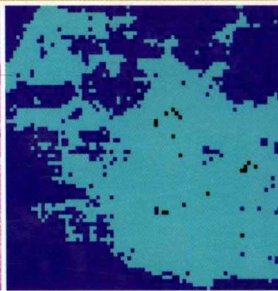
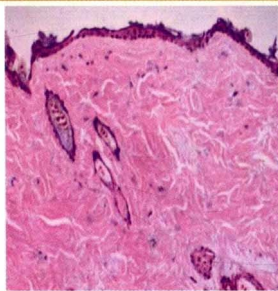
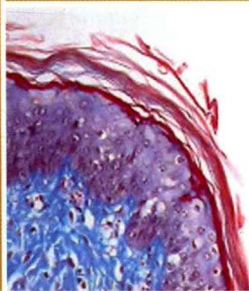


Principles and Practice of

# Skin Toxicology



Editors Robert P. Chilcott and Shirley Price

 WILEY

# **Principles and Practice of Skin Toxicology**

Copyright © 2008

John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester,  
West Sussex PO19 8SQ, England

Telephone (+44) 1243 779777

Email (for orders and customer service enquiries): [cs-books@wiley.co.uk](mailto:cs-books@wiley.co.uk)

Visit our Home Page on [www.wileyeurope.com](http://www.wileyeurope.com) or [www.wiley.com](http://www.wiley.com)

All Rights Reserved. No part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, scanning or otherwise, except under the terms of the Copyright, Designs and Patents Act 1988 or under the terms of a licence issued by the Copyright Licensing Agency Ltd, 90 Tottenham Court Road, London W1T 4LP, UK, without the permission in writing of the Publisher. Requests to the Publisher should be addressed to the Permissions Department, John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex PO19 8SQ, England, or emailed to [permreq@wiley.co.uk](mailto:permreq@wiley.co.uk), or faxed to (+44) 1243 770620.

Designations used by companies to distinguish their products are often claimed as trademarks. All brand names and product names used in this book are trade names, service marks, trademarks or registered trademarks of their respective owners. The Publisher is not associated with any product or vendor mentioned in this book.

This publication is designed to provide accurate and authoritative information in regard to the subject matter covered. It is sold on the understanding that the Publisher is not engaged in rendering professional services. If professional advice or other expert assistance is required, the services of a competent professional should be sought.

#### ***Other Wiley Editorial Offices***

John Wiley & Sons Inc., 111 River Street, Hoboken, NJ 07030, USA

Jossey-Bass, 989 Market Street, San Francisco, CA 94103-1741, USA

Wiley-VCH Verlag GmbH, Boschstr. 12, D-69469 Weinheim, Germany

John Wiley & Sons Australia Ltd, 42 McDougall Street, Milton, Queensland 4064, Australia

John Wiley & Sons (Asia) Pte Ltd, 2 Clementi Loop #02-01, Jin Xing Distripark, Singapore 129809

John Wiley & Sons Canada Ltd, 6045 Freemont Blvd, Mississauga, Ontario, L5R 4J3, Canada

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic books.

#### ***Library of Congress Cataloging-in-Publication Data***

Principles and practice of skin toxicology / editors, Robert P. Chilcott,  
Shirley Price.

p. ; cm.

Includes bibliographical references and index.

ISBN 978-0-470-51172-5

1. Dermatotoxicology. I. Chilcott, Robert P. II. Price, Shirley, Dr.  
[DNLM: 1. Skin Physiology. 2. Skin Absorption. 3. Skin Diseases. WR  
102 P957 2008]

RL803.P75 2008

615'.778 – dc22

2008002901

#### ***British Library Cataloguing in Publication Data***

A catalogue record for this book is available from the British Library

ISBN 978-0-470-51172-5

Typeset in 10/12 Minion by Laserwords Private Limited, Chennai, India

Printed and bound in Singapore by Markono Print Media Pte Ltd

This book is printed on acid-free paper responsibly manufactured from sustainable forestry in which at least two trees are planted for each one used for paper production.

# Principles and Practice of Skin Toxicology

Editors

**Robert P. Chilcott**

*Chemical Hazards and Poisons Division, Health Protection Agency, Chilton, UK*

and

**Shirley Price**

*School of Biomedical and Molecular Sciences, University of Surrey, UK*



John Wiley & Sons, Ltd

## 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!!

# 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**  
Chemical Hazards and Poisons Division,  
Health Protection Agency, Chilton, UK

# 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

# Acknowledgements

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.

