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PRINCIPLES OF SKIN PERMEABILITY RELEVANT TO CHEMICAL EXPOSURE

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16. Abstract (Limit: 200 words) Biological and physicochemical parameters which determine the rate and extent of chemical penetration across the human skin were identified. Such exposures may represent a significant occupational hazard. Anatomical features of the skin that control the barrier to absorption were reviewed. The interaction of the physiological parameters with the physicochemical properties of the dermally contacting chemical were discussed to determine the kinetics and degree of penetration which will be accomplished. The relationship between chemical structure and activity and penetration of the skin was reviewed for n-alkanols, phenols, phenylboronic acids, steroids, nicotinic-acid esters, alkanoic acids, polynuclear aromatics, and nonsteroidal antiinflammatory drugs. Using skin absorption data for the forearm alone it is possible to calculate relative body exposures; to model this process of skin absorption effectively is a complex undertaking. The simplest treatment involves the use of Fick's laws of diffusion and an estimation of total body burden following a dermal exposure. Another approach based on the physicochemical properties of the penetrant was also discussed.

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INTRODUCTION

The objective of this chapter is to identify those biological and physicochemical parameters which determine the rate and extent of chemical penetration across human skin. There is no question that dermal exposure to toxic substances represents a major occupational hazard and that successful anticipation of potential risk could significantly reduce the incidence of this chronic health and environmental problem. Recent interest in the transdermal delivery of drugs to elicit systemic pharmacological effects has stimulated research into the mechanism(s) of percutaneous absorption and a detailed understanding of the skin's barrier function. On the basis of this emerging information, it is now feasible to predict, with a reasonable degree of reliability, the systemic exposure of the body to a chemical following dermal contact. It should then prove possible to determine, on a rational basis, whether a toxicity problem is likely and, if so, what steps should be taken to minimise the risk. To understand dermal penetration and the factors which control this route of chemical entry into the body, it is first necessary to review the salient anatomical features of the skin that control the barrier to absorption. Subsequently, we will discuss how these physiological parameters interact with the physicochemical properties of the dermally-contacting chemical to determine the kinetics and degree of penetration.

SKIN STRUCTURE

The skin is the largest organ of the body and covers a surface area of nearly 2 m^2 in the adult human. The basic structure of skin is a bilaminate membrane comprising the dermis and epidermis. Although the thicknesses of these layers differ from site to site on the body, the microscopic detail is remarkably constant. The major determinants of the barrier function of the skin are the stratum corneum and the viable tissue, the two regions which constitute the epidermis. The viable epidermis evolves from a basal endothelial cell layer. As the cells mature, they migrate towards the skin surface and undergo the process of differentiation. In so doing, a thin, completely keratinised cell layer, the stratum corneum, is formed as a 10 μm thick layer at the surface. The stratum corneum can be depicted as a "brick wall"[1]. The keratin filled corneocytes are the bricks and a complex mixture of apolar lipids[2] form the mortar and confer structural integrity. A principal function of the stratum corneum is to provide a barrier to the transepidermal loss of tissue water. By forming this resistance, it is consequential that the stratum corneum is also an excellent barrier to the inward movement of dermally contacting materials.

The diffusion environment of the stratum corneum is primarily lipophilic (see below). The viable epidermis, on the other hand, is an essentially aqueous region. In addition, the epidermis is avascular, the microcirculation of the skin being confined to the dermis. For a topically applied chemical to reach the systemic circulation, therefore, requires that it transports through both lipophilic and aqueous regions. A schematic representation of the skin is shown in Figure 1.

In most cases, it is the lipoidal stratum corneum which provides the rate limiting step in absorption[3]. However, for very lipophilic substances, slow partitioning from the stratum corneum into the less 'attractive' viable tissue layer can assume overall control of the penetration process. If the latter situation prevails, then a reservoir of chemical can be established within the stratum corneum and can provide a slow release of the agent into the body over a prolonged period of time[4].

ROUTES OF PENETRATION

Previous discussions concerning the routes of chemical penetration across the skin (and, in particular, the stratum corneum) have identified three possible pathways[5] (Figure 2):

(a) transcellular,

(b) intercellular, and

(c) appendageal (primarily, follicular).

On the basis of a number of disparate observations over the last 10-15 years, it now appears that, for the majority of compounds, the intercellular route predominates. In man, transport via the hair follicles and sweat glands is unlikely on the basis of available surface area; in other words, except in isolated regions, humans are not very hairy nor does the skin contain a high number of sweat glands. The transcellular path, although maximising the surface area parameter, requires that transport takes place through the densely packed corneocytes and that multiple partitioning steps between these cells and the intercellular lipids occur. It has been shown, for example, in experiments localising the position of butanol during its passage across the stratum corneum, that the chemical is concentrated in the intercellular domains and is excluded from the interior of the corneocytes[6]. Earlier studies[7], which investigated the passage of nicotinic acid esters across the skin, demonstrated that a transcellular route was physicochemically implausible and that the intercellular path was preferred. More recently, the link between the physical state of the intercellular lipid and the status of the barrier function has been established[8]. There appears to be no question that fluidisation of the lipid 'mortar' is directly correlated with facilitated stratum corneum transport. It is appropriate, therefore, to view the stratum corneum as an essentially lipid membrane. One should also point out that the lipids are organised into broad

lamellar sheets and that these structures can be visualised by careful microscopy[9]. A feature of the lipid compositon comprising the intercellular region is the high fraction of ceramides and the virtual absence of phospholipids. It is possible that some of the ceramides act as "rivets" to hold together adjacent lamellae[10].

Identification of the intercellular lipid domain as the transport path has a significant ramification from the standpoint of dermal exposure to toxic materials. Another key study in the determination of barrier properties involved solvent extraction of the stratum corneum[11]. When the skin is treated with volatile solvents, the barrier to chemical transport is reduced, presumably because of lipid extraction. Replacement of the lipid restores barrier function. This observation is highly relevant: many occupational exposures to toxic chemicals are mediated via the solvents in which the chemicals are dissolved. Hence, not only are these materials contacting the skin, they are being "delivered" to the surface in a vehicle which itself can compromise the barrier.

PHYSICOCHEMICAL DETERMINANTS OF SKIN PENETRATION

The sequential steps involved in percutaneous absorption are schematically illustrated in Figure 3.

The initial process is the partitioning of the chemical into the lipid environment of the stratum corneum. The ease of this event will be determined by both the inherent attraction of the chemical for the lipids and the nature of the 'vehicle' in which the chemical is delivered to the skin surface. If the chemical is in a solid state, e.g., a powder, then the particle size and polymorphism of the material may contribute to the kinetics of this first step in absorption. The material must be in solution before it can partition into the stratum corneum and hence the dissolution rate can contribute to the overall absorption[12]. For an agent that is a liquid or in solution, the partition coefficient ($K_{S/V}$) between the applied phase and the outer layers of the stratum corneum is important. Recent publications have indicated that the solubility parameter of the chemical may be a factor that should be considered in predicting $K_{S/V}$[13].

Having partitioned into the stratum corneum, the chemical must now diffuse through the intercellular lipids. The diffusional barrier of the stratum corneum is high and has been characterised by diffusion coefficients as low as 10^{-13} cm^2/s. However, these values are frequently based on a path-length of transport that ignores the tortuoisty of the intercellular route. As a result, most diffusion coefficients quoted for stratum corneum transport are under-estimates. Further, derivation of diffusion coefficients has usually involved in vitro measurement of a diffusional lag-time[14]. Unfortunately, experimental determination of this parameter is subject to considerable variability. The use of lag-times to calculate

diffusion coefficients, therefore, is, at best, approximate and, more typically, unreliable. There is general agreement that the diffusional resistance of the stratum corneum increases (i.e., the diffusion coefficient decreases) as the molecular size (or weight) of the penetrant increases. The dependence on molecular weight (MW), however, and whether there is a "cut-off" in MW beyond which skin transport does not occur, has not been resolved. It has been suggested that diffusion through the stratum corneum is analogous to transport through a polymer network and that the diffusion coefficient depends exponentially on molecular volume[15]. In the light of the previous statements concerning the nature of the diffusional route, transport is probably modelled better by consideration of a lipid array rather than a polymeric matrix. Therefore, the dependence of diffusion coefficient on molecular size would not be expected to be as severe as that given by an exponential relation. In line with values obtained for diffusion in liquids, it is anticipated that the diffusion coefficient will vary as a function of $(MW)^{-b}$, where $b = 0.3\text{-}0.6$[16]. In predictions of the transdermal delivery of drugs, a cube root dependency has been found to be a satisfactory approximation[17].

