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

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

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

Maternal Factors and Physiologic Status

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

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

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

Chemical Characteristics

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

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

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

PBPK Modeling of the Transfer of Chemicals into Breast Milk

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

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

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

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

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

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

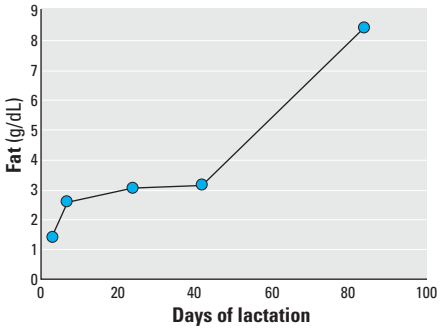

Figure 1. Changes in fat content of human milk during lactation in a group of mothers carrying their infants through normal pregnancy. Data from Bitman et al. (*17*).

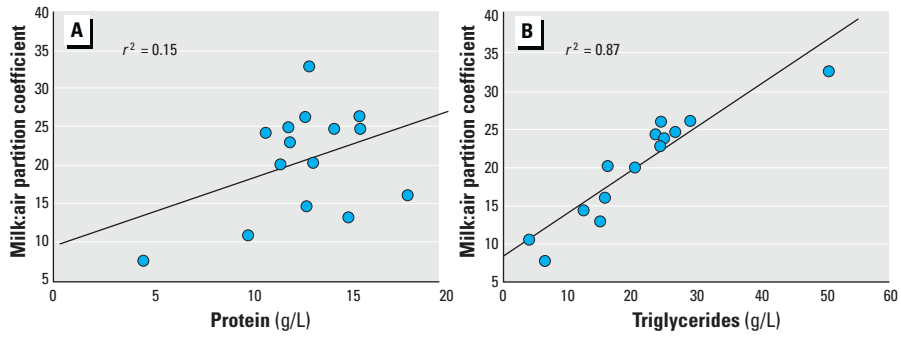

Figure 2. Effects of protein (*A*) and fat (triglyceride) (*B*) content on the human milk:air partition coefficient for benzene. Each point is one milk sample; all samples are from one human subject. Data from Greene et al. (*20*).

