Chemical Contaminants, Pharmacokinetics, and the Lactating Mother

Walter J. Rogan and N. Beth Ragan

Office of Clinical Research, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina

We review the commonly occurring persistent pesticides and industrial chemicals in breast milk. These chemicals are dichlorodiphenyl trichloroethane as dichlorodiphenyl dichloroethene dieldrin, chlordane as oxychlordane, heptachlor, polychlorinated biphenyls, polychlorinated dibenzofurans, and polychlorinated dibenzodioxins. We present a worked example of the kinds of pharmacokinetic assumptions and calculations necessary for setting regulatory limits of contaminants in the food supply, calculating dose of chemical contaminants to the nursed infant, converting risks from lifetime exposure in laboratory animals to risks for short-term exposure in humans, and estimating the excess cancer risk to the nursed infant. — Environ Health Perspect 102(Suppl 11):89–95 (1994)

Key words: breast feeding, lactation, pharmacokinetics, risk assessment, polychlorobiphenyl compounds, DDE, dioxins, furans, oxychlordane, heptachlor, dieldrin

Introduction

Any xenobiotic that the nursing mother absorbs and circulates may contaminate her breast milk; this is documented for components of beverage alcohol (*1–3*) and tobacco smoke (*4*), pharmaceuticals (*5*), persistent pesticides, industrial chemicals, volatiles, and metals (*6*). Pharmaceuticals have been treated in other reviews (*5,7*), and the data for the volatiles and the metals are sparse, so what follows is a review of the commonly occurring persistent pesticides and industrial chemicals in breast milk, and worked examples of the kinds of pharmacokinetic assumptions and calculations necessary for both setting regulatory limits and for estimating the cancer risk to the child. This material is condensed from three papers, which contain more background and more complete references (*8–10*). Although commonly occurring pesticides and industrial chemicals have been banned or were never produced intentionally, our research topic is not archaic, as there have been inadvertent exposures to agents that involved contamination of human milk, and several chemicals are part of the waste stream or are still present in large amounts in the environment. Thus, human exposure will likely continue. Years of small daily doses at levels that contaminate food below the limits of analytic detection can result in measurable levels in fat tissue, with no recollection on the part of the individual that special exposure has taken place. The considerations necessary to evaluate the hazards from these agents are similar to those that will come up with any agent. In particular, assumptions regarding the pharmacokinetics of the agents are inherent in any of these evaluations, and the conclusions may depend heavily on the kinds of assumptions made. All the chemicals discussed are present in trace amounts in a substantial fraction of the breast milk of U.S. women with no obvious known source to account for their presence. There also have been accidental, somewhat higher exposures, and those situations will be presented for context.

This article was presented at the Workshop on Pharmacokinetics: Defining the Dose for Risk Assessment held 4–5 March 1992 at the National Academy of Sciences in Washington, DC.

The authors acknowledge the help of H.A. Tilson, J.L. Jacobson, P.J. Blanton, C.J. Portier, E. Stallard, and B.C. Gladen.

Address correspondence to Dr. Walter J. Rogan, Office of Clinical Research, National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709. Telephone (919) 541-4578. Fax (919) 541-7640.

Chemical Contaminants

DDT. Dichlorodiphenyl trichloroethane enjoyed widespread use from its introduction in the 1930s until its ban by the U.S. Environmental Protection Agency (U.S. EPA) in 1972. DDT and its derivatives are stable in the environment and remain active long after initial application. Once in the food chain, it resists ultimate metabolism and bioconcentrates in predators (*11*). Among those predators is man, and during the 1960s, evidence accrued that residues of DDT or its stable metabolites, especially DDE (dichlorodiphenyl dichloroethene), were detectable with very high prevalence in human fat tissue (as a consequence of their fat solubility) and human milk (as a consequence of its fat content).

Laug (*12*) reported the presence of DDT in human milk in 1951. Since then, there have been many reports of occurrence, some information on factors that vary with the amount of chemical present, and few reports of directly attributable morbidity. Generally, African–Americans have higher DDT levels than whites (*13*), levels go up with age (*14*), and smokers have higher levels than nonsmokers (*15*). Levels decline over the course of lactation; levels after 6 months of breast feeding are about 80% of those at the beginning. Women have lower levels after having breast fed a previous child; pregnancy per se lowers levels very little (*14*).

While reports of morbidity have been lacking, several findings that are plausibly effects of DDT contamination have been reported at least once. O'Leary et al. reported that low birth weight premature babies have higher DDE in whole blood than term infants of higher normal birth weight (*16*). There is a report from Israel showing higher levels in women with premature delivery (*17*). Rogan et al. reported that women with higher DDE levels breast feed for a shorter length of time (*18*); in the same data, however, there was no association with birthweight or with increased incidence of illness (taking into acccount other factors such as smoking).

Heptachlor. Heptachlor is a polyhalogenated cyclodiene pesticide that is routinely detected in human milk samples in the United States; it is metabolized to an intermediate epoxide form and is then

stable in human tissue. Savage et al. reported that, in 1975, there were detectable amounts of heptachlor in about 60% of breast milk samples from 1046 women volunteers recruited from a probability sample of U.S. hospitals (*19*). Limit of detection at that time was 1 ppb (whole milk); depending on the region of the country, medians were around 0.25 ppm, and 95th percentiles ranged from 0.46 to 1.29 ppm (fat basis, assuming 2.5% fat).