The next step in percutaneous penetration is the partitioning of the chemical from the lipid environment of the stratum corneum into the much more aqueous in nature viable epidermis. Chemicals which are extremely lipophilic will be severely rate-limited by this process due to their low solubility in the viable tissue and the resultant slow interfacial transfer kinetics at the lipid-aqueous boundary. The degree of penetrant lipophilicity which leads to this change in transport controlling step is not precisely defined. However, on the basis of simulations of the skin transport process[18] and from analyses of experimentally determined absorption data[19], chemicals with a log (octanol/water) partition coefficient (log P) greater than 3.0 may be expected to be at least partially rate-controlled by the stratum corneum to viable epidermis transfer step. The sensitivity of this component of

percutaneous penetration to the oil/water partition coefficient of the chemical is illustrated in the discussion of kinetic modelling below. As stated previously, an important ramification of this step being kinetically limiting is that a substantial reservoir of chemical can be established in the stratum corneum. For more water-soluble substances, of course, interfacial transport across the stratum corneum - viable tissue interface is a facile and rapid process that does not influence the overall absorption rate.

Having reached the viable epidermis, the penetrant is relatively free to diffuse deeper into the skin towards the cutaneous microcirculation in the upper dermis. The diffusion environment resembles an aqueous protein gel[20] and is characterised by diffusion coefficients of the order of 10^{-7}-10^{-6} cm^2/s. As these values are orders of magnitude greater than those representative of the stratum corneum, it follows that this diffusion step is unlikely to determine the absorption rate unless the outer layer of the skin is damaged.

Finally, the penetrant will encounter a blood vessel and gain entry to the systemic circulation. This will normally be a very efficient process and is one that has been characterised by a first-order rate constant[21] of approximately 10^{-3} s^{-1}. It is possible that certain chemicals may induce significant changes in cutaneous blood flow. Those which cause vasodilatation are unlikely to enhance the overall flux of penetrant in the body because of the general efficiency of the process in the unperturbed state. Vasoconstrictors, on the other hand, may impede their own clearance from the dermis and retard the rate of appearance of the chemical in the body. Deeper penetration into subcutaneous tissues (fat, muscle) may occur and lead to the formation of a long-lived depot[22]. The precise mechanism by which this occurs is not fully understood. However, simple calculations of transfer rates

suggest that passive diffusion alone cannot be responsible for localisation of topically applied agents in the deeper tissues of the skin.

At this point, it is possible to identify certain physicochemical parameters which can give an indication of a molecule's ability to penetrate skin. From the discussion above, it is clear that the relative lipophilicity of the penetrant is a key determinant. Ionised materials are poor penetrants unless they are able to form ion pairs. It can also be shown that skin penetration is inversely related to permeant melting point (MP). For example, in Figure 4, the steady state flux of an unrelated group of compounds across excised human skin in vitro is plotted as a function of penetrant MP[23]; a linear relationship is seen. Not unexpectedly, for this same series of compounds, flux increases proportionately with oil/water partition coefficient. However, as indicated above, penetration does not continue to rise with ever-increasing partition coefficient. At some point, the lipophilicity becomes high enough that transfer out of the stratum corneum is rate-limiting. Hence, flux as a function of partition coefficient will plateau or, if the range of penetrants is sufficiently large, show a parabolic form[24]. The maximum in the parabola occurs at a value of log P of approximately 2. The generality of this observation, though, is not, at this time, fully established. In conclusion, the following basic rules can be deduced:-

[1] Chemicals with a log P between 1 and 2 will be well absorbed.

[2] Poorly soluble substances are not well absorbed.

[3] The lower the melting point of the agent, the better its absorption.

[4] Molecules which can hydrogen bond, diffuse more slowly through the skin.

STRUCTURE-ACTIVITY RELATIONSHIPS IN PERCUTANEOUS PENETRATION

There have been, on the whole, relatively few quantitative attempts to relate percutaneous absorption to the structure and physicochemical properties of the permeant. To do so requires that systematic evaluation of skin penetration be performed on several sets of homologous or analogous chemicals. These experiments are time-consuming and do not necessarily address compounds of immediate significance to a particular therapeutic or toxicologic situation. Nevertheless, there is no question that, ultimately, these studies will form the cornerstone on which valid predictions of dermal exposure can be made. It is important, therefore, that this type of approach be pursued and encouraged. It is equally important that the experiments be conducted in as meaningful a fashion as possible; that is to say: if a model system (animal, in vitro, etc.) is to be used, then some attempt to relate the data obtained to results in humans must be made. In this way, not only may a useful structure-activity relationship be derived, but one may also gain insight as to the degree of extrapolation necessary to convert "model system" information into a risk assessment in man.

With respect to structure-transport studies in skin absorption, the following specific chemical classes have been investigated: n-alkanols[25,26], phenols[27,28], phenylboronic acids[29], steroids[30,31], nicotinic acid esters[28,32], alkanoic acids[33],polynuclear aromatics[34], and non-steroidal anti-inflammatory drugs[35].

n-Alkanols: The steady-state permeability from aqueous solution, of the homologous series of n-alcohols through excised human epidermis in vitro has been measured[25]. The results, plotted as permeability coefficient (Kp) against log P, are shown in Figure 5. Also shown on this graph are the corresponding data for the

same molecules permeating full-thickness hairless mouse skin[26]. The results for human skin are described by the equation[36] :

$$\log Kp = 0.54 \log P - 2.88 \quad (1)$$

with a correlation coefficient of 0.98. A slightly improved correlation is obtained if the stratum corneum - water partition coefficient is used[36]. The hairless mouse data fit the equation:

$$\log Kp = 0.50 \log P - 2.52 \quad (2)$$

with, again, r = 0.98. It follows that, in this case, a result from the animal model would be quite predictive of human skin absorption. Further discussion of animal to man extrapolation is presented below. One may also conclude from these results that, within this series of compounds, a log-linear relationship dependent upon partition coefficient alone is perfectly adequate to assess Kp. As will become apparent, however, it is not necessarily true that the equations above can be used to predict the Kp of a chemical which is not an alcohol. A final point is that the results for transport across human epidermis hint (and are frequently used to demonstrate) that a maximum Kp value has been reached. That is, with nonanol (the most lipophilic alcohol considered), the control of permeation has now transferred to slow transfer out of the stratum corneum into the viable tissue.

Phenols: The permeability of a wide range of phenol derivatives across human epidermis was measured by Roberts et al.[27] The results, plotted as a function of log P, are reproduced in Figure 6. In this case, significant non-linearity in the data is apparent and a parabolic dependence of log Kp on log P may be determined:

$$\log Kp = -0.36(\log P)^2 + 2.39 \log P - 5.2 \quad (3)$$

The correlation coefficient is 0.94.

In an attempt to develop simple models for measuring percutaneous penetration, the permeability characteristics of organic liquid membranes in a rotating diffusion

cell have been considered[28]. The lipid phases employed were isopropyl myristate (IPM) and tetradecane (TD) and were chosen to simulate the apolar nature of the intercellular domains of the stratum corneum. Again, a diverse range of phenols was considered (although there was not complete coincidence with the Roberts' compounds[27]) and this allowed an extensive span of lipophilicity to be evaluated. The permeabilities of the phenols through the two lipid models are presented as a function of log P in Figure 7. Quadratic fits to the results give the following equations:

$$\log Kp\ [IPM] = -0.48(\log P)^2 + 2.32 \log P - 2.2 \qquad [r = 0.96] \qquad (4)$$

$$\log Kp\ [TD] = -0.40(\log P)^2 + 2.55 \log P - 4.0 \qquad [r = 0.96] \qquad (5)$$

As can be seen from Figures 6 and 7, the organic liquid models are more permeable than human epidermis. Nevertheless, the magnitude of the difference is quite constant and predictable (see section below on Miscellaneous Compounds). The functional dependence of log Kp on log P is very similar for the 'real' and 'model' systems (as can be deduced by the similarity of the coefficients pre-multiplying the log P and $(\log P)^2$ terms in eqns. (3), (4) and (5)). Once again, therefore, a reasonable prediction of the Kp of a phenol through human skin may be obtained from an extrapolation based on log P or from a model in vitro experiment.

It is of interest to ask, at this point, the question: "can phenol permeability be predicted from the alkanol structure-transport relationship?" In Figure 8, the phenol permeability coefficients are compared to the dependency predicted by the alcohol results (eqn. (1)). It can be seen that the alkanol data, in general, overestimate phenol penetration and that the discrepancy is most marked in the range $\log P < 2.0$. It follows that the answer to the above question depends on the nature of the penetrant and that this situation is clearly not optimal.

Phenylboronic acids: The percutaneous absorption of meta- and para-substituted derivatives showed linear relationships with log P and with the log (benzene/water) partition coefficient[29]. However, because the measurement of skin penetration differed from a simple Kp determination, it is not possible to compare the structure-activity equations for this set of compounds with those discussed above.

