

PHARMACOKINETIC MODELING:

AN APPROACH TO RISK ASSESSMENT

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Abstract

The United States Environmental Protection Agency (EPA) is sponsoring research on the development of Pharmacokinetic Models to support the Agency's Exposure and Risk Assessment processes. A prototype model, formulated for the chemical hexachlorobenzene (HCB), has been developed to describe this chemical's absorption, distribution, and elimination in humans and animal species. These processes are described by systems of simultaneous coupled first order differential equations. The model provided a useful tool to estimate the total cumulative dose and concentrations of HCB in offspring via the lactational transfer of HCB from the mother.

INTRODUCTION

The public is exposed to low dose levels of many chemicals in the environment. Some of these chemicals are known or suspected to be carcinogenic at sufficiently high dose levels. The U.S. Environmental Protection Agency (EPA) must develop regulations concerning permissible levels of these substances based on public health and other considerations. The development of such regulations is often difficult because there are rarely adequate exposure data and health effects data from humans upon which to base decisions.

The current approach is to estimate the risk of cancer or other health effects based on evidence derived from experiments with laboratory animals. The animals are exposed to doses that are much higher than those appearing in the environment. Their toxic effects occur at accelerated rates, relative to rates that naturally occur at environmental levels. The results observed in the laboratory must then be extrapolated to what might be observed in humans exposed at relatively low doses. Each of these extrapolation steps, from high to low dose and from animal species to humans, must incorporate as much understanding as possible of the underlying biological processes that affect the actions of the chemical in different animal species and at different dose levels.

This research is based on using target organ tissue concentrations instead of externally applied doses for more realistic inferences of health effects. Current extrapolation techniques rely primarily on some function of the body weight differential between species.

METHODOLOGICAL APPROACH

Pharmacokinetic models relate time trends in tissue concentrations to the levels and the time pattern of the externally applied doses. This presentation describes the background, biological foundations,

development, and mathematical description of a set of six multicompartement models describing the absorption, distribution, metabolism, and elimination of one such chemical, hexachlorobenzene (HCB) in the human body. The models serve as a prototype for other model formulations based on other toxic chemicals.

The model's intended use is to provide quantified exposure estimates derived from measurements of the levels of such chemicals in human tissue and fluids. The Environmental Protection Agency is required to conduct quantitative risk assessments to identify "unreasonable" levels that would warrant regulatory action. Such exposure estimates are needed to perform the risk assessment.

Another goal of this modeling effort is to gain insights into the toxicological mechanisms of HCB based on its pharmacokinetics. The principal predictive model contains ten compartments. An additional model has also been developed to consider exposures to fetuses and nursing infants (i.e., the amount of HCB crossing the placental barrier and the flow of HCB into milk during lactation).

Results of single dose and chronic dose pharmacokinetic animal studies with HCB are reviewed. These form the basis for the biological assumptions and parameter values chosen for the model. They also are the basis for the initial evaluation of the predictiveness of the model. Comparisons are made between model predictions and the observed tissue distributions reported in these studies. The model parameters, chosen to obtain model predictions similar to observations reported by Kuiper-Goodman et al., result in long predicted decay half-lives that agree with decay half-lives reported in the literature.

The model consists of a series of coupled differential equations which are solved numerically to determine HCB levels versus time in each of the seven body compartments (liver, kidney, brain, adipose, systemic circulation, intestinal lumen, and lymph poor tissues) and to determine the total amount excreted versus time in the three exit compartments (urine, feces, and metabolites). The model was originally formulated to run using the BMDP statistical computing system to fit pharmacokinetic models. Since this system allows a maximum of ten compartments, an evaluation of more flexible and user-friendly packages was conducted. The model is now being run using IMSL.