Heptachlor was withdrawn from most uses in 1978 because of its persistence and bioaccumulation and because it is a carcinogen in the laboratory. However, the state of Hawaii had an exemption for use on pineapples. In January 1982, the Hawaii state health department found heptachlor in routine analyses of cow's milk at levels above the 0.3 ppm (fat basis) that was permitted as a residue. The contamination was traced to the practice of feeding dairy cows green chop from the pineapple fields. Pineapples are subject to mealybug damage, and mealybugs live commensally with ants. It had long been the practice to kill the ants with one of the persistent pesticides. Pineapple leaves and other materials went into the green chop. No plant that had been sprayed within a year was supposed to be included; although heptachlor does not degrade substantially, the plant grows over that time and dilutes the residue. Retrospective testing of green chop samples showed that heptachlor was present as far back as June 1981. It could not be documented whether milk contamination had gone back that far. Results of routine tests were supposedly negative, but the chromatograms had been discarded and were not available for suspicious review (*20*).

The Hawaiian mothers' milk showed detectable heptachlor epoxide; the median of approximately 200 samples from August 1981 to January 1983 was about 0.1 ppm, with 95th percentile 0.35 ppm fat basis (*21*). The 1979 to 1980 average in the same lab had been 0.035 ppm (*22,23*). Thus the levels had increased 3-fold, but into the range of expected values on the mainland. The tolerance level for residues in food had been set at 0.3 ppm fat on the basis of the technology available to detect the substance in the 1960s, but it was possible in 1981 to detect at 0.1 ppm routinely and lower on a research basis. Application of either number would result in a substantial fraction of women being advised not to breast feed. However, it was not clear what, if any, benefit would accrue to the children, since the tolerance levels were not based on any known or suspected risk but rather on the state of the art of analytic chemistry.

Thus far, there has not been morbidity attributed to the Hawaiian heptachlor exposure. There is preliminary evidence that heptachlor epoxide levels in serum and breast milk in 1989 to 1990 are higher on Oahu than on the neighbor islands, and that levels bear a relationship to current milk consumption, presumably a surrogate for milk consumption during the time of the contamination (*24*).

In 1986, cow's milk in Arkansas was found to be contaminated with heptachlor. This time, the cows had been fed mash left over from the fermentation of grain to produce ethanol for addition to gasoline (*25*). Thus far, despite almost a thousand analyses of breast milk samples, there is no evidence that the contamination was sufficiently severe to raise breast milk levels in Arkansas higher than in the adjoining southeastern states (*26*).

Chlordane. The simplest way in which houses can be protected from termite infestation is by application of one of the persistent cyclodienes such as chlordane; they can be effective for 20 years. Chlordane had widespread use as a termitocide. In 1970, inadvertent injection of chlordane into the heating ducts of a southwestern military home resulted in air contamination when the heat was turned on (*27*). Several incidents like this happened over the next few years; drench application under the slab or ditch application combined with heating ducts that were either in the slab or beneath it resulted in unacceptably high levels when the heat was used. Eventually, the U.S. Air Force did studies in almost 500 dwellings and found that while most values ranged from nondetectable to about 40 $\mu g/m^3$, occasional values had ranged up to 260 $\mu g/m^3$. At the higher levels, people who lived in the building had irritative symptoms and noted a strong "organic" odor. The symptoms abated and the air cleared when repairs were made (*28*).

Breast milk levels increased for up to 5 years among those who lived in treated houses (*29*). Chlordane or its metabolite, oxychlordane, was one of the pesticides found routinely in breast milk. Data from the 1975 U.S. survey noted above (*19*) show that about three-fourths of a national sample of women had oxychlordane detectable in their milk at a sensitivity of 1 ppb whole milk basis. There are not reports of morbidity from chlordane in the general population.

Polychlorinated Biphenyls, Polychlorinated Dibenzofurans, and Polychlorinated Dibenzodioxins. Polychlorinated biphenyls (PCBs) are a family of compounds that share a paired phenyl ring structure with various degrees of chlorination. They were introduced in the 1930s as a dielectric for cables, capacitors, and transformers used in the electrical industry. Other uses included microscope immersion oil, the suspension vehicle for the pigment in carbonless copy paper, fluid insulators in a legion of small electrical parts, cutting oils, and occasionally dispersants for pesticides.

By 1966, Jensen was able to identify peaks in his chromatograms of his wife's breast milk, his child's hair, and a dead North Sea eagle as PCBs (*30*). Because these same peaks had been interfering in the chromatograms of chemists in Europe and the United States who were trying to document the widespread extent of DDT contamination, it became clear that PCBs had become ubiquitous contaminants like DDT.

