vitamin E (required for muscle integrity, resistance of erythrocytes to rupture, and other important functions), vitamin K (essential for the production of blood-clotting factors), vitamin C (essential to collagen synthesis and necessary for several enzyme and hormone systems), and vitamin B complex (compounds necessary for many biochemical functions in the body) (Lawrence & Lawrence, 1999). Minerals in human milk include sodium, potassium, chloride, calcium, and magnesium (Jensen, 1995).

Nucleotides Nucleotides are building blocks of all cells in the human body and are intimately involved with cell function. They are nitrogenous compounds and make up a significant portion of the 18–30% nonprotein nitrogen portion of human milk. Studies suggest that nucleotides may enhance iron absorption, alter lipid metabolism, and influence the growth and development of the intestinal tract (Gill & Uauy, 1995) and the immunocompetence of the breast-fed baby (Carver et al., 1991).

Exogenous Environmental Chemicals Exogenous chemicals may appear in human milk if the mother has been exposed intentionally or unintentionally either through the oral pathway (e.g., ingestion of medication), the inhalation pathway (e.g., smoking cigarettes), and the dermal pathway (e.g., by application of sunscreen lotion or the use of a nicotine patch). These exogenous chemicals are generally referred to as environmental chemicals since they derive from the mother's surroundings, behaviors, and lifestyle. Examples of classes of environmental chemicals to which the mother may be intentionally exposed include medications and recreational and illicit drugs, as described briefly next.

Medications It is the responsibility of the clinician to make decisions regarding whether or not to prescribe medications to a breast-feeding mother. Generally speaking, the number of drugs that are of concern for the breast-feeding mother is limited (AAP, 2001). Certain drugs pose risks to the nursing infant, such as diagnostic radioactive substances or chemotherapeutic drugs, which usually require temporary cessation of breast-feeding. Even more commonly used drugs may raise concerns; for example, acetaminophen (the drug found in Tylenol) and the prescription drug sertraline (Zoloft, used to treat depression), are usually considered compatible with breast-feeding, whereas aspirin should be used with caution because of its association with Reyes syndrome, and lithium (used to treat bipolar disorder) should be used with caution because it is transferred to milk at a high level and has affected central nervous system (CNS) functioning in some infants.

The decision to use nonprescription medications is frequently made independently by the mother. If the mother consults with her health care provider, she can be advised, since there are lists that classify drugs accord-

ing to whether they (1) should not be used by nursing mothers, (2) should be given to nursing mothers with caution, or (3) are acceptable for use by nursing mothers (AAP, 2001). At the same time, the environmental exposure to certain antibiotics and hormones through everyday food sources, such as domestic meats, is one beyond the mother's or health care provider's control.

Recreational drugs and illicit drugs Recreational drugs, such as caffeine, nicotine, and, alcohol, as well as illicit drugs, all have some effect on the CNS and easily cross the blood-brain barrier. Although the concerns regarding use of caffeine and even alcohol and nicotine by the breast-feeding mother are limited to excessive use or use while the baby is very small, illicit drugs are always contraindicated.

Reviews of environmental chemicals reported in human milk have been published (e.g., Jensen & Slorach, 1991; Sonawane, 1995); we provide here an overview of the classes of environmental chemicals reported in human milk with examples in each class. Because many environmental chemicals have had worldwide use, and because many are persistent, exposures to at least some of these chemicals occur in most geographic locations. Exposures to environmental chemicals can occur via the diet, drinking water, occupational exposures, and use of household and personal care products (which, due to frequent exposures, need not necessarily be persistent to be found in human milk). Lipophilic environmental chemicals and those that bind to milk proteins can be found in human milk. It should be noted here that the distinction between voluntary and involuntary exposures is blurred for these chemicals since many of the scenarios that result in exposures to the types of chemicals considered here are voluntary (for example through use of personal care products, household cleaners, cosmetics, etc.).