STRUCTURE OF THE PHYSIOLOGIC PHARMACOKINETIC MODELS

Six models for HCB have been developed, three pertaining to the rat and three to the human. For each species there is a model for the male, one for the nonpregnant female, and one for the pregnant female and offspring. The underlying structures for each of these models are similar. The absorption,

distribution, and elimination processes are described by systems of simultaneous, coupled first order differential equations. These equation systems reflect the mass balance relations among the intake, storage, and excretion compartments; namely any chemical that exits one compartment must enter another or must exit the system. The solutions of the differential equations estimate the time trends in the concentrations of the xenobiotic (non-naturally occurring chemical) within the various internal compartments and the total amounts of xenobiotic that have exited the system.

The models incorporate physiologic descriptions of the organ and tissue volumes and growth rates, of the blood flow characteristics, and of various processes governed by reaction rate constants. The basic structure of the rat and human models are the same. The differences pertain to the specific volume, growth rate, blood flow rate, and other physiological parameters included in them. For example, the body weight of a rat is of the order of 300g whereas that of a human is of the order of 70kg.

Each of the models describes the time trends of the xenobiotic in the systemic circulation (plasma), lymph rich tissue (e.g., skin, muscle), lymph poor tissue (e.g., adipose, bone), kidney, liver, brain, and intestinal lumen, and the amounts of xenobiotic that are excreted in the urine or feces or that are metabolized. In addition, the female model includes a breast compartment and the pregnancy and offspring model also includes a fetal compartment and an offspring compartment. A schematic diagram of the pregnancy lactation human model is shown in Figure 1.

The models incorporate parameters and as few assumptions as possible. These parameters and assumptions are based on experimental data, on values reported in the literature, or on empirical considerations. The growth rates and blood flow rates are almost all physiologic values, determined from experimental data or from the literature.

An important notion that is incorporated into each of the models is the occurrence of both "free" and "sequestered" forms of the xenobiotic in each of the compartments. The chemical concentration within each compartment is partitioned into free, available and sequestered portions, in fixed proportions described by "distribution ratios." Such partitioning in fixed proportions occurs as long as the concentration of the sequestered portion is less than the capacity limit for that compartment. At that point, all further concentration is of the free, available form.

Generally, only the free, available portion of the residue is transported among internal compartments or is eliminated. Thus compartments with large distribution ratios and with high capacity limits will store large amounts of the chemical. Such large distribution ratios and capacity limits describe the ability of the tissue poor (adipose) compartment to retain large amounts of HCB.

The models have been developed specifically to describe the distribution and trends of HCB in the body. However, the structure of the models and many of the physiologic parameters relate to chemicals apart from HCB. Namely the growth rates, the blood flow rates, and the nature of the communications among compartments are generic. Parameters concerning distribution ratios, capacity limits, and rate constants would need to be modified, based on the agent-specific data available in the literature. Additional compartments, such as the muscle, skin, or lung, might be included in a model for another chemical, depending on the nature of exposure and on known toxic effects. The redistribution of metabolite(s) throughout the body might be studied if they are considered to be of importance in toxic occurrences and if such pharmacokinetic data existed.

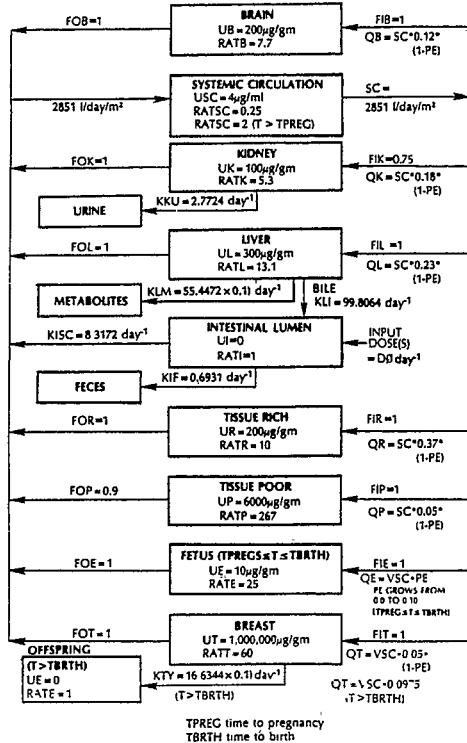
MATHEMATICAL REPRESENTATION OF MODELS

This section contains a discussion of the mathematical representation of the models. The discussion describes the structure of all six models in a unified manner.