Steroids: The steady-state permeability of 14 steroids was measured across human epidermis in vitro[30]. The Kp values are plotted as a function of four organic/aqueous partition coefficients in Figure 9. Linear regression parameters on the results are presented in Table I. The slopes of the lines are quite consistent and the values of the intercepts shift in the direction expected as the solvent dielectric constant increases. Scheuplein et al.[30] also measured stratum corneum - water partition coefficients (K_{SC}) in this study. Linear regression of the permeability data with these values gives[36]:

$$\log Kp = 2.63 \log K_{SC} - 7.54 \qquad (6)$$

with r = 0.93. Clearly, there is discrepancy between this relationship and those given in Table I for the simple organic solvents. Although the exact reason for this difference cannot be identified, two possibilities may be suggested. First, the technique used to measure K_{SC} requires that the tissue be removed from the remainder of the epidermis; it is not known whether the isolation procedure alters, in any way, the nature of the stratum corneum. It is also unclear how to separate partitioning from binding. Secondly, as the intercellular lipids provide the permeation pathway, it is appropriate that a volume correction be applied when calculating K_{SC}.

In a later study, the steady-state flux of hydrocortisone and of a number of its 21-esters (acetate through heptanoate) was measured across hairless mouse skin in vitro[31]. The Kp values determined are plotted as a function of the chemicals'

ether/water partition coefficient ($K_{e/w}$) in Figure 10. The linear relationship (r = 0.95) is described by:

$$\log Kp = 0.56 \log K_{e/w} - 3.39 \quad (7)$$

In this case, it would not be useful to extrapolate from the mouse data to man (see Table I), a conclusion in contrast to the situation for alkanols and, to a certain extent, for phenols. This observation reflects the fact that an animal model, which is applicable to various classes of penetrant, has not been identified for human skin permeation prediction.

Nicotinic acid esters: These compounds are potent vasodilators when applied topically to the skin. Their percutaneous penetration in man has been quantified, therefore, by the time to onset of erythema (skin reddening) following application. In an initial set of experiments using several nicotinates[32], the threshold concentrations (C) necessary to induce visible erythema were determined. The reciprocals of these concentrations are plotted as a function of nicotinate ether/water partition coefficient ($K_{e/w}$) in Figure 11. A classic parabolic relationship is observed. The form of this dependency can be explained on the basis of a change in the rate-controlling step of penetration as discussed above (i.e., a switch from stratum corneum diffusion to slow partitioning at the stratum corneum - viable tissue interface). This structure-activity relationship must reflect transport rather than pharmacological effect since intradermal injection of the different nicotinates has shown that they are equipotent[32].

These results may be compared to the permeabilities (Kp) of a similar range of nicotinates across a tetradecane model membrane[28]. In Figure 11, the two sets of data are juxtaposed and can be seen to be remarkably similar. This further supports the hypothesis proposed above ,in which, physical chemistry rather than

pharmacology controls the structure-activity behaviour observed. Quadratic fits to the data give the following:

$$\log[1/C(mM)] = -0.17 + 0.60 \log K_{e/w} - 0.30 (\log K_{e/w})^2 \quad (8)$$

$$\log[Kp(cm/hr)] = -0.11 + 0.69 \log K_t - 0.27 (\log K_t)^2 \quad (9)$$

(where K_t is the tetradecane/water partition coefficient) with correlation coefficients of 0.90 and 0.99, respectively. Good coincidence in the coefficients is apparent. This agreement is particularly notable (and, potentially, valuable) because of the different nature of the experimental procedures employed. In other words, the results suggest that a measurement of chemical permeation through a model membrane system may be predictive of an in vivo, non-steady state, short-term exposure situation.

Alkanoic acids: The steady-state permeability coefficients of a number of n-alkanoic acids have been measured across excised porcine skin[33]. In one set of experiments, the acids were delivered in their pure state and the results are expressed, together with the corresponding melting points, in Figure 12 for the n = 4-8 homologues. As previously noted, there is an inverse relationship between Kp and melting point.

Polynuclear aromatics: Recently, Roy et al.[34] have determined the in vitro percutaneous penetration of several compounds chosen to represent those typically found in refinery streams. The experimental procedure involved the use of excised rat skin (dermatomed to a thickness of 350 μm) and of a receptor phase, which contained a small (6%) concentration of nonionic surfactant to ensure adequate solubility of the lipophilic penetrants. The data (expressed as % of applied dose absorbed within 96 hours of exposure) were analysed by multivariate regression. The equation derived ,which best characterised the data set, contained four independent variables: molecular surface area, molar refractivity, molecular

moment of inertia, and molecular symmetry. The coincidence between observed and predicted absorption is shown in Figure 13. With the exception of two outliers, there is good agreement between experiment and theory. The authors concluded from their interpretation of the results that skin permeation was not a particularly selective process and that the molecular descriptors identified would impact primarily on dissolution and diffusion phenomena. However, an alternative presentation of the results also implicates (as one might expect from the preceeding discussion) partitioning as a key factor in the determination of percutaneous penetration. In Figure 14, skin permeation, again expressed as % of applied dose absorbed, is plotted as a function of log P. The data for the 3-ring polynuclear aromatics (PNA) are plotted separately from those for the 4- and 5-ring compounds. It can be seen that the two groups lie on separate lines and that, in combination, the effect is to produce an apparent parabolic structure-activity relationship. In constructing Figure 14, the data point for carbazole (a 3-ring PNA), for which absorption was 90% and log P = 3.51, has been ignored. Once again, therefore, there would appear to be evidence for a change in the rate-determining step of skin penetration as the lipophilicity of the permeant becomes large. For the PNAs, however, the maximum absorption occurs at a higher log P than that seen for the other molecular groups considered above. The reason for this difference is not understood. It is possible that the methodology employed may be a contributory factor. For example, rat skin is much more permeable than human skin and is less discriminatory, as a result, to permeant properties. The cumulative dose absorbed at 96 hours is also an imprecise parameter to characterise penetration because it contains essentially no kinetic information. It is difficult, therefore, to extrapolate these results to man Nevertheless, the pattern of behaviour observed is consistent with that demonstrated by other chemical classes discussed in this Chapter and there would appear to be no reason to predict anomalous structure-skin absorption relationships for the PNAs.

Non-steroidal anti-inflammatory drugs (NSAIDs): Yano et al.[35] measured the skin permeability of 18 NSAIDs in vivo in humans. The chemicals tested included a set of eight salicylate derivatives. Percutaneous absorption was quantified as the % of the applied dose which was not recoverable by surface washing following a 4-hour contact period. The chemicals (0.5 mg) were administered in 10 µl of either acetone or methanol. The results are plotted in Figure 15 as a function of the chemicals' log P values. The set of salicylates is highlighted in the figure but is seen to coincide completely with the general pattern of the (once again) parabolic structure-activity relation:

$$\log[\%\ \text{dose abs.}] = 0.42 + 1.14 \log P - 0.23(\log P)^2 \qquad (10)$$

with r=0.96. The coefficients describing this set of experiments may be compared favourably with those characterising the nicotinic acid ester data described above (eqns. (8) and (9)). Although the coincidence may reflect the similarity in structure between the two sets of compounds, the agreement is nevertheless remarkable given the disparate methodology employed in the three investigations.

Miscellaneous: The studies considered so far have focussed upon chemical permeants of similar structure. This may not be typical of the occupational exposure situation in which contact with diverse materials may occur. An important question is whether absorption as a function of physicochemical properties can be predicted for a wide range of compounds? Quantitative and extensive information, which can be used to address this issue, is lacking. However, there have been two recent efforts[37,38] to measure percutaneous absorption of unrelated chemicals and to correlate the behaviour seen with basic chemical properties.

In these experiments, the steady-state fluxes of barbitone, phenobarbitone, butobarbitone, amylobarbitone, hydrocortisone, nicotine, salicylic acid, and isoquinoline were measured across excised human skin in vitro and across four lipid impregnated model membranes in the rotating diffusion cell. It was found that isopropyl myristate (IPM) and tetradecane again provided model membranes, the transport properties of which followed classical behaviour: Kp values increasing with the corresponding lipid/water partition coefficient (see Figure 16). For IPM and tetradecane, the log Kp versus log K data lie on a common line:

$\log Kp = 0.71 \log K - 0.03$ [r=0.97] (11)

The span of log K values is smaller than those considered earlier and this explains why a parabolic dependence is not seen with these data. Also shown in Figure 16 are the Kp results for human skin transport plotted against the log K values for tetradecane/water. The resulting correlation:

$\log Kp = 0.66 \log K - 2.02$ [r=0.89] (12)

is strikingly parallel to the model membrane results and again implies the usefulness of, in particular, tetradecane as a lipoidal representation of stratum corneum. As observed with the phenols and, as expected, the skin is more resistant to permeation than the simple organic liquid membrane. There would appear to be between a 10 and 100-fold difference in permeability coefficient. It is conceivable that this discrepancy results from the fact that stratum corneum transport involves permeation via the intercellular (lipid-filled) channels and that only a fraction of the skin surface can act, therefore, as "productive" area. The lipids in stratum corneum are known to occupy 5-15% of the total membrane volume[39]; given that, for the tetradecane system, essentially all of the membrane is 'available' for solute transport, then the magnitude of the difference between skin and model permeabilities is plausible.