Persistent organic chemicals Chemicals which are considered persistent and have been detected in human milk include chlorinated organic chemicals such as certain pesticides (DDT [trichloro-2,2-bis(*p* chlorophenyl) ethane] and its metabolite DDE [dichloro-2,2-bis(*p*-chlorophenyl)ethylene]), dioxins and furans, and polychlorinated biphenyls (PCBs). Other pesticide chemicals and metabolites that have been detected in human milk include dieldrin, aldrin, endrin, heptachlor and heptachlor epoxide, chlordane, hexachlorocyclohexanes, and hexachlorobenzene. Prohibitions or restrictions on the use of these chemicals exist, and some researchers have begun to observe subsequent declines in concentrations of many of these chemicals in human milk over a period of years (Jensen & Slorach, 1991; LaKind et al., 2001; Smith, 1999; Craan & Haines, 1998).

Some brominated chemicals, including polybrominated biphenyls and certain polybrominated diphenyl ethers, have also been detected in human milk (Brilliant et al., 1978; Darnerud et al., 1998; Norén & Meironyté, 2000; Meironyté et al., 1999).

Heavy metals Heavy metals reported in human milk include arsenic, cadmium, lead, and mercury. Lead and cadmium intake by breast-feeding

infants is the same as or lower than that of infants given formula prepared with local water (Lawrence & Lawrence, 1999).

Volatile chemicals Exposures to high levels of volatile chemicals typically occur in the workplace. For example, the milk of mothers working in dry cleaning operations, or living above these operations, may contain perchloroethylene (Schreiber, 1997). The milk of occupationally exposed women has been shown to contain chemicals such as methylene chloride, ethylene dichloride, and petroleum solvents (WWF-UK, 1999).

Other chemicals Nitro musk and polycyclic musk compounds, used in detergents and cosmetics, have been detected in human milk, as have certain chemicals used in ultraviolet (UV) sunscreens (Liebl & Ehrenstorfer, 1993; WWF-UK, 1999). Industrial chemicals including aromatic amines, used in industrial processes such as the production of plastic, have recently been reported in human milk (WWF-UK, 1999) as has triclosan, an antibacterial agent used in toothpaste and detergents (Adolfsson-Erici et al., 2000).

Complexities Associated with Assessing Risks and Benefits from Various Sources of Infant Nutrition

When assessing potential risks associated with infant exposure to exogenous chemicals in human milk or unwanted chemicals in infant formula, several factors must be considered. The age of the infant at the time of the exposure is an important consideration. For the preterm infant, developmental immaturity may be of concern. For a full-term newborn less than 4 months old, the infant's liver has not fully developed; thus, chemicals that would be of no concern with an older child might be of concern for the young infant. The development of the renal system also has to be considered because of the importance of the urinary excretion pathway. Finally, the dose, timing, and duration of exposure are important in assessing potential risk. For example, is the infant's exposure to an exogenous substance a one-time occurrence (acute), for a limited time (intermittent), or continuous throughout breast-feeding or formula feeding (chronic)? Is the exposure via nursing/formula feeding the only source of exposure, or are there any additional sources of exposure occurring simultaneously, such as secondhand smoke, or exposure to UV sunscreen?

Finally, no comparison of risks and benefits of breast-feeding versus formula feeding is complete without consideration of (1) the numerous chemicals in tap water (from both well water and municipal water) typically used to prepare infant formula, which will vary regionally in the United States, and (2) the numerous important human milk constituents that are absent from infant formulas. In addition, while it is not possible to quantify some of the psychosocial benefits accrued from breast-feeding, these should be included in a qualitative fashion in any risk benefit analysis.

Summary of Known Benefits and Risks to the Infant and Mother from Constituents in Human Milk

The benefits of breast-feeding to the infant are numerous and well-documented and include (Lawrence & Lawrence, 1999; AAP, 1997) nutritional

benefits for normal growth and development, especially from DHA for brain growth; psychologic 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; and significantly reduced risk of ulcerative colitis, bacteremia, bacterial meningitis, urinary-tract infections, lymphoma, allergic diseases, necrotizing enterocolitis, and, as an adult, Crohn's disease.