Finally, we would like to thank all our colleagues at the Health Protection Agency and University of Surrey for their understanding and support during times when things didn't quite go exactly to plan.



# List of contributors

**Alexander Anstey**, Gwent Healthcare NHS Trust, Royal Gwent Hospital, Cardiff Road, Newport, Gwent NP20 2UB, UK.

**David A. Basketter**, St John's Institute of Dermatology, St Thomas' Hospital, London SE1 7EH, UK.

**Mark Birch-Machin**, Dermatological Sciences, Institute of Cellular Medicine, Newcastle-Upon-Tyne, NE2 4AA, UK.

**Keith Brain**, Welsh School of Pharmacy, Cardiff University, Cardiff, CF10 3XF and An-eX, Capital Business Park, Cardiff, CF3 2PX, UK.

**Robert P. Chilcott**, Chemical Hazards and Poisons Division, Centre for Radiation, Chemical and Environmental Hazards, Chilton, Oxfordshire OX11 0RQ, UK.

**Penny Jones**, Safety and Environmental Assurance Centre, Colworth Science Park, Sharnbrook, Bedford, Bedfordshire MK44 1LQ, UK.

**Manjunatha Kalavala**, University Hospital of Wales, Heath Park, Cardiff, CF14 4NJ, UK.

**Jo Larner**, ForthTox Ltd, PO Box 13550, Linlithgow, West Lothian EH49 7YU, UK.

**Chris Packham**, Enviroderm Services, North Littleton, Evesham, WR11 8QY, UK.

**Anthony D Pearse**, Cutest Systems Ltd, 214 Whitchurch Road, Cardiff, CF14 3ND, UK.

**Ruth U. Pendlington**, Safety & Environmental Assurance Centre, Unilever Colworth Science Park, Sharnbrook, Bedford, Bedfordshire MK44 1LQ, UK.

**W. John Pugh**, Welsh School of Pharmacy, Cardiff University, Redwood Building, King Edward VII Avenue, Cardiff, CF1 3XF, UK.

**Jon Spiro**, Capita Health Solutions, Didcot, Oxfordshire OX11 0TA, UK.

**Helen Taylor**, Enviroderm Services, North Littleton, Evesham, WR11 8QY, UK.

**James Wakefield**, Chemical Hazards and Poisons Division, Centre for Radiation, Chemical and Environmental Hazards, Chilton, Oxfordshire OX11 0RQ, UK.

**Simon C. Wilkinson**, Medical Toxicology Research Centre, University of Newcastle, Newcastle-Upon-Tyne, NE2 4AA, UK.

**Adam Woolley**, ForthTox Limited, PO Box 13550, Linlithgow, West Lothian EH49 7YU, UK.

# Contents

<b>Foreword</b>	<b>xv</b>
<b>Preface</b>	<b>xvii</b>
<b>Acknowledgements</b>	<b>xix</b>
<b>List of contributors</b>	<b>xxi</b>
<b>PART I Introduction</b>	<b>1</b>
<b>1 Cutaneous anatomy and function</b>	<b>3</b>
<i>Robert P. Chilcott</i>	
1.1 Introduction and scope	3
1.2 Surface features	3
1.3 Functional histology of the epidermis and associated structures	8
1.4 Species differences	13
Summary	15
References	15
<b>2 Biochemistry of the skin</b>	<b>17</b>
<i>Simon C. Wilkinson</i>	
2.1 Introduction and scope	17
2.2 Protein synthesis and organisation during epidermal differentiation	18
2.3 Lipid synthesis and organisation during epidermal differentiation	19
2.4 Lipid classes in the stratum corneum	20
2.5 Stratum corneum turnover	23
2.6 Biotransformations in skin	24
Summary	42
References	42

