

Toxicology and Risk Assessment

Toxicology and Risk Assessment: A Comprehensive Introduction

Second Edition

Edited By

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Api, Anne Marie Anne Marie Api is Vice President, Human Health Sciences at the Research Institute for Fragrance Materials, Inc. (RIFM). Dr. Api has used her advanced knowledge of fragrance ingredient safety to establish a quality record of managing fragrance ingredient safety at RIFM. She has authored over 100 scientific publications and is a member of numerous scientific organizations. She received for the 2018 Toxicology Forum Philippe Shubik Distinguished Scientist Award.

Bartsch, Rüdiger Dr. Rüdiger Bartsch is certified expert in toxicology (DGPT) and has worked for more than 20 years in the scientific secretariat of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area of the German Research Foundation. His main work is the derivation of occupational exposure levels for industrial chemicals, focusing on the underlying toxic mechanism. Dr. Bartsch is a biologist and received his PhD from the Technical University of Munich.

Bevan, Ruth Dr. Ruth Bevan has considerable expertise in toxicology and human health risk assessment in areas connected with environmental or occupational exposure to chemicals. She has published on a broad range of environment and health issues, notably in the field of occupational cancer burden and biomonitoring of environmental exposures (including via consumer articles, drinking water, food and air).

Blömeke, Brunhilde Brunhilde Blömeke received her PhD in biology and started her academic career as a molecular toxicologist. At present she holds the position of Professor for Environmental Toxicology at the University of Trier, Germany. Her primary research interest is focused on the molecular mechanisms of chemicals and the development of *in vitro* methods for their detection and risk assessment. She serves as member of several advisory committees, including the DFG

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Borm, Paul Paul Borm holds degrees in biochemistry (MSc) and pharmacology (PhD), and has focused his academic career (1984–2004) on inhalation toxicology and risk assessment. Since 2011 Paul Borm has been CSO and shareholder of Nano-Imaging (Aachen), as well as managing director of Nanoconsult. He supports both start-ups in business development and advises major international companies with regard to risk management and product stewardship. In addition he holds a professorship at the University of Düsseldorf and teaches medical imaging.

Calow, Peter Peter Calow is a professor at the Humphrey School of Public Affairs, University of Minnesota and has held previous professorial positions at the universities of Nebraska-Lincoln (USA), Sheffield (UK), and Roskilde (Denmark). His current research is on the interface between science and public policy, with special interest in the better use of risk assessment in environmental policy and regulation. He has written more than 300 articles and edited/authored more than 20 books.

Csanády, György András György András Csanády (1958–2011) studied chemistry at the Eötvös-Loránd-University, Budapest, where he received his PhD. After research positions in Austria and the chemical industry at the Institute of Toxicology, North Carolina he joined the Institute of Toxicology at the federal Research Center in Munich, Germany. His research activities focused on the development of physiological based toxicokinetic models for the risk assessment of chemicals. He held the position of Associate Professor at the Technical University of Munich.

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Dietrich, Daniel Professor Daniel Dietrich, PhD, ERT, FATS, studied biochemistry and biology at the University of Zurich and ETH Zurich, gaining a Master of Science (1984) and a PhD in toxicology (Institute of Toxicology ETH Zurich, 1988). He is head of the Institute of Human and Environmental Toxicology at the University of Konstanz, elected external expert “Life Sciences for Human Well-being” for the European Parliament, ad hoc expert for the High Level Group of the European Commission’s Scientific Advice Mechanism, and Academic Advisor for the European Risk Forum.

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Efferth, Thomas Professor Dr. Thomas Efferth is chair of the Department of Pharmaceutical Biology, Institute of Pharmacy and Biochemistry, Johannes Gutenberg University, Mainz, Germany. He is honorary professor at the Northeast Forestry University, Harbin, and at the Zhejiang Chinese Medical University, Hangzhou, China. Moreover, he is visiting professor at the Zhejiang University of Science and Technology, Hangzhou, China. He has published over 490 PubMed-listed papers in the field of cancer research, pharmacology, and natural products, and is editor-in-chief of the journal *Phytomedicine*. He is scientific advisory board member of the German Pharmaceutical Society and several other institutions.

Filser, Johannes G. Johannes G. Filser, PhD, studied biochemistry at the University of Tübingen; habilitation thesis at the University of Mainz in 1987. His main research topics at the Institutes of Toxicology at the Universities of Tübingen and Mainz and later on at the federal Research Center (former GSF) were toxicokinetics and metabolism of xenobiotics in laboratory animals and humans. Between 1993 and 2012 he served as associate professor at the Technical University of Munich.

