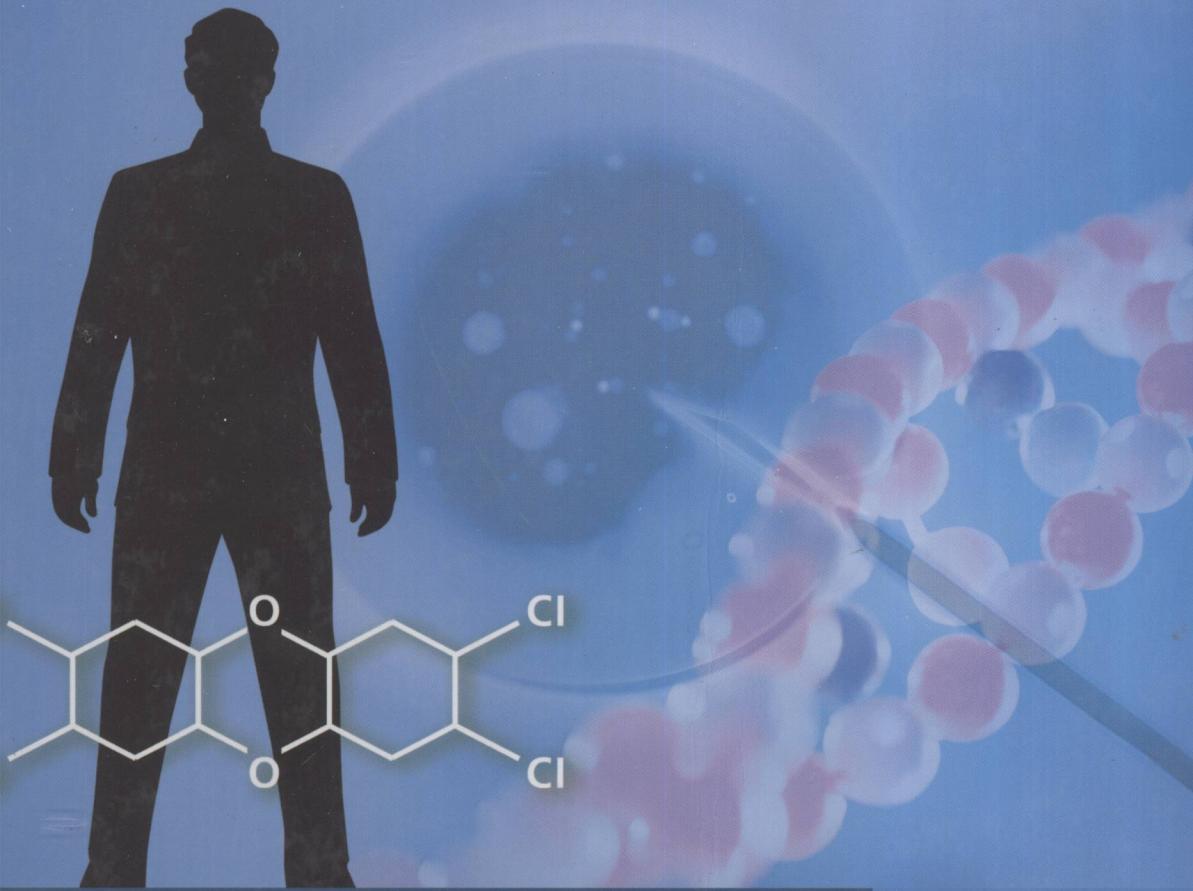


Editors: Helmut Greim and Robert Snyder

Toxicology and Risk Assessment

A Comprehensive Introduction



 WILEY

R99
T755

Toxicology and Risk Assessment: A Comprehensive Introduction

Edited by

HELMUT GREIM, M.D.

Institut für Toxikologie und Umwelthygiene, Technische Universität München

ROBERT SNYDER, Ph.D.

*Environmental and Occupational Health Sciences Institute,
Rutgers, The State University of New Jersey*



E2008001547



John Wiley & Sons, Ltd

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
Visit our Home Page on www.wileyeurope.com or 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, 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.

