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Pig Ear Skin as an In-vitro Model for Human Skin Permeability

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Abstract—Pig skin has been shown to have similar histological and physiological properties to human skin and has been suggested as a good model for human skin permeability. In this series of experiments, the in-vitro permeability of pig ear skin was compared with human (abdominal) skin and rat (dorsal) skin using both hydrophilic (water, mannitol, paraquat) and lipophilic (aldrin, carbaryl, fluazifop-butyl) penetrants. Pig skin was found to have a closer permeability character than rat skin to human skin, particularly for lipophilic penetrants. Electrical conductivity measurements across pig skin membranes showed that skin conductivity could be a useful method for assessing the integrity of membranes, particularly when used in conjunction with water permeability assessments.

Percutaneous absorption studies are important in contributing to our understanding of the dermatotoxicity and pharmacological activity of substances that may come into contact with skin. Human in-vivo percutaneous absorption studies are the most relevant and preferred approach to obtain data pertaining to man. However, human volunteer studies are often difficult to justify, particularly if the dermal application (active ingredient or a component of the formulation) has toxic or irritant properties. Alternatively, skin absorption has been examined using in-vitro techniques, and good agreement with in-vivo experimental data has supported the further use of this approach (Bronaugh et al 1982a; Bronaugh & Maibach 1985; Scott & Ramsey 1987). The similarity between data is primarily due to the fact that the principle barrier to skin penetration is the stratum corneum (Blank & Scheuplein 1969) which is essentially a dead layer of cells that retains its permeability properties after removal from the body. However, for regular use in in-vitro studies, a reliable supply of human skin is required which may cause difficulties. For this reason, more readily available animal models have been used to aid in the prediction of chemical absorption through human skin.

Various animal skin alternatives have been used in absorption studies. Two species which have been reported to have permeability properties closely resembling that of human skin are the pig (Bartek et al 1972; Bronaugh et al 1982b; Hawkins & Reifenrath 1984; Bhatti et al 1988; Roberts & Mueller 1990) and the rhesus monkey (Wester & Maibach 1975; Bronaugh & Maibach 1985; Moody et al 1990). More recently, the perfused isolated porcine skin flap model has been developed to examine the mechanisms involved in percutaneous absorption (Riviere et al 1986; Williams et al 1990). The histological characteristics of pig and human skin have been reported to be comparable, with similarities existing for epidermal thickness and composition (Montagna & Yun 1964; Meyer et al 1978), pelage density (Montagna & Yun 1964), dermal structure (Marcarian & Calhoun 1966), lipid content (Nicolaides et al 1968; Gray & Yardley 1975) and general morphology (Meyer et al 1978; Monteiro-Riviere 1986). However, further investigations of the use of pig skin are necessary to establish its suitability as a model for human skin permeability.

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In the following in-vitro experiments, human abdominal skin and rat dorsal skin were used; these respective regions are commonly used for both in-vivo and in-vitro studies. Although the dorsal area of the pig has been used in some studies (Bartek et al 1972; Bronaugh et al 1982b; Hawkins & Reifenrath 1984), the ear was believed to be a better anatomical site, presenting a reliable supply of skin that has been used by other workers (Bhatti et al 1988; Dyer & Aziza 1989).

A series of both hydrophilic penetrants (water, mannitol, paraquat) and lipophilic penetrants (aldrin, carbaryl, fluazifop-butyl) was applied to pig skin (whole skin and epidermal membranes) and the absorption rates were then compared with data obtained for human and rat skin (a commonly employed model for human skin). In common with similar in-vitro studies, the integrity of all membranes was first assessed by measuring their permeability to water (Scott et al 1986a, b). Another method which may be used to assess the integrity of isolated skin is by measuring its electrical conductivity (Dugard & Scheuplein 1973). In order to determine the usefulness of this technique, the measured electrical conductivities were compared with the water permeabilities obtained for pig skin membranes. Furthermore, by comparing the conductivities obtained before and after the water permeability assessment, any associated loss in skin integrity could be determined.

