# Mathematical Modelling of Percutaneous Absorption

Gary P. Moss[a*], Simon C. Wilkinson[b], Y. Sun[c]

[a]The School of Pharmacy, Keele University, Keele, Staffordshire, UK

[b]Medical Toxicology Centre, Wolfson Building, Institute for Cellular Medicine, Newcastle University, Newcastle-upon-Tyne, UK

[c]School of Engineering & Information Science, University of Hertfordshire, Hatfield, UK

*Corresponding author:

Gary Moss

School of Pharmacy

Keele University

Keele

Staffordshire

ST5 5BG

UK

Tel: +44 (0) 1782 734 776

Fax: +44(0)1782 733326

E-mail: g.p.j.moss@mema.keele.ac.uk

ABSTRACT

This review examines recent progress made in the field of modelling and predicting percutaneous absorption. It describes initial qualitative modelling and how quantitative approaches were pioneered and then developed, particularly in the context of the analysis of specific subsets of data. It then focuses on recent developments, including non-linear modelling and discusses recommendations in model construction, development and validation, suggesting that some models do not fit proposed guidelines.

**Overview and scope**

The percutaneous absorption of exogenous chemicals has been a subject of interest for the last fifty years, in fields as diverse as pharmaceuticals (for delivery of drugs into and across the skin), cosmetics and risk assessment (i.e. exposure and absorption following the use of agrochemicals or industrial chemicals). Modelling of percutaneous absorption provides viable and ethical alternatives to laboratory experimentation. It is also a strategy being considered in a regulatory context, particularly within Europe, e.g.in the framework of the proposed European chemicals strategy; REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals). While many researchers have elucidated aspects of the mechanism of skin absorption based on experimental findings, the quantification of this process has attracted substantial interest, most notably since the early 1990s when Flynn [1] and Potts and Guy [2] developed important semi-quantitative and quantitative models of skin absorption.

The sheer volume of chemicals approved for topical human use ensures that it is virtually impossible to assess solely by experimental means the skin permeability of such materials, particularly in the form of new formulations, where many variations and iterations might require to be tested, and the assessment of new chemical entities. As a consequence, *in silico* models are increasingly employed to assess the risks and hazards associated with exposure of human skin to exogenous chemicals. As well as providing predictions of expected permeation, most models are also presented in the form of a discrete equation with terms usually representing specific physicochemical properties, such as molecular weight, melting point, lipophilicity and so on. This allows insight into the mechanism of absorption and provides opportunities for the design of novel chemicals whose properties are optimized with regard to maximizing percutaneous absorption.

Therefore, it is the aim of this document to review critically the use of mathematical models in predicting percutaneous penetration. Recent advances – in the last three or four years – will provide the main focus of this review, although such advances will be set in the context of preceding research. Clearly, a review of this length and scope cannot be comprehensive and, as such, the reader is directed elsewhere for a comprehensive discussion of the topic [3 – 6].

**Structure of the skin**

The most important aspect of percutaneous absorption remains the skin structure. Despite the application of many novel technologies, including the use of electric currents (iontophoresis), ultrasound (sonophoresis), chemicals that alter the barrier structure of the skin (penetration enhancers) and miniature needles that break the barrier of the skin, allowing drug permeation (microfabricated microneedles), the skin barrier still provides a formidable challenge to scientists seeking to bypass it, particularly for therapeutic uses.