Figure 1 represents the blood flows to and from the various compartments. The interactions among compartments are represented mathematically by systems of coupled differential equations. Such mathematical expression permits mathematical analysis of properties of the models and implementation of the models on computing systems in order to carry out simulations with them.

The growth assumptions incorporated into the models generally vary with time and are nonlinear. Some processes start or stop at particular time points. Such phenomena introduce time dependencies into the model parameters. The existence of capacity constraints on the sequestered pools of many of the compartments introduces nonlinearities into the descriptions of the models. The placental barrier introduces an additional nonlinearity into the pregnancy models. These time dependencies and nonlinearities in the models imply that exact, general

FIGURE 1. PHYSIOLOGIC PHARMACOKINETIC MODEL FOR A GROWING FEMALE HUMAN EXPOSED TO HEXACHLORO BENZENE PREGNANCY (9 MONTHS) AND LACTATION (6 MONTHS)



analytical solutions of the differential equation systems cannot be obtained. However, the time dependencies and nonlinearities present no obstacles to obtaining numerical solutions of the equation systems under a variety of assumptions concerning input dosing patterns and model parameter values. The numerical solutions discussed in this report were obtained using the Gear differential equation solver for stiff systems (2), as implemented in the IMSL routine DGEAR (3).

Form of the Equation System

The system of equations contains an equation for each compartment. The equation represents the inflows of HCB into the compartment (terms with positive coefficients) and the outflows of HCB from the compartment (terms with negative coefficients). The equations for the kidney, the liver, the intestinal lumen, and the fetal compartments are presented for illustration.

Let $C \equiv C(t)$ denote the total HCB concentration in a compartment that has both free, available and sequestered forms present. Let CA and CU denote the concentrations of the free, available and sequestered forms respectively. Let D(t) denote the rate at which HCB is entering the system (mg/kg/hour for rats or mg/kg/day for humans). The model assumes that all the orally administered or consumed HCB enters into the intestinal lumen, from which the majority enters the systemic circulation while the remainder exits the body via the feces.

Kidney

$$\frac{dCK}{dt} - QK*FIK*CSCA/VK - QK*FOK*CKA/VK - KCU*CKA - CK\frac{dVK}{dt}/VK \quad (1)$$

Liver

$$\frac{dCL}{dt} - QL*FIL*CSCA/VL - QL*FOL*CLA/VL - KLI*CLA - KLM*CLA - CL\frac{dVL}{dt}/VL \quad (2)$$

Intestines

$$\frac{dCI}{dt} - D(t)/VI + KLI*CLA*VL/VI - KISC*CIA - KIF*CIA - CI\frac{dVI}{dt}/VI \quad (3)$$

Fetus (Pregnancy Models Only)

$$\frac{dCE}{dt} - QE*FIE*BARRE*CSCA/VE - QE*FOE*CEA/VE - CE\frac{dVE}{dt}/VE$$

$$\frac{dCE}{dt} - 0 \text{ if } t < TPREG$$

$$\frac{dCE}{dt} - 0 \text{ if } t > TPREG + \begin{cases} 480 \text{ hours (rats)} \\ 280 \text{ days (humans)} \end{cases}$$

It is also necessary to specify the initial conditions. For dosing via the diet, the initial conditions would usually be 0 (i.e., $CK(0) = CL(0) = CI(0) = 0$ etc.). For other forms of dosing, such as intravenous dosing, the dose can be assumed to enter the systemic circulation essentially instantaneously, and so $CSC(0)$ would be nonzero.

