PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELLING OF PERCUTANEOUSLY ABSORBED DIBROMOMETHANE UTILIZING MULTIPLE DERMAL SUB-COMPARTMENTS

THESIS

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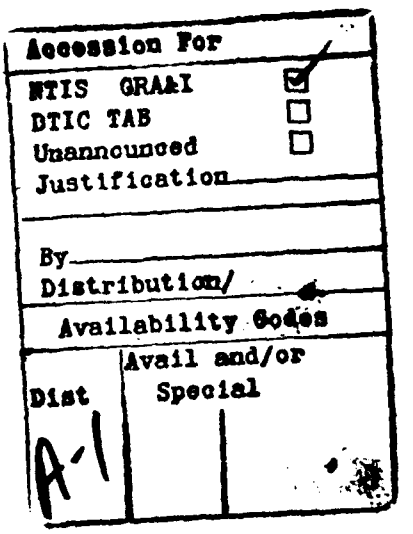

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THESIS

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of the Air Force Institute of Technology
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Christopher R. McDaniel, B.S.
Captain, USAF

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Abstract

The goal of this study was to develop a physiologically based pharmacokinetic (PBPK) model that predicts mammalian blood concentrations of dibromomethane following exposure by dermal absorption more accurately than a previously developed Homogeneous Dermal Model. The Homogeneous Dermal Model contains a dermal compartment with no dermal sub-compartments. The 1:1 Dermal Model developed in this research contains a dermal compartment with a stratum corneum and a composite dermal sub-compartment of equal volume. This model yields predictions which are 21.4 percent more accurate than the original homogeneous model. In order to represent skin anatomy more accurately, the 1:10 Dermal Model variation was developed. The 1:10 Dermal Model contains a dermal compartment with a composite dermal sub-compartment ten times the volume of the stratum corneum sub-compartment. The 1:10 Dermal Model yields predictions which are 17.7 percent more accurate than the original model. Finally, the 1:3:7 Dermal Model was developed which contains a viable epidermis sub-compartment three times the volume of the stratum corneum sub-compartment and a composite dermal sub-compartment which is seven times the volume of the

stratum corneum sub-compartment. This model yields predictions 27.7 percent more accurate than the original model.

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I. Introduction

General Issue

The mission of the Toxicology Division of Armstrong Laboratory is to provide the human health research necessary to preserve Air Force personnel, resources, and the environment. Information that the Toxicology Division provides concerning toxic chemical effects and risks is utilized by the USAF and other consumers including regulatory agencies, in order to create safe handling and protective procedures (McDougal, 1993).

The Toxicology Division uses physiologically based pharmacokinetic (PBPK) models to predict blood and tissue concentrations of a chemical within an organism. In fact, pharmacokinetics is the study of a chemical's transport and distribution within the body (Cohrssen, 1989:369). Scientists study pharmacokinetics by exposing animals to a chemical by various routes which include inhalation, ingestion, or absorption, and subsequently obtain blood and

organ tissue concentrations of the chemical at various times after exposure.

> Although it has formerly been common practice to calculate risk estimates on the basis of administered dose-toxicity/tumor incidence data, it is now recognized that the internal, or target organ dose is a more accurate and direct determinant of the magnitude of injury. (Dallas, 1991:304)

PBPK models not only simulate the pharmacokinetic process in the animal, but also provide information which can be extrapolated to humans. As such, these models are predictive tools of considerable interest to toxicology laboratories (Sultatos, 1990:618).

In 1982 the Air Force Institute of Technology (AFIT), in conjunction with the Toxicology Division, sponsored graduate research to develop a user friendly PBPK model to operate on the laboratory's computer system. The research created a FORTRAN language PBPK model which determined blood and tissue concentrations of styrene during steady-state inhalation at specific concentrations (Mayberry, 1982).

In 1983 a follow-on graduate study was initiated by AFIT and the Toxicology Division. Written in FORTRAN code, the PBPK model developed predicted the blood concentration of inhaled hexane gas in rats. The model was validated using animal data that had been previously obtained by the Toxicology Division (Baird, 1983).

The Toxicology Division has been and continues to be interested in dermal absorption PBPK models. In many PBPK models emphasizing inhalation or ingestion exposure routes, dermal absorption is considered to have a minor effect. However, in some situations and work environments dermal absorption can provide a significant exposure pathway into the body (McDougal, 1985:150).

Problem Statement

The published dermal model has a skin compartment which is homogeneous and well-stirred (McDougal, 1986). Can a dermal PBPK model be developed that more closely resembles the physiology of the skin and provides more accurate predictions of blood concentrations of chemicals following dermal absorption?

Research Goal

The specific goal of this research is to develop a PBPK model with a dermal compartment, consisting of multiple sub-compartments representing anatomical layers of the skin, that will predict mammalian blood concentrations of dibromomethane (CH_2Br_2) following steady-state exposure via percutaneous absorption.

Objectives

The following objectives must be met to achieve the goal stated above.

1. Develop additional mathematical equations to model the anatomical layers of the skin taking into account mass balance as with other PBPK models.
2. Incorporate the additional dermal equations into the dermal compartment of a previously developed dermal PBPK model, thereby creating a new model.
3. Estimate the accuracy of the new PBPK model using previously obtained Toxicology Division dibromomethane data.
4. Optimize the parameters for the new PBPK dermal model to achieve predictions closer to actual Toxicology Division results.

Scope

The purpose of this research is to simulate only the dermal absorption of dibromomethane in rats. This simulation will focus on the blood concentration of the chemical instead of the effect these chemicals may have on the tissue or the animal.

All dibromomethane dosage and rat blood concentration data received from the Toxicology Division's prior experiments are assumed to be accurate. It is not the purpose of this research to evaluate the in vivo animal techniques used by the Toxicology Division.

Definition of Terms

The following definitions are provided for further clarification.

Dibromomethane - CH_2Br_2, Chemical Abstract Service Registry Number 74-95-3 (Howard, 1992: I-95, II-316).

Homogeneous Dermal Model - a dermal PBPK model previously developed which contains a dermal compartment without dermal sub-compartments. This model is similar to a model developed by McDougal et al. as described in the research proposal, "Species Differences in Skin Penetration."

In vitro - experiments or tests that use animal tissue but take place outside the animal (Cohrssen, 1989:364).

In vivo - experiments or tests that use and take place inside living animals (Cohrssen, 1989:364).

Percutaneous - passage through the skin (Webster, 1978: 1331).

Pharmacokinetics - the study of the transport, distribution, and disposition of a drug or chemical in the body (Cohrssen, 1989:369).

Physiology - "the functions and vital processes of living organisms or their parts and organs" (Webster, 1978: 1354).

Sub-compartment - a division of a PBPK model tissue compartment. Each sub-compartment is modelled by an equation.

1:1 Dermal Model - this study's PBPK model whose dermal sub-compartments represent the stratum corneum and a composite dermal sub-compartment which have equal volume.

1:10 Dermal Model - this study's PBPK model whose dermal sub-compartments represent a stratum corneum and a composite dermal sub-compartment with a volume ten times that of the stratum corneum sub-compartment.

1:3:7 Dermal Model - this study's PBPK model whose dermal sub-compartments represent the stratum corneum, viable epidermis, and a composite dermal sub-compartment. The volume of the viable epidermis sub-compartment is three times that of the stratum corneum sub-compartment. The volume of the composite dermal sub-compartment is seven times that of the stratum corneum sub-compartment.

Significance of Study

As compared to a previously developed homogeneous dermal compartment PBPK model, the dermal PBPK model developed in this study more accurately predicts dibromomethane blood concentrations in rats while being more anatomically correct with regard to the skin. The model utilizes two lumped dermal sub-compartments to simulate skin and to achieve greater predictive accuracy. This model will

lead to further, more detailed dermal absorption models for dibromomethane and other chemicals.

Summary

This thesis contains four chapters and several appendices following this introduction. Chapter II, the Literature Review, includes a general discussion of PBPK models, and specific discussions on skin anatomy and dermal PBPK models. The methodology used to conduct this research is explained in Chapter III. Chapter IV contains the findings and analysis of the research and Chapter V contains the conclusion and recommendations for further research. The appendices contain the FORTRAN program codes for the models developed in this study in addition to the data generated by these models.

II. Literature Review

Evaluating chemical transport and tissue concentrations in an animal can be a challenging, but not an impossible proposition. Difficulties arise due to the complex nature of biological systems which include exposures routes, convective and diffusive chemical transport in the circulatory system, and diffusive chemical transport across sub-compartment membranes (Himmelstein, 1979:127). This research will develop a physiologically based pharmacokinetic model which will simulate rat blood concentrations of dibromomethane following steady-state dermal exposure.

This chapter contains a discussion of physiologically based pharmacokinetic (PBPK) models and an anatomical description of mammalian skin. Also, this literature review includes a discussion of mathematical representations of dermal absorption and their inclusion in PBPK models.

Physiologically Based Pharmacokinetic Models

> The most fundamental premise of experimental toxicology is that coherent relationships exist between the intensity of a particular toxic effect and the concentration of toxic chemical at the target tissue in the organism. (Andersen, 1981:383)

In order to establish these relationships between toxic effect and tissue chemical concentration, it is necessary to

determine the distribution, disposition , and elimination, i.e., pharmacokinetics, of the chemical that has been absorbed by the animal (Himmelstein, 1979:127). One method to predict a chemical's pharmacokinetics is mathematical modelling.

A PBPK model is a mathematical model used to estimate the pharmacokinetics of a chemical within the body of an animal. A PBPK model uses mass-balance differential equations grouped into sets or compartments to represent the animal's body. Each compartment represents either individual or groups of organs or tissues (Ramsey, 1984:159). The equations and organ compartments can be as simple or as complex as necessary to describe chemical concentrations in the various tissues (Himmelstein, 1979:130). Ultimately, the differential equations "describe the fate of the chemical within each compartment, and solution of these equations, simultaneously by computer, yields predictions of tissue levels of the chemical" (Sultatos, 1990:611).

Figure 1 is a portion of a PBPK model used by Ramsey and Andersen to determine tissue concentrations of inhaled styrene.