As excellent descriptions of the skin physiology can be found elsewhere (i.e. [5]) this review will focus on the nature of the *stratum corneum*, the outermost layer of the skin and the main barrier to percutaneous absorption. Classically, the *stratum corneum* skin barrier has classically been described using a "bricks and mortar" model, with the bricks representing the tightly-packed corneocytes. These flattened, hexagonal, highly proteinaceous cells are the endpoint of keratinocyte differentiation and are interconnected by structures termed corneodesmosomes (Figure 1). These "bricks" are enclosed within a continuous and highly ordered lipid phase, which is lamellar in structure. The most important component of this phase for barrier function is the ceramides, polar lipids with hydroxylated alkyl side chains which, under normal conditions are packed hexagonally and orthorhombically. In all, this barrier forms a continuous poly-proteinaceous structure whose thickness and exact composition varies across different body sites. The "bricks" of the skin barrier may hydrate extensively and cause significant changes in the packing and structure – as well as the permeability – of the *stratum corneum* [6 – 14]. Thus, it is now understood that the *stratum corneum* does not simply form a homogenous bricks and mortar structure. Rather, the nature of the corneocytes changes in morphology and biochemical function as they progress from the lower levels of the *stratum corneum* to the higher levels. Such a transition is also associated with an increase in transglutaminase-mediated protein crosslinking and increased levels of inter-corneocyte ceramides and fatty acids, resulting in a progression from fragile to rigid structures, where non-peripheral corneodesmosomes exhibit reduced interdigitation as the structure progresses to the outer layers of the barrier, concomitant with an increase in the occurrence of (pro)filaggrin, a protein thought to play a role in the aggregation of keratin filaments within corneocytes [6]. It has been shown that the presence of fragile corneocytes increases in diseased skin where the barrier is compromised [15].

Significant advances have been made in the elucidation of the *stratum corneum* structure and barrier function in the last ten years. While new species of ceramides, and the synthetic pathways

that generate them, are still being identified, substantial advances have been made in our understanding of the *stratum corneum* structure and function. The lamellar arrangement of the *stratum corneum* lipids was characterised by electron microscopy and X-ray diffraction. More recently, Norlen and colleagues [11, 13, 14] have used a cryoelectron microscopy method to propose the existence of a single gel phase model and suggested that cryoelectron microscopy failed to show the expected presence of the trilamellar-conformation long periodicity phase (LPP). Further, a "sandwich" lipid model has been proposed by Bouwstra and colleagues [15] which accounts for differences in *stratum corneum* lipid packing that accounts for differing periodicity phases reported in the barrier lipids, while further highlighting the importance of a fluid phase, the latter being dictated by the presence of ω-esterified long-chain acylceramides. As the stratum corneum changes as it progresses outwards from the body – from "*stratum compactum*" to "*stratum disjunctum*" – changes in its arrangement are also observed. In terms of the packing of ceramide side chains, a transition to a less tightly-packed hexagonal phase occurs closer to the skin surface. In addition, the lamellar phase is normally missing from the outer layers of the *stratum corneum*, and it has recently been shown that the presence of long-chain fatty acids are required to induce the formation of the orthorhombic packing in mixtures of ceramide and cholesterol [15]. This orthorhombic packing, along with the presence of LPP, was defined by Rawlings, in his excellent review of skin barrier biology, as defining "ultimate lipid barrier functionality" [6].

One of the classic characteristics of the stratum corneum barrier function is the nature of the main route of absorption through the skin lipid layers. While it is a longer and more tortuous route across the stratum corneum compared to the transcellular pathway, it does not require the potential partitioning between the stratum corneum lipids and corneocytes, but relies on partitioning into the stratum corneum lipids from the formulation vehicle and diffusion across the stratum corneum predominately in this single phase. The other proposed route across the skin, that of permeation via skin appendages such as hair follicles and sweat glands, is limited by the occurrence of such structures (on average, they represent approximately 0.1% of the total skin surface). Therefore, from the point of view of understanding absorption in the context of skin biology, the nature of the stratum corneum lipids appear to govern the percutaneous absorption of exogenous chemicals. However, it should be noted that the other potential routes can also play a role in the overall absorption process and may be influence by external factors, such as humidity in the case of the transcellular route.