CALCULATIONS OF BODY EXPOSURE FROM SKIN ABSORPTION DATA

There have been a number of investigations designed to evaluate percutaneous absorption in man[40]. The majority of these studies have involved topical application of the chemical in question to a small area on the ventral forearm. While these data are of considerable value, it is useful to know how (or whether) one can extrapolate the findings to a 'real' exposure situation in an occupational or environmental setting. To do so requires two key pieces of information: First, and relatively easily, the area of contact between the chemical and skin must be known. If one assumes that the amount of chemical absorbed into the body is a linear function of contact area (an assumption for which no contrary evidence exists), then a simple correction can be made. Second, and more difficult, the relative permeability of the forearm compared to other anatomic sites must be understood. The latter information is available for only three cases, namely for hydrocortisone[41] and for the pesticides, malathion and parathion[42]. The results from these studies indicate that the skin of the genitalia is, on average, 25 times more permeable than that of the forearm; that of the trunk is 2.5 times more permeable, while the face and head is approximately 5-fold more permeable. Absorption across leg skin is similar to that on the forearm.

Given this data, it is possible to calculate relative body exposures on the basis on forearm data alone or on the basis of differential penetration at specific skin sites[43]. For example, it can be shown that total body exposure based on forearm absorption data will underestimate actual exposure by a factor of 2. One can also demonstrate that an exposure limited to the hands and face could result in 3 to 4-fold higher absorption compared to that estimated from the single value of forearm permeability.

While these calculations are usefully illustrative, it must be emphasised that they are based on a small amount of information from only three compounds. Therefore, before one can use the approach predictively for compounds, which are not closely similar to hydrocortisone, malathion and parathion, it will be necessary to assess skin penetration, as a function of anatomic position, for a range of chemicals of diverse physicochemical characteristics.

MATHEMATICAL MODELLING OF SKIN PENETRATION

Percutaneous absorption is complex and involves many variables. To model this process mathematically, therefore, is a substantial task. Inevitably, one runs the risk either of formulating a model, which is simplistic and incapable of subtle prediction, or of producing a simulation too complex for testing in any reasonable experimental system. Hence, there is a need to tread a delicate path between these extremes if progress is to be made. An ideal model will be sufficiently flexible to incorporate the important variables of skin penetration and will be both sensitive to the biology and condition of the skin, and to the physicochemical characteristics of the permeant. The schematic shown in Figure 17 includes the key steps of percutaneous absorption and a number of additional processes which may impact upon the overall kinetics and extent of penetration. Clearly, a mathematical model which completely described the scheme as shown would be extremely complicated and could only be handled by an efficient computer. To explore the possible utility of a model, therefore, requires that the problem be broken down into more manageable pieces so that the relative significance of the constituent parts can be rationally assessed.

In the simplest case, the problem is treated using Fick's laws of diffusion and an estimation of total body burden following a dermal exposure is found. When skin is contacted with a chemical, the amount penetrating into the body as a function of time is shown in Figure 18. Two situations are illustrated:- in the infinite dose case, a constant driving force is maintained on the skin surface and, following a lag-time (t_L), the amount of chemical crossing the skin increases linearly with time (the so-called steady state situation). In the finite dose case, the skin is exposed to a limited amount of chemical. Initially, the amount reaching the body increases with time

but then slows down as the chemical on the surface is depleted. There may be a region of the finite dose case which is coincident with the steady-state behaviour following infinite dosing. However, it is not easy to determine where the two situations may overlap. Most in vitro evaluations of skin penetration have used an experimental design in which the infinite dose situation applies (see above). At steady-state, the flux (J) of chemical across the skin is given by Fick's 1st law of diffusion:

$$J = A.Kp.\Delta C \qquad (13)$$

where A is the area of exposed skin, Kp is the permeability coefficient of the chemical across the skin and ΔC is the difference ($C_d - C_r$) in chemical concentration between the donor solution on the skin surface and the receptor solution beneath the skin. In designing an infinite dose experiment, two criteria should be met: (i) C_d should be sufficiently large that significant depletion of chemical does not occur, and (ii) C_r should not rise above 1/10th of the saturation solubility. Under these conditions

$$Kp = J/A.C_d \qquad (14)$$

With a knowledge of Kp, an estimation of body burden following a dermal exposure can be made. If an area A is contacted by chemical at concentration C for a time t, then the amount of chemical (M) which will enter the body is given by

$$M = A.Kp.C.t \qquad (15)$$

Depending upon the anatomic site of contact, eqn.(15) may need to be modified to take into account the site dependency of penetration as discussed above.

Some caveats to this approach should be noted. The infinite dose technique often produces complete hydration of the skin tissue. It is well-documented that hydration of skin lowers the barrier to chemical penetration. Secondly, most occupational or environmental exposures do not involve an infinite dose of chemical. Typically, contact times will be relatively short and, following exposure, the chemical will be washed from the skin surface. It follows that a prediction of

body burden by eqn.(15) will overestimate the true exposure level. This latter contention is appropriate, however, only when the skin is intact. If the barrier is broken, then much freer passage is possible[44], particularly for polar, water-soluble chemicals. If the skin is diseased, then there is also the potential for altered barrier function. The extent to which different skin diseases impact upon absorption, though, is not well-understood and cannot be rationally modelled at this time. The straightforward approach detailed above does not address the complex sequelae of diffusion and partitioning illustrated in Figure 17. To do so requires that non-steady state solutions to Fick's 2nd law of diffusion, with appropriate boundary conditions, be obtained. This sophistication has been reported and relationships applicable to short contact exposures have been derived[45-47]. The amount of chemical penetrating the skin can be shown to depend upon basic physicochemical parameters (diffusion coefficients, partition coefficients, transport path lengths, etc.) and the effect of changes in these parameters on the penetration kinetics can be explored. However, experimental determination of these key descriptors is difficult and simple testing of the model predictions requires significant approximations and assumptions. Furthermore, this more rigorous approach does not include other important processes. For example, a volatile chemical will be subject to concomitant evaporation and absorption; reducing thereby the total bioavailability. The skin is a metabolically active organ and activation, or detoxification, of absorbing molecules is possible[48]. Little is known of the magnitudes of the possible effects due to these "loss" processes. Again, mathematical modelling has been carried out[49,50] but validation of the conclusions deduced awaits appropriate experimentation.

Another approach, which is also based on the physicochemical properties of the penetrant, can be adopted to model skin absorption . In this case, the diffusion and

partitioning are approximated by a series of first order rate constants[51,52] as depicted in Figure 19:

k_1 describes diffusion through the stratum corneum. For intact skin, this rate constant will be relatively small and will depend upon the molecular size of the penetrant. This dependency has been suggested to follow a simple cube-root function[51] although a more severe exponential function has been recently proposed[15].

k_2 describes chemical permeation through the viable epidermis. The rate constant is again size-dependent but has a magnitude characteristic of diffusion through an aqueous protein gel[20]. The value of k_2 is therefore greater than that of k_1.

k_3 measures the relative affinity of the chemical for the stratum corneum compared to the more aqueous in nature viable epidermis. The ratio k_3/k_2 may be regarded, therefore, as an effective 'stratum corneum-viable epidermis' partition coefficient of the chemical. The larger the value of k_3, the higher the affinity of the chemical for the stratum corneum and the slower the transfer of molecules from stratum corneum to viable tissue. It has been shown that k_3 may be determined empirically from the octanol/water partition coefficient (determined at pH 7.4) of the chemical[51]: $k_3/k_2 = P/5$.

k_4 characterises the elimination half-life ($t_{1/2}$) of the chemical:

$k_4 = \ln 2/t_{1/2}$.

The model can be used to predict the percutaneous absorption of a diverse range of chemicals on the basis of their molecular weights and octanol/water partition coefficients. Reasonably good agreement between the model and in vivo human skin penetration data has been found[51]. The correlation is adequate for the prediction of both plasma concentration[53] and urinary excretion rate data[51]. As an example, the coincidence between experimental data and model prediction for the insect repellant diethyl-m-toluamide is shown in Figure 20.