Materials and Methods

Chemicals

[^{14}C]Mannitol (sp. act. 60 mCi mmol^{-1}), [^{14}C]carbaryl (sp. act. 60 mCi mmol^{-1}) and [^{3}H]H_2O (sp. act. 270 mCi mmol^{-1}) were supplied by Amersham International, Amersham, UK. [^{14}C]Paraquat (sp. act. 90 mCi mmol^{-1}) was supplied by Radiochemical Laboratory, Billingham, ICI plc, UK. Tritiated water was diluted in physiological saline (0·9% NaCl) to give a final activity of approximately 2·5 mCi L^{-1}.

[^{14}C]Mannitol was diluted in distilled water to give a final activity of approximately 2·5 mCi L^{-1}, and made up to a concentration of 1 g L^{-1} with unlabelled mannitol (supplied by Sigma Chemical Co., Poole, UK). [^{14}C]Carbaryl was diluted in acetone to give a final activity of approximately 15 mCi L^{-1}, and made up to a concentration of 1·6 g L^{-1} with unlabelled carbaryl. [^{14}C]Paraquat was diluted in distilled water to give a final activity of approximately 2·5 mCi L^{-1}, and made up to a concentration of 1 g L^{-1} with unlabelled paraquat. Unlabelled paraquat, carbaryl and a concentrate fluazifop-butyl formulation (containing 125 g L^{-1}) were supplied by ICI Agrochemicals, Jealott's Hill, Bracknell, UK. An aqueous dilution of the concentrate fluazifop-butyl formulation was prepared immediately before application at a concentration of 1·88 g L^{-1} in distilled water. Aldrin was supplied by Shell, Sittingbourne, UK, and dissolved in methanol to give a final concentration of 1·6 g L^{-1}. Optiphase MP scintillation fluid was supplied by LKB and manufactured by FSA Laboratory Supplies, Loughborough, UK.

Membrane preparation

Pig ears (Cheshire White Pigs) were obtained from a local abbatoir and after cleaning under cold running water, the outer region of the ear was shaved with clippers before careful removal of the whole skin membrane from the underlying cartilage. Epidermal membranes were prepared by soaking the whole skin membranes in water at 60°C for 70 s, followed by blunt dissection, they were then floated onto aluminium foil.

Human abdominal skin was obtained from cadavers within 24 h of death. Whole skin membranes were prepared by removal of subcutaneous fat, and epidermal membranes were prepared using a heat separation technique where whole skin membranes were soaked in water at 60°C for 45–60 s. The epidermis was then removed by blunt dissection, and floated onto aluminium foil (Scott & Ramsey 1987).

Wistar-derived Alderley Park rats (Alpk:APfSD strain) were supplied by the Animal Breeding Unit, ICI Pharmaceuticals Division, Alderley Park, Macclesfield, UK. The animals were anaesthetized by exposure to fluothane vapour (Halothane BP, ICI Pharmaceuticals Division) followed by cervical dislocation. The fur from the dorsal region was shaved using clippers before removal of whole skin from this region. Epidermal membranes were prepared using a chemical separation procedure which involved soaking whole skin membranes in 1·5 M sodium bromide for 16–20 h. The epidermis was then removed by blunt dissection, and floated onto aluminium foil (Scott et al 1986a).

All membranes were either used immediately or stored at −20°C for up to 7 days. This has been reported to be a satisfactory method of storage for human skin (Harrison et al 1984).

In-vitro percutaneous absorption studies

The assessment of in-vitro skin permeability was performed as described previously (Scott & Corrigan 1990). Prepared membranes were mounted on horizontal-membrane static glass diffusion cells (exposure area 2·54 cm^2) maintained at 30°C in a water bath. The integrity of the membranes was initially assessed by measuring the tritiated water permeability on day 1. Human skin membranes that had water permeabilities above $1{\cdot}5 \times 10^{-3}$ cm h^{-1} and rat epidermal membranes with water permeabilities above $2{\cdot}5 \times 10^{-3}$ cm h^{-1} were not included in the study (Scott et al 1986b). An upper limit of $5{\cdot}0 \times 10^{-3}$ cm h^{-1} was set for the water permeability of pig ear membranes (Bhatti et al 1988). Electrical conductivity measurements were made across pig skin membranes hydrated in saline for 30 min while mounted in the diffusion cells, both before and after the water permeability assessment. The instrument used in these determinations was AIM 6401 LCR Databridge (H. Tinsley, Croydon, Surrey).