Known benefits of breast-feeding to the mother include (Lawrence & Lawrence, 1999; AAP, 1997) improved postpartum recovery, psychological benefits, including a feeling of empowerment and the development of a strong human bond between mother and infant; decreased risk of osteoporosis and hip fractures; protection against ovarian cancer; reduced risk of premenopausal breast cancer; increased birth interval and decreased prematurity as a result (Brody & Bracken, 1987); and a natural method of birth control for first 6 mo postpartum with exclusive breast-feeding and increased intervals between births of approximately 20 to 24 mo, an optimal spacing associated with decreased neonatal and infant mortality (Rawlings et al., 1995; Ferraz et al., 1988; Lang et al., 1990; Brody & Bracken, 1987).

Some scientists have addressed the issue of whether breast-feeding is indeed the best form of nutrition, given the fact that human milk is likely to contain environmental chemicals such as the chlorinated organic chemicals described in this article. This is a most certainly a complex undertaking, and without prospective, longitudinal information on infant health, the results will be colored by considerable uncertainty. However, those investigators who have undertaken this type of analysis have provided a starting point that can be used and improved upon by future investigators (e.g., Rogan et al., 1986, 1987). What is not mentioned in these types of analyses is an assessment of infant formulas, especially those prepared with tap water, which can contain environmental chemicals, and that any risk evaluation should consider a "risk-risk" comparison as well.

The risks versus the benefits of being breast-fed have been estimated by comparing the potential increase in cancer risk from exposure to environmental chemicals in breast milk with risk of infant mortality from not breast-feeding (Rogan et al., 1991). It was noted that "there is no clear advantage to avoiding breast feeding; there may be a disadvantage [in not breast-feeding]" (Rogan et al., 1991).

In a qualitative assessment of the benefits versus hazards of breast-feeding, the following was noted by Hoover (1999): "Even for health endpoints that could be adversely affected by exposure to organochlorines, such as neurodevelopmental, the benefits of breast milk appear stronger."

The International Joint Commission, a Canada-United States group that follows the progress in cleaning up the Great Lakes, has said that despite

the environmental contaminants found in the milk of mothers in that region, "breast is still the best" (Frank & Newman, 1993).

Kacew (1994), in a comprehensive review of numerous environmental contaminants that were detected in human milk, concluded that "even in the presence of mammary toxicants, breast-feeding should be promoted and maintained."

TRENDS OF ENVIRONMENTAL CHEMICALS IN HUMAN MILK

Data derived from current studies can be used as the baseline for analyzing future trends of environmental chemicals in human milk and for identifying chemicals of emerging concern. Trends analysis is essential to the evaluation of the efficacy of restrictions on use/release of chemicals.

As an example, Smith (1999) compiled international data on levels of the pesticide DDT and its metabolites in human milk to determine if the ban on the use of DDT in many countries, which occurred in the 1970s, led to a subsequent decline in human milk concentrations. While recognizing the uncertainties inherent in summarizing and comparing human milk data collected over a period of five decades, Smith noted that since 1970, DDT levels in human milk have declined. In the United States and Canada, Smith reported an 11% to 21% per year reduction in average DDT concentrations in human milk after 1975, which coincides with the time when restrictions on DDT use were put in place by these countries. Similarly, for many of the countries for which dioxin toxic equivalency quotients (TEQs) in human milk have been reported, the data indicate a decrease in human milk levels of dioxin TEQs over time (LaKind et al., 2001). In contrast, studies of pooled, stored human milk samples (sampled from 1972 to 1997) showed an increase in levels of certain brominated flame retardants (polybrominated diphenyl ethers) (Norén & Meironyté, 2000).

Because of the number of factors influencing the concentrations of environmental chemicals in human milk (for example, time postpartum and time of day when sample is collected, how the sample is collected, age of mother, number of children breast-fed), a uniform protocol for sampling and analysis, as described in the accompanying articles in this volume, will improve our ability to draw conclusions about trends in concentrations of environmental chemicals in the United States and elsewhere.