The Publisher and the Author make no representations or warranties with respect to the accuracy or completeness of the contents of this work and specifically disclaim all warranties, including without limitation any implied warranties of fitness for a particular purpose. The advice and strategies contained herein may not be suitable for every situation. In view of ongoing research, equipment modifications, changes in governmental regulations, and the constant flow of information relating to the use of experimental reagents, equipment, and devices, the reader is urged to review and evaluate the information provided in the package insert or instructions for each chemical, piece of equipment, reagent, or device for, among other things, any changes in the instructions or indication of usage and for added warnings and precautions. The fact that an organization or Website is referred to in this work as a citation and/or a potential source of further information does not mean that the author or the publisher endorses the information the organization or Website may provide or recommendations it may make. Further, readers should be aware that Internet Websites listed in this work may have changed or disappeared between when this work was written and when it is read. No warranty may be created or extended by any promotional statements for this work. Neither the Publisher nor the Author shall be liable for any damages arising herefrom.

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 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

Toxicology and risk assessment : a comprehensive introduction / edited by Helmut Greim and Robert Snyder.

p. ; cm.

Includes bibliographical references and index.

ISBN 978-0-470-86893-5 (cloth : alk. paper)

1. Toxicology. 2. Poisons—Risk assessment. 3. Health risk assessment.

I. Greim, Helmut. II. Snyder, Robert, 1935-

[DNLM: 1. Poisoning. 2. Hazardous Substances—toxicity. 3. Risk Assessment. QV 600 T75566 2007]

RA1211.T6348 2007

615.9—dc22

2007021098

British Library Cataloguing in Publication Data

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

ISBN 978-0-470-86893-5

Typeset in 10/12 pt Times by Thomson Digital, India

Printed and bound in Great Britain by Antony Rowe Ltd, Chippenham, Wiltshire, England

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.

Toxicology and Risk Assessment

This book is dedicated to Professor Herbert Remmer (1919–2003), late Director of the Institute of Toxicology of the University of Tübingen. He was a pathfinder in the biomedical sciences, a dedicated teacher, and an inspiration to all of his friends and colleagues. His work established a standard of excellence for generations of scientists to come. He is sorely missed.

Preface

About 30 years ago the need for trained toxicologists in the German chemical industry prompted Professors Herbert Remmer and Helmut Greim to organize a 3-year toxicology training program for 20 chemists. Using this experience the German Society of Pharmacology and Toxicology developed criteria to receive a certificate designating the 'Fach-Toxikologe' and initiated a broad training program to provide the information required. It became obvious that a text book was needed to accompany the classroom work to meet the needs of the students. The book* was published in the German language in 1995 and subsequently in Italian.** When time came for a new edition, the publishers, who were interested in expanding the market, suggested that a new edition, which could service a broader representation of the community of scholars in toxicology, should be written in English. The editors, Helmut Greim and Robert Snyder, decided to prepare a completely new book to ensure that recent achievements in toxicology are covered and each chapter produced by the faculty contained essential knowledge for a toxicologist. The authors and editors hope that the book proves useful to students and provides information at a level that will enable them to successfully study toxicology.

The current book is intended for people with a broad range of toxicological interests, including both practical and mechanistic subjects. References at the end of each chapter will allow the reader to go beyond this book into the toxicological literature. Furthermore, coverage extends into areas such as the 'omics,' biomarkers, molecular and cell biology, and newer approaches to risk assessment. It stresses the important need for overlap between mechanistic studies and safety assessment.

There are two famous admonitions in toxicology. The first, by Paracelsus, appears in the introduction. The second has been credited to any of several of our colleagues: 'Toxicology can be learned in two lessons, each 20 years long.' We hope that this book can start students down the path toward an exciting and productive career in toxicology.

Helmut Greim and Robert Snyder

**Toxikologie. Eine Einführung für Naturwissenschaftler und Mediziner.* H. Greim und E. Deml eds, (Wiley)-Verlag Chemie, Weinheim, 1995.