Other advantages of the kinetic model are apparent. In addition to the fact that it is a non-steady state simulation, it can be adapted and expanded to take into account surface evaporation of penetrant[54], cutaneous metabolism[55], and different chemical input functions (zero-order, first-order, etc.)[18]. Furthermore, the approach offers, at least, the potential to extrapolate data acquired in animals to man. It is anticipated that the value of k_1 will be the most species-dependent parameter since it will be a function of stratum corneum thickness, the number of cell layers and the diffusional path length. It is unlikely that k_2 is significantly different between species and the partitioning process between lipophilic stratum corneum and hydrophilic viable tissue (common features of all animal models and man) should remain quite constant. Hence, if a scale of relative k_1 values for different species could be developed, then the absorption process in man might be deduced from an animal experiment. Of course, the value of k_4 may also depend upon the animal used but this parameter can be found with relative ease by experiment. Unfortunately, the ability to extrapolate from one species to another does not presently exist because of the paucity of comparative data across animals for a wide range of compounds. Although there have been a few studies[56-58] in which the penetration of a number of chemicals across different animal skins has been measured, the results are insufficient to formulate simple rules for human absorption prediction from animal data. Qualitatively, however, it is possible to draw the following conclusions about the predictability of absorption data from various animal models[40]:

1. Small "hairy" animals (e.g. rats, rabbits) usually yield penetration values much higher than those seen in man.

2. The rhesus monkey has been shown to be a valuable in vivo model for human percutaneous absorption.

3. Newer models, such as the weanling (or mini or micro-) pig and the human skin grafted rat, offer alternatives of considerable promise.

CONCLUSIONS

At present, our understanding of the skin permeation process has reached a reasonable level. General rules governing the penetration of chemicals have been established and the impact of structural and/or physical changes is being intensively studied. However, while correct qualitative statements about percutaneous absorption can be made, there is much less certainty when quantitative conclusions are required. Obviously, in the area of risk assessment and dermal exposure prediction, this is a serious drawback. In this chapter, we have attempted to highlight those areas in which progress has been made and those in which considerable further work needs to be done. The discussion on quantitative structure-activity relationships indicates a fruitful path for additional study. The power of this type of approach has been demonstrated in other fields of biological transport and pharmacology - one is optimistic that skin penetration will also prove amenable to this analysis. On the other hand, comprehension of the role of skin metabolism, for example, and the optimal use of animal model experiments remain problems of substance. There is no question, in our opinion, that the skin is a complex membrane, the transport properties of which deserve greater attention and considerable respect. Until these properties are unravelled, prediction of dermal exposure to toxic chemicals will be, at best, qualitative and, in less favourable circumstances, wrong.

ACKNOWLEDGMENTS

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Figure Legends

1. A schematic representation of the structure of the skin.

2. Potential pathways of drug penetration through the skin.

3. The sequential physicochemical steps involved in drug transfer in percutaneous absorption.

4. The relationship between the steady state flux for a number of compounds across excised full thickness skin and their melting points. The compounds are:- ATR, atropine; CHL, chlorpheniramine; DEC, diethylcarbamazine; DIG, digitoxin; EPH, ephedrine; EST; œstradiol; FEN, fentanyl; GTN, glyceryl trinitrate; OUA, ouabain; SCOP, scopolamine.

5. The relationship between permeability and octanol-water partition coefficient or a series of n-alkanols. The similarity between human and hairless mouse data is demonstrated.

6. The relationship between the permeability of human skin and the octanol-water partition coefficient for a series of phenols.

7. The relationship between the resistance to transport across model skin lipid membranes and the octanol-water partition coefficient of a series of phenols. The two model membranes are:- ▲ tetradecane; ■ isopropyl myristate.

8. The variation of the permeability of human skin with log P for a series of phenols. The linear relationship shows the predicted values based on the alcohol data described by equation 1.

9. The relationship between the permeability of human skin and various solvent-water partition coefficients for a series of steroids. The solvents are:- ♦, hexadecane; □, amyl caproate; ▲, ether; ■, octanol. The linear relationships shown are given in Table I.

10. The relationship between the permeability of hairless mouse skin and the ether-water partition coefficient for a series of 21-esters of hydrocortisone.

11. A parabolic relationship between the reciprocal threshold concentration (c) required to induce erythema and the ether-water partition coefficient for a series of nicotinates (□). Also shown is a similar relationship for the permeabilities across a tetradecane model membrane (■), and the tetradecane-water partition coefficient. [the ether-water partition coefficient for octyl nicotinate has been estimated by extrapolation of the values for the lower homologues. The value quoted in reference 32 (log K =1.49) seems implausible].

12. The relationship between permeability (♦) of porcine skin and carbon number for a series of alkanoic acids. The inverse relationship between melting point (□) and permeability is also demonstrated.

13. The percentage dose absorbed through rat skin within 96 hours has been predicted for a series of polynuclear aromatics. The prediction includes four independent variables, molecular surface area, molar refractivity,

molecular moment of inertia, and molecular symmetry (reference 34). Good correlation with experimental data is shown.

14. The relationship between percentage dose absorbed through rat skin within 96 hours and log P for a series of polynuclear aromatic compounds. The substances have been separated into 3-ring compounds (□) and 4 and 5-ring aromatics (■).

15. The percutaneous absorption of a series of non steroidal anti-inflammatory agents, including salicylates (■), plotted as a function of log P. All the data presented in reference 35 has been used with the exception of naproxen which was clearly an outlier. The values given for naproxen were:- % absorbed; 1.3; log P, 3.18.

16. The relationship between permeability and partition coefficient for a series of miscellaneous compounds. The permeability has been measured across excised human skin (*), and membranes impregnated with isopropyl myristate (□) and tetradecane (■).

17. A typical profile showing the amount of substance penetrating the skin as a function of time for infinite and finite dose application.

18. A kinetic description of dermal absorption using first order rate constants.

19. The theoretical and experimental (■) urinary excretion data for diethyl-m-toluamide. The theoretical profile has been generated using the kinetic model and the physicochemical properties of the permeant.

Table I. The relationships between observed steroid permeabilities and their partition coefficients between various solvents and water. Linear regression analysis was applied to the data presented in Figure 9 using the equation log Kp = αlog K(solvent) -β. R is the correlation coefficient.

	α	β	R
solvent			
octanol	1.04	6.51	0.85
hexadecane	0.81	3.55	0.86
amyl caproate	1.26	5.21	0.93
ether	0.89	5.17	0.96

Figure 1.

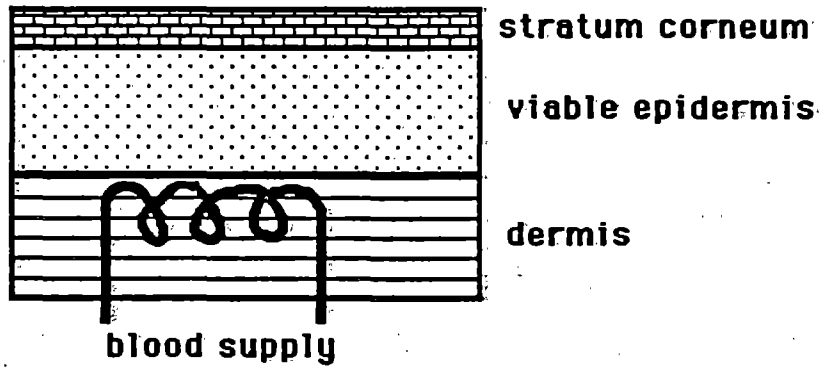
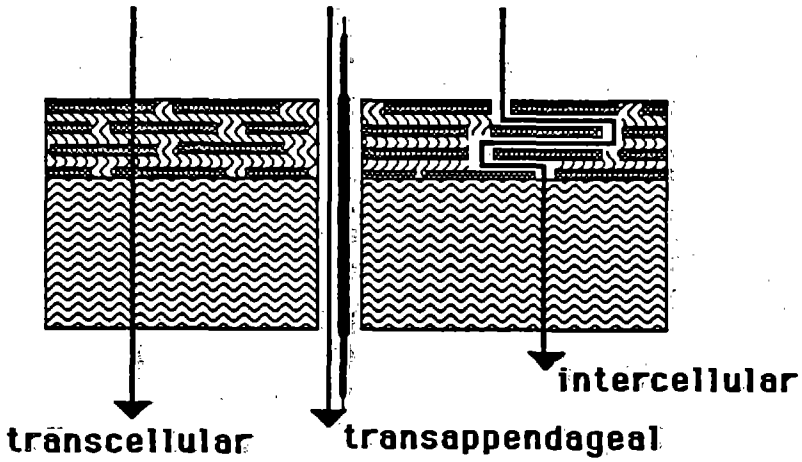


Figure 2.



