Principles and Practice of Skin Toxicology

Editors

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and

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Dedications

(RC) For all my teachers, lecturers and professors. Especially the ones that were left in despair.

For Emlyn Evans and Trefor Pedrick. True gentlemen of knowledge.

For all of my family.

For the young ladies in my life:

*Caroline, Florence Megan and Charlotte Rose.*

(SP) For my partner in crime, Rob Chilcott, the more verbose member of the partnership, and Carolyn, for her patience

For Pete, my husband, and for Jessica and Jonathan for their patience during the editing of this document

For my mentors who taught me the essence of Toxicology – I am still learning!!
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*Keith R. Brain and Robert P. Chilcott*

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Foreword

Dermatologists seldom tire of telling us that the skin is a large and important organ. They are correct. The skin and the lungs are the two organ systems that are in constant and direct contact with the environment from birth to death and are thus, also, of great interest to toxicologists. The skin is susceptible to damage by a range of physical and chemical agents and responds to insult in a variety of ways. In some cases chronic exposure to chemicals leads to serious damage to the skin and to a loss of its essential protective function. Responses also include malignant changes and these, far from being protective, are sometimes lethal.

This book deals with many aspects of skin biology and skin toxicology and the editors, Dr Robert Chilcott and Dr Shirley Price, are to be congratulated on drawing together a distinguished team of authors and on producing a book that will, I think, take a leading place in the literature of his subject. The reader will find that the subject has been addressed in a systematic way beginning, appropriately, with normal structure and function and going on to consider the effects of an unusually wide range of toxic compounds. On reading this book I was struck by the truly scientific approach adopted wherever possible. This, for example in the sections dealing with the physico-chemical aspects of absorption of chemicals, has led to discussion that the beginner will find challenging. But this is appropriate in an advanced monograph and the quantitative approach developed by the authors is both very welcome and much needed in this, and other, areas of toxicology.

This book is the first from the Toxicology Unit of the Chemical Hazards and Poisons Division of the Health Protection Agency: its high standard is the best possible advertisement for our work.

Professor Robert L. Maynard CBE, FBTS
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Preface

The idea for this book was first conceived during the planning of a module in dermal toxicology as part of the Modular Training Programme in Applied Toxicology at the University of Surrey. In preparing a background reading list for the course, it became apparent that there was a niche for a basic, introductory text on the subject. We were very fortunate in that many of the experts who lectured on the course kindly agreed to contribute chapters in their specialist area. Furthermore, considerable effort has been made to ensure that the book is not just a collection of separate monographs on discrete areas of skin toxicology but is an integrated body of general information which draws across a broad spectrum of disciplines.

We hope that this book will succeed in being a useful aid for those wishing to acquire a basic understanding of the principles and practice of skin toxicology.

Robert P. Chilcott
Shirley Price
March 2008
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Firstly, we wish to thank Professor Robert Maynard for his support, advice and encouragement and for reviewing the draft manuscript.

Perhaps rather obviously, this text would have not been possible without the time and effort of the contributors to whom many thanks are due.

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PART I:
Introduction
1 Cutaneous anatomy and function

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Primary Learning Objectives

• Appreciation of the highly variable morphology of the skin, particularly between anatomical regions (intra-individual variation) and between species.
• Basic understanding of the functional anatomy of the epidermis in relation to skin barrier properties.

1.1 Introduction and scope

In terrestrial mammals, the integument contributes to a variety of physiological functions including thermoregulation, immune defence and the prevention of catastrophic water loss. It is the barrier property of skin that is of specific relevance to dermal toxicology (dermatotoxicology), so the purpose of this chapter is to outline the anatomical and histological features that contribute to skin barrier function. Therefore, this chapter concentrates on the outermost (epidermal) layers associated with protecting the skin from the ingress of xenobiotics. More detailed information on the structure and function of the dermis and hypodermis may be found elsewhere (Forslind et al. 2004; Freinkel and Woodley 2001; Montagna 1962).

1.2 Surface features

The skin is not a homogenous covering. Its structure and function vary considerably, resulting in regional variations in permeability that may span several orders of magnitude.

The protective function of the human integument is reflected by its relatively small surface area (∼2 m²). In contrast, the lung and gastrointestinal tract have evolved to facilitate absorption and so have much higher surface areas (∼150 and 200 m², respectively).
Human skin can essentially be divided into two types; glabrous (non-hairy) and non-glabrous. The former is generally thicker and less permeable than the latter and is limited to areas such as the palms of the hand, soles of the feet and lips.