***Toxicology.* H. Greim and E. Deml eds, Zanichelli, Bologna, 2000.

List of Contributors

Ilse-Dore Adler Institut für Genetik, GSF-Forschungszentrum für Umwelt & Gesundheit, Neuherberg, Germany

Marion W. Anders Department of Pharmacology, University of Rochester, NY, USA

Ulrich Andrae Institut für Toxikologie, GSF-Forschungszentrum für Umwelt & Gesundheit, Neuherberg, Germany

Rüdiger Bartsch Institut für Toxikologie und Umwelthygiene, Technische Universität München, Germany

Michael G. Bird Toxicology & Environmental Sciences Division, ExxonMobil Biomedical Sciences, Inc., Annandale, New Jersey, USA

Paul J. A. Borm Centre of Expertise in Life Sciences, Zuyd University, Heerlen, The Netherlands

Jeroen T. M. Buters Zentrum Allergie & Umwelt, Klinik & Poliklinik für Dermatologie & Allergologie der Technischen Universität München, Germany

Peter Calow Department of Environmental, Social and Spatial Change, Roskilde University, Denmark

György Csanády Institut für Toxikologie, GSF-Forschungszentrum für Umwelt & Gesundheit, Neuherberg, Germany

Gisela H. Degen Institut für Arbeitsphysiologie an der Universität Dortmund, Germany

Wolfgang Dekant Institut für Pharmakologie und Toxikologie der Universität Würzburg, Germany

Gunter P. Eckert Pharmakologisches Institut deo Universität Frankfurt, Germany

Thomas Efferth Deutsches Krebs Forschungs-Zentrum, Heidelberg, Germany

Victor J. Feron TNO Quality of Life, Business Unit Toxicology & Applied Pharmacology, Zeist, Netherlands

Johannes G. Filser Institut für Toxikologie, GSF-Forschungszentrum für Umwelt & Gesundheit, Neuherberg, Germany

Valery E. Forbes Department of Environmental, Social and Spatial Change, Roskilde University, Denmark

Kristian W. Fried Department of Pharmacology, Toxicology and Therapeutics, University of Kansas Medical Center, Kansas City, USA

Carol R. Gardner Department of Pharmacology and Toxicology, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, NJ, USA

Helmut Greim Institut für Toxikologie und Umwelthygiene, Technische Universität München, Germany

Stefan Halbach Institut für Toxikologie, GSF-Forschungszentrum für Umwelt & Gesundheit, Neuherberg, Germany

Franz Hofmann Institut für Pharmakologie und Toxikologie, Technische Universität München, Germany

Diana Jonker TNO Quality of Life, Business Unit Toxicology & Applied Pharmacology, Zeist, Netherlands

Bernd Kaina Institut für Toxikologie, Universität Mainz, Germany

Herrmann Kappus Klinik für Dermatologie, Charite, Campus Virchow-Klinikum, Berlin, Germany

Peter Kasper Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn, Germany

Ines M. Lanzl Augenklinik und Poliklinik Rechts der Isar der Technischen Universität München, Germany

Debra L. Laskin Department of Pharmacology and Toxicology, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, NJ, USA

Stephan Madle Bundesinstitut für Risikobewertung, Berlin, Germany

Pearl Moy ChemRisk, Inc., San Francisco, USA

Walter E. Müller Pharmakologisches Institut für Naturwissenschaftler, Johann Wolfgang Goethe-Universität, Frankfurt am Main, Germany

J. William Owens The Procter and Gamble Company, Central Product Safety, Cincinnati, Ohio, USA

Ulrike Pabel Bundesinstitut für Risikobewertung, Berlin, Germany

Jürgen Pauluhn Bayer AG, Institut für Toxikologie IC, Wuppertal, Germany

Dennis J. Paustenbach ChemRisk, Inc., San Francisco, USA

Karl K. Rozman Department of Pharmacology, Toxicology and Therapeutics, University of Kansas Medical Center, Kansas City, USA

Tibor A. Rozman Department of Pharmacology, Toxicology and Therapeutics, University of Kansas Medical Center, Kansas City, USA

Jens Schlossmann Institut für Pharmakologie und Toxikologie, Technische Universität München, Germany