QK represents the blood flow through the kidney compartment. $QK*CSCA$ represents the amount of available HCB in the arterial plasma entering the kidney and FIK represents the proportion of that available HCB within the plasma that may diffuse across the interstitial membrane. $QK*CKA*FOK$ represents the amount of available HCB in the venous blood leaving the kidney. In a bloodflow limited model, FIK and FOK would both be 1. Similar interpretations apply for the liver and the fetus compartments.

Certain HCB transport processes are independent of the plasma flow. These include kidney to urine, liver to intestines, liver to metabolites. Such processes are modeled in terms of reaction rate constants (K's). For example, in the equation for the liver, the term $-KLI*CLA$ represents the rate at which HCB exits the liver and enters the intestines. This rate is proportional to the concentration of available HCB in the liver. The rate constant, KLI, is inversely proportional to the half life of the process. The relation between KLI and the half life is

$$KLI = 0.6931/TLI \quad (5)$$

where TLI is the half life.

Placenta

The placenta is modeled as a barrier between the systemic circulation and the fetus. It slows down the rate of inflow of HCB into the fetal compartment. The greater the available HCB concentration in the systemic circulation, the more that the placenta slows down the transfer of HCB. The placenta is denoted as BARRE in the equations for the systemic circulation and the fetus compartments in the pregnancy and lactation models. The functional form of BARRE is:

$$BARRE = (1 - CE)/[1 + \exp(BE*(\ln(CSCA) - AE))]$$

BARRE is approximately 1-CE for relatively low concentrations and decreases asymptotically to 0 as the concentration CSCA increases. The BARRE factor is $(1-CE)/2$ when $\ln(CSCA) = AE$. The parameters CE, AE, BE are constants which can be varied to affect the amount of uptake into the fetus. $1-CE$ ($0 < CE < 1$) is the upper asymptote of BARRE. AE is the natural logarithm of the concentration at which BARRE is midway between its lower asymptote of 0 and its upper asymptote of 1-CE. BE ($0 < BE < 2/3$) affects the steepness of the BARRE factor; large values of BE result in a rapidly decreasing curve, while small values of BE result in a slowly decreasing curve.

Blood Brain Barrier

Each of the models contains a barrier between the systemic circulation and the brain, called the "blood-brain" barrier. This barrier has the same functional form as the placenta and it assumes the same role; it slows down the rate of inflow of HCB into the brain.

The greater the available HCB concentration in the systemic circulation, the more that the blood brain barrier slows down the transfer of HCB. The barrier is denoted as BARR in the equations. The functional form for BARR is

$$BARR = (1-C)/[1+\exp(B*(\ln C-A))]$$

In the present models we have chosen not to implement the blood brain barrier. This is done by simply including the line of code, BARR=1.0, following the expression for BARR. However, BARR could be utilized in the future, if it is so desired.

Capacity Limits (U) and Distribution Ratios (RAT)

The capacity limit and distribution ratio parameters are used to determine the portion of the total HCB concentration in a compartment that is free, available and the portion that is sequestered. Let C denote the total HCB concentration in a compartment that has both free, available and sequestered forms present. Let CA and CU denote the concentrations of the free, available and sequestered forms respectively. Let U and RAT denote the upper limit on the available pool and the distribution ratio of sequestered to free, respectively. Then

$$CU/CA - RAT \quad \text{if } CU = U$$

otherwise

$$CU - U$$

Since C = CA + CU,

it follows that

$$CU = \min \left[C \left(\frac{RAT}{1+RAT} \right), U \right]$$

$$CA = C - CU = \max \left[\frac{C}{1+RAT}, C - U \right]$$

This relation holds for each of the systemic circulation, tissue rich, tissue poor, kidney, liver, brain, breast, and fetus compartments.

Mobilization of HCB During Lactation

During lactation, HCB in the adipose is mobilized from the lymph poor tissue (adipose) compartment and enters the systemic circulation. HCB moves into the systemic circulation, eventually reaching the breast, from which the HCB is transferred to the offspring via the milk.