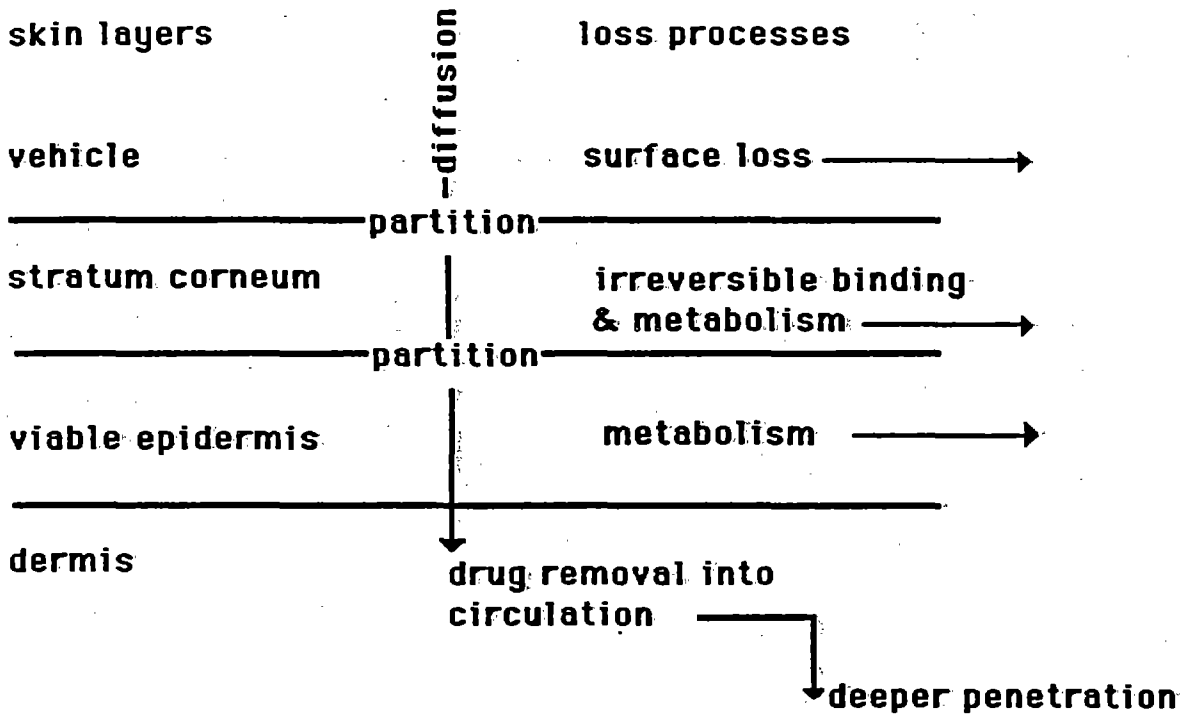
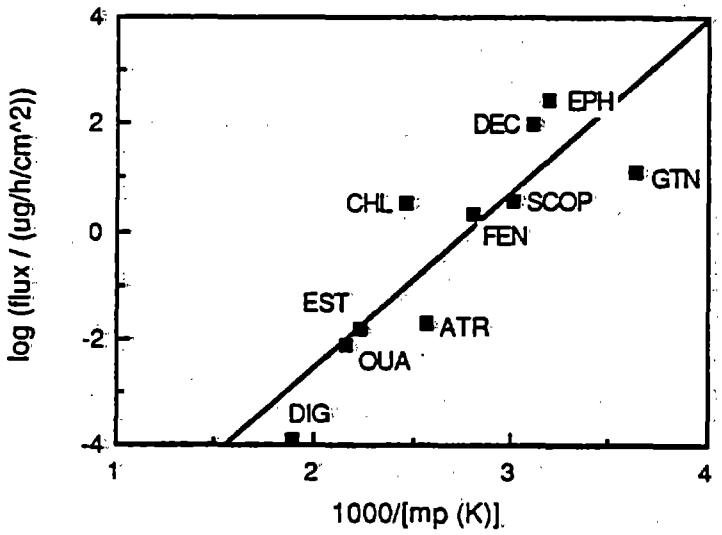

skin layers
loss processes
diffusion
vehicle
surface loss
partition
stratum corneum
irreversible binding
& metabolism
partition
viable epidermis
metabolism
dermis
drug removal into
circulation
deeper penetration

Figure 3.

Figure 4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1000/[mp (K)]
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2
0
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-4
1
2
3
4
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DEC
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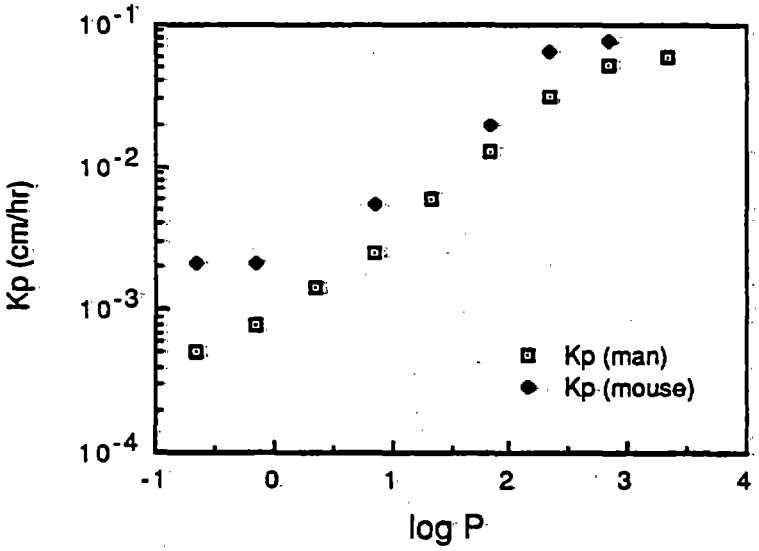
CHL
SCOP
FEN
EST
ATR
OUA
DIG

Figure 5



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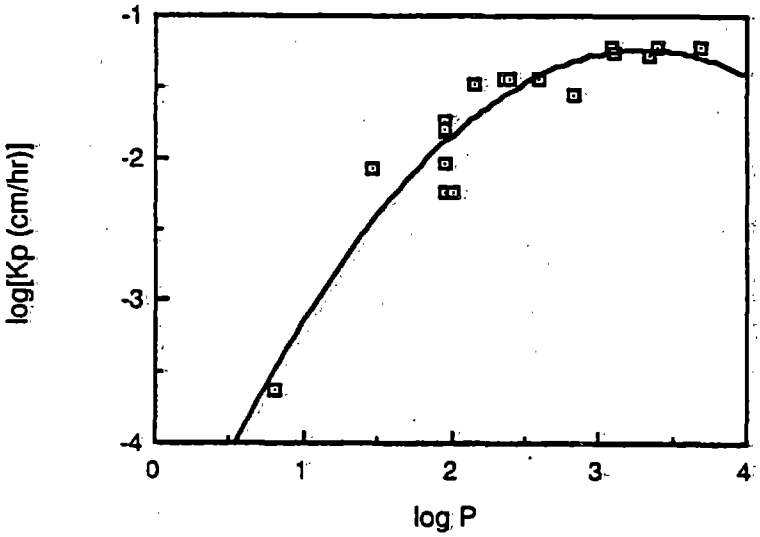
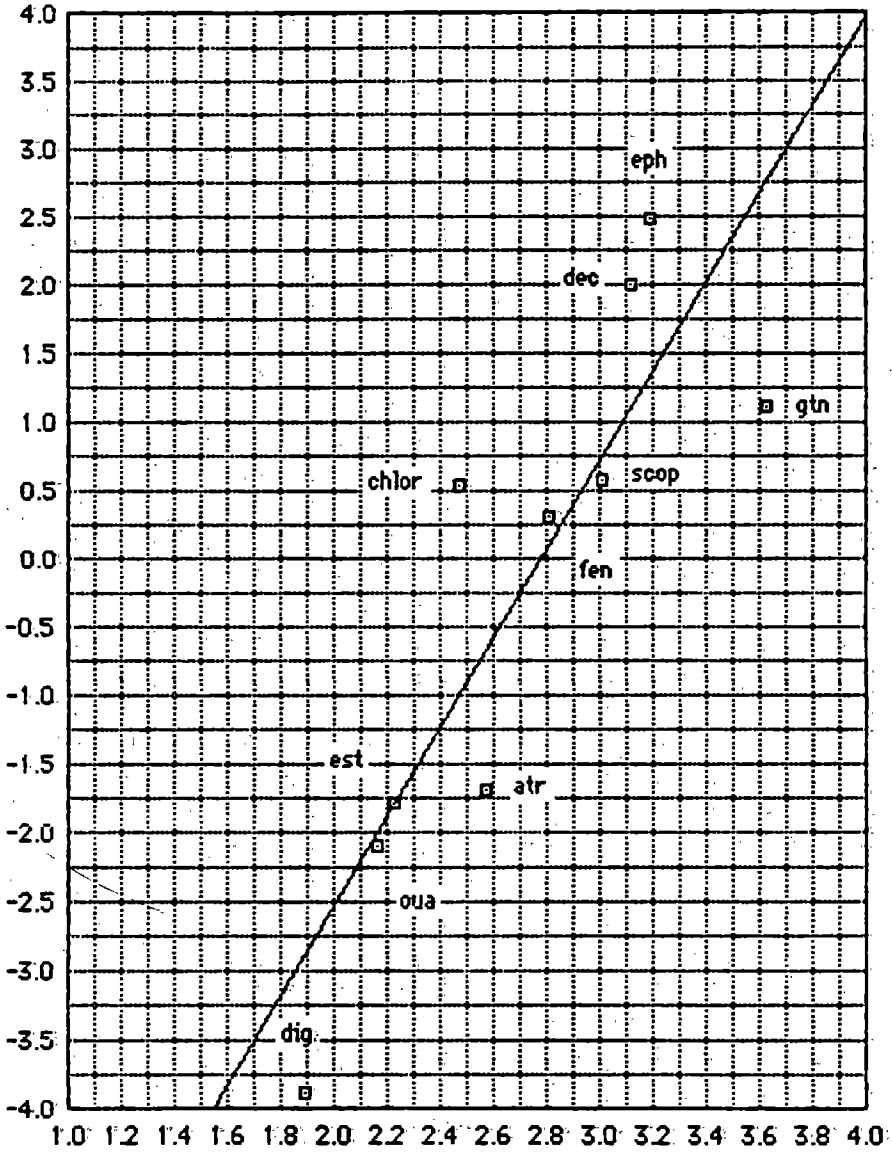