The absorption of the test penetrant was then studied over a 3 day period, and the steady-state absorption rates calculated and expressed as either permeability coefficients (K_p: units, cm h^{-1}, for the hydrophilic penetrants which were in solution in the same vehicle) or absorption rates (units, μg cm^{-2} h^{-1}, which were applied in a variety of vehicles).

These studies were done over a period of time, and not all the dose levels were the same. Tritiated water was applied at a rate of 400 μL cm^{-2} skin, and mannitol and paraquat were applied at a rate of 200 μL cm^{-2} skin, followed by occlusion. Physiological saline was used as the receptor phase for the hydrophilic penetrants. All applications of lipophilic penetrants were unoccluded, carbaryl and aldrin being applied at a rate of 25 μL cm^{-2} skin and fluazifop-butyl (concentrate and aqueous dilution) at a rate of 10 μL cm^{-2} skin. The higher application volumes for water, mannitol and paraquat corresponded to dose regimes used in comparable studies to provide classic steady-state absorption profiles for human and rat skin membranes. The lower application volumes for aldrin, carbaryl and fluazifop-butyl are commonly used for in-vivo studies, and are considered to be representative of realistic occupational exposures. In order to avoid the technical problem that the solubility of the lipophilic penetrant in the receptor fluid may affect the absorption rate (Bronaugh & Stewart 1984; Scott & Ramsey 1987), a 50% ethanol:water solution was used with these chemicals.

It is not possible to use these data for the lipophilic penetrants, which were applied in a variety of vehicles at different concentrations, for inter-compound comparisons. However, all the data can be used for interspecies comparisons as the same vehicle and concentration of penetrant was used with each species.

Results

Electrical conductivity measurements

The skin conductivities obtained before the tritiated water permeability assessment for pig skin were plotted against the water permeabilities (Fig. 1). The linear regression fitted lines demonstrated that the whole skin conductivities were slightly higher than for epidermal membranes with similar water permeabilities, possibly due to increased hydration of the dermis of whole skin. However, the correlation between conductivity and water permeability was better for whole skin ($r^2 = 0{\cdot}80$) than for epidermal membranes ($r^2 = 0{\cdot}52$). The pre-water permeability assessment for skin conductivities were also compared with the conductivity values obtained immediately after the water permeability assess-