Let VP denote the adipose compartment volume (pregnancy + nonpregnancy related portions of growth). The HCB in the adipose mobilized by time t following birth is

$$VP * [1 - (1 + \theta * (t - TBRTH))^{-0.5}] \quad t \geq TBRTH$$

The parameter θ takes on different values in the rat model and in the human model. In the rat model, θ is selected so that 75 percent of the HCB is mobilized during 28 days of lactation; in the human model, θ is selected so that 50 percent of the HCB is mobilized during 6 months (180 days) of lactation.

Goodness of Fit/Model Validation

Physiological pharmacokinetic models for HCB have been developed for the growing female and male Sprague-

Dawley rats, and for the physiological states of pregnancy and nursing of the offsprings. The female model estimates reasonably accurately the kinetics of HCB in tissues and the elimination of HCB and its metabolites. Multiphasic half-lives are observed for HCB, whereas the model only estimates a single-long half-life. This major difference in half-lives between the model estimates and observed has minimal consequences in the chronic-dosed studies, e.g., Kuiper-Goodman et al. (4, 6) and Koss et al. (5) but will overestimate the estimated concentrations in tissues at early times in single dosed pharmacokinetic studies. In general the model for the female Sprague-Dawley rats approximates the observed results of Kuiper-Goodman et al. (4), Koss et al. (5), Koss and Koransky (7), Cripps (8) and Iatropoulos et al. (9). Table I illustrates the goodness of fit of tissue concentrations predicted by the model with the experimental data of Kuiper-Goodman et al. (4).

TABLE I

COMPARISON OF TISSUE CONCENTRATIONS PREDICTED BY THE PHARMACOKINETIC MODEL WITH THE EXPERIMENTAL DATA OF KUIPER-GOODMAN ET AL.

Dose mg/Kg	Tissue	15 weeks		Model Predictions $\mu\text{g/gm}$
		Males ^a	Females ^a	
0.5	Serum	0.42	0.46	0.45
	Adipose	111	209	152
	Kidney	3.32	2.61	2.6
	Liver	11.7	8.0	7.9
	Brain	2.6	5.4	4.2
2	Serum	1.68	1.28	1.8
	Adipose	325	439	606
	Kidney	14.3	11.0	10.4
	Liver	27.7	22.3	31.7
	Brain	11.9	13.2	15.7
8	Serum	3.35	6.37	7.2
	Adipose	1,460	1,485	2,428
	Kidney	59.1	29.7	41.5
	Liver	122.0	81.6	127
	Brain	51.4	48.5	49.5
32	Serum	19.4	30.9	22.1
	Adipose	3,902	6,065	6,147
	Kidney	72.8	100.3	153
	Liver	186.8	267.6	307
	Brain	89.7	170.1	118

^a Data of Kuiper-Goodman et al.

The physiological pharmacokinetic model for HCB that was developed for the male Sprague-Dawley rats does not do as well as the female model in estimating the observed concentration of HCB in tissues (4). At present, there is not a ready solution to resolving the poor estimations by the male model. The much shorter estimated half-lives (55 days) greatly

underestimate the observed concentrations in tissues, upon stopping dosing, and the absence of any biphasic elimination half-lives further complicates the elimination of HCB in tissues of male Sprague-Dawley rats after single dose studies; e.g. Koss and Koranski (7).

The pregnant female model was the most difficult to develop because the physiological state of pregnancy superimposes growth characteristics of a fetal compartment, adipose, systemic circulation, and breast in addition to the normal growing female Sprague-Dawley rat. Many of these pregnancy-related parameters were scaled from the human data and in several instances the numbers were empirical. At this time, the model estimates must be viewed with some reservation, since there were relatively few results that could challenge the validity of the model. Nevertheless, the model estimated reasonably accurately the minimal transfer of HCB to the fetal compartment and the extensive mobilization of HCB to the nursing offspring.