Figure 7


log (flux / (ug/h/cm**2))
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3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0
1.0 1.2 1.4 1.6 1.8 2.0 2.2 2.4 2.6 2.8 3.0 3.2 3.4 3.6 3.8 4.0
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chlor
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est
oua
dig

Figure 8

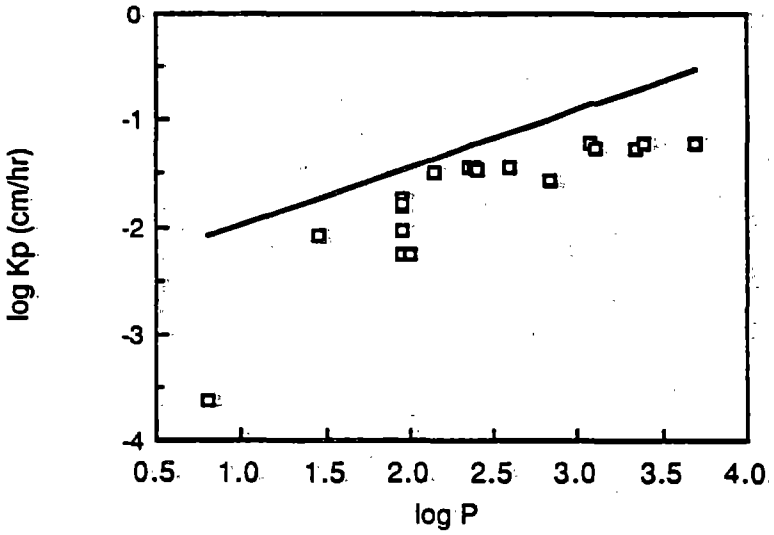


Figure 9

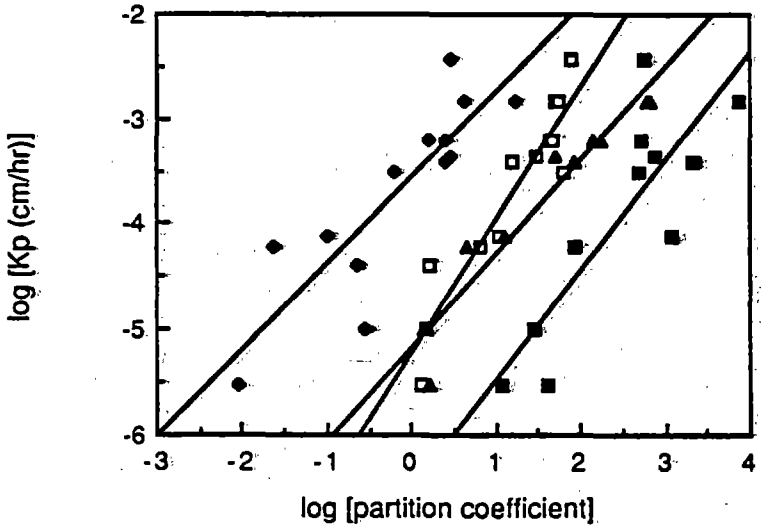


Figure 10

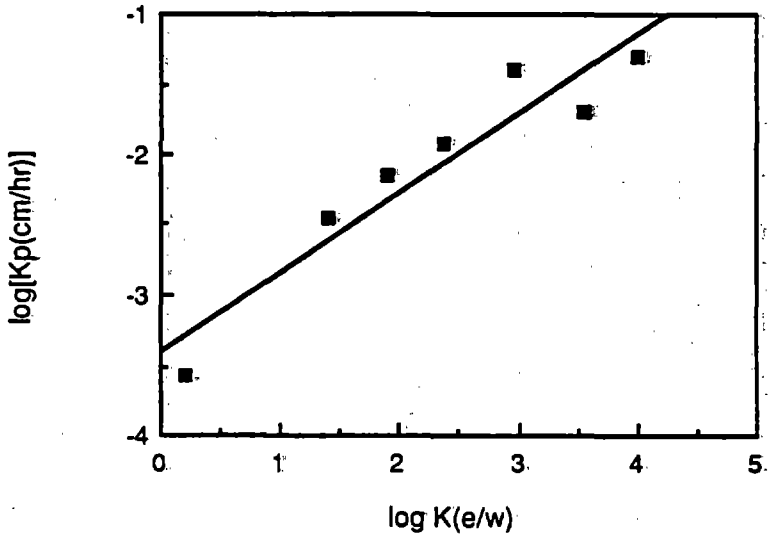


Figure 11

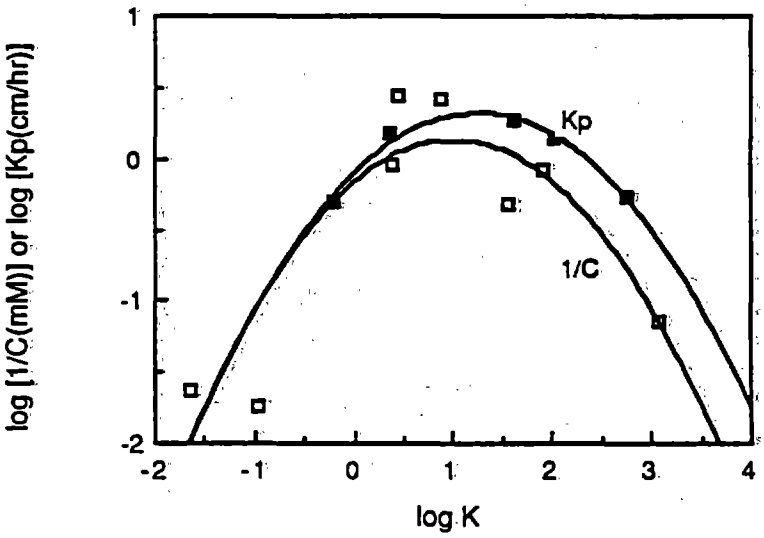


Figure 12

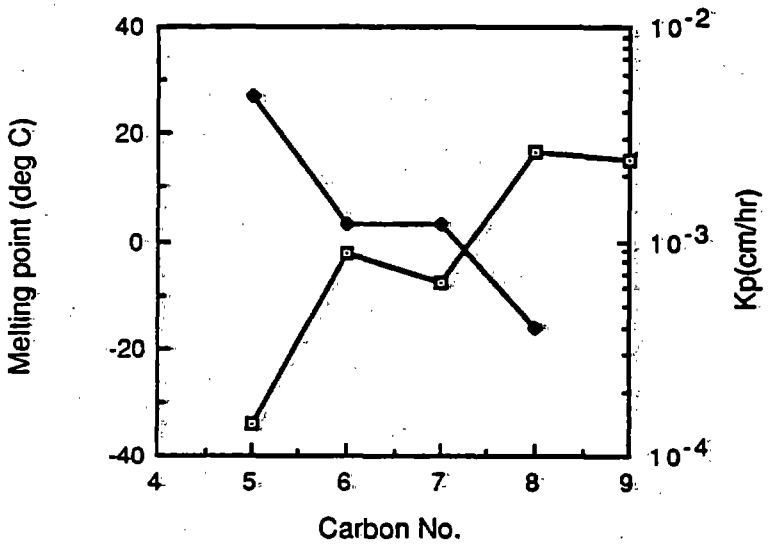
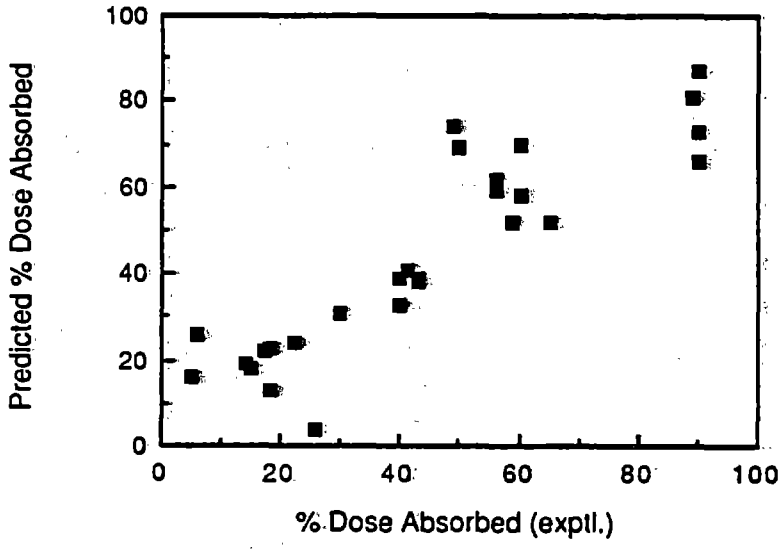

40
20
0
-20
-40
4
5
6
7
8
9
Carbon No.
Melting point (deg C)
10^{-2}
10^{-3}
10^{-4}
Kp(cm/hr)

Figure 13


Predicted % Dose Absorbed
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60
40
20
0
0
20
40
60
80
100
% Dose Absorbed (exptl.)