Leslie Schwarz Institut für Toxikologie, GSF-Forschungszentrum für Umwelt & Gesundheit, Neuherberg, Germany

Michael Schwenk Medizinische Hochschule Hannover, Germany

Andreas Seeber Institut für Arbeitsphysiologie an der Universität Dortmund, Germany

Thomas Singer F. Hoffmann-La Roche AG, Basel, Switzerland

Robert Snyder Associate Dean for Research and Professor of Pharmacology and Toxicology, Ernest Mario School of Pharmacy and the Environmental and Occupational Health Sciences Institute, Rutgers the State University of New Jersey, Piscataway, USA

Günter Speit Institut für Humangenetik, Universität Ulm, Germany

Horst Spielmann Bundesinstitut für Risikobewertung, Berlin, Germany

Lesley Stanley Consultant in Investigative Toxicology, Fife, Scotland

Myriam Straube Bundesinstitut für Arzneimittel und Medizinprodukte

Karl-Heinz Summer Institut für Toxikologie, GSF-Forschungszentrum für Umwelt & Gesundheit, Neuherberg, Germany

Laura Suter-Dick F. Hoffmann-La Roche AG, Basel, Switzerland

Ladislaus Szinicz Institut für Pharmakologie und Toxikologie, Sanitätsakademie der Bundeswehr, München, Germany

Jürgen Timm Institut für Statistik der Universität Bremen, Germany

Kurt Ulm Institut für Medizinische Statistik und Epidemiologie des Klinikums Rechts der Isar der Technischen Universität München, Germany

John B. Watkins Medical Sciences, Indiana University School of Medicine, Bloomington, IN, USA

Thomas Zilker Toxikologische Abteilung der II. Medizinischen Klinik und Poliklinik Rechts der Isar der Technischen Universität München, Germany

Contents

Preface	xv
List of Contributors	xvii
1 Introduction to the Discipline of Toxicology	1
<i>Helmut Greim and Robert Snyder</i>	
1.1 Introduction	1
1.2 The Risk-Assessment Process	2
1.2.1 Hazard Identification	2
1.2.2 Dose–Response and Toxic Potency	3
1.2.3 Exposure Assessment	4
1.2.4 Risk Characterization	5
1.3 Toxicological Evaluation of New and Existing Chemicals	6
1.3.1 General Requirements for Hazard Identification and Risk Assessment	6
1.3.2 General Approach for Hazard Identification and Risk Assessment	11
1.3.3 Toxicological Issues Related to Specific Chemical Classes	12
1.3.4 Existing Chemicals	13
1.3.5 Classification of Carcinogens	16
1.4 Summary	17
2 Principles	19
2.1 Toxicokinetics	19
<i>Johannes G. Filser</i>	
2.1.1 Definition and Purpose	19
2.1.2 Absorption, Distribution, and Elimination	20
2.1.3 Toxicokinetic Models	33
2.1.4 Summary	48
2.2A Phase I Metabolism	49
<i>Jeroen T.M. Buters</i>	
2.2A.1 Introduction	49
2.2A.2 The Enzymes Involved in Phase I Metabolism	55