In 1968, an epidemic of severe acne among residents of Kyushu province in Japan was traced to the use of cooking oil that had been contaminated by PCBs during processing. Over 1000 people were eventually diagnosed as having Yusho (oil disease) by the local health authorities (*31*). Yusho was essentially chloracne with liver and nerve function abnormalities along with alterations in fat metabolism. PCBs appeared in the breast milk of cases, although levels were not remarkably different from controls. Breast-fed children had higher levels in their serum than bottle-fed children. Follow up of children up to 9 years later, including some cases that were reported to have been produced by breast milk transmission alone, showed apathy, lethargy, and soft neurological signs (*32*). Chemical analysis at the time could do no better than to show 2000 to 3000 ppm total organic chlorine; subsequent analyses showed that degradation of the PCBs had taken place and that polychlorinated terphenyls, quaterphenyls, and dibenzofurans were present (*33*). The toxicity of these compounds is similar in the laboratory to that of PCBs; however, the dose at which they are active is substantially lower.

Following Yusho, two lines of research were pursued through the 1970s: documentation of the degree of exposure of human beings to PCBs and explication of toxicity in the laboratory. The monitoring literature is fairly consistent, showing a very high to universal prevalence of detectable PCB contamination in unselected groups of people. In the general population, levels go up with age and are sometimes higher in African-Americans

than whites. Thus far, no groups have reliably higher levels except for persons who work around PCBs and persons who regularly consume sport fish from polluted waters (commercial fish are regulated, and are removed from the market if the amount present exceeds the Food and Drug Administration [FDA] action level).

In 1979, there was an outbreak of acne among school children in Taichung province of Taiwan. Investigation proceeded much more rapidly than had been the case in Japan 11 years earlier, and contaminated rice oil was again the vector (*34–36*). Although the specific machine was not identified, residue under the site of a scrapped machine showed PCB-contaminated cooking oil. Over 2000 patients are still followed by health authorities. The symptoms, signs, and laboratory findings are roughly similar to the Japanese outbreak.

Much of the toxicity in the Asian outbreaks is likely because of polychlorinated dibenzofurans (PCDFs), a thermal degradation product of PCBs. Although these chemicals occur in the rice oil mixtures at levels 10^4 below the PCBs, they are much more toxic. PCDFs and polychlorinated dibenzo-*p*-dioxins (PCDDs) have similar physical and chemical properties. PCDFs have one oxygen that bridges the phenyl rings. The dioxins have two oxygens; the most toxic of the dioxins are among the most toxic substances known. PCDFs and PCDDs occur in the environment from ill-defined sources; possible sources include contamination of pesticides during manufacture, the bleaching process in paper making, and combustion of chlorine-containing waste material. Both classes of chemicals occur at low but detectable levels in breast milk samples from persons without known exposures.

Risk Assessment and Regulation

Reference Dose for the Mother. Since the agents reviewed above occur as trace contaminants in the food supply, regulatory agencies such as FDA must establish a concentration below which a class of foods can still be sold, because permitting no detectable residue is thought to cause great economic hardship with little benefit for public health. The FDA calls these concentrations action levels, and they are arrived at by different methods depending on the toxicity of the agents involved and the degree to which they are avoidable or unavoidable contaminants (*37*). These regulations concern only commercial foods; breast milk cannot be regulated, and fish or game caught by individuals may be subject to advisories but cannot be regulated. All these agents are now unavoidable, in the sense that they are no longer directly used and their appearance is because of environmental contamination or accident rather than current use.

For toxicity other than carcinogenicity, the regulatory agencies use a safety factor approach, in which the levels of exposure thought to be associated with toxicity in either humans or animals are divided by some factors of ten, depending on the uncertainty. For example, if the only data available show toxicity at the lowest dose in the experiment, or if there are no data available for humans but only animal data, or there is thought to be genetic varation in the response, then the lowest observed effect level (LOAEL) or the no-observed effect level (NOAEL) is divided by 10 for each kind of uncertainty to arrive at the reference dose, the dose at which no morbidity is expected to occur. Here we will work through the safety factor approach for determining the reference dose for PCBs, because sufficient data exist to use human rather than animal data. Taken together with data on food consumption or other routes of exposure, this would be one step toward arriving at what levels of PCBs might be permitted in specific foods or what exposure level from a waste source requires intervention.

To estimate a reference dose for PCBs from all sources, we estimate the dose to the mother that results in the kinds of PCB levels that we now see, and use data from observational studies of PCB toxicity to get the relationship between that maternal exposure and morbidity in the child. There are two studies of morbidity in children occurring from background exposure PCBs in the United States, one in central North Carolina (the NC study) (*38*) and the other near Lake Michigan (the MI study) (*39*). Both were cohort studies in which mothers were identified at or near term, the levels of PCBs were measured in breast milk and other fluids, and the children tested for neurodevelopmental status over time. In both studies, abnormalities of development were noted that bore a relationship to prenatal exposure rather than to exposure through breast milk (*40,41*). Thus far, these studies show morbidity from PCBs at exposures lower than any other studies, and so it is this morbidity we wish to prevent by limiting the mother's exposures.

Dose information is not available for the women who participated in these studies, and we need to make a number of assumptions to estimate maternal dose (*38*). In the NC study, the measure of prenatal exposure is the estimated amount of PCBs in the fat of breast milk at term. If we assume that this breast milk fat is in steady state with the rest of the body's fat, then we can calculate a body burden, the mass of PCBs accumulated by the mother up to that point.