Figure 14

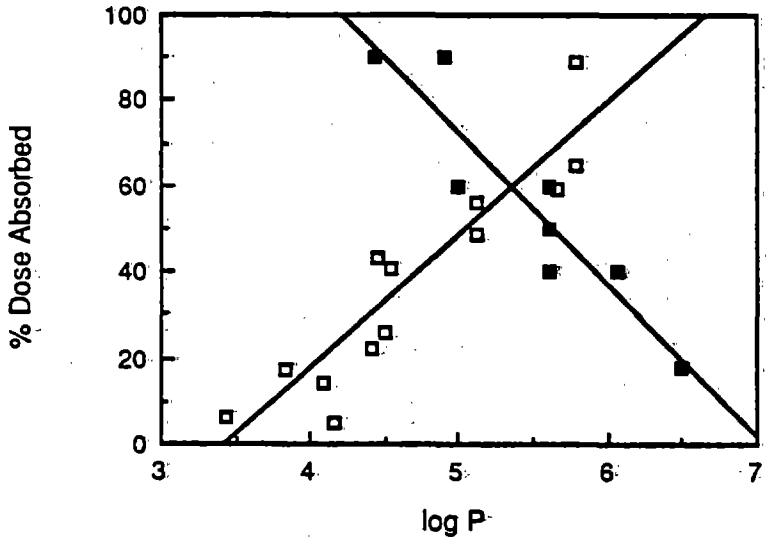


Figure 15

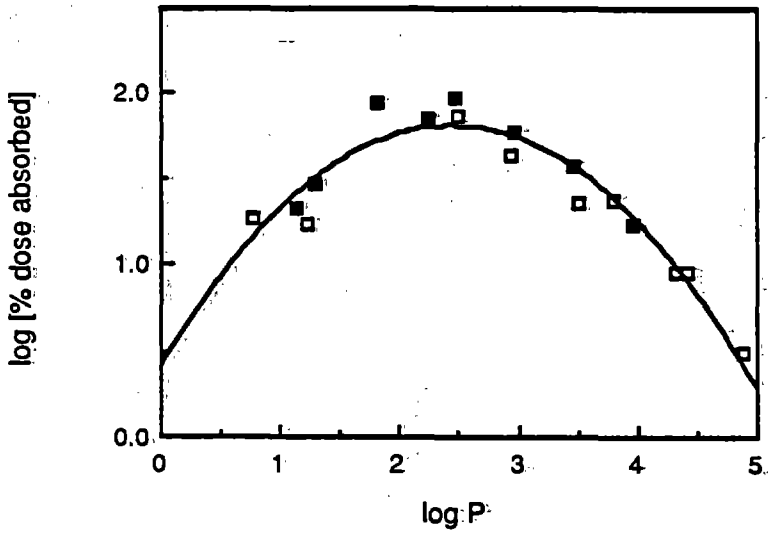


Figure 16

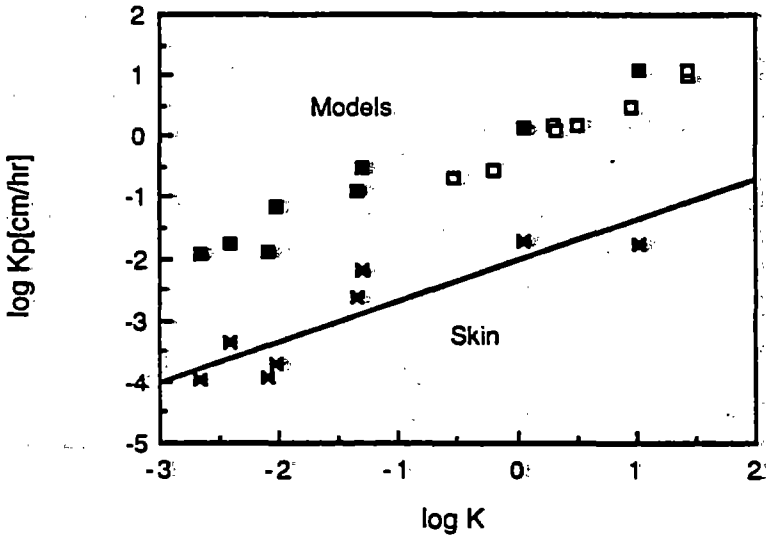
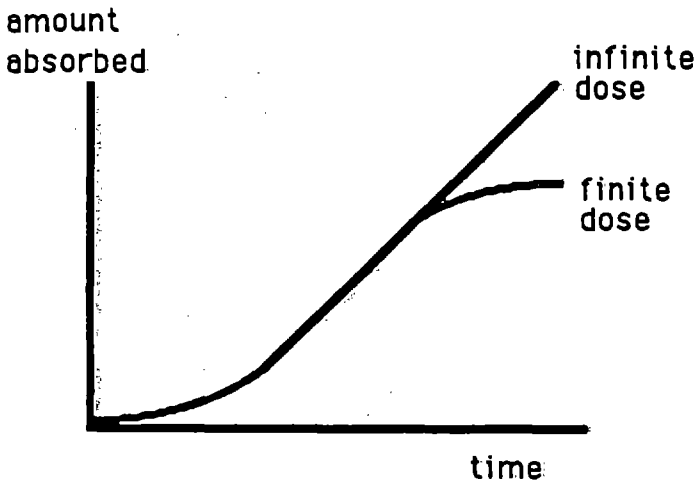


Figure 17



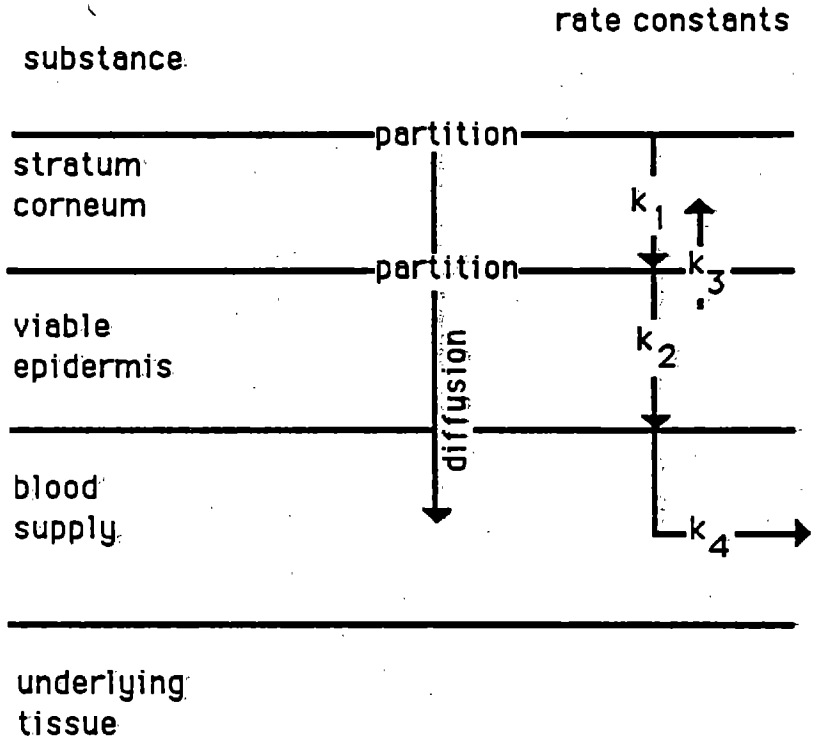

rate constants
substance
partition
stratum corneum
partition
viable epidermis
diffusion
blood supply
underlying tissue
k_1
k_2
k_3
k_4

Fig 18

Figure 19