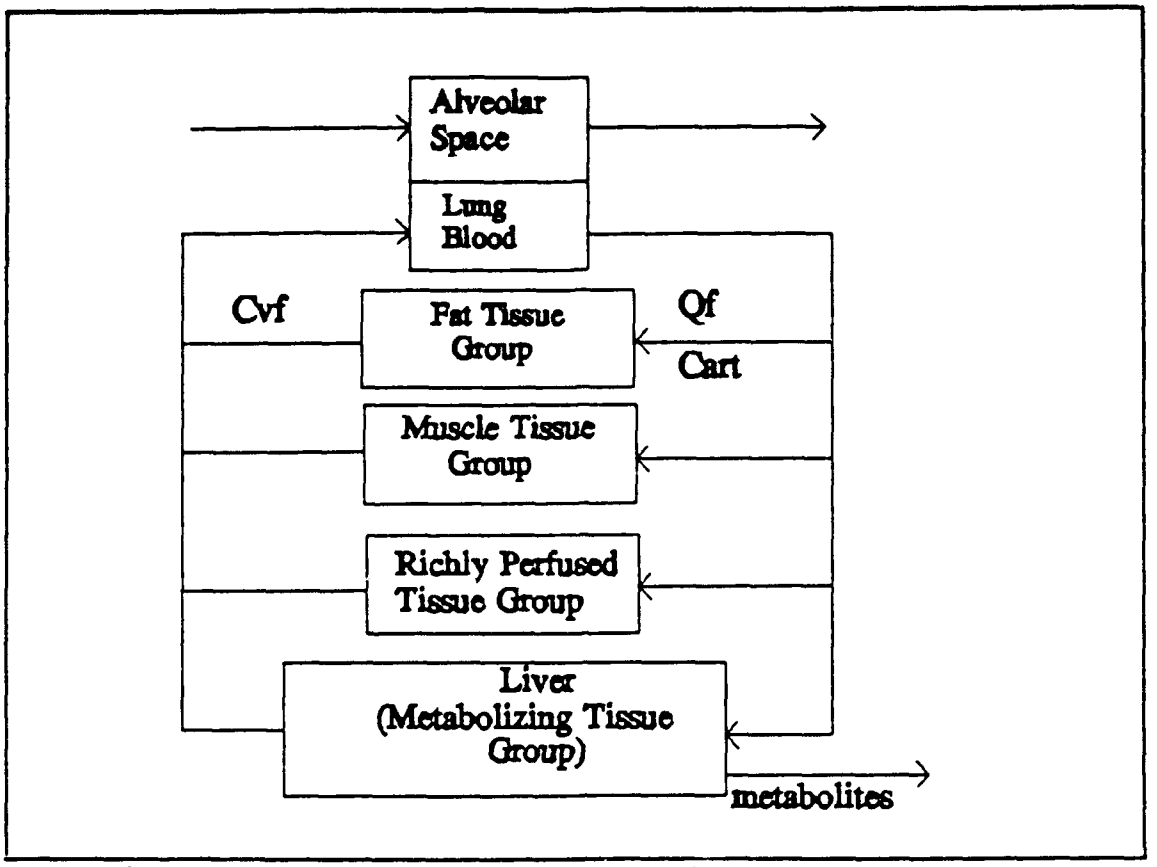


Figure 1. Inhalation PBPK Model (Ramsey, 1984:160)

The equation that represents the fat compartment for this model is:

$$dA_F/dt = Q_F(C_{ART} - C_{VF}) \qquad (1)$$

where

dA_F/dt = rate of accumulation of the chemical

Q_F = blood flow through the fat compartment

C_{ART} = chemical concentration in arterial blood

C_{VF} = chemical concentration in venous blood leaving the fat compartment

A more general expression that represents any tissue compartment is

$$dA_i/dt = Q_i(C_{ART} - C_{VF}) \qquad (2)$$

where i = tissue compartment. (Ramsey, 1984:173; McDougal, 1986:289; Shelley, 1992)

Other mass-balance equations can be developed to represent air-to-blood exchanges in the lungs, metabolism of the chemical in the liver, and chemical absorption through the skin.

The accuracy of a PBPK model is dependent upon the reliability of the parameters and the equations that estimate physiological, anatomical, and chemical-specific characteristics (Sultatos, 1990:612). Normally, only a few parameters of a PBPK model are adjusted to achieve accuracy because changing all parameters by the small increments required can be time consuming (Bois, 1991:85). A model has been validated when a single set of physiological parameters accurately predicts chemical concentrations at multiple chemical exposure levels (Shelley, 1992).

"A comprehensive PBPK model should integrate the variety of metabolic and physiological observations that determine the metabolic fate and distribution of a compound" (Frederick, 1992:246). However, even the most comprehensive models have drawbacks. Large amounts of data from in vitro and in vivo animal studies are required to validate these

models. Also, this disadvantage applies to validating models that have been scaled-up from animals to represent humans (Himmelstein, 1979:132). A potential disadvantage is that PBPK models are created for specific chemicals, routes of exposures, and target tissue groups. Therefore, if not carefully developed, extrapolation to conditions different from ones to which the models were fitted could lead to dubious results (Bois, 1991:86).

The functions and limitations of PBPK models have been established. Before proceeding to PBPK modelling of dermal chemical absorption, it is necessary to discuss the anatomy of the skin.

Skin Anatomy

As the largest organ of a mammal, the skin comprises around ten percent of the total body weight (McDougal, 1992:3). Generally, skin is a significant barrier for the body against the outside environment. Indeed, if the skin is damaged or removed, the body's absorption of water-soluble chemicals could be approximately 1000 times greater than normal (Scheuplein, 1971:702).

Mammalian skin is comprised of several layers and structures. Figure 2 depicts a cross-section of mammalian skin to include hair follicles and sweat pores. Figure 3 shows the blood distribution in the layers of mammalian skin.

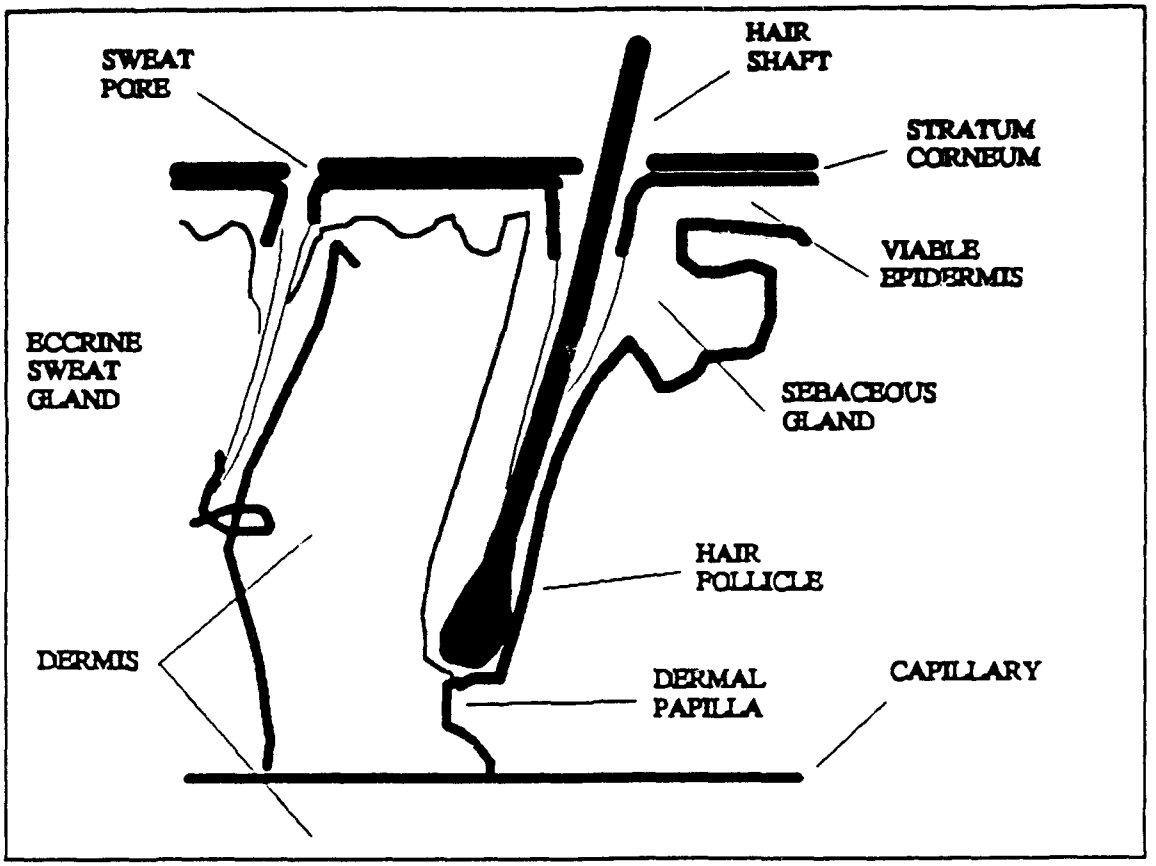


Figure 2. Skin Cross-section (Shroot, 1986:122)

The outer layer of the skin is known as the stratum corneum or horny layer. This layer is made up of dead sub-compartments which originate in the epidermis. Of all the skin layers, it is the stratum corneum that is the most effective barrier against chemical absorption, especially water-based chemicals (Scheuplein, 1971:705-706).

The viable epidermis is the layer of mammalian skin under the stratum corneum. The viable epidermis is comprised of living cells and functions as a

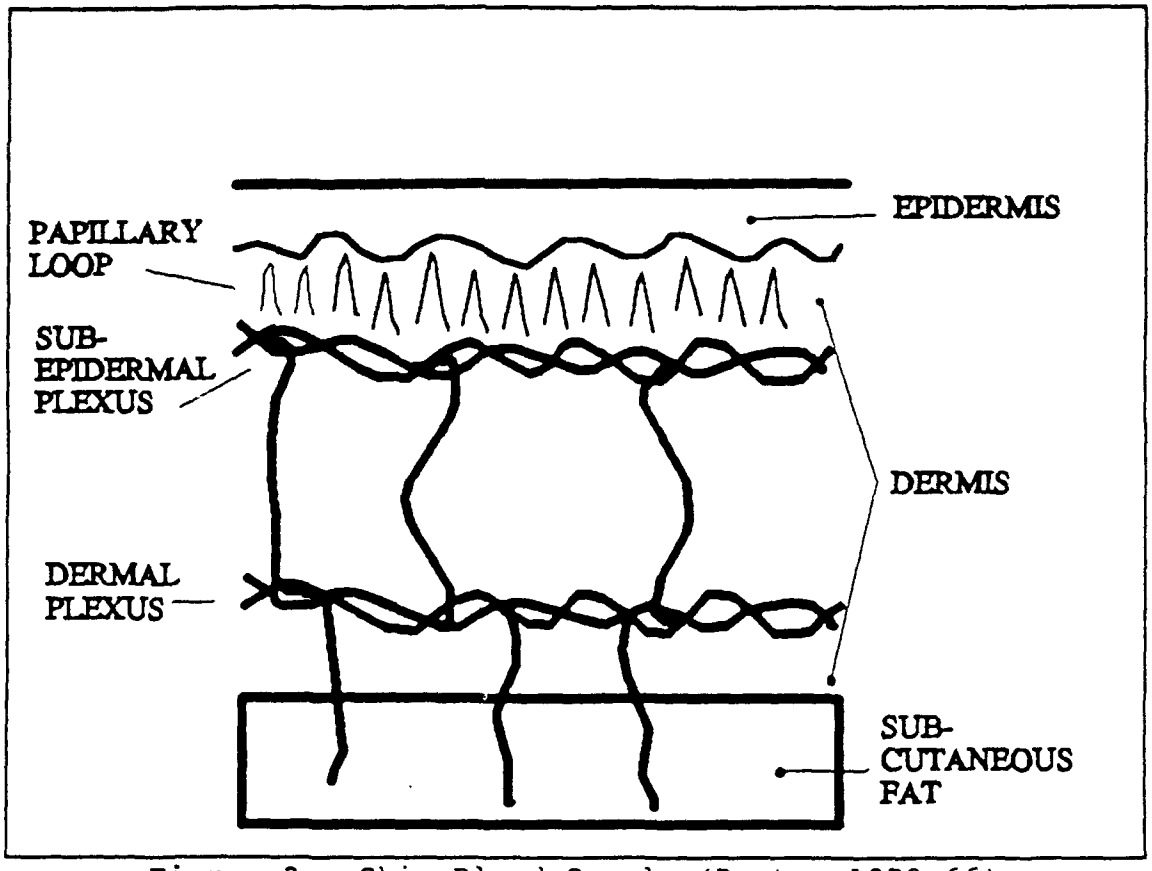


Figure 3. Skin Blood Supply (Burton 1979:66)

reservoir of cells for the stratum corneum. Also, the epidermal layer surrounds hair follicles, even into lower skin layers (Schaefer, 1982:548-549). The epidermis is not as effective as the horny layer in resisting chemical absorption.