Forbes, Valery Valery Forbes is Dean of the College of Biological Sciences at the University of Minnesota, a position she has held since July 2015. A marine biologist by training, Dr. Forbes' research aims to improve the science underlying risk assessments of chemicals and other stressors on ecological systems.

Gebel, Thomas Professor Dr. Thomas Gebel is head of the toxicology unit at the German BAuA, the Federal Institute for Occupational Safety and Health. He deals with the toxicological evaluation of workplace chemicals with respect to both hazard classification and occupational exposure limit setting. He is associate professor for environmental toxicology at the Technical University of Dortmund.

Göen, Thomas Professor Dr. Thomas Göen is a chemist and expert in the human metabolism of hazardous substances as well as analytical procedures for the determination of such substances and their metabolites in biological matrices. He is a member of the DFG Senate Commission for the Investigation of Hazardous Compounds in the Work Area and the Human Biomonitoring Commission of the German Federal Environment Agency. He is also engaged in the organization of the German External Quality Assessment Scheme, which offers the proficiency control of laboratories worldwide for about 200 biomonitoring parameters.

Greim, Heidrun Heidrun Greim has a PhD in chemistry and has been involved in toxicology for many years. As head of the scientific secretariat of the GDCH Advisory Committee on Existing Chemicals and the DFG Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (German MAK Commission), the focus of her work is the hazard as well as the risk assessment of chemicals and the regulatory toxicology.

Greim, Helmut Helmut Greim is Professor Emeritus at the Technical University of Munich. After receiving his MD in Pediatrics he joined the Institute of Pharmacology of the Freie University at Berlin. In 1955 he moved to the Institute of Toxicology at the University of Tübingen and after holding a Research Associate Professorship at the Department of Pathology at the Mount

Sinai School of Medicine, New York between 1970 and 1973 he became director of the Institute of Toxicology of the Gesellschaft für Strahlen- und Umweltforschung in Munich, Germany in 1975 and between 1987 and 2003 was Director and Chairman of the Institute of Toxicology of the Technical University of Munich. He has served as member or chairman of many national and international committees such as the Health Effects Institute, Boston, the Health and Environmental Safety Institute, Washington DC, the Research Institute of Fragrance Materials (Woodcliff NJ, chair 2000–2008), Scientific Committee on Health and Environmental Risks (chair 2004–2012), the Risk Assessment Committee of the European Chemicals Agency and the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area of the German Research Foundation (chair 1992–2007). Dr. Greim's major research interest has been the metabolism and mechanisms of toxic chemicals, alternative methods to animal testing as well as training in toxicology.

Griem, Peter Dr. Peter Griem studied biochemistry in Berlin and Tübingen, Germany and did his PhD in the area of immunotoxicology at Düsseldorf University, completing postgraduate training in toxicology (DGPT, ERT, DABT). After working with FoBiG GmbH, Wella AG, and Clariant AG Dr. Griem joined Symrise AG in 2011 as Head of Toxicology. Throughout his professional career the interaction of chemicals with the immune system has stayed one of his focal points of interest.

Harrison, Paul Professor Paul Harrison has an impressive depth and range of experience in the field of toxicological risk assessment, having for many years investigated the linkages between environmental quality and human health. His principal areas of expertise are dust and fiber toxicology, indoor air quality, endocrine disruption and chemical risk assessment. He has held positions on numerous expert groups and committees and has published many scientific papers and articles on a broad range of toxicological issues.

Hartung, Thomas Thomas Hartung, MD, PhD, is the Doerenkamp-Zbinden-Chair for Evidence-based Toxicology with a joint appointment for Molecular Microbiology and Immunology at Johns Hopkins Bloomberg School of Public Health, Baltimore. He holds a joint appointment as Professor for Pharmacology and Toxicology at University of Konstanz, Germany. He also is Director of Centers for Alternatives to Animal Testing (CAAT). CAAT hosts the secretariat of the Evidence-based Toxicology Collaboration, the Good Read-Across Practice Collaboration, the Good Cell Culture Practice Collaboration, the Green Toxicology Collaboration and the Industry Refinement Working Group. As PI, he heads the Human Toxome project funded as an NIH Transformative Research Grant. He is the former Head of the European Commission's Center for the Validation of Alternative Methods, Ispra, Italy, and has authored more than 500 scientific publications.

Hartwig, Andrea Andrea Hartwig is Full Professor and Chair of the Department of Food Chemistry and Toxicology at the Karlsruhe Institute of Technology, Karlsruhe, Germany. Her main research area focuses on the impact of carcinogenic metal compounds, including metal-based nanoparticles, as well as essential trace elements on genomic stability, with special emphasis on DNA damage induction and DNA damage response systems. Since 2007 she has been chair of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (German MAK commission).