PHARMACOKINETIC PROJECTIONS FOR HCB EXPOSURE IN HUMANS

Using the physiological pharmacokinetic model for a growing female human exposed to HCB, the concentrations of HCB in tissues are estimated using a dosing schedule identical to Kuiper-Goodman et al. (4,6) for female rats. Results are shown in Figures 2-4. The exposure to HCB begins at 15 years of age (5,400 days) and continues for 15 weeks. The doses were 0.5, 2, 8 and 32 mg/kg/day. The estimated concentrations of HCB in all tissues, during the 15 weeks of dosing of humans, approximate the experimentally determined concentrations in similar tissues of female (nonpregnant) rats. Upon stopping dosing at 5,505 days, all tissues except adipose showed a byphasic elimination of HCB. The initial elimination is most apparent at the 32 mg/kg/day dosing schedule, when the adipose compartment becomes saturated. The second elimination phase in the humans has an estimated half-life of 215 days, which is considerably longer than the 80 days in rats. Since none of the experimentally derived parameters for HCB in rats were modified in the human model, this longer half-life must reflect the differences in the physiologically defined characteristics between humans and rats.

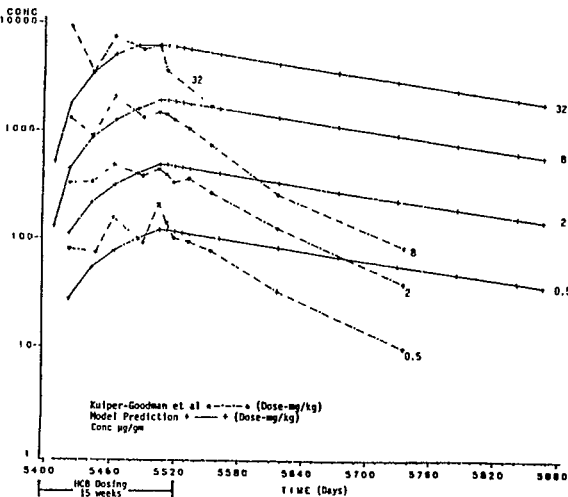


FIGURE 2. PROJECTED CONCENTRATIONS OF HCB IN ADIPOSE TISSUE OF HUMAN FEMALES (NON-PREGNANT) USING A DOSING SCHEDULE IDENTICAL TO KUIPER-GOODMAN ET AL (27) FOR FEMALE RATS

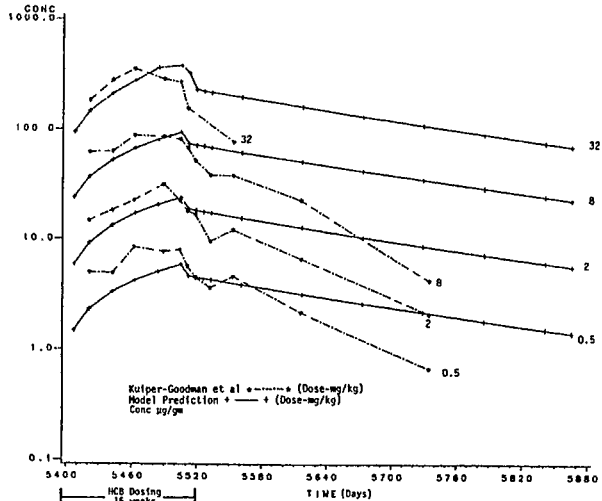


FIGURE 3. PROJECTED CONCENTRATIONS OF HCB IN LIVER TISSUE OF HUMAN FEMALES (NON-PREGNANT) USING A DOSING SCHEDULE IDENTICAL TO KUIPER-GOODMAN ET AL (27) FOR FEMALE RATS