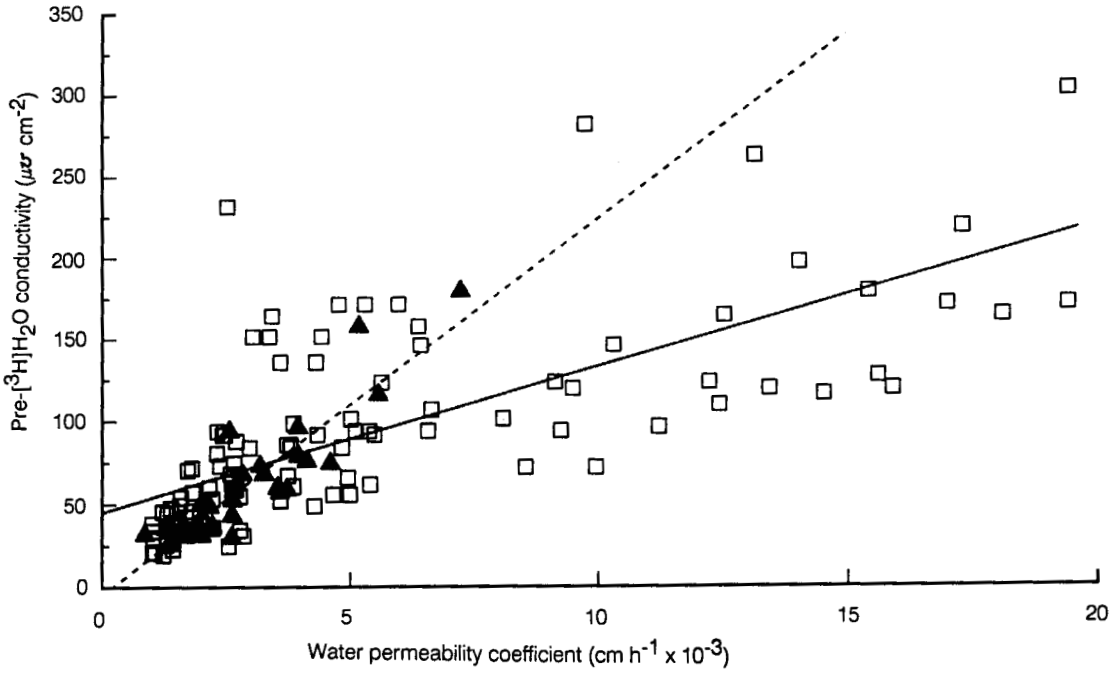

FIG. 1. Comparison between the water permeability and the pre-tritiated water (pre-[^{3}H]H_2O) skin conductivity measurement when used as indicators of pig skin integrity. Pig epidermis □, pig whole skin ▲.

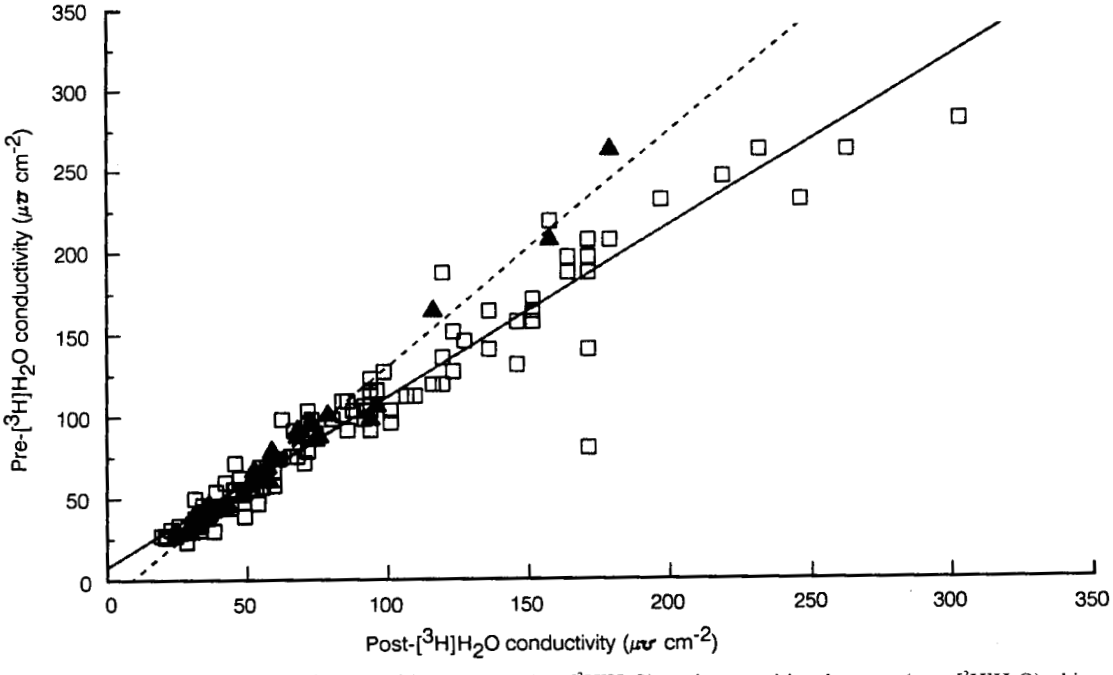

FIG. 2. Comparison between the pre-tritiated water (pre-[^{3}H]H_2O) and post-tritiated water (post-[^{3}H]H_2O) skin conductivity measurements used as indicators of pig skin integrity. Pig epidermis □, pig whole skin ▲.

ment (Fig. 2). For the epidermal membranes, the slope of the linear regression fitted line ($r^2 = 0{\cdot}92$) was 1·04 showing that there was no difference between pre- and post-conductivities. For whole skin membranes, the slope of the fitted line ($r^2 = 0{\cdot}98$) was 1·44 suggesting a very slight increase in conductivity after the permeability assessment, possibly due to further hydration of the dermal layer.