RISK ASSESSMENT AND REGULATORY DECISION MAKING

Toxicological risk assessment of infant nutrition sources requires a careful analysis of the goals of the assessment and an understanding of various methods that will support those goals. In this context, it is worthwhile to consider briefly the different types of applications of risk assessment methodology. Often, risk assessments are used to assist regulatory decision making where the goals are to protect human health and the environment. Examples include the setting of values for acceptable workplace exposure

levels, allowable levels of contaminants in air, surface water, drinking water, soils, and sediments, and for the production and use of industrial chemicals, pesticides, and consumer products. In each of those applications, a level of conservatism is typically built into the characterization of risk because the consequences of underestimating risk could be deleterious to human health or the environment. Often, pollution control or exposure reduction methods can be used to mitigate such risks.

Toxicological risk assessments may also be used in other contexts where the goals of the assessment are to support risk–benefit decisions, such as in regulating pharmaceutical agents, making decisions about drug therapy and surgical procedures, and making recommendations regarding human nutrition, including infant nutrition. In these applications, exposure reduction must be balanced against the direct health benefits of exposure to the product or process. For such purposes, the risk characterization must strive for scientific accuracy rather than conservatism, because the consequences of overestimating risks could be as deleterious to health as underestimating risks. For risk–benefit analysis, using conservative assumptions to assess risk becomes problematic because a situation is created in which theoretical health risks are weighed against more definitive health benefits (Hoover, 1999). This concern holds particularly for breast-feeding, where using overly conservative assumptions to estimate health risks may not protect infants or mothers and may actually pose a health risk of its own, specifically, the risk that concerned individuals will deny themselves or others health benefits by not breast-feeding.

Risk management decisions, based on sound science, must be integrated with policy that is formulated to be appropriate for the particular situation. In this regard, it must be acknowledged that infants derive health benefits from feeding regardless of whether they are breast-fed or formula fed. Because of these benefits, it is difficult to compare any potential health risks from infant nutritional sources using the current risk assessment methodologies for environmental chemicals. Thus, comparing risk estimates from infant nutrition sources with acceptable daily intakes (ADIs), reference doses (RfD), or cancer slope factors, derived using standard risk assessment assumptions and methodologies—as has been done currently for environmental chemicals in human milk—does not necessarily provide a useful tool for making public health decisions. ADIs, RfDs, and cancer slope factors are typically based on chronic toxicity hazards, which are probably not applicable to infant exposure patterns from human milk. Furthermore, risk estimates are typically derived assuming static, or averaging of, exposure concentrations, which are likely to produce an overestimate of risk for exposure scenarios in which environmental chemical concentrations are declining, as discussed later for certain chemicals in human milk.

Risk assessment of environmental chemicals in human milk should have the goal of providing a basis for physicians and public health care providers to:

1. Know when and how to estimate or measure the level of an environmental chemical in human milk.
2. Reassure mothers whose milk does not pose health risks to their nursing infants.
3. Counsel mothers whose milk contains a level of environmental chemicals that could be harmful to their nursing infant.
4. Choose the most appropriate nutrition source to recommend for infants.

For such effects to be realized, risk assessments must achieve an acceptable level of accuracy based on sound science rather than merely reflecting use of the Precautionary Principle, as advocated by some.

As is true for most dietary exposures, environmental chemicals in human milk are present as mixtures rather than as single chemicals. Mixture risk assessment methods commonly call for assessing the effects of chemicals with similar mechanisms of toxicity or similar target organs by dose-additive rather than independence (response-additive) models. Dose additivity relies on the assumption that chemicals act so similarly that their combined effect occurs as if they were simply different dilutions of the same chemical. Conversely, independence (response additivity) assumes that each chemical exerts its effect, or lack thereof, as if other chemicals in the mixture were not present. An empirical basis for such an assumption is currently lacking for chemicals identified in human milk, but the choice of models can have a profound impact on the estimated risk (ATSDR, 2001a, 2001b; U.S. EPA, 1986, 1988, 1989, 2000). Clearly, risk assessment methods for environmental chemicals in human milk must weigh these assumptions carefully because inaccuracies could result in a recommendation to cease breast-feeding when, on balance, it would be the best available nutrition source for the infant.