Neither the NC nor the MI data have been modeled using techniques to estimate thresholds of morbidity, and the linear models used to control confounding assume no threshold. For our purposes, we therefore use the crude data, in which the outcome variable (here, percent abnormals or mean scores on various developmental tests of children) is arrayed by level of PCBs in milk fat (*14,42*) and estimate a NOAEL by inspection. For the NC data, that level appears to be about 3.4 ppm in breast milk fat, and for the MI data, about 1.0 ppm. The estimated body burden of PCBs in a theoretical 25-year-old, primiparous, 60-kg bw (U.S. median for 165-cm tall female) (*43*), 25% body fat mother is

$$\begin{aligned}&\text{estimated body burden at NOAEL (mg)}\\&= [\text{av bw}] \times [\text{av \% body fat}] \times [\text{NOAEL}]\\&= 60\ \text{kg} \times 25\% \times 3.4\ \text{ppm}\\&= 51\ \text{mg}\end{aligned} \qquad [1]$$

If we assume that the mother accumulated this body burden from equal daily doses over her lifetime, that she has as her only means of excretion either pregnancy or lactation, and that she is primiparous, then her daily dose associated with any given level in breast milk is the body burden at that level divided by age in days.

$$\begin{aligned}&\text{daily dose}\left(\text{mg/day}\right)\\&= \frac{\text{body burden}}{\text{age in days}}\\&= \frac{51\ \text{mg}}{25\ \text{years} \times 365.25\ \text{days/year}}\\&= 5.6 \times 10^{-3}\ \text{mg/day}\\&\text{daily dose (mg/kg/day)}\\&= \frac{5.6 \times 10^{-3}\ \text{mg/day}}{60\ \text{kg}}\\&= 9.3 \times 10^{-5}\ \text{mg/kg/day}\end{aligned} \qquad [2]$$

Applicable safety factors would be divided by 10 for variation in susceptibility among exposed humans.

$$\text{reference dose (mg/kg/day)} = \frac{\text{daily dose (mg/kg/day)}}{\text{safety factor}} = \frac{9.3\times10^{-5}\ \text{mg/kg/day}}{10} = 9.3\times10^{-6}\ \text{mg/kg/day} \quad [3]$$

This yields a reference dose of 9.3×10^{-6} mg/kg/day; for 1.0 ppm in milk fat, the reference dose would be 2.7×10^{-6} mg/kg/day. In Table 1, we briefly review PCB reference dose comparisons, including animal data and current U.S. EPA estimates.

For comparison, the median concentration in breast milk fat in the MI data is 0.8 ppm, which would have been achieved under these assumptions by a daily dose of 2.2×10^{-5} mg/kg/day, an order of magnitude above the reference dose. By an entirely different method, involving analysis of foods commonly consumed in the United States (the Market Basket Survey), FDA estimated that dietary intake in the United States in 1978 was 3×10^{-5} mg/kg/day, but by 1982 was 3×10^{-6} mg/kg/day (*44*), essentially at the estimated reference dose.

Thus, using human data on toxicity and several assumptions concerning the pharmacokinetics of PCBs, we find that the U.S. food supply, at least as it was in the 1960s and 1970s when the women in these studies were growing up, provides no margin of safety for PCBs. This conclusion is robust against most of the assumptions that need to be made because some persons in the population are already being affected; thus, any process that seeks to prevent morbidity in the population at large should reach the conclusion that the extant levels are too high. If we had data only on workers or persons with exceptional exposures and were trying to extrapolate down to the general population, the process would be much more sensitive to the assumptions.

Risk of Cancer to the Child. Historically, PCBs have been regulated both as toxic substances without regard to carcinogenicity and as carcinogens; in the previous section, we estimated a dose to the mother that would be expected to prevent morbidity from occurring in the child as a consequence of prenatal exposure. In this section, we attempt to estimate the risk to the child posed by the presence of carcinogenic substances in breast milk. All of these agents are known or suspected carcinogens in the laboratory. To estimate the exposure for which the risk of excess cancer is considered minimal, usually one in 10^6, the regulatory agencies use formal risk assessment procedures that have their basis in the mathematical modeling of the carcinogenic process and the use of experimental data from animals. We will work through the estimate of the cancer risk for the nursed infant for all the agents. Exposure to breast milk cannot be regulated, but some estimate of the degree of toxicity expected from the concentrations of chemicals that are prevalent should help with questions about the testing of breast milk and the interpretation of the results of the tests.

The dose to the child consists of three parts: the concentration of the chemical in milk, the amount that the child consumes, and the duration of breast feeding, i.e., the time from birth until weaning. We use the data of Savage et al. (*45*) for dieldrin (another commonly found cyclodiene pesticide), oxychlordane, and heptachlor epoxide. We use the data of Rogan et al. for PCBs and DDE (*14*). The data on TCDDs (tetrachlorodibenzo-*p*-dioxins) are quite sparse. We use data of Schecter et al. (*46*), which are based upon pooled samples; thus, we cannot calculate percentiles. There are very few data on the dibenzofurans, and no bioassay data to estimate carcinogenicity, and so we ignore the dibenzofurans for these calculations.

We use the methods of Rogan and Gladen (see below) to calculate the child's typical dose of PCBs and DDE (*18,38*). For the other agents, we use the same method but with a fixed rather than declining concentration over the course of lactation, because the concentrations are much lower. Using these methods, we estimate the dose to the child from several combinations of breast feeding durations and percentile concentrations of chemicals (Table *2*).