<b>3</b>	<b>Skin photobiology</b>	<b>51</b>
	<i>Mark A. Birch-Machin and Simon C. Wilkinson</i>	
3.1	Introduction and scope	51
3.2	Photoprotection and melanogenesis	51
3.3	Increased environmental ultraviolet radiation exposure and its link with photoageing and skin cancer	55
3.4	Mitochondrial DNA as a biomarker of sun exposure in human skin	60
3.5	Apoptosis	61
3.6	Sun protection	63
	Summary	65
	References	65
	 <b>PART II Skin Absorption</b>	 <b>69</b>
<b>4</b>	<b>Skin as a route of entry</b>	<b>71</b>
	<i>Simon C. Wilkinson</i>	
4.1	Salient anatomical features of the stratum corneum – the ‘brick and mortar model’	71
4.2	Species and regional variation in skin structure	72
4.3	Species and regional variation in skin permeability	74
4.4	Intra- and inter-individual variation in percutaneous absorption	75
4.5	Effect of age on skin barrier function	76
4.6	Role of skin appendages	77
4.7	The <i>in vitro</i> skin sandwich model	78
4.8	Penetration of particles through appendages	79
	Summary	80
	References	80
<b>5</b>	<b>Physicochemical Factors Affecting Skin Absorption</b>	<b>83</b>
	<i>Keith R. Brain and Robert P. Chilcott</i>	
5.1	Introduction	83
5.2	Physicochemical properties	84
5.3	Exposure considerations	89
	Summary	91
	References	91
<b>6</b>	<b>Principles of Diffusion and Thermodynamics</b>	<b>93</b>
	<i>W. John Pugh and Robert P. Chilcott</i>	

6.1	Introduction and scope	93
6.2	Some definitions pertaining to skin absorption kinetics	94
6.3	Basic concepts of diffusion	97
6.4	Fick's Laws of diffusion	97
6.5	Thermodynamic activity	98
6.6	Skin absorption of a substance from two different vehicles	99
6.7	Partitioning	101
6.8	Diffusivity	102
6.9	Skin absorption data and risk assessments	105
	Summary	106
	References	106
<b>7</b>	<b><i>In vivo</i> measurements of skin absorption</b>	<b>109</b>
	<i>James C. Wakefield and Robert P. Chilcott</i>	
7.1	Introduction and scope	109
7.2	Why conduct <i>in vivo</i> studies?	110
7.3	Ethics and legislation	110
7.4	Standard methodology: OECD Guideline 427	115
7.5	Alternative <i>in vivo</i> methods	119
	Summary	126
	References	126
<b>8</b>	<b><i>In vitro</i> percutaneous absorption measurements</b>	<b>129</b>
	<i>Ruth U. Pendlington</i>	
8.1	Introduction and scope	129
8.2	Regulatory guidelines	129
8.3	Why assess percutaneous absorption <i>in vitro</i> ?	130
8.4	Basic principle of <i>in vitro</i> percutaneous absorption measurements	131
8.5	Choice of diffusion cell	131
8.6	Skin membrane considerations	136
8.7	Integrity measurements	137
8.8	Choice of receptor fluid and sampling considerations	138
8.9	Test material considerations	139
8.10	Application of test preparation to the skin	140
8.11	Examples of results from <i>in vitro</i> skin absorption studies	142
8.12	What is considered to be absorbed?	146
8.13	Micro-autoradiography	147
	Summary	147
	References	147

<b>PART III Toxicological Assessment</b>	<b>149</b>
<b>9 Skin immunology and sensitisation</b>	<b>151</b>
<i>David A. Basketter</i>	
9.1 Introduction	151
9.2 Definitions	151
9.3 Skin sensitisation	152
9.4 Identification of skin sensitisers	155
9.5 Risk assessment	160
9.6 Other types of allergic skin reaction	163
9.7 Future prospects	164
Summary	164
References	165
<b>10 <i>In vitro</i> phototoxicity assays</b>	<b>169</b>
<i>Penny Jones</i>	
10.1 Introduction and scope	169
10.2 <i>In vitro</i> strategies for phototoxicity testing	169
10.3 The UV/visible absorption spectrum as a pre-screen for phototoxicity	171
10.4 <i>In vitro</i> assays for phototoxicity using monolayer cultures	172
10.5 <i>In vitro</i> assays for photoallergenicity	174
10.6 <i>In vitro</i> assays for phototoxicity using human 3-D skin models	177
Summary	181
References	181
<b>11 <i>In vitro</i> alternatives for irritation and corrosion assessment</b>	<b>185</b>
<i>Penny Jones</i>	
11.1 Introduction and scope	185
11.2 Acute dermal irritation/corrosion	185
11.3 Validation/regulatory status of <i>in vitro</i> assays for skin corrosion	186
11.4 <i>In vitro</i> tests for skin corrosion	188
11.5 Validation/regulatory status of <i>in vitro</i> assays for skin irritation	194
11.6 <i>In vitro</i> tests for skin irritation	195
Summary	197
References	198
<b>12 Instruments for measuring skin toxicity</b>	<b>201</b>
<i>Helen Taylor</i>	
12.1 Introduction and scope	201