The layer of skin under the viable epidermis is the dermis or corneum. This layer contains capillary loops and the roots of hair follicles and sweat glands (Schaefer 1982:549). It is in the dermis that absorbed chemicals are

transferred from dermis tissue to the blood stream and vice versa.

As stated previously, the stratum corneum is the main barrier to chemical absorption. However, hair follicles and sweat ducts act as shunts or direct pathways for some chemicals from the skin surface to the dermis. In effect, the horny layer is by-passed. The total fractional area of the skin comprised of hair follicles and sweat ducts is approximately 10^{-3}. Therefore, chemical absorption through shunt pathways, under steady-state conditions, is negligible (Scheuplein, 1971:706). Equations developed by Scheuplein reveal that for the initial phases of chemical absorption, when compared to the stratum corneum, "diffusion through the follicles and through the sweat ducts can be much greater" (Schaefer, 1982:604).

Skin is not a uniform organ. An animal's skin varies with its location on the body, and with humidity, temperature, and skin health (Bartek, 1972:119). Also, skin differs in thickness, density of hair follicles and sweat glands, and structure (McDougal, 1992:3). Not only must the differences be taken into account when developing representative models, but variances between species must likewise be noted.

Dermal Modelling

A dermal absorption PBPK model "would provide a valuable tool for understanding hazards involved in dermal exposures" (McDougal, 1986:286). In order to create an effective model, appropriate mathematical representations of the skin must be developed.

The following equation represents the movement of a chemical through the skin compartment.

$$X(dC/dt) = tD(d^2C/dX^2) \qquad (3)$$

where

C = chemical concentration (mass/volume)

t = time

X = distance of chemical penetration

D = diffusion coefficient (length^2/time)

(Schaefer, 1982:589)

Equation (3) is known as Fick's diffusion law and its integrated form is represented by equation (4).

$$J_s = DA(\Delta C)/\ \delta \qquad (4)$$

where

J_s = steady-state flux of the chemical (mass/time)

δ = compartment thickness

A = area

ΔC = change in concentration

(Scheuplein, 1971:713-714, McDougal 1986:287)

Depending on the goals of the modelling, equations can be included to represent other processes such as metabolism and binding.

Conclusion

This literature review has covered three areas. Initially, the composition, capability and limitations of PBPK models were discussed. For purposes of this research, the anatomy and function of the skin was reviewed. Finally, methods and equations used to create dermal models were given. With these components established, the next chapter will identify the methodology used to accomplish this research.

III. Methodology

Introduction

The Toxicology Division of the Armstrong Laboratory and researchers around the world use physiologically based pharmacokinetic (PBPK) models to determine drug or chemical concentrations in animal tissue following exposures through various routes. While dermal PBPK modelling is not a recent development, the Toxicology Division remains interested in improving this approach to achieve better predictive capabilities concerning the dermal absorption of chemicals.

This research developed a PBPK model with a dermal compartment which contains multiple dermal sub-compartments in order to more accurately predict the blood concentrations of dibromomethane in a mammal following exposure by percutaneous absorption.

Skin Modelling

As discussed in the literature review, skin is composed of several layers each of which can be considered a compartment in a PBPK model, depending upon the level of detail the researcher may require. Figure 4 is a general schematic of a cross-section of skin developed by McDougal in his article "Physiologically Based Pharmacokinetic Modelling." Each of the layers represented can be modelled

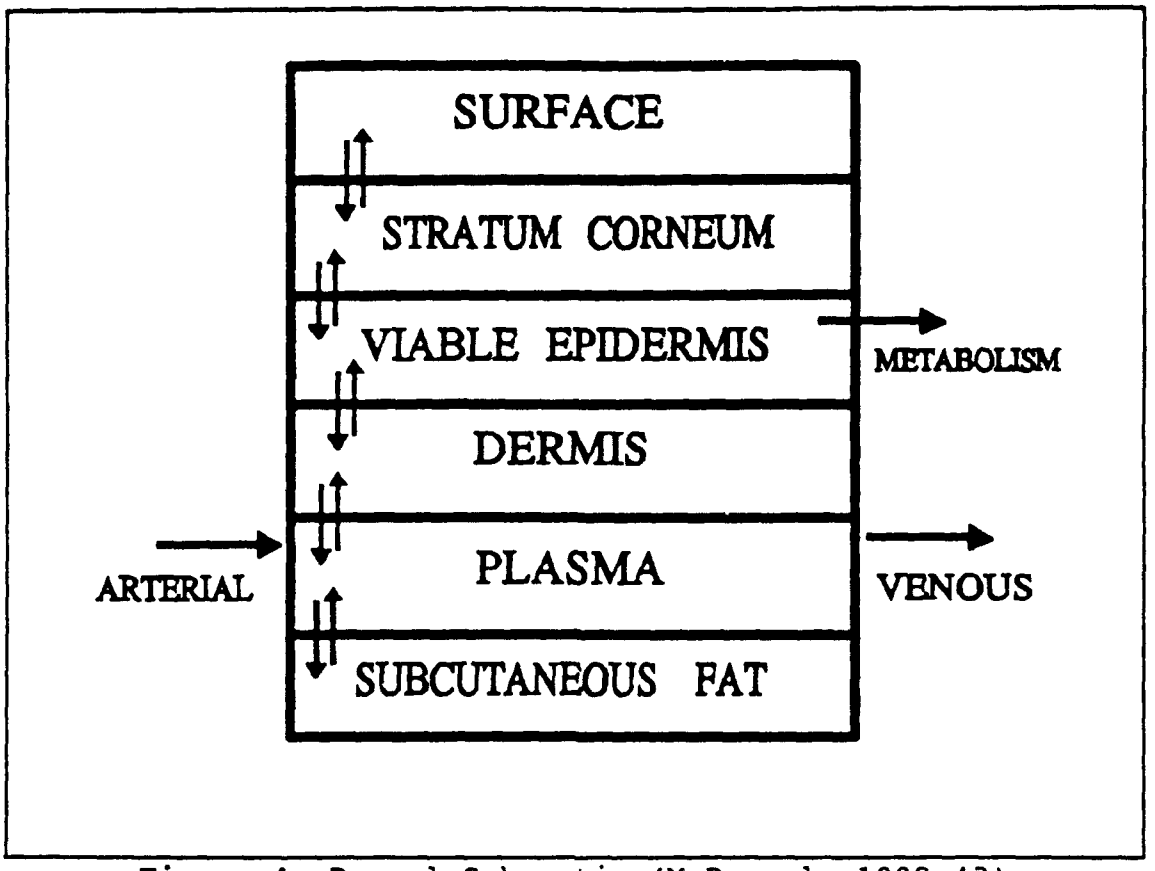


Figure 4 Dermal Schematic (McDougal, 1992:43)

as a sub-compartment or lumped together as a composite sub-compartment. In this research, some layer consolidation was used to obtain a simpler, but reasonably accurate model.

A dermal PBPK model which had been developed prior to this research utilizes a single homogeneous dermal compartment to represent the skin. This model is shown in Figure 5. This research improved upon this model. The Homogeneous Dermal Model was used as a reference to evaluate whether improvements in predictive capabilities had been

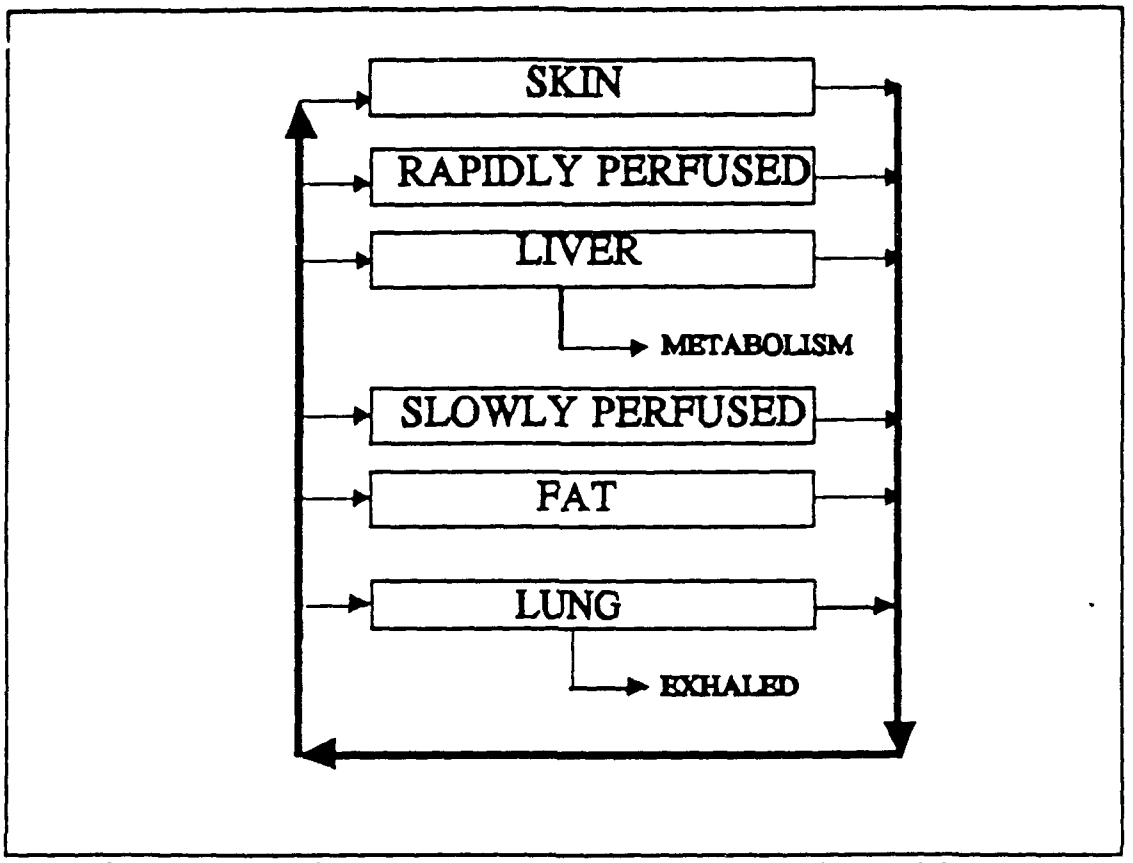


Figure 5. Tissue Compartments (McDougal, 1986:288)

achieved. The following equations were used to describe the mass-balance of the Homogeneous Dermal Model (McDougal, 1986). These equations, once solved, yielded blood concentrations of a chemical with respect to time.