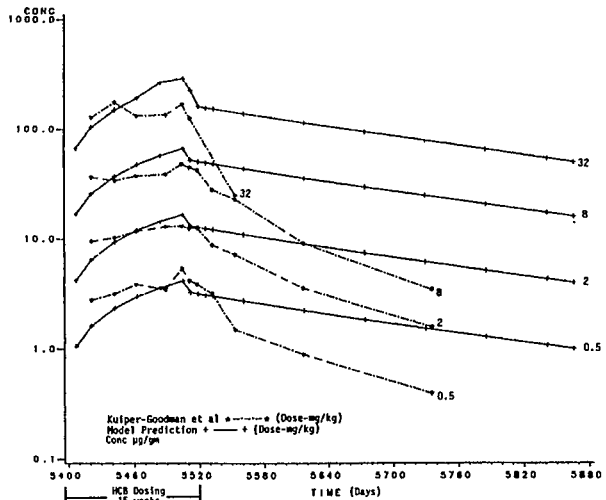


FIGURE 4. PROJECTED CONCENTRATIONS OF HCB IN BRAIN TISSUE OF HUMAN FEMALES (NON-PREGNANT) USING A DOSING SCHEDULE IDENTICAL TO KUIPER-GOODMAN ET AL (27) FOR FEMALE RATS

The 215 day half-life in all tissues indicates that an equilibrium between the intake and elimination of HCB by humans will occur within approximately 7 half-lives or approximately 4 years of continuous exposure. Thus, in using adipose concentrations to reflect past exposures to HCB, a constant adipose concentration in an individual over a 3- to 5-year period indicates that the person has been exposed to a constant level of HCB. On the other hand, an increase or decrease in adipose concentrations within a 3- to 5-year period strongly implies that the environmental exposure to HCB has increased or decreased respectively.

DISCUSSION

Lactational transfer of hexachlorobenzene is the major excretory route for the dam and large quantities of hexachlorobenzene are transferred to the litter in breast milk (5,6). Courtney and Andrews (10) show that mice redistribute hexachlorobenzene from adipose stores during gestation, and Linder et al. (11) suggest substantial redistribution and elimination of maternal adipose stores can occur during lactation. During lactation, hexachlorobenzene in breast milk can come from two sources: from the dam's experimental dose and from the mobilized adipose stores. Thus, the litter can receive a larger exposure to hexachlorobenzene than the dam ever saw. Use of a pharmacokinetic model allowed the calculation of this effective dose. In fact, the pharmacokinetic model shows that the litter received higher concentrations and total cumulative amounts of hexachlorobenzene than any of the pre-gestational dam's critical organs. (Figure 5)

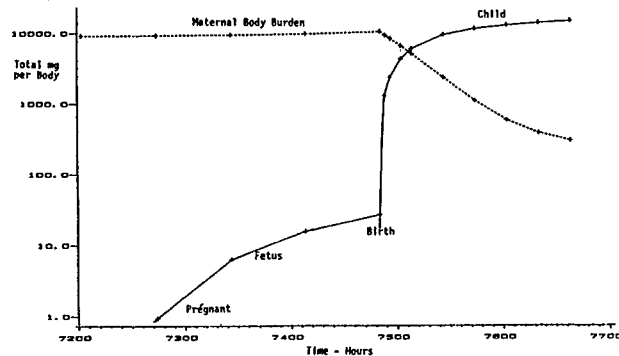


FIGURE 5. ANTICIPATED TRANSFER OF HCB FROM THE BODY OF A PREGNANT HUMAN TO THE FETUS DURING 40 WEEKS OF PREGNANCY AND TO THE CHILD DURING SIX MONTHS OF LACTATION. THE FEMALE WAS ASSUMED TO HAVE BEEN EXPOSED TO 0.5 mg/kg FOR AT LEAST 3 YEARS PRIOR TO PREGNANCY AND THEREAFTER DURING PREGNANCY AND LACTATION.

The use of an estimated concentration of hexachlorobenzene was a better indicator of exposure for the litter. Between 220 and 310 $\mu\text{g/g}$ of hexachlorobenzene in the litter caused a relatively high increase (50%) in the number of litters with a 10% or greater mortality.