**Models pre-1990**

The majority of early studies, with possibly the exception of Higuchi's work on drug release from ointments [16] were based on the analysis of homologous, or closely related, series of molecules where often relatively small numbers of compounds were assessed. Many of these studies revealed a linear relationship between increasing hydrophobicity and increased skin permeation [17, 18]. It is interesting to note, in the context of the development and establishment of linear models, that some studies also reported a parabolic relationship with hydrophobicity, particularly where highly hydrophobic compounds were included (cf. [17]). While such studies showed that it was possible to derive quantitative models of skin penetration, each model existed in isolation for a particular chemical class, or series of compounds, an issue observed much later when research focused on the analysis of small subsets taken from larger datasets, a matter that is discussed in greater detail below. Moss et al. [3] described the problems of such analyses, including the lack of physicochemical variety in the dataset and the subsequent inability to decouple co-linear effects, such as hydrophobicity and molecular weight. Excellent reviews on modelling the skin permeability of homologous, or closely related, series of compounds exist [19 – 22] to which the reader is referred.

**Early quantitative models**

Thus, the mathematical modelling of percutaneous absorption is not new and has contributed to our understanding of transport across the skin in general, and the stratum corneum in particular, for approximately twenty years. The physicochemical properties of a molecule are known to influence its permeation into and across the skin. Prior to 1990, the vast majority of work in this field relied on inferences drawn from experiments, particularly those that examined closely related, or homologous, series.

One exception to the above comment is the study by Brown and Rossi [23]. They developed a simple model, based solely on a representation of the stratum corneum as a simple lipophilic barrier. They developed two mathematical relationships between permeability and the lipophilicity of a penetrant:

$$K_p = 0.1\left[\frac{P_{oct}^{0.75}}{120+ P_{oct}^{0.75}}\right] \qquad (1)$$

$$I = C_W.A.T.0.2\left[\frac{P_{oct}^{0.75}}{120+P_{oct}^{0.75}}\right] \quad (2)$$

Where $K_p$ is the permeability coefficient (cm/hr); I is the dermally absorbed intake (mg), $C_W$ is the concentration of the penetrant in water (mg/cm$^3$); A is the area of skin exposed to permeation (cm$^2$); T is the time of exposure (hr); $P_{oct}$ is the octanol-water partition coefficient.

This work was followed by two key studies – those by Flynn and Potts and Guy [1, 2]. These studies were significant milestones in the drive to develop quantitative models of percutaneous absorption. Flynn [1] published a dataset of 97 permeability coefficients for 94 compounds *in vitro* through human skin (with the exception of *in vivo* studies for toluene, ethylbenzene and styrene) from 15 different literature sources. This provided the first large, and until relatively recently the largest, database of skin permeability values measured in a single species. It is from the analysis of this dataset that Flynn drew a series of conclusions (summarised in Table 1) showing that a clear relationship was observed between the permeability of a permeant and its lipophilicity (log P) and molecular size. Flynn presented a series of simple algorithms for low and high molecular weight compounds which simply stated that very hydrophilic and hydrophobic compounds had low and high skin permeability, respectively, and that different hydrophobicity-dependent QSARs could be used to predict skin permeability for high and low molecular weight compounds. No statistical measures of fit were provided at this time.

This was later quantified by Potts and Guy in their seminal work [2] which quantified the relationship between permeability and the physicochemical properties of a molecule. For 93 of the compounds in Flynn's dataset they reported the following relationship:

$$logK_p = 0.71logK_{ow} - 0.0061MW - 6.3 \quad (3)$$

[n = 93; $r^2$ = 0.67; s not reported; F not reported]

where: $K_p$ Where $K_p$ is the permeability coefficient (cm/s); log $K_{ow}$ is the $\log_{10}$ octanol-water partition coefficient; MW is the molecular weight; n is the number of observations; r is the correlation coefficient; s is the standard error of the estimate; F is Fisher's statistic.

It was recognised by Cleek and Bunge [24] that highly lipophilic penetrants would encounter diffusional resistance during percutaneous absorption because of the aqueous properties of the viable epidermis. They developed a modified version of (3) that accounts for the, effects of these properties on the percutaneous absorption of highly lipophilic penetrants.