Skin compartment:

$$V_{sk}(dC_{sk}/dt) = Q_{sk}(C_a - C_{sk}/R_{sk/b}) + P_{sk}A_{sk}(C_{sfc} - C_{sk}/R_{sk/sfc}) \quad (5)$$

Rapidly perfused tissue compartment:

$$V_{rp}(dC_{rp}/dt) = Q_{rp}(C_a - C_{rp}/R_{rp/b}) \quad (6)$$

Liver compartment:

$$V_l(dC_l/dt) = Q_l(C_a - C_l/R_{l/b}) - V_{max}C_l/(K \circ R_{l/b} + C_l) \quad (7)$$

Slowly perfused tissue compartment:

$$V_{sp}(dC_{sp}/dt) = Q_{sp}(C_a - C_{sp}/R_{sp/b}) \quad (8)$$

Fat tissue compartment:

$$V_f(dC_f/dt) = Q_f(C_a - C_f/R_{f/b}) \quad (9)$$

Arterial concentration (including $Q_{al}/P_{b/air}$ exhalation term):

$$C_a = Q_cC_v/(Q_{al}/P_{b/air} + Q_c) \quad (10)$$

where

V = volume
v = venous
C = concentration (mass/volume)
c = cardiac
t = time
Q = flow (volume/time)
R = partition coefficient
P = permeability (distance/time)
A = area
K = Michaelis constant - metabolism (mass/volume time)
sk = skin
a = arterial blood
b = blood
sfc = surface
rp = rapidly perfused tissue
l = liver
sp = slowly perfused tissue
f = fat tissue

(McDougal, 1986: 289, 1991:45-49)

In this research, each of the above equations were retained except equation (5) which was altered to account for new dermal sub-compartments. The first approach that was used in this research was to represent the skin

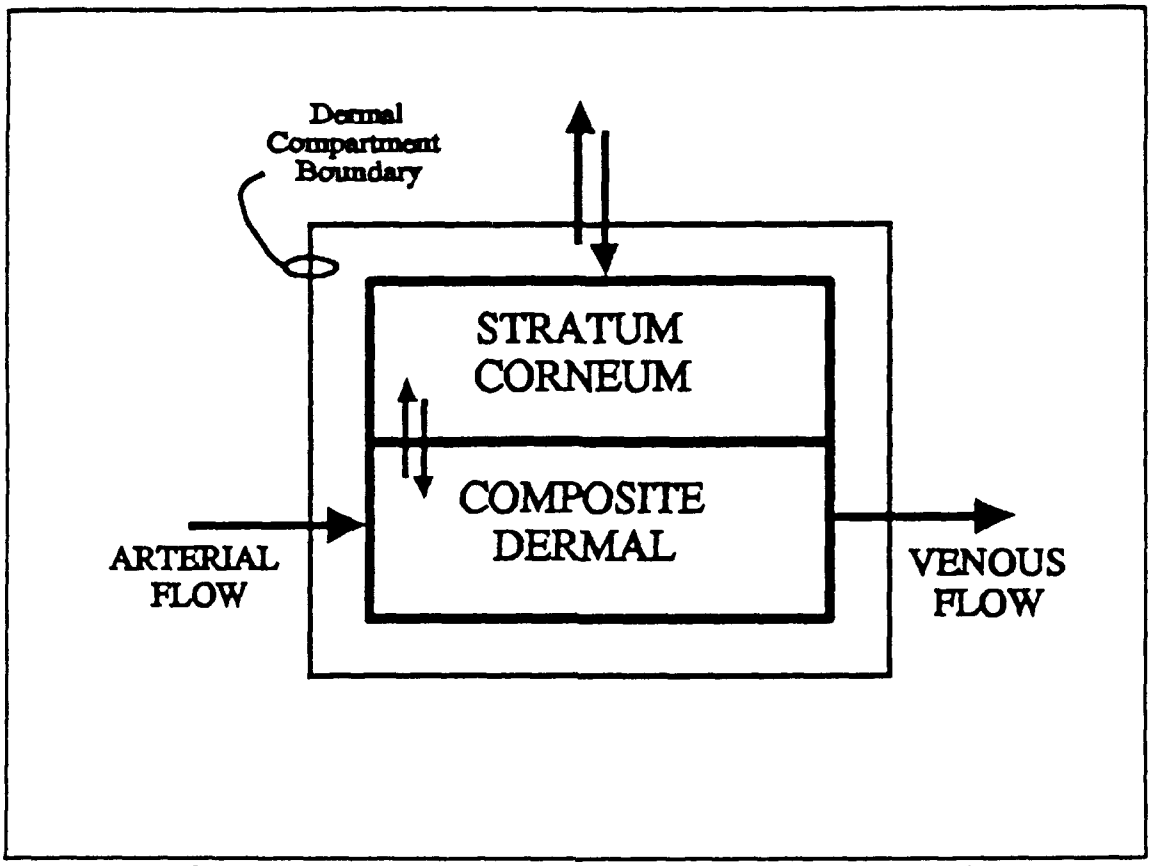


Figure 6. Two Sub-compartment Dermal Model

compartment as two equivalent volume sub-compartments. This model is referred to as the 1:1 Dermal Model. As shown in Figure 6, the two sub-compartments represent the stratum corneum and a composite of all the other skin layers. Blood exchange occurs only in the second sub-compartment. The following equations, each representing a sub-compartment, combine to form the PBPK model's skin compartment.

Stratum corneum sub-compartment:

$$V_{sc}(dC_{sc}/dt) = P_{sc}A_{sc}(C_{sfc} - C_{sc}/R_{sc/sfc}) + P_{cd}A_{cd}(C_{cd} - C_{sc}/R_{sc/cd}) \quad (11)$$

Composite dermal sub-compartment:

$$V_{cd}(dC_{cd}/dt) = P_{cd}A_{cd}(C_{sc}/R_{sc/cd} - C_{cd}) + Q_{cd}(C_a - C_{cd}/R_{cd/b}) \quad (12)$$

where

cd = composite dermal sub-compartment.

These two equations replace equation (5) of the Homogeneous Dermal Model. The equations have been coded into FORTRAN for use on AFIT's UNIX based computer system. The programs utilized a sub-routine called IVPAG which is a program in the IMSL library that is capable of solving simultaneously a set of ordinary differential equations.

The model has been run using initial skin surface concentrations of dibromomethane of 500, 1000, 5000, and 10000 ppm. Also, the model generates blood concentration predictions over a four hour time period.

The following parameters have been estimated to obtain better prediction results.

R_{12} - partition coefficient between skin sub-compartments one and two

P_{sk1} - permeability parameter for sub-compartment 1

$R_{2/b}$ - partition coefficient between skin sub-compartment 2 and the blood

Only the unknown parameters associated with the skin compartment have been estimated and optimized. Since this model is a modification of the Homogeneous Dermal Model noted earlier, the parameters associated with the other compartments were already optimized.

Model Assumptions

The 1:1 Dermal Model is based upon two simplifying assumptions. First, chemical binding in the skin compartment is not represented. Second, chemical metabolism other than in the liver is not modelled. Both of these factors will be left to future research effort.

Validation

The model has been validated using experimental rat data obtained in previous research and provided by the Toxicology Division. Over the four hour period, the model's predictions at 500, 1000, 5000, and 10000 ppm skin surface concentrations of dibromomethane are compared to experimental data at the same concentrations. The weighted deviation sum of squares is calculated for each model over the range of dibromomethane initial skin surface concentrations at 0.5, 1.0, 2.0, 3.0, and 4.0 hours. The weighting is calculated as follows:

$$DEV = (CA - DIBRO)/WEIGHT \qquad (13)$$

$$SD = \Sigma\ DEV^2 \qquad (14)$$

where

CA - predicted blood concentration at some time and initial dibromomethane skin surface concentration

DEV - deviation

DIBRO - dibromomethane experimental data at CA's time and initial dibromomethane skin surface concentration

SD - weighted sum of square deviation

WEIGHT - weighting factor linked to the initial dibromomethane skin surface concentration. Values are:

1.3 - 500 ppm

3.5 - 1000 ppm

45.8 - 5000 ppm

144.7 - 10000 ppm

The weighting factors are average values for the experimental blood concentrations at each initial skin surface concentration (Quinn, 1991:198).

1:10 Dermal Model

Following the presentation of the 1:1 Dermal Model to the Toxicology Division, it was suggested that the composite dermal sub-compartment's volume be increased to ten times that of the stratum corneum sub-compartment in order to be more representative of the skin's anatomy. As a result, the 1:10 Dermal Model was developed.

The 1:10 Dermal Model utilizes the skin sub-compartment Equations 11 and 12; however, the composite sub-compartment's volume is increased to ten times the size of the stratum corneum sub-compartment.

1:3:7 Dermal Model

The third and final PBPK model developed in this research was the 1:3:7 Dermal Model. This model was developed in conjunction with the 1:10 Dermal Model in an effort to determine if the two sub-compartment model could be improved upon.

The 1:3:7 Dermal Model contains a skin compartment which consists of three dermal sub-compartments. As shown in Figure 7, these sub-compartments represent the stratum corneum, the viable epidermis, and a composite of the remaining skin layers. Blood exchange occurs only in the third sub-compartment. The volume of the viable epidermis sub-compartment was set to three times the volume of the stratum corneum, while the volume of the third composite sub-compartment was set to seven times that of the stratum corneum. These volumes were set arbitrarily only ensuring that the combined viable epidermis and composite dermal sub-compartment volume was ten times that of the stratum corneum.

The equations used to describe these sub-compartments are similar to the two sub-compartment variation. The

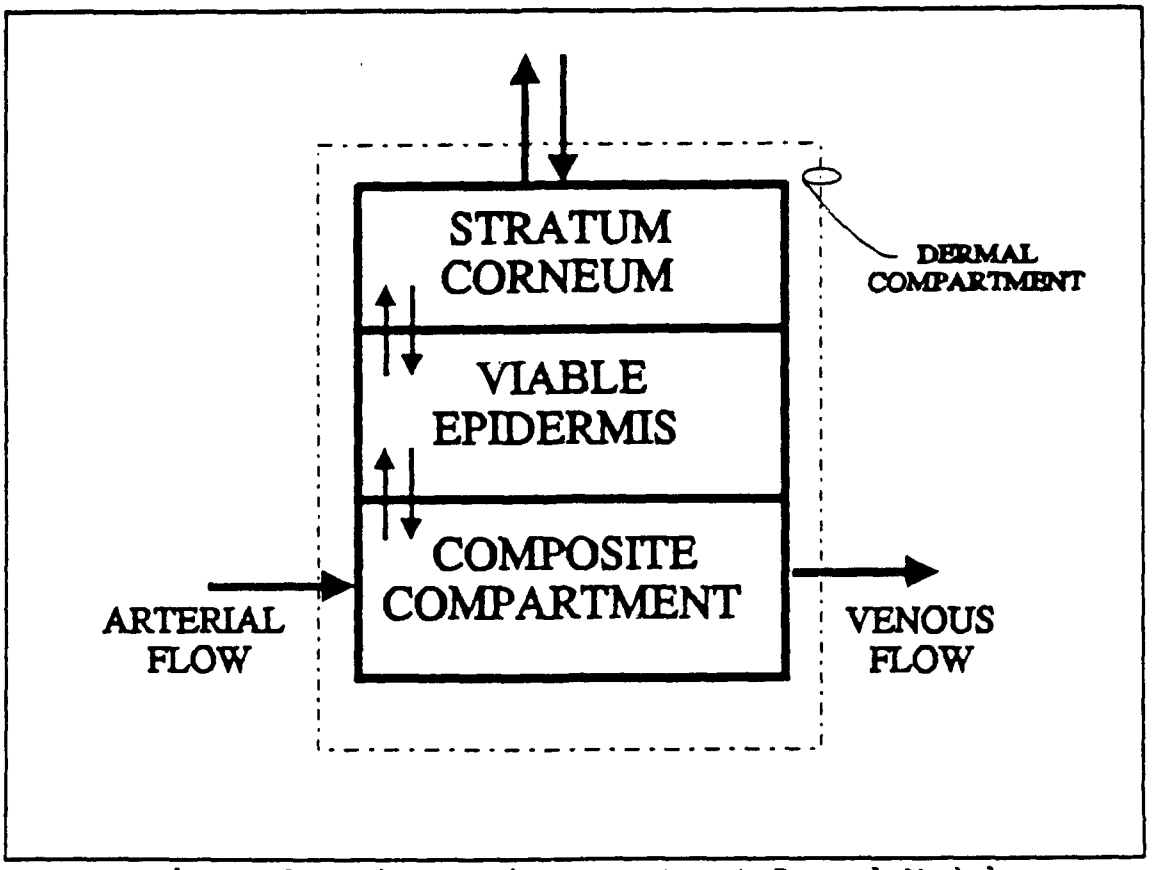


Figure 7. Three Sub-compartment Dermal Model

symbols are the same as those in Equations 5 - 10. In the 1:3:7 Dermal Model, Equation (5) is replaced with equations (15), (16), and (17) which are as follows:

Stratum corneum sub-compartment:

$$V_{sc}(dC_{sc}/dt) = P_{sc}A_{sc}(C_{stc} - C_{sc}/R_{sc/stc}) + P_{ve}A_{ve}(C_{ve} - C_{sc}/R_{sc/ve}) \quad (15)$$

Viable epidermis sub-compartment:

$$V_{ve}(dC_{ve}/dt) = P_{ve}A_{ve}(C_{sc}/R_{sc/ve} - C_{ve}) + P_{cd}A_{cd}(C_{cd} - C_{ve}/R_{ve/cd}) \quad (16)$$

Composite dermal sub-compartment:

$$V_{cd}(dC_{cd}/dt) = P_{cd}A_{cd}(C_{ve}/R_{ve/cd} - C_{cd}) + Q_{cd}(C_a - C_{cd}/R_{cd/b}) \quad (17)$$

where

ve = viable epidermis

The parameters which were estimated in the 1:3:7 Dermal Model are the following:

R_{12} - partition coefficient between sub-compartment 1 and 2

R_{23} - partition coefficient between sub-compartment 2 and 3

P_{sk1} - permeability parameter for sub-compartment 1

P_{sk2} - permeability parameter for sub-compartment 2

$R_{3/b}$ - partition coefficient between sub-compartment 3 and blood

Objective

The objective has been to minimize the weighted deviation sum squares by altering several parameters within physiological limits. Also, each set of predictions have been plotted against the experimental data for visual verification of the model's accuracy. These results will be presented in the next chapter.