Clinical experience suggests that strict additivity of pharmacological and toxicological action is probably rare, even when therapeutic levels of drugs are consumed. For example, humans often consume various adrenergic stimulants from a variety of sources, such as caffeine in coffee, tea, and carbonated beverages, and sympathomimetic amines in over-the-counter cold and allergy remedies. For this reason, medical conditions are rarely treated by the simultaneous administration of two drugs that work via a similar mechanism of action. Risk calculations typically assume a static or average estimate of exposure over the exposure interval of interest without considering how chemical concentrations may change over that interval. Current "safe" or "acceptable" levels of chemicals in human milk are estimated without consideration of the decrease in concentrations over the course of lactation. However, the concentration of chemicals in human milk is a function of maternal depuration rate, a process that can result in a reduction in the concentrations of certain environmental chemicals during the course of lactation (see LaKind et al., 2001, for review). Failure to account for declining

chemical concentrations can have a surprisingly large impact on risk estimates, as has previously been demonstrated for exposure to chemicals in contaminated soils (Borgert et al., 1995). Utilization of empirical values for depuration will produce more realistic estimates of infant body burdens and related acceptable exposure levels. Models of infant exposure to chemicals in human milk have demonstrated that depuration (as well as reduced half-life in the infant) results in markedly decreasing human milk levels and infant body burdens of persistent organic chemicals over the first years of life (LaKind et al., 2000; Lorber & Phillips, 2002).

Regardless of whether one calculates risk as a function of the dose received from human milk or as a function of infant body burden, risk estimates that consider declining chemical concentrations over the exposure interval produce markedly lower risk estimates. For example, if declining body burdens of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) were taken into account, there would be a twofold decrease in cancer risk estimates for infants breast-fed for 24 mo versus using levels measured at 5 mo of age. This calculation is based on formulas from Borgert et al. (1995) and mean and 95th percentile data for TCDD body burdens from LaKind et al. (2000).

Reducing the use of overly conservative assumptions in toxicological risk assessments should not result in ignoring factors that would underestimate risk. Germane to the assessment of infant nutrition sources is 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). Thus, depending on the assay, animal toxicity studies may not measure the response of neonatal animals and therefore the extrapolation of the study results to human neonates may be less appropriate than extrapolation to adult humans. Several critical organ systems—including the central nervous system, immune system, digestive system, and reproductive system—may be more or less vulnerable to chemical insult during the neonatal period as they continue to develop and mature. Toxicological studies that include a neonatal exposure period often are not available to support the development of regulatory guidance values. Neonatal exposures also provide a longer latency period for an organism to develop cancer, a factor not typically assessed in rodent carcinogenicity bioassays. A careful consideration of all factors unique to the human neonate and the developing infant, as well as the fact that all feeding carries risk is necessary in order that risk assessments used for comparative assessment or for risk–benefit analysis are as accurate and clinically useful as possible.

CONCLUSIONS

The benefits of breast-feeding to the infant and mother are numerous, well documented, and have been cited earlier in the article. Whether a

woman breast-feeds or formula feeds must be her own informed decision. However, the emphasis is on "informed," and information gathered as part of ongoing and future human milk surveillance and research programs must convey the results of their studies such that information on benefits accruing to mother and infant are not lost.