12.2	Skin surface pH	202
12.3	Biomechanical properties	204
12.4	Sebum	205
12.5	Skin surface contours	205
12.6	Thickness	205
12.7	Desquamation	205
12.8	Applications and measurement of transepidermal water loss	206
12.9	Guidance for TEWL measurements	208
12.10	Hydration measurement	209
12.11	Guidance for hydration measurements	212
12.12	Relationship between hydration and dermal toxicity	213
12.13	Colour measurement	213
12.14	Measurement of vascular perfusion	215
12.15	A final word of caution	216
	Summary	217
	References	217
<b>PART IV Clinical Aspects</b>		<b>221</b>
<b>13</b>	<b>Introduction to dermatology</b>	<b>223</b>
	<i>Manjunatha Kalavala and Alex Anstey</i>	
13.1	Introduction and scope	223
13.2	Clinical assessment of patient with skin disease	224
13.3	Cutaneous manifestations of disease following exposure to chemicals and pharmaceutical formulations	234
13.4	Overview of standard treatments	241
	Summary	243
<b>14</b>	<b>Clinical aspects of phototoxicity</b>	<b>245</b>
	<i>Anthony D. Pearse and Alex Anstey</i>	
14.1	Introduction and scope	245
14.2	UV-induced skin reactions	247
14.3	Phototoxicity (photoirritancy) reactions	247
14.4	Photosensitive reactions	251
	Summary	256
	References	256
<b>15</b>	<b>Occupational skin diseases</b>	<b>259</b>
	<i>Jon Spiro</i>	

15.1	Introduction and scope	259
15.2	Dermatitis	260
15.3	Development of occupational dermatitis	263
15.4	Patterns of occupational dermatitis	264
15.5	Incidence of occupational dermatitis	265
15.6	Effects of dermatitis on work	265
15.7	The outlook in occupational dermatitis	266
15.8	Identification of occupational dermatitis	266
15.9	Other occupational skin disorders	267
15.10	Investigation of a case of dermatitis at work	270
	Summary	276
	References	276
<b>16</b>	<b>Prevention of occupational skin disease</b>	<b>279</b>
	<i>Chris Packham</i>	
16.1	Prevention of occupational skin disease	279
16.2	Defining the problem	280
16.3	Material safety data sheets	282
16.4	Chain of responsibility	283
16.5	Managing dermal exposure	284
16.6	Selection and use of personal protective equipment	289
16.7	Protective or 'barrier' creams: do they have a role?	294
16.8	The role of education and training	294
16.9	Conclusions	294
	Summary	294
	References	294
<b>PART V</b>	<b>Regulatory</b>	<b>297</b>
<b>17</b>	<b>Occupational skin exposures: legal aspects</b>	<b>299</b>
	<i>Chris Packham</i>	
17.1	Introduction and scope	299
17.2	Brief overview of current United Kingdom legislation	300
17.3	The employer's perspective	303
17.4	Hazard identification	304
17.5	Risk assessment	306
17.6	Gloves: a note of caution	309
	Summary	310
	References	310

<b>18 Safety assessment of cosmetics: an EU perspective</b>	<b>311</b>
<i>Jo Larner</i>	
18.1 Introduction and scope	311
18.2 Overview and scope of Cosmetics Directive 76/768/EC	312
18.3 Overview of the requirements of the EU Cosmetics Directive	315
18.4 Scientific advice	316
18.5 Influence of other legislation	317
18.6 Adverse effects from cosmetics	318
18.7 Toxicity of cosmetic ingredients	320
18.8 The safety assessment	326
18.9 A final consideration	328
Summary	329
References	329
Appendix 18.1 Additional obligations for cosmetic suppliers	330
<b>19 Regulatory dermatotoxicology and international guidelines</b>	<b>333</b>
<i>Adam Woolley</i>	
19.1 Introduction	333
19.2 Regulatory context	334
19.3 Product groups and the human context	335
19.4 Dermal toxicology with the different product groups	336
19.5 Factors in dermal toxicity	338
19.6 Repeat dose dermal toxicology	339
19.7 Classic short-term dermal toxicity studies	341
19.8 Pragmatic considerations	344
Summary	345
References	345
<b>20 Glossary of main terms and abbreviations</b>	<b>347</b>
<i>James C. Wakefield</i>	
<b>Index</b>	<b>358</b>



# **PART I: Introduction**