IV. Results and Discussion

The purpose of this research was to develop a dermal PBPK model consisting of multiple dermal sub-compartments that is capable of predicting dibromomethane blood concentration in a mammal following percutaneous absorption. The 1:1 Dermal Model developed in this study generated predictions of modest improvement over those given by the original Homogeneous Dermal Model. Two other dermal PBPK models were developed in addition to the initial model created in this research. The predictions and relative accuracy of each model are presented in this chapter.

The predictions generated by the original Homogeneous Dermal Model were plotted and are given in Figure 8 for comparison purposes.

1:1 Dermal Model Results

The original Homogeneous Dermal Model developed prior to this study predicted the blood concentration of dibromomethane reasonably well. The weighted deviation sum of squares for this model was 0.599.

The 1:1 Dermal Model achieved a weighted sum of squared deviation of 0.471. This translates into a 21.4 percent increase in accuracy of this model over the original. A plot of the predicted concentrations over time is given in

Figure 9. Dibromomethane: 1:1 Dermal Model

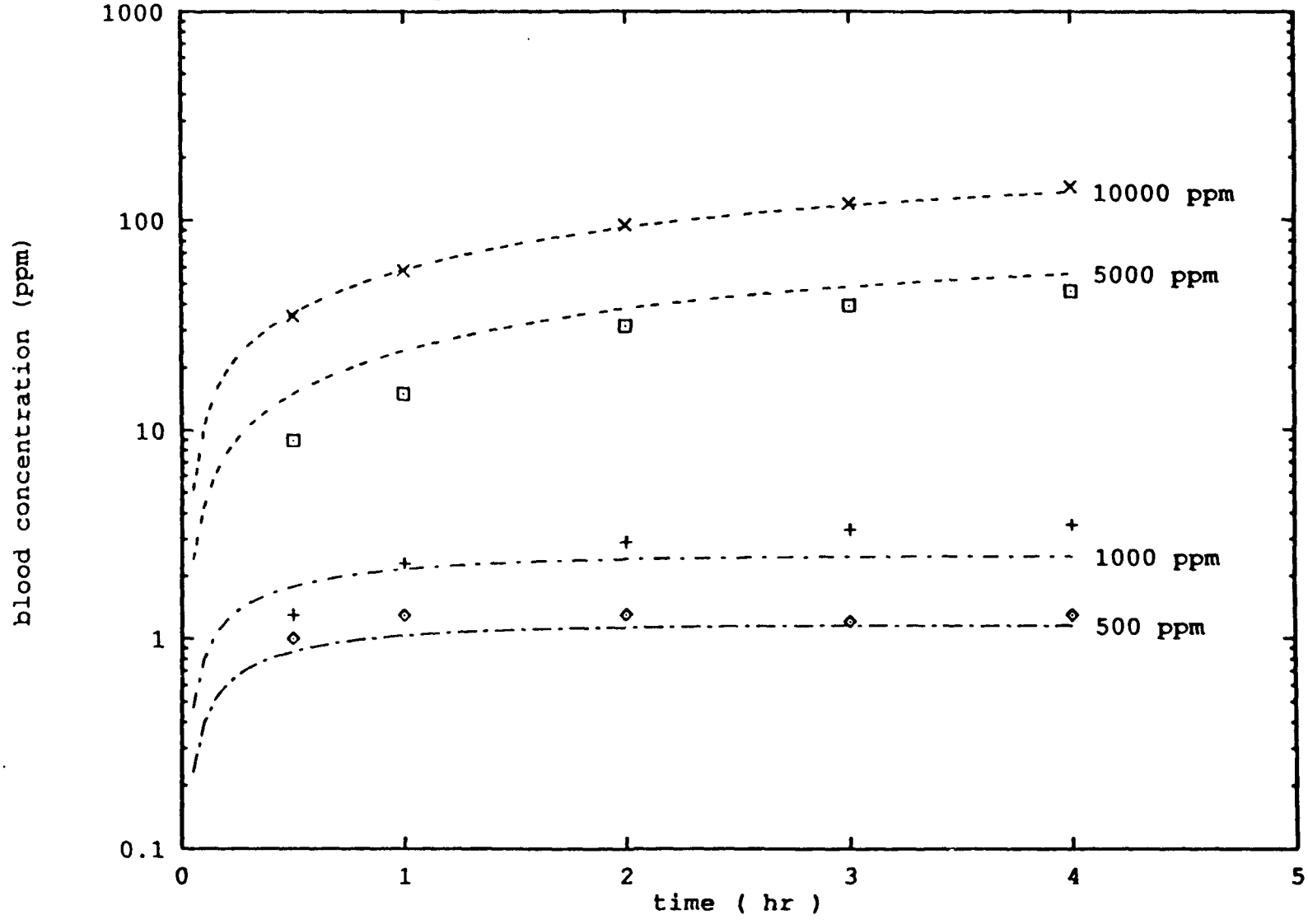


Figure 9 and results from the parameter estimation process is given in Table 1 located at the end of this chapter. Note that partition coefficients are represented in the tables as P2B, P3B, P12, and P23. Likewise, permeability parameters are represented in the tables as PSK1 and PSK2. These representations in this chapter match the coded program variables given in the Appendices.

The coded program for the 1:1 Dermal Model may be found in Appendix B with a definition of relevant variables located in Appendix A.

1:10 Dermal Model Results

The 1:10 Dermal Model obtained a weighted sum of squared deviation of 0.493. This result is a 17.7 percent increase in predictive accuracy over the homogeneous model, but slightly worse than the 1:1 Dermal Model. Despite the decrease in predictive accuracy of this model, as stated in the previous chapter, it is anatomically more accurate than the 1:1 Dermal Model. The 1:10 Dermal Model's predictions were plotted and are shown in Figure 10. The model's program code is given in Appendix C. Table 2 at the end of this chapter contains the results of the parameter estimation for this model.

Figure 10. Dibromomethane: 1:10 Dermal Model

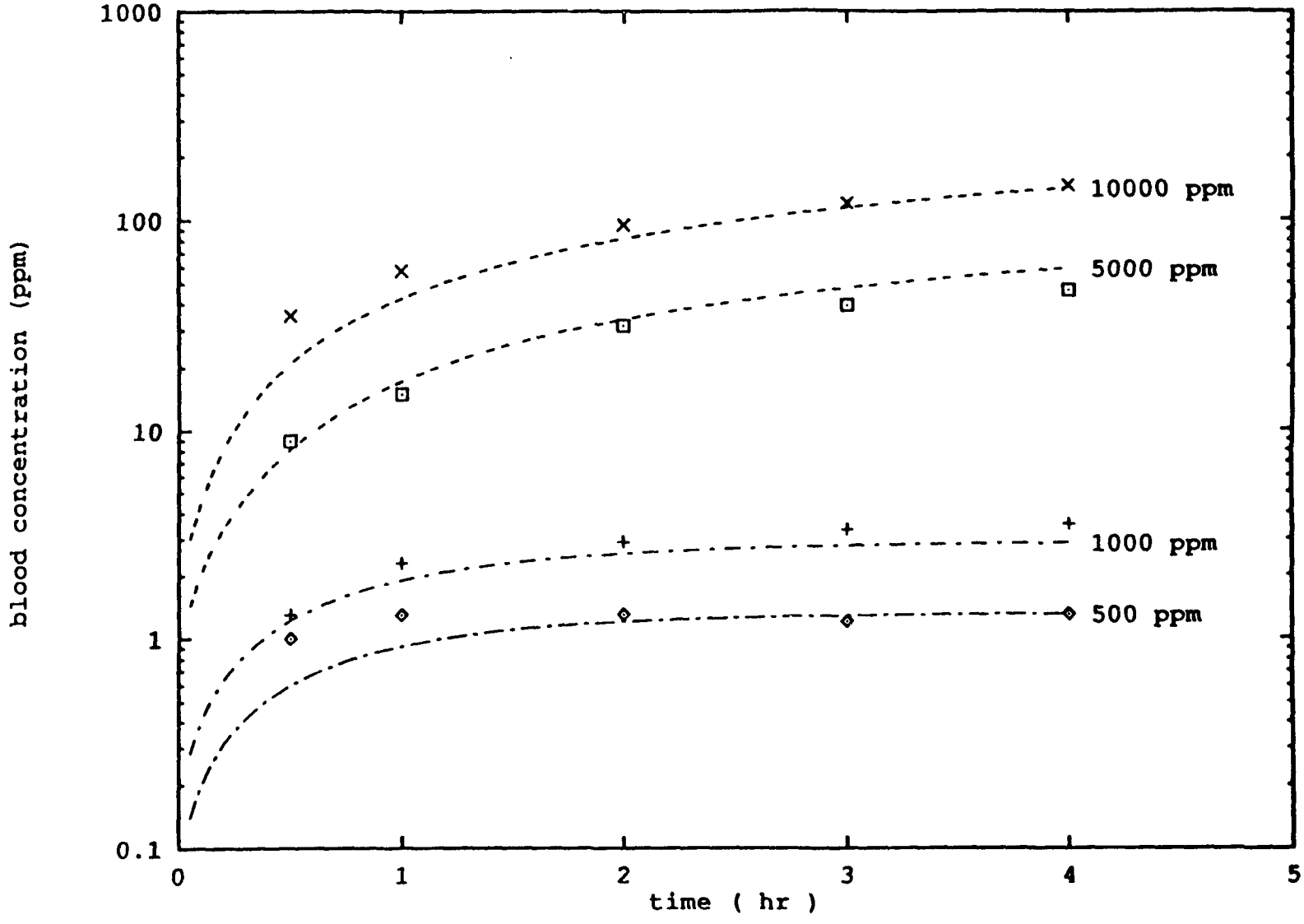
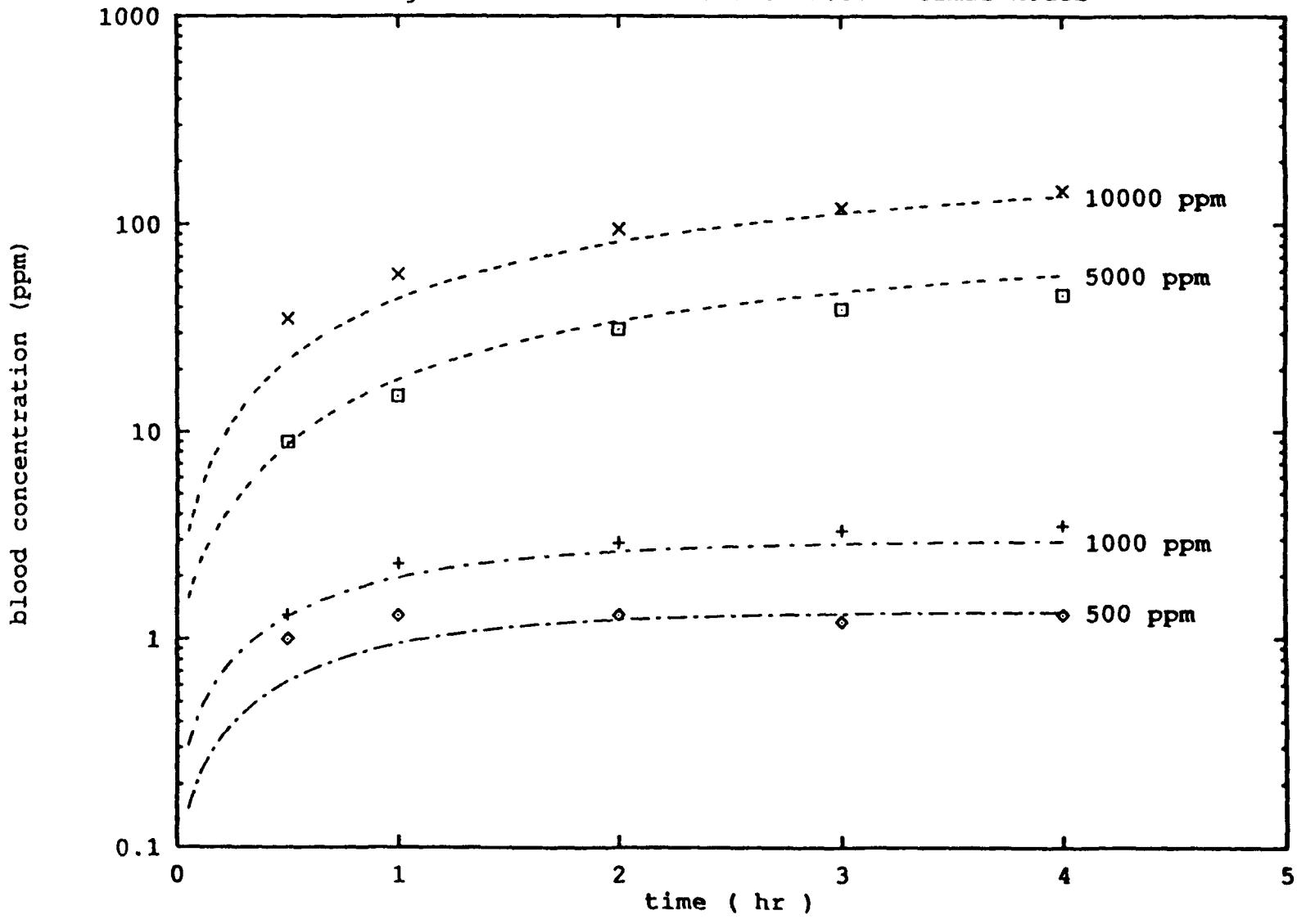