2.2A.3 Phase III (Metabolism)	70
2.2A.4 Summary	73
2.2B Drug Metabolism	74
<i>Leslie Schwarz and John B. Watkins</i>	
2.2B.1 Conjugation	74
2.2B.2 Hydrolysis	90
2.2B.3 Summary	94
2.3 Toxicogenetics	96
<i>Lesley Stanley</i>	
2.3.1 Introduction	96
2.3.2 Genotyping and Phenotyping	97
2.3.3 Correlating Genotype and Phenotype	98
2.3.4 The Role of Polymorphisms in Influencing Susceptibility to Toxic Agents	99
2.3.5 Acute Toxicity	107
2.3.6 Polymorphic Drug Transporters	108
2.3.7 Polymorphic Xenobiotic Receptors	109
2.3.8 Summary	110
2.4 Cytotoxicity	112
<i>Leslie Schwarz and John B. Watkins</i>	
2.4.1 Introduction	112
2.4.2 The Cell	115
2.4.3 Cellular Targets of Toxic Chemicals	119
2.4.4 Mechanisms Underlying Cell Death	127
2.4.5 Summary	131
2.5 Receptor-Mediated Mechanisms	132
<i>Jens Schlossmann and Franz Hofmann</i>	
2.5.1 Introduction	132
2.5.2 Ligand–Receptor Interactions	133
2.5.3 Receptor-signal Transduction	137
2.6 Mixtures and Combinations of Chemicals	139
<i>Victor J. Feron and Diana Jonker</i>	
2.6.1 Introduction	139
2.6.2 Types of Mixed Exposures	140
2.6.3 Types of Joint Actions and Their Role in Safety Evaluation	141
2.6.4 Designs for Toxicity Studies of Mixtures or Combinations	143
2.6.5 Safety Evaluation	146
2.6.6 Summary	150
2.7 Chemical Carcinogenesis: Genotoxic and Nongenotoxic Mechanisms	151
<i>Thomas Efferth and Bernd Kaina</i>	
2.7.1 Introduction	151
2.7.2 Mechanisms of DNA Damage, Repair, and Carcinogenesis	153
2.7.3 Cancer Development	164

2.7.4	Nongenotoxic Mechanisms of Carcinogenesis	175
2.7.5	Implications of Initiation and Promotion for Risk Assessment	178
2.7.6	Summary	179
2.8	Reproductive Toxicology	180
<i>Horst Spielmann</i>		
2.8.1	Introduction	180
2.8.2	Characteristics of Reproductive Toxicology	181
2.8.3	Adverse Effects on Female and Male Fertility	182
2.8.4	Pre- and Postnatal Toxicology	185
2.8.5	Summary	192
2.9	Ecotoxicology: Not just Wildlife Toxicology	194
<i>Peter Calow and Valery E. Forbes</i>		
2.9.1	Introduction	194
2.9.2	Protection Targets	194
2.9.3	Necessary Information	195
2.9.4	Risk Assessment	200
2.9.5	Fast-track Approaches	202
2.9.6	Summary	203
3	Organ Toxicology	205
3.1	The Gastrointestinal Tract	205
<i>Michael Schwenk</i>		
3.1.1	Introduction	205
3.1.2	Structure and Function	206
3.1.3	Fate of Xenobiotics in the GI Tract	208
3.1.4	Toxicology	211
3.1.5	Summary	215
3.2	The Liver	216
<i>Leslie Schwarz and John B. Watkins</i>		
3.2.1	Introduction	216
3.2.2	Structure and Function	216
3.2.3	Toxicology	220
3.2.4	Summary	226
3.3	The Respiratory System	227
<i>Jürgen Pauluhn</i>		
3.3.1	Introduction	227
3.3.2	Structure and Function	228
3.3.3	The Respiratory System as Target for Toxicity	235
3.3.4	Test Systems to Detect Toxic Effects of Inhaled Materials	242
3.3.5	Summary	243
3.4	The Nervous System	244
<i>Gunter P. Eckert and Walter E. Müller</i>		
3.4.1	Structure and Function of the Nervous System	244
3.4.2	The Nervous System - Site of Attack for Toxins	255