Percutaneous absorption assessments

The absorption data for the hydrophilic penetrants (presented as calculated permeability coefficients) through human, pig and rat skin are presented in Figs 3, 4 for whole skin and epidermal membranes, respectively. Data from pig and rat skin (whole skin and epidermis) significantly overestimated the permeability of all three penetrants through

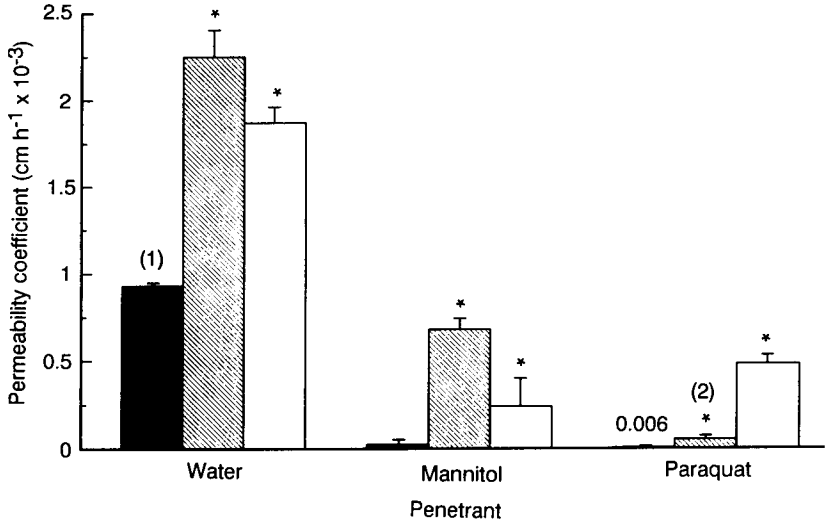

FIG. 3. Mean permeability coefficient + s.e.m. ($7 < n < 38$) for several hydrophilic penetrants through human (■), pig (▧) and rat (□) whole skin membranes, with a two-sided Student's *t*-test comparing human and animal skin permeabilities. (*$P < 0.01$). Additional data obtained from (1) Scott et al (1986b) and (2) Bhatti et al (1988).

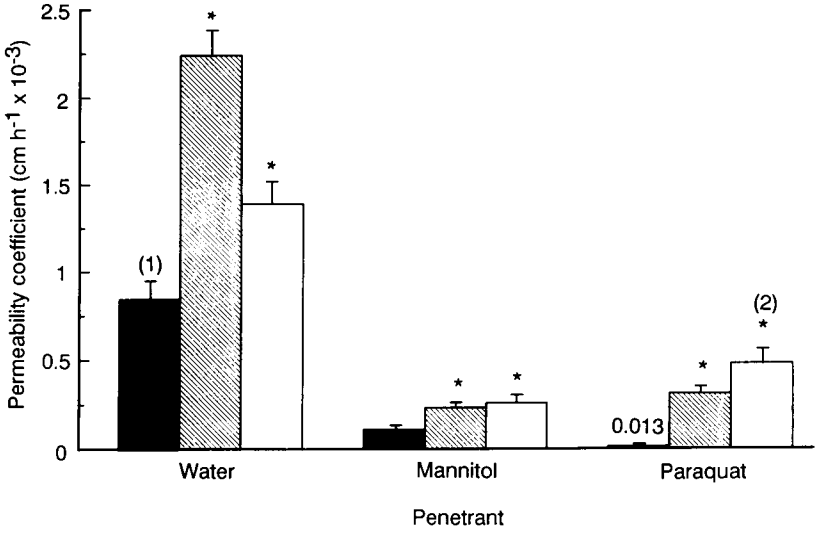

FIG. 4. Mean permeability coefficient + s.e.m. ($6 < n < 38$) for several hydrophilic penetrants through human (■), pig (▧) and rat (□) epidermal membranes, with a two-sided Student's *t*-test comparing human and animal skin permeabilities. (*$P < 0.01$). Additional data obtained from (1) Scott et al (1986b) and (2) Scott et al (1986a).

human skin membranes (two sided Student's *t*-test: $P < 0.01$). There were no significant differences found between the permeabilities of pig and rat skin for water (whole skin), mannitol (epidermis) and paraquat (epidermis) ($P > 0.05$).

For the lipophilic penetrants, with the exception of carbaryl absorption through pig skin ($P > 0.05$), the animal skin permeability data were significantly higher than for human skin ($P < 0.01$). However, the data obtained for pig skin were closest to human skin, rat skin permeabilities being significantly larger than pig skin permeabilities ($P < 0.01$).