Figure 11. Dibromomethane: 1:3:7 Dermal Model



1:3:7 Dermal Model Results

After being compiled and executed, the 1:3:7 Dermal Model achieved a weighted sum of square deviation of 0.433. This is a 27.7 percent improvement over the Homogeneous Dermal Model. This model's prediction plot is presented in Figure 11, while its program code appears in Appendix D, and the parameter estimation results are given in Table 3.

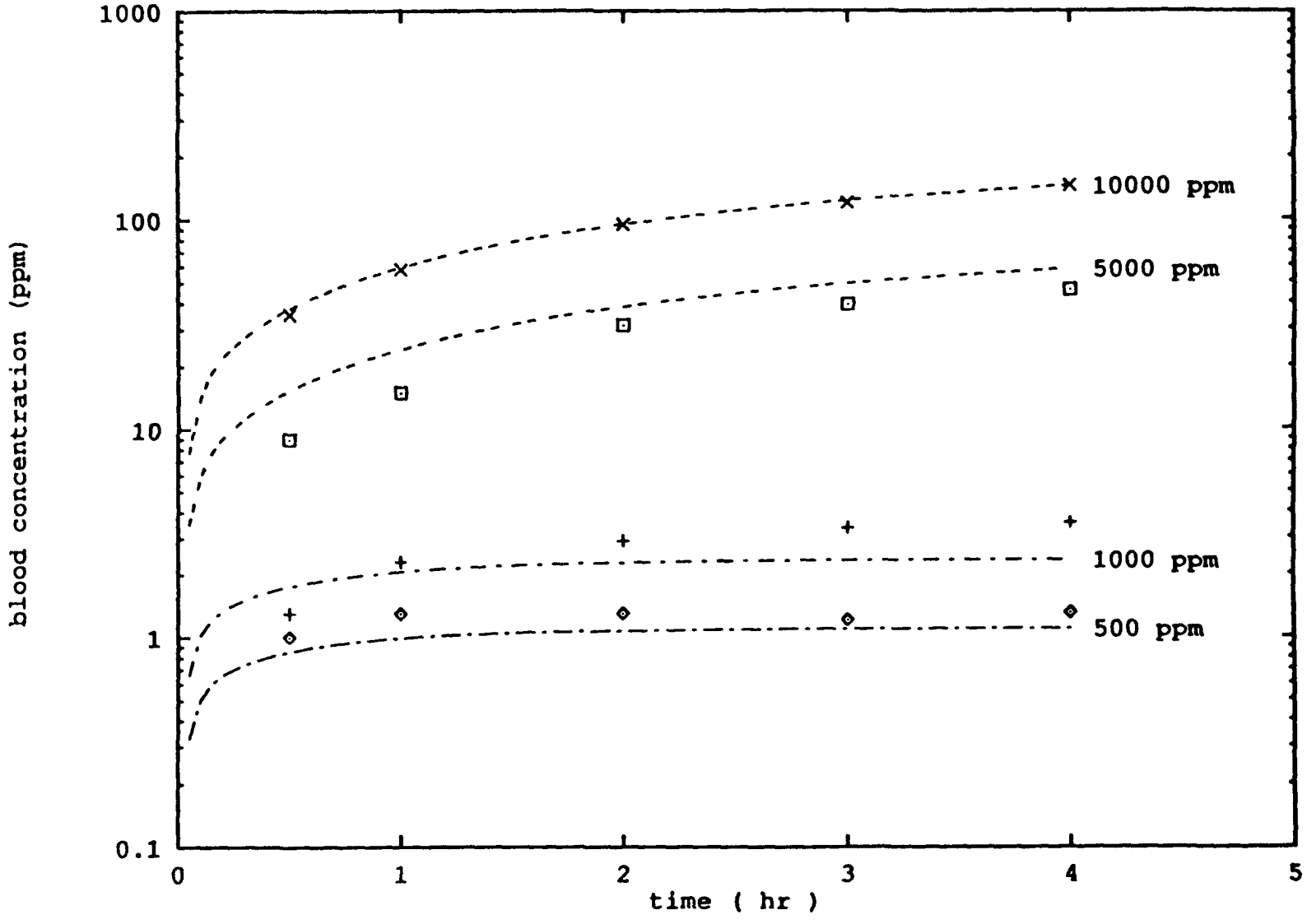
Discussion of Results

Each dermal model developed in this research generates reasonable predictions of dibromomethane concentrations in rats following dermal exposure. However, while the 1:10 Dermal Model does not yield better predictions than the 1:1 Dermal Model, it is more representative of the skin anatomy and therefore is an improvement over both the Homogeneous Dermal Model and the 1:1 Dermal Model.

The results of the 1:3:7 Dermal Model suggest that improvements can be made with additional sub-compartments; however, a point of diminishing returns may be reached. With more research, the 1:3:7 Dermal Model can be more physiologically representative with respect to sub-compartment volumes. Again, additional complexity may not prove beneficial with marginal increases in accuracy.

Subsequent to the completion of this research, it was discovered that a fault exists within the estimation of the sub-compartment partition coefficient. An additional

Figure 8. Dibromomethane: Homogeneous Dermal Model



constraint is required when forming sub-compartment partition coefficients. This constraint takes the form of the following equation:

$$1/R_o = \Sigma\ 1/R_n \qquad (18)$$

where

R = partition coefficient

o = original homogeneous compartment

n = sub-compartment 1 through n

(McDougal, 1993)

It is not known how this adjustment will affect the model predictions presented in this paper. It must be left to future research efforts to determine this effect.

TABLE 1

RESULTS FROM PARAMETER ESTIMATION FOR
1:1 DERMAL MODEL

P12	M1 (PSK1=M1∘P)	M2 (P2B=M2∘ PSKB)	SD
1.0	1.0	1.0	0.9622174
1.1	1.0	1.0	2.6951764
0.9	1.0	1.0	0.4753195
0.8	1.0	1.0	0.8335980
0.89	1.0	1.0	0.4783762
0.91	1.0	1.0	0.4804890
0.9	1.1	1.0	0.4832967
0.9	1.2	1.0	0.4952881
0.9	0.9	1.0	0.4749715
0.9	0.8	1.0	0.4890361
0.9	0.89	1.0	0.4754832
0.9	0.91	1.0	0.4744299
0.9	0.92	1.0	0.4740500
0.9	0.94	1.0	0.4739079
0.9	0.96	1.0	0.4739265
0.9	0.95	1.0	0.4737312
0.9	0.94	1.1	0.8216658
0.9	0.94	0.9	0.6592712
0.9	0.94	0.99	0.4712904
0.9	0.94	0.97	0.4810873
0.9	0.94	0.98	0.4736753
0.9	0.94	0.99	0.4712904

TABLE 2

RESULTS FROM PARAMETER ESTIMATION FOR
1:10 DERMAL MODEL

P12	M1 (PSK1=M1*P)	M2 (PSKB=M2* PSKB)	SD
1.0	1.0	1.0	0.5241103
1.1	1.0	1.0	0.7284113
0.9	1.0	1.0	0.8556208
0.99	1.0	1.0	0.5355669
1.01	1.0	1.0	0.5179490
1.03	1.0	1.0	0.5223331
1.02	1.0	1.0	0.5173553
1.02	1.1	1.0	0.5303404
1.02	0.9	1.0	0.5124760
1.02	0.8	1.0	0.5238835
1.02	0.95	1.0	0.5138880
1.02	0.93	1.0	0.5128970
1.02	0.91	1.0	0.5125576
1.02	0.89	1.0	0.5127838
1.02	0.9	1.1	0.7957720
1.02	0.9	0.9	0.5575377
1.02	0.9	0.95	0.4958929
1.02	0.9	0.96	0.4927654
1.02	0.9	0.97	0.4929826
1.02	0.9	0.96	0.4927654