3.4.3	Clinical Signs and Symptoms Induced by Neurotoxins	262
3.4.4	Summary	263
3.5	Behavioral Neurotoxicology	265
<i>Andreas Seeger</i>		
3.5.1	Introduction	265
3.5.2	Exposure Assessment	265
3.5.3	Methods	267
3.5.4	Neurobehavioral Effects in Humans	275
3.5.5	Summary	278
3.6	The Skin	279
<i>Tibor A. Rozman, Myriam Straube and Karl K. Rozman</i>		
3.6.1	Structure	280
3.6.2	Function	281
3.6.3	Toxicology of the Skin and the Anterior Segment of the Eye	284
3.6.4	Summary	294
3.7	The Kidney and Urinary Tract	295
<i>Helmut Greim</i>		
3.7.1	Introduction	295
3.7.2	Anatomy and Function	295
3.7.3	Toxicology	298
3.7.4	Summary	304
3.8	Toxicology of the Blood and Bone Marrow	305
<i>Robert Snyder</i>		
3.8.1	Introduction	305
3.8.2	Hematopoiesis	306
3.8.3	Toxicological Features of Circulating Blood Cells	308
3.8.4	Leucocytosis and Leukemia	313
3.8.5	Summary	315
3.9	Immunotoxicology	316
<i>Carol R. Gardner and Debra L. Laskin</i>		
3.9.1	Introduction	316
3.9.2	Anatomical Organization of the Immune System	318
3.9.3	Effects of Toxicants on the Immune System	322
3.9.4	Procedures for Assessing Immunotoxicity	325
3.9.5	Summary	327
3.10	The Eye	329
<i>Ines M. Lanzl</i>		
3.10.1	Introduction	329
3.10.2	Structure and Function of the Eye	329
3.10.3	Routes of Delivery of Xenobiotics to the Eye	332
3.10.4	Specific Toxicology of the Eye	333
3.10.5	Summary	342
3.11	The Cardiovascular System	343
<i>Helmut Greim</i>		
3.11.1	Structure and Function	343

3.11.2 Toxicology	346
3.11.3 Summary	351
4 Methods in Toxicology	353
4.1 OECD Test Guidelines for Toxicity Tests <i>in vivo</i>	353
<i>Rüdiger Bartsch</i>	
4.1.1 Introduction	353
4.1.2 Requirements for <i>in vivo</i> Tests	354
4.1.3 Acute Toxicity	356
4.1.4 Skin and Eye Irritation	359
4.1.5 Skin Sensitization	361
4.1.6 Toxicity after Repeated Dosing	362
4.1.7 Reproductive Toxicity	366
4.1.8 Other Test Guidelines	370
4.1.9 Summary	370
4.2A Mutagenicity Tests <i>in vivo</i>	371
<i>Ilse-Dore Adler</i>	
4.2A.1 Introduction	371
4.2A.2 Chromosomal Mutations in Somatic Cells	373
4.2A.3 Gene Mutations in Somatic Cells	375
4.2A.4 Chromosome Mutations in Germ Cells	376
4.2A.5 Gene Mutations in Germ Cells	381
4.2A.6 Summary	383
4.2B <i>In vitro</i> Tests for Genotoxicity	385
<i>Ulrich Andrae and Günter Speit</i>	
4.2B.1 Introduction	385
4.2B.2 Xenobiotic Metabolism <i>in vitro</i>	386
4.2B.3 Test Systems Employing Bacteria	388
4.2B.4 Test Systems Employing Mammalian Cells	391
4.2B.5 Cell-Transformation Assays	404
4.2B.6 Summary	405
4.2.C Strategies for the Evaluation of Genotoxicity	406
<i>Stephan Madle, Peter Kasper, Ulrike Pabel and Günter Speit</i>	
4.2C.1 Introduction	406
4.2C.2 Basics of Genotoxicity Testing	407
4.2C.3 Current Approaches for Assessing Genotoxicity	409
4.2C.4 Summary	417
4.3 Biomonitoring	418
<i>Michael G. Bird</i>	
4.3.1 Introduction	418
4.3.2 History	420
4.3.3 Biomonitoring Programs	421
4.3.4 Study Design	422
4.3.5 Case Study Examples	424
4.3.6 Summary	425