Calculation of factor of difference

A comparison of pig and rat skin permeabilities relative to human skin is displayed in Table 1. Factors of difference (FoD values) were calculated for each penetrant using the following expression:

$$\text{FoD value} = \frac{\text{rate of absorption through animal skin}}{\text{rate of absorption through human skin}}$$

The FoD values further indicated that human skin had closer permeability properties to pig skin than to rat skin, particularly with the liphophilic penetrants tested. For paraquat, rat skin was approximately 9 and 1·5 times more permeable than pig skin for whole skin and epidermal membranes, respectively. For carbaryl and the concentrate and aqueous dilution of the fluazifop-butyl formulation, rat epidermis was about 30, 6 and 10 times, respectively, more permeable than pig

Table 1. Comparison of the permeability data obtained for pig and rat skin relative to human skin.

Penetrant	Membrane	Factor of difference		
		Man	Pig	Rat
Water	Whole skin	1·0	2·7	1·9
	Epidermis	1·0	2·4	2·0
Mannitol	Whole skin	1·0	28·3	10·0
	Epidermis	1·0	21·3	23·5
Paraquat	Whole skin	1·0	8·5	79·2
	Epidermis	1·0	23·5	36·9
Carbaryl	Epidermis	1·0	1·2	35·0
Aldrin	Epidermis	1·0	2·8	—
Fluazifop-butyl (concentrate)	Epidermis	1·0	5·4	35·0
Fluazifop-butyl (aqueous dilution)	Epidermis	1·0	4·3	44·0

epidermis. Conversely, mannitol penetrated pig whole skin 3 times faster than rat whole skin.

Discussion

Electrical conductivity was investigated as a rapid alternative to water permeability assessments of skin integrity. In these studies, pig skin membranes with a water permeability below 5×10^{-3} cm h^{-1} were deemed intact. Consequently, an upper limit of a conductivity of 100 $\mu\upsilon$ cm^{-2} was proposed since all pig whole skin membranes with water permeabilities $< 5 \times 10^{-3}$ cm h^{-1} had conductivities below this value. The same proportion of epidermal membranes (nearly 70%) was deemed intact by either water permeability or conductivity measurements. It would therefore appear that below 100 $\mu\upsilon$ cm^{-2}, skin conductivity is indicative of acceptable water permeability. It should be noted, however, that just over 10% of the membranes judged to be intact by conductivity measurements had water permeabilities $> 5 \times 10^{-3}$ cm h^{-1}.

It may be more appropriate, however, to use conductivity measurements as an initial screen of damage to pig skin, and use water permeability as an ultimate assurance of membrane integrity. In practice, however, either method could be used and the final choice is governed by availability of equipment and experimental protocols. There was no difference between pre- and post-water permeability assessment for skin conductivities for epidermal membranes, and although there was a minor increase in whole skin conductivity after the water permeability assessment, this was not considered to be significant. These observations demonstrate that the permeability assessment of membrane integrity does not affect the permeability properties of skin.

Since the skin may be exposed to chemicals with various physicochemical properties, a potentially useful animal model should, ideally, predict the permeability of human skin to both lipophilic and hydrophilic penetrants. During in-vitro studies, the absorption of hydrophilic penetrants may be assessed using whole skin or epidermal membranes; however, only epidermal membranes can be used to study the absorption of lipophilic chemicals. This is because the hygroscopic nature of the dermal layer of isolated whole skin acts as an aqueous barrier to lipophilic penetrants, resulting in an under-estimation of in-vivo absorption data (Scheuplein & Blank 1973; Scott et al 1986a). Consequently, there must be a suitable method for preparing intact epidermal membranes from the animal skin being investigated. It may also be advantageous if the same method is used to prepare epidermal membranes from both animal and human skin.

In this study, both pig and human epidermal membranes were prepared using heat separation techniques. The integrity of the prepared membranes was assessed by comparing the water permeabilities through whole skin and epidermis, with no significant difference being found for pig and human skin (two-sided Student's t-test: $P > 0{\cdot}05$). Heat separation of rat epidermis was unsuccessful (unpublished data), possibly due to the higher pelage density. An alternative chemical separation method was used instead and the integrity of these membranes was also confirmed (no significant difference between whole skin and epidermal permeabilities to water ($P > 0{\cdot}05$)).