TABLE 3

RESULTS FROM PARAMETER ESTIMATION FOR
1:3:7 DERMAL MODEL

P12	P23	M1 (PSK1= M1*P)	M2 (PSK2= M2*P)	M3 (P3B=M3* PSKB)	SD
1.0	1.0	1.0	1.0	1.0	0.7151995
1.01	1.0	1.0	1.0	1.0	0.7814474
0.99	1.0	1.0	1.0	1.0	0.6566185
0.9	1.0	1.0	1.0	1.0	0.4548367
0.8	1.0	1.0	1.0	1.0	0.8087665
0.91	1.0	1.0	1.0	1.0	0.4503877
0.92	1.0	1.0	1.0	1.0	0.4526393
0.91	1.01	1.0	1.0	1.0	0.4530610
0.91	0.99	1.0	1.0	1.0	0.4513902
0.91	1.0	1.01	1.0	1.0	0.4514778
0.91	1.0	0.99	1.0	1.0	0.4492975
0.91	1.0	0.9	1.0	1.0	0.4439190
0.91	1.0	0.8	1.0	1.0	0.4486297
0.91	1.0	0.89	1.0	1.0	0.4440323
0.91	1.0	0.91	1.0	1.0	0.4447286
0.91	1.0	0.9	1.01	1.0	0.4441657
0.91	1.0	0.9	0.99	1.0	0.4445271

TABLE 3 (CONTINUED)

RESULTS FROM PARAMETER ESTIMATION FOR
1:3:7 DERMAL MODEL

P12	P23	M1 (PSK1= M1°P)	M2 (PSK2= M2°P)	M3 (P3B=M3° PSKB)	SD
0.91	1.0	0.9	1.0	1.01	0.4524778
0.91	1.0	0.9	1.0	0.99	0.4381944
0.91	1.0	0.9	1.0	0.9	0.4845310
0.91	1.0	0.9	1.0	0.97	0.4327300
0.91	1.0	0.9	1.0	0.95	0.4364229
0.91	1.0	0.9	1.0	0.96	0.4335011
0.91	1.0	0.9	1.0	0.98	0.4342730
0.91	1.0	0.9	1.0	0.97	0.4327300

V. Conclusions and Recommendations

Conclusions

The goal of this research was to develop a dermal PBPK model with multiple dermal sub-compartments that predicted mammalian blood concentrations of dibromomethane following dermal exposure. This goal was successfully achieved with three separate dermal PBPK models. These three models included a 1:1 Dermal Model, a 1:10 Dermal Model, and a 1:3:7 Dermal Model.

Each model predicted blood concentrations of dibromomethane more accurately than the Homogeneous Dermal Model developed prior to this research. The 1:10 Dermal Model has been validated more extensively than the 1:3:7 Dermal Model so there is more confidence in the 1:10 Dermal Model at this time. Both the 1:10 and the 1:3:7 Dermal Models achieved modest improvements over the predictive ability of the original Homogeneous Dermal Model, and also represents mammalian skin more correctly.

The 1:3:7 Dermal Model generated the most accurate predictions of the four models and with further development it can be even more physiologically representative than the other models.

As noted in Chapter IV, the parameter estimation for the dermal sub-compartment partition coefficients must be altered to reflect the relationship established in Equation (18). It is not known how this will affect the accuracy of these models' predictions with respect to the Homogeneous Dermal Model.

Recommendations

There are several subjects to consider for future research. The first is to evaluate chemical binding in various compartments. This research assumed no binding in the various tissue compartments. Depending upon the chemical, there may be a potential to bind to the sub-compartments within the tissue to be released at a later time. The effect could possibly reduce the amount of chemical immediately reaching the blood stream and lengthen the blood chemical concentration decay after the exposure has ceased.

The second subject which could be evaluated is in tissue metabolism. In this research, metabolism was only considered in the liver. However, chemical metabolism may occur in other tissue. Again, consideration of this effect may alter the amount of chemical reaching the blood stream and the decay rate after exposure has ceased.

The final subject to consider is to develop a more anatomically representative dermal compartment for a PBPK

model. Other sub-compartments to consider include hair follicles and sweat glands, which could act as shunt pathways for a chemical, completely by-passing the resistive effect of the stratum corneum. Also, adding a sub-cutaneous fat compartment may have an additional bearing on how well the model is able to predict blood concentrations of a chemical over time. The results of the 1:3:7 Dermal Model suggest that achieving more anatomical correctness in dermal modelling will be a worthy objective in obtaining more accurate predictions of chemical concentrations in the blood following exposure. However, this effort will be tempered by increasing complexity in conjunction with marginal accuracy improvements.

Appendix A: Program Variables

The following list contains pertinent variables found in the program code in Appendices B, C, and D. The original program was designed not only to generate predictions of tissue concentrations of dibromomethane, but also to perform sensitivity analyses on several other predictions of chemical concentrations. Only variables associated directly with the models described in this document will be identified. Most of the extraneous program code has been eliminated.

A - area of exposed skin (cm)
ASK1 - area of skin compartment 1 impacted (cm)
BW - body weight (mg)
BWE - experimental body weight (mg)
CA - arterial blood chemical concentration (mg/l)
CI - inhaled chemical concentration
CV - venous blood chemical concentration (mg/l)
CVF - venous blood chemical concentration, fat compartment (mg/l)
CVL - venous blood chemical concentration, liver compartment (mg/l)
CVR - venous blood chemical concentration, rapidly perfused tissue compartment (mg/l)
CVS - venous blood chemical concentration, slowly perfused tissue compartment (mg/l)
CZ - chemical concentration on skin surface (mg/l)
DEPTH - thickness of stratum corneum skin compartment, skin compartment 1 (cm)
DF - tissue compartment ordinary differential equation
DFRDXI - weighted deviation
DIBRO - experimental dibromomethane concentration data
I - counter
II - counter
IR - counter

J - counter
N - number of tissue compartment differential equations
NPP - number of points in time to generate predictions
PB - blood to air partition coefficient
PCBF - fat tissue volume adjustment (1/mg)
PCBM - slowly perfused tissue volume adjustment (1/mg)
PCL - liver tissue volume adjustment (1/mg)
PCO - rapidly perfused tissue volume adjustment (1/mg)
PF - fat to blood partition coefficient
PL - liver to blood partition coefficient
PR - rapidly perfused tissue to blood partition coefficient
PS - slowly perfused tissue to blood partition coefficient
PSK - permeability of the skin compartment (homogeneous model
PSK1 - permeability, skin sub-compartment 1
PSK2 - permeability, skin sub-compartment 2
P12 - partition coefficient between skin compartment 1 and 2
P23 - partition coefficient between skin compartment 2 and 3
P2B - partition coefficient between skin compartment 2 and blood
P3B - partition coefficient between skin compartment 3 and blood
QC - total cardiac blood output, body weight adjusted (l/hr)
QCC - total cardiac blood output (l/kg/hr)
QF - fat compartment blood flow rate (l/hr)
QL - liver compartment blood flow rate (l/hr)
QP - pulmonary ventilation rate, body weight adjusted (l/hr)
QPC - pulmonary ventilation rate (l/kg/hr)
QR - rapidly perfused tissue compartment blood flow rate (l/hr)
QS - slowly perfused tissue compartment blood flow rate (l/hr)
QSK - skin compartment blood flow rate (l/hr)
RAMT - rate of chemical metabolism in liver (mg/hr)
SD - weighted sum of square deviation
T - time (hr)
TEND - time increment for predictions (hr)
VF - volume of fat compartment (l)
VL - volume of liver compartment (l)
VMAX - metabolism, maximum velocity body weight adjusted
VR - volume of rapidly perfused tissue compartment (l)
VS - volume of slowly perfused tissue compartment (l)
VSK - volume of skin compartment, original model (l)
VSK1 - volume of skin compartment 1 (l)
VSK2 - volume of skin compartment 2 (l)
VSK3 - volume of skin compartment 3 (l)
WEIGHT - weighting factor for square deviation calculation

Appendix B: FORTRAN Program:

1:1 Dermal PBPK Model

This program was developed and executed in FORTRAN in a UNIX environment. The program calls the IVPAG subroutine in the IMSL library. The subroutine simultaneously solves the tissue compartment ordinary differential equations. IVPAG is similar to Simusolve in the ACSL programming language which operates in a PC based environment.

```
program main
dimension X(7),A(7,2),DF(7),XN(7),FR(81),FN(81)
dimension DIBRO(4,8),CARBOX(4,8),BROM(4,8)
dimension TIME(8)
COMMON/OBSERV/DIBRO,CARBOX,BROM,TIME,NUMMAX
EXTERNAL FUNCT,FCN,FCNJ
DATA (DIBRO(1,J),J=1,8)/-1.,1.,1.3,-1.,1.2,-1.,1.2,1.3/
DATA (DIBRO(2,J),J=1,8)/-1.,1.3,2.3,-1.,2.9,-1.,3.3,3.5/
DATA (DIBRO(3,J),J=1,8)/-1.,8.9,14.9,-1.,31.3,-1.,
39.,45.8/
DATA (DIBRO(4,J),J=1,8)/5.4,30.9,59.4,84.8,103.7,
115.7,142.,-1./
DATA (CARBOX(1,J),J=1,8)/-1.,1.5,1.9,-1.,3.7,-1.,
4.7,4.2/
DATA (CARBOX(2,J),J=1,8)/-1.,1.8,5.3,-1.,9.8,-1.,
11.9,11.9/
DATA (CARBOX(3,J),J=1,8)/-1.,6.5,12.,-1.,16.7,-1.,
18.3,19.9/
DATA (CARBOX(4,J),J=1,8)/1.,5.4,11.,13.6,14.5,15.1,
15.4,-1./
DATA (BROM(1,J),J=1,8)/-1.,-1.,-1.,-1.,-1.,-1.,-1.,.6/
DATA (BROM(2,J),J=1,8)/-1.,-1.,-1.,-1.,-1.,-1.,-1.,1.1/
DATA (BROM(3,J),J=1,8)/-1.,-1.,-1.,-1.,-1.,-1.,-1.,2.9/
DATA (BROM(4,J),J=1,8)/-1.,-1.,-1.,-1.,-1.,-1.,15.4,-1./
DATA(TIME(J),J=1,8)/.25,.5,1.,1.5,2.,2.5,3.,4./
DATA (A(I,1),I=1,2)/.1,.1/
DATA (A(I,2),I=1,2)/100.,100./
NX=2
```

```
      DATA (X(I),I=1,2)/1.,1./
      NF=22
      NUMMAX=1
      NUM=1
      print 977
  977 format(1x,'two compartments, P12=0.9, psk1=p,derm6.f')
      CALL FUNCT(NX,X,NF,FR,FMINR)
      PRINT 999,(X(I),I=1,NX),FMINR
      IF(NUMMAX.EQ.1) STOP
          .          .          .          .          .
          .          .          .          .          .
                     (EXTRANEOUS CODE REMOVED)
          .          .          .          .          .
          .          .          .          .          .
  999 FORMAT(1X,7F12.7)
      END
      SUBROUTINE FUNCT(NX,X,NF,FN,FMIN)
      dimension X(NX),FMIN
      real a(1:1),param(50)
      dimension FN(NF)
      dimension DIBRO(4,8),CARBOX(4,8),BROM(4,8)
      dimension TIME(8),WEIGHT(4),dibexp(4,5)
      INTEGER N,METH
      dimension f(7),df(7),T,TOL,TEND,H
      EXTERNAL FCN,FCNJ
      COMMON/OBSERV/DIBRO,CARBOX,BROM,TIME,NUMMAX
      COMMON/PARM1/CA,VWC,BW
      common/parm2/irun
      COMMON/DIST/DX,XK,XH,XL,CZ
      DATA WEIGHT/1.3,3.5,45.8,144.7/
      data (dibexp(1,j),j=1,5)/1.0,1.3,1.3,1.2,1.3/
      data (dibexp(2,j),j=1,5)/1.3,2.3,2.9,3.3,3.5/
      data (dibexp(3,j),j=1,5)/8.9,14.9,31.3,39.0,45.8/
      data (dibexp(4,j),j=1,5)/35.3,57.8,94.6,119.8,144.7/
      N=6
      XK=X(1)
      XH=X(2)
      II=0
      tol=.001
      DO 150 IR=1,4
      h=.000001
      METH=2
      do 5 i=1,50
    5 param(i)=0.0
      param(12)=meth
      param(1)=h
      param(4)=100000.
      print 997,param(4)
      ido=1
  997 FORMAT(1X,'PAR=',4F16.7)
```

```
      IRUN=IR
      PRINT 996
  996 FORMAT(7X,1HT,11X,2HCA)
      DO 10 I=1,N
   10 F(I)=0.
      T=0.
      npp=80
      DO 100 KK=1,npp
      tend=4.*float(kk)/float(npp)
      call ivpag(ido,n,fcn,fcnj,a,t,tend,tol,param,f)
      call fcn(n,t,f,df)
      IF(NUMMAX.EQ.1) PRINT 999,T,CA
      IF(IER.GT.128) GO TO 200
      DO 50 J=1,8
      IF(TEND.NE.TIME(J))GO TO 50
      IF(DIBRO(IR,J).LT. 0.) GO TO 50
      II=II+1
      FN(II)=(CA-DIBRO(IR,J))/WEIGHT(IR)
      GO TO 50
   30 IF(CARBOX(IR,J).LT. 0.) GO TO 40
      II=II+1
      FN(II)=(F(7)-CARBOX(IR,J))/CARBOX(IR,J)
   40 IF(BROM(IR,J).LT. 0.) GO TO 50
      II=II+1
      FN(II)=(F(7)-BROM(IR,J))/BROM(IR,J)
   50 CONTINUE
  100 CONTINUE
      IF(NUMMAX.GT.1) GO TO 150
      cz=-1.
      PRINT 999,CZ,BW
      print 998,ii,nf
      do 140 i=1,5
      tttt=float(i)-1.
      if(i.eq.1) tttt=.5
  140 print 999,tttt,dibexp(ir,i)
      ido=3
      call ivpag(ido,n,fcn,fcnj,a,t,tend,tol,param,f)
  150 CONTINUE
      FMIN=0.
      DO 175 J=1,NF
  175 FMIN=FMIN+FN(J)*FN(J)
  999 FORMAT(1X,5e14.5)
      RETURN
  200 PRINT 998,IER,N,METH,MITER,INDEX,TOL,(F(J),J=1,N),
      TEND,T
  998 FORMAT(1X,5I5,8F10.5)
      STOP
      END
      SUBROUTINE FCN(N,T,F,DF)
      dimension F(N),DF(N),T,akm
```

```
      dimension CIV(4),BWE(4)
      COMMON/PARM1/CA,VWC,BW
      common/parm2/irun
      COMMON/DIST/DX,XK,XH,XL,CZ
      DATA CIV/500.,1000.,5000.,10000./
      DATA BWE/.187,.212,.209,.260/
      DATA QCC,QPC,PB,VMAXC,akm,PL,akfc,
     1 P,PF,PS,PR,VBSKC,QSKC/
     1 15.,15.,74.1:10.6,.36,.919,.557,
     3 1.1:10.8,.546,.9,.0028,.05/
      CI=0.
      CZ=.001*173.85*CIV(IRUN)/24450.
      BW=BWE(IRUN)
      IF(T.GT.6.) CI=0.
  999 FORMAT(1X,5e14.5)
      QC=QCC*BW**0.74
      QL=.2*QC
      QF=.09*QC
      A=9.1*(1000.*BW)**.666 - 60.
      QSK=A*QSKC*QC/.906/BW**0.7
      QS=.15*QC-QSK/1000.
      QR=.56*QC
      QP=QPC*BW**0.74
      PCL=.04
      PCBF=.07
      PCBM=.75
      PCO=.05
      VF=PCBF*BW
      VL=PCL*BW
      VS=PCBM*BW
      VR=PCO*BW
      VMAX=VMAXC*BW**0.7
      VBSK=A*VBSKC
      akf=akfc/BW**.3
      PSK=266.
      PSKB=PSK/PB
      DEPTH=.01
      VSK=A*DEPTH
      P12=0.9
      p2b=pskb*0.99
      VSK1=VSK
      VSK2=VSK
      ASK1=A
      PSK1=P*0.94
      CVF=F(N-3)/PF
      CV=QF*CVF+QL*F(N)/PL+QS*F(N-2)/PS+QR*F(N-1)/PR+QSK
         *F(1)/PSKB
      CV=CV/QC
      CA=(QC*CV+QP*CI)/(QP/PB+QC)
      DF(1)=(P*A*(CZ-F(1)/PSK)+PSK1*ASK1*(F(2)-F(1)/P12))/VSK1
```

```
DF(2)=(PSK1*ASK1*(-F(2)+F(1)/P12)+QSK
   *(CA/1000.-F(2)/P2B))/VSK2
DF(N-3)=QF*(CA-F(N-3)/PF)/VF
RAMT=VMAX*F(N)/(akm*PL+F(N)) + akf*VL*F(N)/PL
DF(N)=(QL*(CA-F(N)/PL) - RAMT)/VL
DF(N-2)=QS*(CA-F(N-2)/PS)/VS
DF(N-1)=QR*(CA-F(N-1)/PR)/VR
RETURN
END
SUBROUTINE FCNJ(N,T,F,PD)
integer n
real t,f(n),pd(*)
RETURN
END
```

Appendix C: FORTRAN Program

1:10 Dermal PBPK Model

The following FORTRAN program code is an excerpt from the 1:1 Dermal Model developed in this research. The composite dermal sub-compartment is ten times the volume of the stratum corneum dermal sub-compartment. Only a portion of this model is included here as the remainder is identical to the code presented in Appendix B. The significant code changes have been underlined.

```
QC=QCC*BW**0.74
QL=.2*QC
QF=.09*QC
A=9.1*(1000.*BW)**.666 - 60.
QSK=A*QSKC*QC/.906/BW**0.7
QS=.15*QC-QSK/1000.
QR=.56*QC
QP=QPC*BW**0.74
PCL=.04
PCBF=.07
PCBM=.75
PCO=.05
VF=PCBF*BW
VL=PCL*BW
VS=PCBM*BW
VR=PCO*BW
VMAX=VMAXC*BW**0.7
VBSK=A*VBSKC
akf=akfc/BW**.3
PSK=266.
PSKB=PSK/PB
DEPTH=.01
VSK=A*DEPTH
P12=1.02
p2b=pskb*0.96
VSK1=VSK
```

```
      VSK2=VSK*10
      ASK1=A
      PSK1=P*0.9
      CVF=F(N-3)/PF
CV=QF*CVF+QL*F(N)/PL+QS*F(N-2)/PS+QR*F(N-1)/PR+QSK*F(1)/PSKB
      CV=CV/QC
      CA=(QC*CV+QP*CI)/(QP/PB+QC)
DF(1)=(P*A*(CZ-F(1)/PSK)+PSK1*ASK1*(F(2)-F(1)/P12))/VSK1
DF(2)=(PSK1*ASK1*(-F(2)+F(1)/P12)+QSK*(CA/1000.-F(2)/P2B))/V
SK2
      DF(N-3)=QF*(CA-F(N-3)/PF)/VF
      RAMT=VMAX*F(N)/(akm*PL+F(N)) + akf*VL*F(N)/PL
      DF(N)=(QL*(CA-F(N)/PL) - RAMT)/VL
      DF(N-2)=QS*(CA-F(N-2)/PS)/VS
      DF(N-1)=QR*(CA-F(N-1)/PR)/VR
      RETURN
      END
      SUBROUTINE FCNJ(N,T,F,PD)
      integer n
      real t,f(n),pd(*)
      RETURN
      END
```

Appendix D: FORTRAN Program

1:3:7 Dermal PBPK Model

The following FORTRAN program code is an excerpt from the 1:3:7 Dermal Model developed in this research. The composite dermal sub-compartment is seven times the volume of the stratum corneum dermal sub-compartment while the viable epidermis sub-compartment is three times the volume of the stratum corneum. Only a portion of this model is included here as the remainder is identical to the code presented in Appendix B. The significant code changes have been underlined.

```
QC=QCC*BW**0.74
QL=.2*QC
QF=.09*QC
A=9.1*(1000.*BW)**.666 - 60.
QSK=A*QSKC*QC/.906/BW**0.7
QS=.15*QC-QSK/1000.
QR=.56*QC
QP=QPC*BW**0.74
PCL=.04
PCBF=.07
PCBM=.75
PCO=.05
VF=PCBF*BW
VL=PCL*BW
VS=PCBM*BW
VR=PCO*BW
VMAX=VMAXC*BW**0.7
VBSK=A*VBSKC
akf=akfc/BW**.3
PSK=266.
PSKB=PSK/PB
DEPTH=.01
```

```
      VSK=A*DEPTH
      P12=0.91
      P23=1.0
      p3b=pskb*0.97
      VSK1=VSK
      VSK2=VSK*3
      VSK3=VSK*7
      ASK1=A
      ASK2=A
      PSK1=P*.9
      PSK2=P
      CVF=F(N-3)/PF
CV=QF*CVF+QL*F(N)/PL+QS*F(N-2)/PS+QR*F(N-1)/PR+QSK*F(1)/PSKB
      CV=CV/QC
      CA=(QC*CV+QP*CI)/(QP/PB+QC)
DF(1)=(P*A*(CZ-F(1)/PSK)+PSK1*ASK1*(F(2)-F(1)/P12))/VSK1
DF(2)=(PSK1*ASK1*(F(1)/P12-F(2))+PSK2*ASK2*(F(3)-F(2)/P23))/
VSK2
DF(3)=(PSK2*ASK2*(F(2)/P23-F(3))+QSK*(CA/1000.-F(3)/P3B))/VS
K3
      DF(N-3)=QF*(CA-F(N-3)/PF)/VF
      RAMT=VMAX*F(N)/(akm*PL+F(N)) + akf*VL*F(N)/PL
      DF(N)=(QL*(CA-F(N)/PL) - RAMT)/VL
      DF(N-2)=QS*(CA-F(N-2)/PS)/VS
      DF(N-1)=QR*(CA-F(N-1)/PR)/VR
      RETURN
      END
      SUBROUTINE FCNJ(N,T,F,PD)
      integer n
      real t,f(n),pd(*)
      RETURN
      END
```

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Vita

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The goal of this study was to develop a physiologically based pharmacokinetic (PBPK) model that predicts mammalian blood concentrations of dibromomethane following exposure by dermal absorption more accurately than a previously developed Homogeneous Dermal Model. The Homogeneous Dermal Model contains a dermal compartment with no dermal sub-compartments. The 1:1 Dermal Model developed in this research contains a dermal compartment with a stratum corneum and a composite dermal sub-compartment of equal volume. This model yields predictions which are 21.4 percent more accurate than the original homogeneous model. In order to represent skin anatomy more accurately, the 1:10 Dermal Model variation was developed. The 1:10 Dermal Model contains a dermal compartment with a composite dermal sub-compartment ten times the volume of the stratum corneum sub-compartment. The 1:10 Dermal Model yields predictions which are 17.7 percent more accurate than the original model. Finally, the 1:3:7 Dermal Model was developed which contains a viable epidermis sub-compartment three times the volume of the stratum corneum sub-compartment and a composite dermal sub-compartment which is seven times the volume of the stratum corneum sub-compartment. This model yields predictions 27.7 percent more accurate than the original model.

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