A number of studies have since reported similar conclusions to those presented by Potts and Guy, often by a number of different approaches. While most of these have been summarised previously by Moss et al. [3], a few are noteworthy in the context of this review. For example, Pugh and Hadgraft [25] used a novel *ab initio* approach to analyse the Flynn dataset. This was a fragment approach based on a range of molecular substructures and features, and is not to be confused with *ab initio* approaches used for the calculation of molecular orbital properties. Their analysis yielded 11- and 17-descriptor models which produced results similar, but not statistically better than, Potts and Guy's approach. Pugh and Hadgraft were able to identify a number of significant outliers (including atropine, estroil, naproxen, nicotine and sucrose) by their analysis. Cronin et al. [26] used an expanded database and identified several outliers, yielding an equation similar to that produced by Potts and Guy [1]. Wilshut et al. [27] validated a series of existing models and also considered separately the influence of protein and lipid fractions on permeation. Barratt [28] also analysed the full Flynn [1] dataset, producing a quantitative structure-permeability relationship after subdividing the original dataset into a subset of 60 which included small molecules and steroids, but excluded the hydrocortisone derivatives. He extended the Potts and Guy [2] approach and used melting point (possibly being indirectly related to hydrogen bonding phenomena) and molecular volume (as a measure of molecular size), and derived a relationship between permeability and both hydrophobicity and melting point. Table 2 lists some of the currently most cited models for the prediction of percutaneous absorption including those described above.

Mitragotri et al. [29] considered solute permeation through four possible routes in the stratum corneum – free-volume diffusion through lipid bilayers, lateral diffusion among lipid bilayers, diffusion through pores, and diffusion through shunts). The first route includes solute diffusion through lipid bilayers by a process of "hopping" across lamellar bilayers, and was considered important for transport of low molecular weight hydrophobic solutes (MW < 400Da). The second route includes solute motion due to lateral diffusion of lipid molecules, considered important for high molecular weight solutes (MW > 400Da) that partition in lipid bilayers, albeit slowly due to their

large size. The third route includes solute diffusion through pores and the fourth includes solute diffusion through shunt pathways. The authors commented that the last two pathways are important for the permeation of hydrophilic solutes. Patel et al. [30] found molecular weight to be a significant predictive model and also that it has the advantage of being easy to calculate, thus giving their model – and similar models – wide applicability particularly to users who may not have access to the software required to calculate complex molecular descriptors.

**Modelling of subsets**

Barratt [29] also found that hydrocortisone derivatives modelled consistently poorly (Table 2), an issue that was later addressed by Johnson et al. [31] who demonstrated that the steroid data used in the Barratt, and preceding, models was at odds with a larger volume of data for the same chemicals that appeared in the literature. In re-modelling this dataset by including Johnson's proposed "new" data from the literature, Moss and Cronin [32] proposed a QSPR similar to those that had been previously published (Table 2) [2, 26] but which did not return the steroid derivatives as outliers.

Importantly, Potts and Guy [33] investigated the role of hydrogen bonding by examining a subset of 37 non-electrolytes from the Flynn dataset. They developed a QSPR that included a term for molecular volume as well as descriptors for solute hydrogen bond acidity and hydrogen bond basicity:

$$\log K_p = 0.0256MW - 1.72\sum \alpha_2^H - 3.93\sum \beta_2^H - 4.85 \quad (4)$$

[n = 37; $r^2$ = 0.94; s not reported; F = 165]

where: $K_p$ Where $K_p$ is the permeability coefficient (cm/s); MW is the molecular weight; $\sum \alpha_2^H$ is the solute hydrogen bond acidity; $\sum \beta_2^H$ is the solute hydrogen bond basicity.