With the increase in popularity of breast-feeding, a question must be raised as to risks for human infants. Data from the National Human Adipose Tissue Survey in the United States show that 100% of 83 samples analyzed in 1983 had detectable levels of hexachlorobenzene (12). Assuming that the human critical exposure level to hexachlorobenzene is equal to that observed for rats, the pharmacokinetic model scaled to a human estimated that the mother's pre-pregnancy adipose concentration would have to be 54 to

76 $\mu\text{g/g}$ to have a concentration of 220 to 310 $\mu\text{g/g}$ hexachlorobenzene in her infant. These estimates were made assuming the woman maintained the same chronic exposure level and breast-feed for six months.

This adipose level is 1,000 fold higher than the median adipose levels reported for U.S. women between 18 and 37 years of age. Median concentrations for these women ranged between 0.03 and 0.04 ppm. The 90th percentiles showed a wider range: 18 to 22 years, 0.04 ppm; 23 - 26 years, 0.05 ppm; 27 - 30 years, 0.07 ppm; and 35 - 37 years, 0.06 ppm. A safety factor of 1000 is recommended by Jackson (13) for irreversible diseases such as terata. For a small group of women aged 27 to 34 years of age, this safety factor, however, is less than 1,000. As U.S. women delay first pregnancy into their late twenties and early thirties, the concern over lactation transfer of hexachlorobenzene is valid and should be considered worthy of future human studies.

SUMMARY

Hexachlorobenzene has been shown to produce reproductive effects in man and animals. The risks associated with hexachlorobenzene exposure have been determined for a litter using data from a feeding study by Kitchin et al. (14).

The total cumulative amount and the concentration of hexachlorobenzene in the litter is estimated from a pharmacokinetic model. This estimate is consistent with the works of Kitchin et al. (14), Courtney and Andrews (10), and others which demonstrate that a large amount of hexachlorobenzene is transferred to the litter, and this quantity increases as a function of the number of lactating days. The transfer of large quantities of hexachlorobenzene in the litters caused a significant increase in the number of litters with 10% or greater mortality when the total amount of hexachlorobenzene in the litter was between 29 to 56 mg. This total amount was equivalent to a concentration of hexachlorobenzene in the litter of 220 to 310 $\mu\text{g/g}$.

The pharmacokinetic model provided a useful tool to estimate the total cumulative effective dose and concentration of hexachlorobenzene in the litter via the dam's experimental dose. The pharmacokinetic model, also, enabled us to calculate equivalent human exposure so as to compare hexachlorobenzene levels from human monitoring data.

REFERENCES

1. Dedrick, R.L., *Journal of Pharmacokinetics and Biopharmaceutics*, 1973, 1, 435, .
2. Gear, C.W., "Numerical Initial Value Problems in Ordinary Differential Equations", Prentice Hall, Inc., Englewood Cliffs, N.J., 1971.
3. IMSL Library, 9th ed., Revised June, 1982.
4. Kuiper-Goodman, T. et al., *Toxicology and Applied Pharmacology*, 1977, 40, 529.
5. Koss, G. et al. *Arch. Toxicol.*, 1978, 40, 285.
6. Kuiper-Goodman, T., Food Directorate, Health Protection Branch, National Health and Welfare, Canada, personal communication.

7. Koss, G. and Koransky, W., Arch. Toxicol., 1975, 34, 203.
8. Kripps, D.J., Univ. Wisconsin, Center for Health Sciences, Task 5, Experiment 2, EPA Contract 68-01-5002.
9. Iatropoulos, M.J., et al. Environ. Res., 1975, 10, 384.
10. Courtney, K.D., Andrews, J.E., et al., Environ. Res., 1979, 19, 1.
11. Linder, R.E., et al., Toxicol. Letters, 1983, 15, 237.
12. Robinson, P.E., et al., Evaluation of HCB Body Burden in General U.S. Population, IARC Symposium on HCB, Lyon, France, 1985.
13. Jackson, B.A., J. American Vet. Med., 1980, 176, 1141.
14. Kitchin, K.T., Toxicol., 1982, 23, 33.

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