As an example of the procedure used to estimate the child's exposure, we give the detailed calculation for one of the PCB combinations — the 90th percentile of exposure for 9 months of breast feeding. The 90th percentile for the concentration of PCBs in breast milk is 2.97 ppm in fat of breast milk (Table 2). To get the dose to the child, we assume that breast milk is on the average 2.5% fat and that the concentrations of PCBs decline by 20% in 6 months because of the chemical's excretion into milk. The child drinks about 700 g of milk per day. Total dose is the area under the curve of daily dose versus days breast fed. Daily dose is the concentration of chemical in milk fat that day times milk volume times the average percent fat in breast milk. For PCBs, 9 months at the 90th percentile gives 12.4 mg total dose, assuming first-order kinetics [an assumption used by others (*47*) for dioxin].

Carcinogenicity. To estimate the excess risk of cancer from a given dose of these (or any other) chemicals, we assume that risk is some increasing linear function of dose and use an estimate of the slope of the dose–response curve, which can be thought of as a potency. There are no data to allow us to estimate the potency of these agents directly in humans. The few experiments designed specifically to evaluate the risk from exposure through breast feeding do not provide sufficient data to estimate potency (*48,49*); there are, however, data from lifetime exposure studies in laboratory animals. For all but DDE, the U.S. EPA has conducted formal risk assessments, and estimated an upper bound on potency for lifetime exposure to the agents in adult humans (*50*). For DDE, we used a computer program,

Table 1. Polychlorinated biphenyls reference dose comparison.

Type of effect	Reference dose, mg/kg/day[a]
Rodents	
Fetotoxicity; reproduction	3.2×10^{-2}
Postnatal body weights	2.0×10^{-2}
Motor activity	2.0×10^{-4}
Learning and memory	1.0×10^{-2}
Rhesus monkeys	
Fetotoxicity; chloracne; postnatal body weights	1.4×10^{-4}
Motor activity; learning/memory; performance	1.4×10^{-5}
Humans	
Developmental abnormalities (NC study)	9.3×10^{-6}
Developmental abnormalities (MI study)	2.7×10^{-6}
Carcinogenicity, risk = 1×10^{-6} (U.S. EPA quantitative estimate, lifetime exposure) (*56*)	1.3×10^{-7}
Current U.S. EPA reference dose (based on low birthweight in rhesus monkeys) (*56*)	1.0×10^{-4}

[a]For animal experiments, intra- and interspecies variability were considered. For human data, only interspecies variability was considered. Adapted from Tilson et al. (*9*).

Table 2. Estimated excess risk of cancer by concentrations of chemicals and duration of breast feeding.

Chemical	Concentration of chemical in breastmilk, ppm (fat) 50th percentile	90th percentile	Total dose, mg 9 months 90th percentile	q*, mg/kg/day^{-1}	Average daily dose, mg/kg/day. 9 months 90th percentile	Excess risk ($\times 10^{-5}$) by duration and level of infant exposure 6 weeks median	3 months 90th percentile	6 months median	9 months 90th percentile
DDE	2.51	5.33	21.5	0.5	1.3×10^{-4}	0.96	3.65	2.63	6.99
Dieldrin	< 0.01	0.12	0.6	20.0	3.6×10^{-6}	0.02	3.48	0.03	7.15
Heptachlor Epoxide	0.01	0.10	0.5	9.1	3.0×10^{-6}	0.08	1.32	0.24	2.71
Oxychlordane	0.03	0.10	0.5	1.3	3.1×10^{-6}	0.03	0.20	0.08	0.41
PCBs	1.74	2.97	12.4	7.7	7.9×10^{-5}	10.19	31.72	28.37	60.72
TCDD	5×10^{-6} (pooled sample)		2.1×10^{-5}	156,000	1.4×10^{-10}	0.56	1.04	1.65	2.14
					TOTAL	11.84	41.41	33.00	80.12

GLOBAL 82 (*51*), to extrapolate the results of the National Cancer Institute DDE study (*52*) to low doses using the methods of the U.S. EPA (*53*). These techniques estimate the 95% upper bound of the slope of the dose–response curve, and adjust for interspecies differences on the basis of differences in surface area. The potencies (conventionally called q*) are given in Table 2. The estimated risks are for daily intake in milligrams per kilograms body weight over a lifetime.

There are numerous ways, but no agreed upon method, to convert risks from lifetime exposure in laboratory animals to risks for short-term exposure in humans. One way is to calculate the average difference over a lifetime in the exposure of a breast-fed and nonbreast-fed child. This is total dose from breast feeding averaged over an effective lifetime (because of the latency between exposure and the development of cancer, exposure after some age is without risk, because its consequences do not occur in the life-span). We use 65 years for this effective lifetime. Note that exposure to these agents does not cease between the termination of breast feeding and 65 years; however, the exposure is much lower and is the same for both breast-fed and bottle-fed children and thus does not enter into the calculations of excess risk from breast feeding. Similarly, we could base the analysis on total lifetime dose rather than average daily dose by changing the units of the potency estimate. This allows for the fact that the chemicals accumulate in the exposed organism. The results of these procedures are excess lifetime cancer risks, of unspecified site and age at occurrence. For either exposure estimate, we assume no synergy among the compounds and simply add the excess risks from all the contaminants.