While (4) is important in illustrating the importance of hydrogen bonding in the permeation of non-electrolytes it is clearly different from the previous model reported by the same authors [1], suggesting very clearly that the nature of the model output is dependent upon the nature of the data used to construct it. Abrahams et al. [34] found similar results when analysing a slightly larger subset (n = 46) of the same dataset.

A large number of studies were subsequently conducted on subsets of the Flynn dataset [1], and also on a number of new datasets. Lien and Gao [35] analysed a subset of the Flynn dataset (22 compounds; $r^2 = 0.96$). Other studies, such as Barratt [28], discussed above, have selected subsets of a larger database or examined a small number of compounds from which quantitative models were developed. Abrahams *et al*.,[34, 36] examined, respectively, 46 and 53 compounds taken from Flynn, and a number of other studies examined 20,[37] 16 (in two different studies, by both Lee et al.[38], and Morimoto *et al*.[39]) or as few as four compounds [40].In common with studies using substantially larger datasets inferences were made concerning the mechanism of percutaneous absorption of these compounds and, by inference, those that may be chemically similar.

Moss et al. [41] illustrated the pitfalls of developing models based on small datasets. They demonstrated this by determining the quality of a range of models for various mammalian skins and an artificial membrane, polydimethylsiloxane, which has found use as a replacement for human skin, based on a range of parameters including the size of the dataset. They concluded that the over-riding issue in the development of models for skin absorption was "the nature and quality of the data used to construct the model and that Cronin and Schultz's comments on model development should be considered when constructing mathematical representations of percutaneous absorption to avoid the generation of false positive or false negative results" [41]. The issue of data availability (and the underlying distribution of that data) is a key limiting factor to model quality, however, and perhaps the analysis of smaller datasets should be considered within such a context, for example in experiments where a finite dose is applied to the skin. It is perhaps unsurprising that very few recent studies in this field have analysed subsets of the size described above.

Clearly, the seminal work of Potts and Guy [2, 33] raises an important issue in this matter. They constructed two models from Flynn's dataset (one, in 1995 [33], being a subset of the whole dataset, used in their initial study [2]). Both models, discussed above, are substantially different. However, both models exhibit high correlation coefficients. More generally, in the case of smaller datasets this may suggest over-fitting of the data or that the data abstracted from the larger whole yields an unrealistic representation of the statistical nature of these models [41 – 43]. The inclusion by Moss et al. [41] of a deliberately small dataset addresses this concern and shows clearly the impact that the volume – or lack of it – of data can exert on a model, possibly resulting in a misleading model. Such comments echo those made by Cronin and Schultz [44] on the design of successful approaches for the development of valid mathematical models of biological processes.

Clearly, the key theme in this analysis is the reduction in the size of the dataset and, with this, the corresponding lack of relevance to a wider "molecular audience", resulting in these models drawing conclusions from small datasets, conclusions that have relevance only for a narrow range of chemicals. An excellent context can be found for this work in the review of the pitfalls of QSARs by Cronin and Schultz [44]. Briefly, such an understanding of both the size and distribution of the data used to develop models will impact on the quality of analysis. Their conclusions are summarised in Table 3. Further, it may be suggested that the provision of large databases of consistent quality, with transparent information on their origin (i.e. Sangester [45]) will be required to advance the field.

It is interesting at this point to reflect on the role of hydrogen bonding in modelling of percutaneous absorption, and to comment upon this in the context of the subset analyses discussed above, and to contextualise this with some findings reported in the literature prior to the development of a number of QSPR models. Significantly, Roberts [18] demonstrated the importance of hydrogen bonding to percutaneous absorption over 30 years ago. Partition phenomena, particularly the development of the solvatochromic theory [46] coupled with a developing understanding in skin permeability have indicated the importance of hydrogen bonding acceptor and donor group properties in percutaneous absorption [34, 46, 47]. Most strikingly, Roberts et al. [48] showed that the introduction of one hydrogen bonding group to a molecule significantly decreased its epidermal permeability, and the addition of further groups resulted in smaller decreases in permeability. They concluded that hydrogen bonding was the key factor in the diffusion of chemicals across the stratum corneum, and that lipophilicity was more important for partitioning, being possibly related to the $pK_a$ (and therefore ionisation state) of the penetrant. Clearly, as well as showing the importance of hydrogen bonding and ionisation this study also showed the fundamental non-linearity associated with increasing the number of hydrogen bonding groups – a substantial contrast to the understandings associated with studies – both qualitative and quantitative – based on small subsets of similar molecular, particularly homologous series.