REFERENCES

- Adolfsson-Erici, M., Pettersson, M., Parkkonene, J., and Sturve, J. 2000. Triclosan, a commonly used bactericide found in human milk and in the aquatic environment. *Organohalogen Compounds* 48: 83–86.
- Agency for Toxic Substances and Disease Registry. 2001a. *Guidance manual for the assessment of joint toxic action of chemical mixtures*. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry Division of Toxicology.
- Agency for Toxic Substances and Disease Registry. 2001b. *Guidance for the preparation of an interaction profile*. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry Division of Toxicology.
- American Academy of Pediatrics. 1997. American Academy of Pediatrics Work Group on Breast-feeding. Policy Statement: Breastfeeding and the use of human milk. *Pediatrics* 100:1035–1039.
- American Academy of Pediatrics. 1999. *Handbook of pediatric environmental health*, Chapter 16 [referencing the work of Jensen, A. A. 1983. Chemical contaminants in human milk. *Residue Rev.* 89: 1–128]. Elk Grove Village, IL: American Academy of Pediatrics.
- American Academy of Pediatrics. 2001. American Academy of Pediatrics, Committee in Drugs. Transfer of drugs and other chemicals into human milk. *Pediatrics* 108:776–789.
- Bernt, K. M., and Walker, W. A. 1999. Human milk as a carrier of biochemical messages. *Acta Paediatr. Suppl.* 430:27–41.
- Birch, E. E., Hoffman, D. R., Uauy, R., Birch, D. G., and Prestidge, C. 1998. Visual acuity and the essentiality of docosahexaenoic acid and arachidonic acid in the diet of term infants. *Pediatr. Res.* 44:201–209.
- Borgert, C. J., Roberts, S. M., Harbison, R. D., and James, R. C. 1995. Influence of soil half-life on risk assessment of carcinogens. *Regul. Toxicol. Pharmacol.* 22:143–151.
- Brilliant, L., Amburg, G. V., Isbister, J., Humphrey, H., Wilcox, K., Eyster, J., Bloomer, A. W., and Price, H. 1978. Breast-milk monitoring to measure Michigan's contamination with polybrominated biphenyls. *Lancet* 2:643–646.
- Brody, D. J., and Bracken, M. B. 1987. Short interpregnancy interval: A risk factor for low birthweight. *Am. J. Perinatal.* 4:50–54.
- Burr, M. L., Limb, E. S., Maguire, M. J., Amarah, L., Eldridge, B. A., Layzell, J. C. M., and Merrett, T. G. 1993. Infant feeding, wheezing, and allergy: A prospective study. *Arch. Dis. Child* 68:724–728.
- Carver, J. D., Pimentel, B., Cox, W. I., and Barness, L. A. 1991. Dietary nucleotide effects upon immune function in infants. *Pediatrics* 88:359–363.
- Champe, P. C., and Harvey, R. A. 1994. *Biochemistry*, 2nd ed. Lippincott's Illustrated Reviews. Philadelphia: J. B. Lippincott.
- Craan, A. G., and Haines, D. A. 1998. Twenty-five years of surveillance for contaminants in human breast milk. *Arch. Environ. Contam. Toxicol.* 35:702–710.
- Darnerud, P. O., Atuma, S., Aune, M., Cnattingius, S., Wernroth, M.-L., and Wicklund-Glynn, A. 1998. Polybrominated diphenyl ethers (PBDEs) in breast milk from primiparous women in Uppsala county, Sweden. *Organohalogen Compounds* 35:411–414.
- Davis, M. K., Savitz, D. A., and Graubard, B. I. 1988. Infant feeding and childhood cancer. *Lancet* 2:365–368.
- Ferraz, E. M., Gray, R. H., Fleming, P. L., and Maia, T. M. 1988. Interpregnancy interval and low birth weight: Findings from a case control study. *Am. J. Epidemiol.* 128:1111–1116.
- Frank, J. W., and Newman, J. 1993. Breast-feeding in a polluted world: Uncertain risks, clear benefits. *Can. Med. Assoc. J.* 149:33–37.