To continue with the PCB example, to get average daily dose, we divide total dose (in milligrams) by the effective lifetime (in days) and by interpolated median weight of the child during 9 months of breast feeding (*54,55*), which yields the dose on a milligram per kilogram basis during breast feeding, and by the effective lifetime (in days), as follows:

$$\text{average daily dose (mg/kg/day)} = \frac{\text{total dose}}{\text{median weight during 9 months of breastfeeding}} \div \text{effective lifetime}$$

$$= \frac{12.4 \text{ mg}}{(365.25 \text{ days/year} \times 6.61 \text{ kg})} \div 65 \text{ years}$$
$$= 7.9 \times 10^{-5} \text{ mg/kg/day} \quad [4]$$

An upper bound on the excess estimated lifetime cancer risk based upon average daily exposure is estimated by multiplying the average daily dose by q* (Table 2); q* is defined as the 95% upper bound of the slope of the dose-response curve, as estimated by the U.S. EPA. For PCBs, q* is 7.7 (mg/kg/day)$^{-1}$. The estimated upper bound on excess cancer risk in a lifetime from 9 months of breast feeding at the 90th percentile of the PCB distribution is then:

$$\text{excess cancer risk}_{\text{daily dose}} = \text{av daily dose} \times q^*$$
$$= 7.9 \times 10^{-5} \text{ mg/kg/day} \times 7.7 \text{ (mg/kg/day)}^{-1}$$
$$= 61 \times 10^{-5} \quad [5]$$

To obtain risk based upon total dose, we must first convert q* to units of milligram per kilogram^{-1} instead of milligram per kilogram per day^{-1}. This is q* divided by the length of the animal experiment in days. Total dose is 12.4 mg, average weight over a lifetime is 70 kg, and thus estimated risk based on total dose is then

$$\text{excess cancer risk}_{\text{total dose}} = \frac{q^*}{\text{length of animal experiment}} \times \frac{\text{total dose}}{\text{av lifetime weight}}$$

$$= \frac{7.7 \text{(mg/kg/day)}^{-1}}{\sim 2 \text{ years}} \times \frac{12.4 \text{ mg}}{70 \text{ kg}}$$
$$= 1.054 \times 10^{-2} \text{(mg/kg)}^{-1} \times 0.177 \text{ mg/kg}$$
$$= 186.7 \times 10^{-5} \quad [6]$$

Thus, excess risk based on total dose is about three times higher than the estimate based on average daily dose. Risk based on total dose is not commonly used and involves some extreme assumptions; we thus present risks based on average daily dose in Table 2. However, greater extremes are possible; we could assume that all risk from short-term exposure comes from the first exposure, which would magnify the risk by about 2000-fold to a lifetime excess risk of cancer of 16%, or about an 80% increase. While this seems implausible, differences in cancer risk of this magnitude are at about the resolving power of epidemiologic studies, and thus empirical confirmation of these sorts of calculations within several orders of magnitude are largely impossible.

Conclusion

Pharmacokinetic data, assumptions, and calculations are necessary for either risk estimation or standard setting. In the specific case of the lactating woman, the environmental toxicologist is usually in a different situation

than that of the pharmacologist, because the level in breast milk may be known, and it is the dose that the mother might have gotten that is unknown. In general, data are unavailable with which to quantify precisely absorption, distribution, persistence, etc., and guesses of varying degrees of education are required. Even in simple cases, the plausible range of these guesses may result in predictions that vary by several orders of magnitude. The only responsible tactic in such situations is to make all assumptions as explicit as possible, estimate the sensitivity of the conclusions to the assumptions, attempt to use experimental data where it exists, and recognize ignorance when it is found.