A comparison of whole skin and epidermal permeabilities for each penetrant showed no significant difference for water, mannitol and paraquat absorption through skin membranes ($P > 0{\cdot}05$). Also, no significant difference was observed for water and paraquat absorption through human skin, and water absorption through pig ear membranes ($P > 0{\cdot}05$). Human and pig whole skin were 2·2 and 2·9 times, respectively, more permeable than epidermal membranes to mannitol, but this could be attributed to inter-experimental variation (see later discussion). However, pig epidermis was 6 times more permeable to paraquat than pig whole skin, and the magnitude of this difference was considered too large to be ascribed to variation between experiments. It may be that upon the detachment of the epidermis using the described procedures, some of the hairs remain embedded in the dermis leaving potential pathways in the epidermal sheet where the follicles slipped free.

The pelage density of pig skin has been shown to be very similar to that in man (pig = 11 follicles cm^{-2} (Bronaugh et al 1982b), human = 6 follicles cm^{-2} (Scott et al 1991)), but the follicular diameter is much greater for pig (pig = 177 μm (Bronaugh et al 1982b), man = 70 μm (Scott et al 1991)). The larger holes that would be formed by detached pig follicles may be sufficient to provide increased shunt pathways to certain penetrants, and may have a significant effect on the permeability of slowly absorbed chemicals such as paraquat.

To assess the usefulness of an animal model to predict human percutaneous absorption, it is necessary to find a satisfactory degree of correlation between animal and human skin permeabilities. Analysis of the individual data for each determination in this study (unpublished), showed that the permeability may differ by up to threefold between cadavers of the same species, and this factor could be considered representative of typical inter-experimental variations. It is proposed, therefore, that an animal model may be predictive of human skin permeability if the FoD value in permeability between species is < 3. Applying this criterion to our data, FoD values of < 3 were obtained for pig skin with the penetrants, water, carbaryl and aldrin, and for rat skin, with water only (Table 1). However, there were FoD values as high as 28 for pig skin (mannitol absorption) and 79 for rat skin (paraquat absorption) demonstrating a subsequent compound—specific variability in FoD values.

Other inconsistencies in the degree of correlation between animal and human skin permeability have been observed for

many animal models and appear to become greater as the physicochemical nature of the chemicals involved vary. Hawkins & Reifenrath (1984) suggested that the FoD value between pig and human skin increased as the lipophilicity of the penetrant increased. They demonstrated good agreement between in-vivo human and in-vitro pig skin absorption data for hydrophilic penetrants (FoD value ~1: caffeine, benzoic acid, fluocinolone acetonide, M-diethyltoluamide, malathion), but a loss of correlation as the lipophilic character of the penetrant increased (FoD value: testosterone < parathion < progesterone < lindane < DDT). However, the essentially aqueous Tyrode solution used as the receptor fluid in the in-vitro model may have limited the absorption of the lipophilic species. Bartek et al (1972) obtained FoD values of less than 3 between pig and human in-vivo absorption data for both lipophilic (butter yellow, DDT, haloprogin, lindane, testosterone) and hydrophilic penetrants (caffeine, acetylcysteine, cortisone). Notably, for rat skin, FoD values >3 were obtained for both hydrophilic (cortisone, FoD ~7) and lipophilic penetrants (testosterone, FoD ~4; haloprogin, FoD ~4).

In this study, the variation and magnitude of the FoD values for pig skin were, overall, much less for lipophilic penetrants than for hydrophilic penetrants (and less than rat skin FoD values). The absorption rate of paraquat through pig whole skin was found to be much lower than that obtained for several species (Scott et al 1986b), with FoD values ranging from 280 for guinea-pigs to 1520 for hairless mice. In other reported studies using hydrophilic chemicals, Bronaugh et al (1982b) found similar permeabilities between pig and human skin for acetylsalicylic acid and urea (FoD ~1) (the FoD values for rat skin were approx. 1 and 5, respectively). Bhatti et al (1988) obtained a FoD value of 0·5 for benzoic acid through pig ear skin and Dick et al (1992) obtained a FoD value of 1·0 for ethanol diffusion through pig flank skin.

In conclusion, the data in this study provides further evidence that pig skin, whilst not a perfect model for human skin permeability, has closer permeability properties than several species including the rat, particularly when lipophilic penetrants are used.

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