- Gaull, G. E. 1989. Taurine in pediatric nutrition: Review and update. *Pediatrics* 83:433–442.
- Gill, A., and Uauy, R. 1995. Nitrogenous compounds in milk. In *Handbook of milk composition*, ed. R. G. Jensen, pp. 436–464. San Diego: Academic Press.
- Gruskay, F. L. 1982. Comparison of breast, cow, and soy feedings in the prevention of onset of allergic disease. *Clin. Pediatr.* 21:486–491.
- Hamosh, M. 2001. Bioactive factors in human milk. *Pediatr. Clin. North Am.* 48:69–86.
- Hamosh, M., Bitman, J., Wood, L., Hamosh, P., and Mehta, N. R. 1984. Lipids in milk and the first steps in their digestion. *Pediatrics* 75:146–150.
- Harvard. 1998. Commentary. Improving public understanding: Guidelines for communicating emerging science on nutrition, food safety, and health. *JNCI* 90:194–199.
- Health InSight. 1999. *10 Questions to help you make sense of health information*. <http://www.health-insight.com> and www.health-insight.harvard.edu.
- Hoover, S. M. 1999. Exposure to persistent organochlorines in Canadian breast milk: A probabilistic assessment. *Risk Anal.* 19:527–545.
- Jensen, A. A., and Slorach, S. A. 1991. *Chemical contaminants in human milk*. Boca Raton, FL: CRC Press.
- Jensen, R. G., ed. 1995. *Handbook of milk composition*. San Diego: Academic Press.
- Jensen, R. G., Bitman, J., Carlson, S. E., Couch, S. C., Hamosh, M., and Newburg, D. S. 1995. Human milk lipids. In *Handbook of milk composition*, ed. R. G. Jensen, pp. 495–542. San Diego: Academic Press.
- Kacew, S. 1994. Current issues in lactation: Advantages, environment, silicone. *Biomed. Environ. Sci.* 7:307–719.
- Kaufman, K. R., Petrucha, R. A., Pitts, F. N., and Weekes, M. E. 1983. PCP in amniotic fluid and breast milk: Case report. *J. Clin. Psychiatry* 44:269–270.
- Koldovsky, O. 1995. Hormones in milk. *Vitamin Hormones* 50:77–149.
- Koldovsky, O., and Strbak, V. 1995. Hormones and growth factors in human milk. In *Handbook of milk composition*, ed. R. G. Jensen, pp. 428–436. San Diego: Academic Press.
- LaKind, J. S., Berlin, C., Park, C., Naiman, D. Q., and Gudka, N. J. 2000. Methodology for characterizing distributions of incremental body burdens of 2,3,7,8-TCDD and DDE from breast milk in North American nursing infants. *J. Toxicol. Environ. Health A* 59:605–639.
- LaKind, J. S., Berlin, C., and Naiman, D. Q. 2001. Infant exposure to chemicals in breast milk in the United States: What we need to learn from a breast milk monitoring program. *Environ. Health Perspect.* 109:75–88.
- Lang, J. M., Lieberman, E., Ryan, K. J., and Monson, R. R. 1990. Interpregnancy interval and risk of preterm labor. *Am. J. Epidemiol.* 132:304–309.
- Lawrence, R. A., and Lawrence, R. M. 1999. *Breastfeeding: A guide for the medical profession*, 5th ed. St. Louis, MO: Mosby.
- Liebl, B., and Ehrenstorfer, S. 1993. Nitro musks in human milk. *Chemosphere* 27:2253–2260.
- Lorber, M., and Phillips, L. 2002. Infant exposure to dioxin-like compounds in breast milk. *Environ. Health Perspect.* 110:A325–A332.
- Meironyté, D., Norén, K., and Bergman, A. 1999. Analysis of polybrominated diphenyl ethers in Swedish human milk. A time-related trend study, 1972–1997. *J. Toxicol. Environ. Health A* 58:329–341.
- Mennella, J. A., and Beauchamp, G. K. 1993. Beer, breast feeding, and folklore. *Dev. Psychobiol.* 26:459–466.
- Natural Resources Defense Council. 2002. Healthy milk, healthy baby: Chemicals and mother's milk. <http://www.nrdc.org/breastmilk/>
- Norén, K., and Meironyté, D. 2000. Certain organochlorine and organobromine contaminants in Swedish human milk in perspective of past 20–30 years. *Chemosphere* 40:1111–1123.
- Peterson, J. A., Patton, S., and Hamosh, M. 1998. Glycoproteins of the human milk fat globule in the protection of the breast-fed infant against infections. *Biol. Neonate* 74:143–162.
- Potter, J. M., and Nestel, P. J. 1976. The effects of dietary fatty acids and cholesterol on the milk lipids of lactating women and the plasma cholesterol of breastfed infants. *Am. J. Clin. Nutr.* 29:54–60.