REFERENCES

1. Mennella JA, Beauchamp GK. The transfer of alcohol to human milk. Effects on flavor and the infant's behavior. N Engl J Med 325:981–985 (1991).
2. Jason J. Breast-feeding in 1991. N Engl J Med 325:1036–1038 (1991).
3. Mennella JA, Beauchamp GK. Maternal diet alters the sensory qualities of human milk and the nursling's behavior. Pediatrics 88:737–744 (1991).
4. Ferguson BB, Wilson DJ, Schaffner W. Determination of nicotine concentrations in human milk. Am J Dis Child. 130:837–839 (1976).
5. Wilson JT, Brown RD, Hinson JL, Dailey JW. Pharmacokinetic pitfalls in the estimation of the breast milk/plasma ratio for drugs. Annu Rev Pharmacol Toxicol 25:667–689(1985).
6. Jensen AA. Chemical contaminants in human milk. Residue Rev 89:1–128 (1983).
7. Committee on Drugs, American Academy of Pediatrics. The transfer of drugs and other chemicals into human breast milk. Pediatrics 72:375–383 (1983).
8. Rogan WJ, Blanton PJ, Portier CJ, Stallard E. Should the presence of carcinogens in breast milk discourage breast feeding? Regul Toxicol Pharmacol 13:228–240 (1991).
9. Tilson HA, Jacobson JL, Rogan WJ. Polychlorinated biphenyls and the developing nervous system: cross-species comparisons. Neurotoxicol Teratol 12:239–248 (1990).
10. Rogan WJ. Epidemiologic assessment of the health hazards of persistent pesticides. In: Management of Hazardous Agents: Industrial and Regulatory Approaches. Only One Earth Series (LeVine D,Upton A, eds). Westport, CT:Praeger Publishers, 1992.
11. Bevenue A. The "bioconcentration" aspects of DDT in the environment. Residue Rev 61:37–112 (1976).
12. Laug EP, Kunze FM, Prickett CS. Occurrence of DDT in human fat and milk. Arch Ind Hyg Occup Med 3:245–246 (1951).
13. Kutz FW, Yobs AR, Strassman SC. Racial stratification of organochlorine insecticide residues in human adipose tissue. J Occup Med 19:619–622 (1977).
14. Rogan WJ, Gladen BC, McKinney JD, Carreras N, Hardy P, Thullen JD, Tingelstad J, Tully M. Polychlorinated biphenyls (PCBs) and dichlorodiphenyl dichlorethene (DDE) in human milk: effects of maternal factors and previous lactation. Am J Public Health 76:172–177 (1986).
15. Bradt PT, Herrenkohl RC. DDT in human milk—what determines the levels. Sci Total Environ 6:161–163 (1976).
16. O'Leary JA, Davies JE, Edmundson WF. Correlation of prematurity and DDE levels in fetal whole blood. Am J Obstet Gynecol 106:939–940 (1970).
17. Wasserman M, Ron M, Bercovici B, Wasserman D, Cucos S, Pines A. Premature delivery and some organochlorine compounds. Environ Res 28:106–112 (1982).
18. Rogan WJ, Gladen BC, McKinney JD, Carreras N, Hardy P, Thullen JD, Tingelstad J, Tully M. Polychlorinated (PCBs) and dichlorodiphenyl dichloroethene (DDE) in human milk: effects on growth, morbidity, and duration of lactation. Am J Public Health 77:1294–1297 (1987).
19. Savage EP, Keefe TJ, Tessari JD, Wheeler HW, Applehans FN, Goes EA, Ford SA. National study of chlorinated hydrocarbon insecticide residues in human milk, USA. I. Geographic distribution of dieldrin, heptachlor, heptachlor epoxide, chlordane, oxychlordane, and Mirex. Am J Epidemiol 113:413–422 (1981).
20. Smith RJ. Hawaiian milk contamination creates alarm. Science 217:137–140 (1982).
21. Pesticide Hazard Assessment Project. Hepatochlor Epoxide in Mother's Milk, Oahu, August 1981–November 1982. Manoa, HI:University of Hawaii, 1983.
22. Casarett LJ, Fryer GC, Yanger WL, Klemmer HW. Organochlorine pesticide residue in human tissue—Hawaii. Arch Environ Health 17:306–311 (1968).
23. Takahashi W, Saidin D, Takei G, Wong L. Organochlorine pesticide residues in human milk in Hawaii, 1979–1980. Bull Environ Contam Toxicol 27:506–511 (1981).
24. Baker D. Estimation of Human Exposure to Heptachlor Epoxide and Related Pesticides in Hawaii. Proceedings of a symposium, January 17–18, 1991. Sponsored by U.S. EPA, Hawaii Department of Health, Hawaii Medical Association, UC Davis Agricultural Health and Safety Center, NIOSH cooperative agreement no. U07/CCU906162-01, 312–319.
25. Stehr-Green PA, Wohlleb JC, Royce W, Head SL. An evaluation of serum pesticide residue levels and liver function in persons exposed to dairy products contaminated with heptachlor. JAMA 259:374–377 (1988).
26. Mattison DR, Wohlleb J, To T, Lamb Y, Faitak S, Brewster MA, Walls RC, Selevan SG. Pesticide concentrations in Arkansas breast milk. J Ark Med Soc 88:553–557 (1992).
27. Livingston JM, Jones CR. Living area contamination by chlordane used for termite treatment. Bull Environ Contam Toxicol 27:406–411 (1981).
28. Lillie TH. Chlordane in Air Force housing. San Antonio, TX: USAF Occupational and Environmental Health Laboratory, Brooks Air Force Base, 1981.
29. Taguchi S, Yakushiji T. Influence of termite treatment in the home on the chlordane concentration in human milk. Arch Environ Contam Toxicol 17:65–71 (1988).
30. Anonymous. Report of a new chemical hazard. New Scientist 32:612 (1966).
31. Kuratsune M. Yusho, with reference to Yu-Cheng. In: Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins, and Related Products, 2nd fully revised ed. Topics in Environmental Health, Vol 4 (Kimbrough RD, Jensen AA, eds). Amsterdam:Elsevier, 1989;381–400.
32. Harada M. Intrauterine poisoning: clinical and epidemiological studies of the problem. Bull Inst Const Med 25:1–60 (1976).
33. Masuda Y, Kuroki H, Haraguchi K, Nagayama J. PCB and PCDF congeners in the blood and tissues of yusho and yucheng patients. Environ Health Perspect 59:53–58 (1985).
34. Rogan WJ. Yu-Cheng. In: Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Products, 2nd revised ed. Topics in Environmental Health, Vol 4 (Kimbrough RD, Jensen AA, eds). Amsterdam:Elsevier, 1989;401–415.
35. Rogan WJ, Gladen BC, Hung K, Koong S, Shih L, Taylor JS, Wu Y, Yang D, Ragan NB, Hsu CC. Congenital poisoning by polychlorinated biphenyls and their contaminants in Taiwan. Science 241:334–336 (1988).
36. Hsu ST, Ma CI, Hsu SK, Wu SS, Hsu NH, Yeh C, Wu SB. Discovery and epidemiology of PCB poisoning in Taiwan: a four year follow-up. Environ Health Perspect 59:5–10 (1985).
37. FDA. Action levels for poisonous or deleterious substances in human food and animal feed, January 6, 1978 ed. Washington:Food and Drug Administration, 1978.