Skin surface morphology varies according to anatomical region and this is particularly evident in humans where localised, functional adaptations have resulted in overt differences in appearance (Figure 1.1). Regional differences include variation in epidermal thickness and the density of hair follicles, sweat and sebaceous ducts (Table 1.1). Other differences include the presence or absence of ridges and sulci (dermatoglyphs), flexure lines, surface roughness and extent of oily (sebaceous) deposits. It is conceivable that the presence of furrows, wrinkles or dermatoglyphs may affect the skin surface distribution of liquids applied to the skin by providing a means for capillary motion away from the point of contact, thus facilitating skin surface spreading and so increasing the area of skin contamination (Figure 1.2). However, the influence of the skin surface micro-relief on skin absorption has not been thoroughly investigated. The human integument is also characterised by lines of cleavage referred to as Langer's lines, which result from the (congenital) orientation of collagen fibres within the dermis. The lines of Langer are of clinical significance in surgical procedures: incisions made

![Figure 1.1](image)

**Figure 1.1** Skin surface over the inner ear (A), hand (dorsum) (B) and wrist (ventral aspect) (C). Some dermatoglyphs are discernible on the inner ear site, but the main feature of the picture is the enlarged sebaceous duct (SD) specific to this anatomical region. The duct is surrounded by fine (velous) hairs, which provide some limited protection against foreign objects. Dermatoglyphics are pronounced on the back of the hand and are occasionally punctuated by hair follicles (HF) sprouting hair of medium coarseness. The wrist area is largely free of hair but flexure lines (indicated by small arrows) can be clearly seen running in parallel. Also visible are superficial veins (SV) of this region. Photographs courtesy of Dr Helen Packham, Enviroderm Services. A full-colour version of this figure appears in the colour plate section of this book.
### Table 1.1 Selection of quantitative data of human skin characteristics

<table>
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<th>Temperature</th>
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<td>Epidermis (µm)</td>
<td>Dermis (µm)</td>
<td>Turnover (days)</td>
<td>Desquamation (g m⁻² day⁻¹)</td>
<td>Glands (cm⁻²)</td>
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<tr>
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<td>547</td>
<td>1207</td>
<td>0–50</td>
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<td>2.1</td>
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Turnover (kinetics) refers to the average time taken for a cell in the stratum basale to reach the stratum corneum.
Figure 1.2  Surface autoradiograph of pig skin exposed to a single, discrete droplet (100 µl) of 14C-radiolabelled benzene under unoccluded conditions. Radioactive material (indicated by the dark areas) can be seen to preferentially partition into hair follicles (F) and hair shafts (S). Dermatoglyphics can be seen radiating from (and interconnecting) adjacent hair follicles (RD), indicative of capillary movement along the sulci.

parallel to Langer’s lines generally heal more readily and are less likely to form scar tissue (Monaco and Grumbine 1986).

Numerous studies have demonstrated that skin permeability is also subject to anatomical variation (Feldmann and Maibach 1967, Maibach et al. 1971, Rougier et al. 1986). Whilst epidermal thickness is commonly considered to be a prime determinant of regional skin permeability, such generalisations should be interpreted with caution (for example, see Figure 1.3) as other factors such as the regional lipid content (Table 1.1) or morphology of the stratum corneum may be implicated (Rougier et al. 1988).

There is a superficial ‘layer’ of skin that is often overlooked in dermal toxicology: the ‘acid mantle’. This forms a thin film on the skin surface and is comprised of sebum, corneocyte debris and residual material from sweat. This mixture of substances generally imparts a low pH on the skin surface owing to the presence of free fatty acids and, being predominantly lipophilic, may conceivably influence the partitioning of substances into the skin or act as an adsorbent matrix to trap microscopic particles such as dirt, dust or powders.

The predominant component of the acid mantle is sebum, considered by some to be vestigial (Kligman 1963). Sebum is mainly composed of triglycerides, wax esters and squalene, with the actual composition (and amount being secreted) varying according to anatomical location (Figure 1.4).

The evolutionary significance of sebum has been subject to much debate and several putative functions including anti-microbial activity, ‘water-proofing’ and ‘sweat-sheet’ formation have been proposed (Porter 2001). However, sebum may represent a significant route of excretion for lipophilic substances (Faergemann et al. 1993; Iida et al. 1999) and may be of physiological significance for the delivery of vitamin E to the skin surface where it could act as a superficial antioxidant (Thiele et al. 1999).