Therefore, it may be clearly stated, as has been previously reported [3, 26, 44] that the nature of the model is absolutely reliant on the nature of the dataset – specifically, in terms of its size and distribution of data (in the context of physicochemical descriptors) therein. Considerations should therefore be given to understanding the nature of how the model was constructed before paying too much attention to what the model states.

**Linear or non-linear models?**

Cronin and Schultz [44] also commented that biological processes were seldom non-linear in nature and that modelling of such processes was unlikely to be successful without considering non-linearity. However, the vast majority of studies described above utilise linear methods. While attempts have been made to employ non-linear methods in this field, their use has, until recently, been confined to adjusting or correcting previous models. In most cases non-linear models appear to be of limited value as they can readily over-fit data, resulting in simply modelling the error present in the data – given the range of literature sources that the datasets are constructed from, and the range of experimental protocols used to generate the data, past considerations of non-linear modelling have been cautious but, ultimately, reasonable. This is particularly relevant to the modelling of smaller datasets.

Moss et al. [51] took a novel approach to the modelling of skin permeability by applying machine learning techniques, notably Gaussian Processes, to a large skin permeability dataset. In doing so they worked in a manner recommended by Cronin and Schultz [44] – that is, in a multi-disciplinary group of researchers whose expertise extends across all parts of the study and its methodology, particularly mathematics and statistics. The therefore initially examined the underlying nature of the skin permeability dataset used (an extension of the Flynn dataset) using simple methods of data visualisation and more complex methods such as principal and canonical [50] component analysis. They demonstrated the fundamentally non-linear nature of the skin dataset, which validated their choice of non-linear methods of analysis but which is also in stark contrast to the vast majority of studies in this field which have been carried out using (multiple) linear regression analysis and similar methods.

The main issue with their [49] work is its lack of transparency as the Gaussian Process, and related, methods used do not produce explicit functional representations of data – that is, equations such as those shown above and in Tables 1 and 2 that represent the relationship between the transport of a permeant across the skin and its physicochemical properties. The latter are represented as discrete terms in an equation. Lam et al. [42] addressed this issue by the use of Machine Learning methods, most notably Feature Selection, which is able to rank the significance of contributions made by each of the physicochemical parameters used in their study. They found that models of equal statistical quality and predictive ability could be constructed from certain range of physicochemical

parameters, and that certain parameters were effectively interchangeable, or possibly co-linear. Such apparent interchangeability of physicochemical descriptors – in a study to use one of the largest datasets analysed in the modelling of percutaneous absorption – perhaps reflects the myriad of conflicting models discussed above, and further suggests that the use of small datasets, or subsets, may bias the output of models to particular physicochemical parameters. It certainly reflects the importance of hydrogen bonding, as described by Roberts [18] in the context of models produced by Potts and Guy [2], among others. Non-linear methods have also recently been applied to this problem domain by Neely et al. [51], who produced a statistically robust model by integrating quantitative structure-permeability relationships, genetic algorithms and neural networks. Their model suggested that size/shape and polarity descriptors accounted for approximately 70% of the permeability information in their model.