4.4 Epidemiology	426
<i>Kurt Ulm</i>	
4.4.1 Introduction	426
4.4.2 Measures to Describe the Risk	426
4.4.3 Standardization	429
4.4.4 Types of Epidemiological Studies	431
4.4.5 Statistics	433
4.4.6 Causality, Bias, Confounding, Chance	434
4.4.7 Summary	436
4.5 Omics in Toxicology	437
<i>Laura Suter-Dick and Thomas Singer</i>	
4.5.1 Introduction	437
4.5.2 Concept of Toxicogenomics	437
4.5.3 Technology Platforms	438
4.5.4 Bioinformatics and Biostatistics	443
4.5.5 Applications of Toxicogenomics	444
4.5.6 Summary	448
4.6 Introduction to the Statistical Analysis of Experimental Data	449
<i>György Csanády</i>	
4.6.1 Introduction	449
4.6.2 Descriptive Statistics	452
4.6.3 Error Propagation	455
4.6.4 Probability Distribution	456
4.6.5 Inferential Statistics	461
4.6.6 Regression Analysis	470
4.6.7 Probit Analysis	473
4.6.8 Experimental Designs	474
4.6.9 Statistical Software	475
4.6.10 Summary	476
5 Risk Assessment	479
5.1 Mathematical Models for Risk Extrapolation	479
<i>Jurgen Timm</i>	
5.1.1 Introduction	479
5.1.2 Methods of Extrapolation	482
5.1.3 Consideration of the Time Aspect	483
5.1.4 Methods for Determination of Benchmark Doses and Unit Risks	485
5.1.5 Dose-conversion	487
5.1.6 Models of Carcinogenesis	487
5.1.7 Assumptions and Limits of Extrapolation in Mathematical Models	490
5.1.8 Summary	492

5.2	Regulations Regarding Chemicals and Radionuclides in the Environment, Workplace, Consumer Products, Foods, and Pharmaceuticals	494
<i>Dennis J. Paustenbach and Pearl Moy</i>		
5.2.1	Introduction	494
5.2.2	Occupational Health Regulations	495
5.2.3	Food and Drug Regulation	498
5.2.4	Environmental Regulation	500
5.2.5	Consumer Product Regulation	505
5.2.6	Radionuclides Regulation	506
5.2.7	Governmental Agencies on Human Health	507
5.2.8	Regulations in the European Union (EU) and United Kingdom (UK)	509
5.2.9	International Chemical Regulations	509
5.2.10	Summary	511
6	Toxicity of Selected Chemicals	513
6.1	Persistent Polyhalogenated Aromatic Hydrocarbons	513
<i>Kristian W. Fried and Karl K. Rozman</i>		
6.1.1	Introduction	513
6.1.2	PCDDs and PCDFs	513
6.1.3	Polychlorinated Biphenyls (PCBs)	515
6.1.4	DDT	517
6.1.5	HCB	518
6.1.6	Properties	519
6.1.7	Toxicity	520
6.1.8	Mechanisms of Action	526
6.1.9	Metabolism	530
6.1.10	Enzyme Induction	530
6.1.11	Kinetics	531
6.1.12	Summary	533
6.2	Metals	534
<i>Karl-Heinz Summer, Stefan Halbach, Herrmann Kappus and Helmut Greim</i>		
6.2.1	Introduction	534
6.2.2	Toxicity	535
6.2.3	Carcinogenicity	537
6.2.4	Toxicity of Individual Metals	539
6.2.5	Summary	564
6.3	Toxicology of Fibers and Particles	565
<i>Paul J.A. Borm</i>		
6.3.1	Introduction	565
6.3.2	Particle Toxicology: Basic Concepts	565
6.3.3	Particle Properties	573
6.3.4	Nanoparticles: A Special Case?	577
6.3.5	Special Particle Effects	578
6.3.6	Summary	581

6.4	Xenoestrogens and Xenoantiandrogens	583
	<i>Gisela H. Degen and J. William Owens</i>	
6.4.1	Introduction	583
6.4.2	Toxicities	584
6.4.3	Modes of Action and Testing	586
6.4.4	Compound Assessment	592
6.4.5	Summary	602
6.5	Toxicology of Solvents	604
	<i>Wolfgang Dekant and Marion W. Anders</i>	
6.5.1	Introduction	604
6.5.2	Toxicology of Selected Solvents	607
6.5.3	Summary	619
6.6	Noxious Gases	621
	<i>Ladislau Szinicz</i>	
6.6.1	Introduction	621
6.6.2	Airborne Systemic Poisons	621
6.6.3	Respiratory Tract Irritants	628
6.6.4	Irritant Gases	629
6.6.5	Summary	634
6.7	Animal and Plant Toxins	635
	<i>Thomas Zilker</i>	
6.7.1	Introduction	635
6.7.2	Animal Toxins	635
6.7.3	Plant Toxins	645
6.7.4	Summary	653
	Index	657