38. Rogan WJ, Gladen BC. Study of human lactation for effects of environmental contaminants: The North Carolina Breast Milk and Formula Project and some other ideas. Environ Health Perspect 60:215–221 (1985).
39. Fein GG, Jacobson JL, Jacobson SW, Schwartz PM, Dowler JK. Prenatal exposure to polychlorinated biphenyls: effects on birth size and gestational age. J Pediatr 105:315–320 (1984).
40. Rogan WJ, Gladen BC, McKinney JD, Carreras N, Hardy P, Thullen JD, Tingelstad J, Tully M. Neonatal effects of transplacental exposure to PCBs and DDE. J Pediatr 109:335–341 (1986).
41. Jacobson SW, Fein GG, Jacobson JL, Schwartz PM, Dowler JK. The effect of intrauterine PCB exposure on visual recognition memory. Child Dev 56:853–860 (1985).
42. Gladen BC, Rogan WJ, Hardy P, Thullen J, Tingelstad J, Tully MR. Development after exposure to polychlorinated biphenyls and dichlorodiphenyl dichloroethene transplacentally and through breast milk. J Pediatr 113:991–995 (1988).
43. Frisancho AR. New standards of weight and body composition by frame size and height for assessment of nutritional status of adults and the elderly. Am J Clin Nutr 40:808–819 (1984).
44. Gartrell MJ, Craun JC, Podrebarac DS, Gunderson EL. Pesticides, selected elements, and other chemicals in adult total diet samples, October 1980–March 1982. J Assoc Off Anal Chem 69:146–159 (1986).
45. Savage EP, Keefe TJ, Wheeler HW, Tessari JD, Aaronson MJ. Second national study to determine levels of hydrocarbon insecticides and polychlorinated biphenyls in human milk. Fort Collins, Colorado: Colorado State University, 1984.
46. Schecter A, Ryan JJ, Constable JD. Polychlorinated dibenzo-*p*-dioxin and polychlorinated dibenzofuran levels in human breast milk from Vietnam compared with cow's milk and human breast milk from the North American Continent. Chemosphere 16:2003–2016 (1987).
47. Hoover S, Zeise L, Krowech G. Exposure to environmental contaminants through breast milk. In: The Analysis, Communication, and Perception of Risk. Advances in Risk Analysis, Vol 9. New York:Plenum Press, 1991;257–266.
48. Anderson LM, Ward JM, Fox SD, Isaaq HJ, Riggs CW. Effects of a single dose of polychlorinated biphenyls to infant mice on *N*-nitrosodimethylamine-initiated lung and liver tumors. Int J Cancer 38:109–116 (1986).
49. Anderson LM, van Havere K, Budinger JM. Effects of polychlorinated biphenyls on lung and liver tumors initiated in suckling mice by *N*-nitrosodimethylamine. J Natl Cancer Inst 71:157-163(1983).
50. U.S. EPA. Health assessment document for beryllium. No. EPA/600/8-84/026F Research Triangle Park, NC:U.S. Environmental Protection Agengy, 1987.
51. Howe RB, Crump KS. GLOBAL 82: a computer program to extrapolate quantal animal toxicity data to low doses. No.41 USC252C3. Washington:Occupational Safety, and Health Administration, 1982.
52. National Cancer Institute. Bioassays of DDT, TDE, and p,p′-DDE for Possible Carcinogenicity. CAS No. 50-29-3, 72-54-8, 72-55-9. Carcinogenesis Technical Report Series, No. 131. Washington:U.S. DHEW, 1978.
53. Anderson EL. Carcinogen Assessment Group of the U.S. Environmental Protection Agency. Quantitative approaches in use to assess cancer risk. Risk Anal 3:277–295 (1983).
54. Nelson WE, Vaughan VC, McKay RJ Jr, Behrman RE, eds. Nelson Textbook of Pediatrics, 11th ed. Philadelphia:WB Saunders, 1979.
55. McKinney JD, Moore L, Prokopetz A, Walters DB. Validated extraction and cleanup procedures for polychlorinated biphenyls and DDE in human body fluids and infant formula. J Assoc Off Anal Chem 67:122–129 (1984).
56. Agency for Toxic Substances and Disease Registry. Toxicological profile for selected PCBs (Aroclor-1260, -1254, -1248, -1242, -1232, -1221, and -1016). Oak Ridge, TN: Oak Ridge National Laboratories, 1987.