While such methods may superficially appear to lack "real-world" relevance, particularly as they do not yield an easily digestible equation, their relevance was demonstrated by Lam et al. [42] when they compared the ability of their Gaussian Process model to the Potts and Guy [2] model. The results are shown in Figure 3, and are characterised by the difference not only in proximity of each model to its intended experimental target, but in the overall pattern of predictions across the whole dataset. Further, Moss et al. [43] have shown the relevance of Gaussian Process methods in a "real-world" situation when they examined a dataset of chemical penetration enhancers. They were able to show that the Machine Learning methods were able to provide fewer classification errors than discriminant analysis and were able to generate predictions of enhancement, something which discriminant analysis was not able to achieve. Therefore, while still a novel method the use of Machine Learning shows great potential but it does so – as all such studies should – within the framework for developing robust mathematical models of biological process described by Cronin and Schultz [44].

**Conclusions**

This is clearly a relatively brief and subjective overview of the field of modelling percutaneous absorption. It is a field fraught by subjective opinions and analyses. However, the key principles are relatively clear. From Roberts' important work [48] to Flynn's dataset [1] and Potts and Guy's landmark model [2], through later iterations of that approach, clear advances were made in both our mechanistic understanding of percutaneous absorption and in the predictive ability of models to

estimate absorption, potentially providing ethically and financially viable shortcuts to the screening of percutaneous absorption. An expansion of the field, mostly in the 1990s, saw a narrowing of focus to specific subsets, and with that a loss of the broad applicability of the best predictive models, but also an increased understanding of the permeation of specific compounds, which strongly suggested that a single holistic model was not perhaps the best approach to modelling skin absorption.

However, several authors [3, 44] suggested that the focus of model quality should be on the source of the data, not the methods used to analyse datasets. Aspects of data redundancy, data quality and uniformity have been raised by these authors and others, and continue to be the focus of research into developing better models [43]. In recent years, concomitant with advances in information technology, a range of new methods have been applied to the field. These include artificial neural networks, fuzzy logic and Machine Learning including ensemble models employing nearest-neighbour theories, which often utilise large pools of theoretical molecular descriptors in their modeling and simulation methods for stratum corneum lipids [41 – 43, 49 – 56]. Such methods have failed to establish themselves so far, probably as they are difficult to apply to non-experts and, in the case of Machine Learning methods in particular, insufficiently transparent as they do not develop a specific functional representation of the data.

Therefore, great advances have been made through the modelling of percutaneous absorption in our understanding of the mechanisms underpinning skin absorption. The increasing application of novel techniques, such as dermatopharmacokinetics, Confocal Raman spectroscopy and mass spectrometry-based imaging techniques to the characterisation of percutaneous absorption will provide detailed and specific endpoints currently unavailable to many researchers, and should open up the possibilities of modelling these phenomena in greater detail.

Finally, while such models are beginning to find initial application into an emerging regulatory framework concerned with the prediction of dermal absorption (for example, the excellent model developed by Frasch [57]), it is perhaps fitting to focus at this point on the work of Cronin and Schultz [44] once more. Their study has been refined by the authors and has informed the OECD Principles for the Validation of (Q)SAR Models (available at http://www.oecd.org/document/4/0,3746,en_2649_34379_42926724_1_1_1_1,00.html). As well as understanding the fundamental nature of the data being examined [41 – 43, 49, 50] the need to develop models that are based on the sound principles proposed by Cronin and Schultz (Table 3) will underpin future successes in this field, such as the approach of Hansen et al. [58], who combined

experimental and theoretical approaches to understand the mechanism of permeant-corneocyte interactions, recent work where flux, rather than the permeability coefficient, was modelled [59] or the microscopic multiphase diffusion models of Wang and colleagues [60, 61]. These approaches, and that of Naegel et al. [62], suggests that we have perhaps come full circle, and that a full understanding of skin biology, as emphasised at the beginning of this review, is as important as the design and construction of data sets.

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The first substantial work to examine the underlying nature of skin permeability data and to apply it in a real-world environment using the technique of feature selection.

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An excellent and novel study that has set a benchmark in the field.