- Rawlings, J. S., Rawlings, V. B., and Read, J. A. 1995. Prevalence of low birth weight and preterm delivery in relation to the interval between pregnancies among white and black women. *N. Engl. J. Med.* 332:69–74.
- Rogan, W. J., Gladen, B. C., McKinney, J. D., Carreras, N., Hardy, P., Thullen, J., Tingelstad, J., and Tully, M. 1986. Polychlorinated biphenyls (PCBs) and dichlorodiphenyl dichloroethene (DDE) in human milk: Effects of maternal factors and previous lactation. *Am. J. Public Health* 76:172–177.
- Rogan, W. J., Gladen, B. C., McKinney, J. D., Carreras, N., Hardy, P., Thullen, J., Tingelstad, J., and Tully, M. 1987. Polychlorinated biphenyls (PCBs) and dichlorodiphenyl dichloroethene (DDE) in human milk: Effects on growth morbidity and duration of lactation. *Am. J. Public Health* 77:1294–1297.
- Rogan, W. J., Blanton, P. J., Portier, C. J., and Stallard, E. 1991. Should the presence of carcinogens discourage breast feeding? *Regul. Toxicol. Pharmacol.* 13:228–240.
- Schreiber, J. 1997. Transport of organic chemicals to breast milk: Tetrachloroethene case study. In *Environmental toxicology and pharmacology of human development*, eds. S. Kacew and G. H. Lambert, pp. 95–143. Washington, DC: Taylor & Francis.
- Shu, X. O., Linet, M. S., Steinbuch, M., Wen, W. Q., Buckley, J. D., Neglia, J. P., Potter, J. D., Reaman, G. H., and Robison, L. L. 1999. Breast-feeding and risk of childhood acute leukemia. *JNCI* 91: 1765–1772.
- Smith, D. 1999. Worldwide trends in DDT levels in human breast milk. *Int. J. Epidemiol.* 28:179–188.
- Sonawane, B. R. 1995. Chemical contaminants in human milk: An overview. *Environ. Health Perspect.* 103(suppl. 6):197–205.
- Speight, T. M., and Holford, N. H. G., eds. 1997. *Avery's drug treatment*, 4th ed. Auckland, New Zealand: ADIS International.
- U.S. Department of Health and Human Services. 2000. *Breastfeeding, HHS Blueprint for Action on Breastfeeding*. Washington, DC. Available at <http://www.4woman.gov/owh/pub/breastfeeding>.
- U.S. Environmental Protection Agency. 1986. *Guidelines for the health risk assessment of chemical mixtures*. Washington, DC: U.S. EPA.
- U.S. Environmental Protection Agency. 1988. *Risk assessment forum. Technical support document on risk assessment of chemical mixtures*. EPA/600/8-90/064. Washington, DC: U.S. EPA.
- U.S. Environmental Protection Agency. 1989. *Risk assessment guidance for superfund, vol. 1, Human health evaluation manual (Part A), Interim final*. EPA/540/1-89/002. NTIS (PB90-155581). Washington, DC: U.S. EPA, Office of Emergency and Remedial Response.
- U.S. Environmental Protection Agency. 2000. *Supplementary guidance for conducting health risk assessment of chemical mixtures*. August. EPA/630/R-00/002. Washington, DC: U.S. EPA.
- U.S. Food and Drug Administration. 1998. *Breast milk or formula. Making the right choice for your baby*. eds. R. D. Williams and I. Stehlin. June 1996 *FDA Consumer*, Revised as USFDA Publication No. 98-2309. September.
- van der Strate, B. W., Beljaars, L., Molema, G., Harmsen, M. C., and Meijer, D. K. 2001. Antiviral activities of lactoferrin. *Antiviral Res.* 52:225–239.
- Wiggins, R. C., Rolsten, C., Ruiz, B., and Davis, C. M. 1989. Pharmacokinetics of cocaine: Basic studies of route, dosage, pregnancy and lactation. *Neurotoxicology* 10:367–382.
- World Health Assembly. 2001. *World Health Assembly Endorses WHO's Strategic Priorities*, Press release, WHA 54/6, 22 May.
- World Wildlife Fund-UK. 1999. *Chemical trespass. A toxic legacy*. Surrey, UK, June.

Copyright © 2002 From *Journal of Toxicology and Environmental Health Part A*, by LaKind JS, Birnbach N, Borgert CJ, Sonawane BR, Tully MR, Friedman L. Reproduced by permission of Taylor & Francis Group, LLC., <http://www.taylorandfrancis.com>