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

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

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

PBPK Model for Perchlorate-Induced Inhibition of Thyroid Iodide Uptake

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

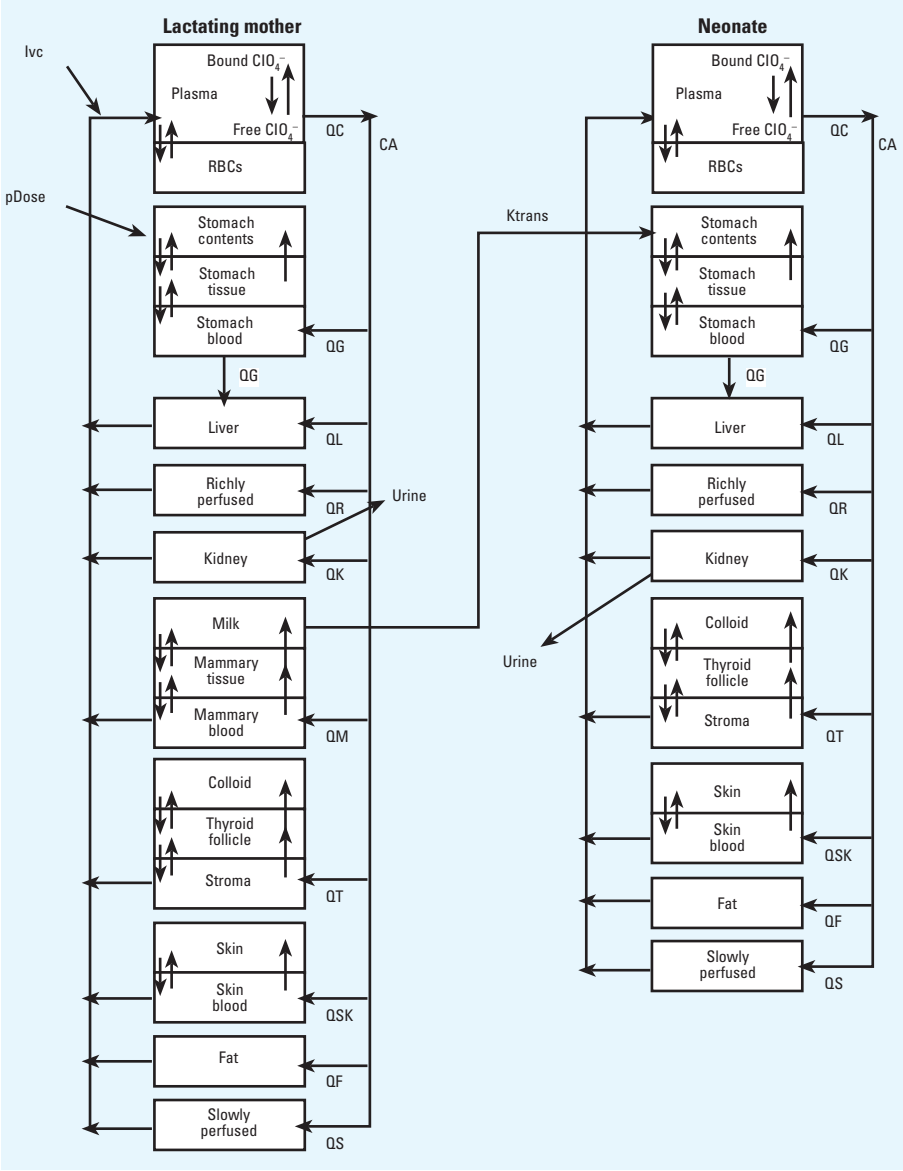

Figure 3. Model schematic for the lactational transfer of perchlorate and iodide from the mother to the neonate. Abbreviations: CA, arterial blood concentration; Ktrans, suckling rate; pDose, drinking water dose; QC, cardiac output; QF, blood flow total; RBCs, red blood cells.

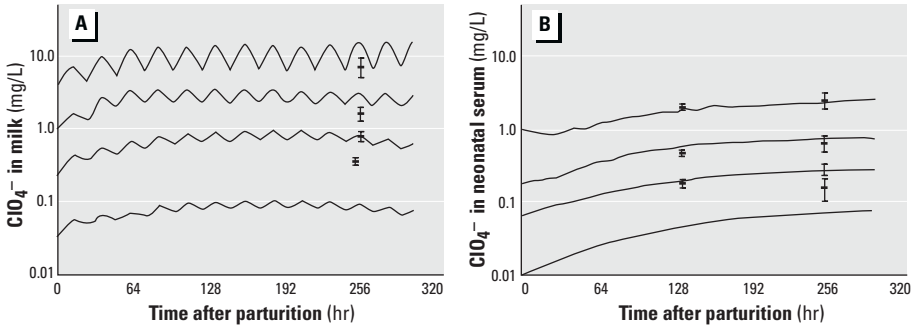

Figure 4. Perchlorate concentration in maternal milk (*A*) and male neonatal serum (*B*) after exposing lactating rats to 0.01, 0.1, 1.0, or 10.0 mg/kg/day ClO_4^- in drinking water. Solid lines indicate model prediction and cross-bars indicate mean ± SD of the data. Daily perchlorate dosing via maternal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

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

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

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

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

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

Summary

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

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

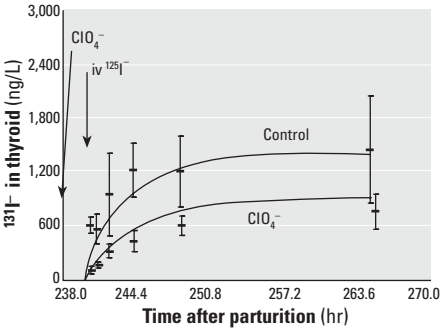

Figure 6. $^{131}I^-$ concentration in maternal thyroid of rats after an intravenous (iv) dose of 1.87 ng/kg $^{125}I^-$ to the dam, with or without an iv dose of 1.0 mg/kg ClO_4^- 2 hr later. Solid lines indicate model prediction and cross-bars indicate mean ± SD of the data. The iv doses of $^{131}I^-$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

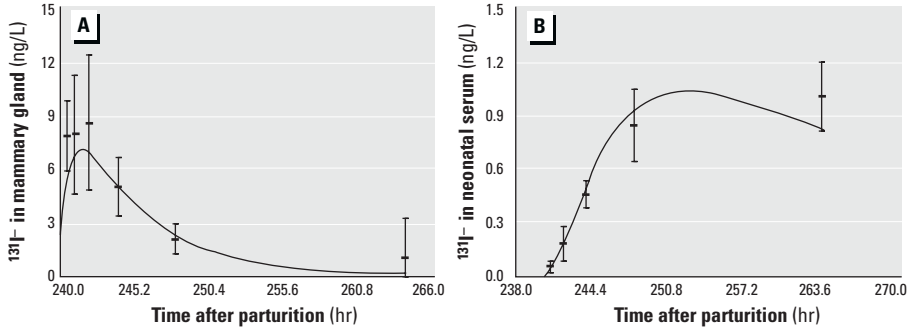

Figure 5. $^{131}I^-$ concentration in maternal mammary gland (*A*) and male neonatal serum (*B*) after exposing lactating rats to 2.19 ng/kg $^{125}I^-$ via intravenous injection. Solid lines indicate model prediction and cross-bars indicate mean ± SD of the data. Daily perchlorate dosing began via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

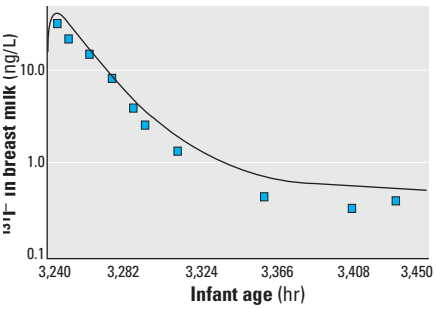

Figure 7. $^{131}I^-$ concentration in human milk of one mother after an oral dose of 77.4 ng $^{131}I^-$. Data from Dydek and Blue (*47*). Solid lines indicate model prediction and points indicate individual data points. The single intravenous dose of $^{131}I^-$ was given at 3,240 hr (fourth month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

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