Hengstler, Jan G. Jan G. Hengstler studied medicine, began his research work at the institute of Toxicology in Mainz, became Professor of Molecular Toxicology at the Leipzig University, and currently is director of the Leibniz Research Center in Dortmund. His research interests include

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Hofmann, Franz Professor Dr. Franz Hofmann studied medicine at the Universities of Heidelberg, Munich and Berlin. He started his academic career at the Institute of Pharmacology at the University of Heidelberg, worked between 1973 and 1975 at the Department of Biological Chemistry, in the Medical School at the University of California, Davis, USA and after returning to pharmacology in Heidelberg he became Chairman and Professor of Physiological Chemistry at the University of the Saarland in 1985. Between 1990 and his retirement in 2007 he served as chairman and Professor of Pharmacology and Toxicology at the Technical University of Munich. His research activities focused on the function, distribution and mechanisms of the cAMP- and cGMP-dependent protein kinases. He also paid special attention to cardiac and smooth muscle function, and carried out experiments to understand the role and function of the cAMP- and cGMP-dependent protein kinases in these tissues.

Holmes, Philip Philip Holmes has over 40 years' experience as a toxicologist and chemical risk assessor, having worked in pharmaceutical and agrochemical development, academia, and consultancies. During this time he has studied a wide range of chemical classes in relation to the risk posed to humans from occupational or environmental exposure, as well as the application of toxicological and epidemiological data to the socioeconomic analysis of chemical regulation options.

Jahnke, Gunnar Gunnar Jahnke studied food chemistry and did his PhD thesis in the field of metal toxicology and DNA repair in the group of Andrea Hartwig at the Technical University of Berlin, Germany. Since 2007 he has been a member of the scientific secretariat of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (German MAK Commission). He is a European Registered Toxicologist.

Kaina, Bernd Professor Bernd Kaina obtained his PhD in genetics in 1976. He completed his postdoctoral training at the Institute of Genetics in Gatersleben (Germany), the Department of Molecular Biology in Leiden (The Netherlands), the German Cancer Research Center in Heidelberg and, as a Heisenberg fellow, at the Department of Genetics at the Nuclear Research Center in Karlsruhe, Germany. In 1993 he obtained a full professorship at the Institute of Toxicology of the University in Mainz, and since 2004 has acted as director of the Institute. His working fields are DNA repair and damage signaling, regulation of cell death, and mechanisms of carcinogenesis.

Kehe, Kai Colonel (MC) PD Dr. Kai Kehe received his doctorate in medicine from the Technical University of Munich in 1991 and was a postdoctoral fellow at the Bundeswehr Institute of Pharmacology and Toxicology and the Walther-Straub Institute of Pharmacology and Toxicology, Ludwig-Maximilians-University of Munich. Dr. Kehe specializes in pharmacology and toxicology, and is lecturer and assistant professor in pharmacology and toxicology at the Ludwig-Maximilians-University of Munich. In 2016 he earned a Master of Business Administration for medical doctors from the University of Neu-Ulm, Germany. Dr. Kehe is currently head of the Medical CBRN Defense Division at the Bundeswehr Medical Academy in Munich, Germany.

Lanzl, Ines Professor Dr. med. Ines Lanzl is currently teaching ophthalmology at the Medical School of the Technical University of Munich and is practicing ophthalmology in the city of Prien, Bavaria, Germany. Her research and clinical focus is on a multidisciplinary approach to ophthalmic pathology with a special interest in ocular surface, immunology, and perfusion as well as increasing disease awareness and patient compliance.

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Lilienblum, Werner Dr. Werner Lilienblum, a chemist by training, received his PhD at the University of Marburg, Germany, became a certified toxicologist (Fachtoxikologe DGPT) at the University of Göttingen in 1983 and is a EUROTOX Registered Toxicologist. He headed the State Authority for Occupational Safety and the Environment, Hannover and Hildesheim, Germany. Since retirement he has been a toxicology consultant and independent researcher. He served as a member of the Scientific Committee for Consumer Safety of the European Commission, sat on many scientific national boards, and served as a member of the German Society of Toxicology.

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Paustenbach, Dennis Dennis Paustenbach has been the President of ChemRisk for more than 20 years. About 5 years ago, ChemRisk merged with Cardno, an Australian environmental services firm. Dr. Paustenbach has a BS in chemical engineering from the Rose-Hulman Institute of Technology (Terre Haute), an MS in industrial hygiene and toxicology from the University of Michigan (Ann Arbor) and a PhD in toxicology from Purdue University. He did postgraduate work at the Wright-Patterson Air Force Base and the Harvard School of Public Health. He has authored more than 250 peer-reviewed publications, about 50 book chapters, and two books on risk assessment that are used by many graduate schools of public health and medicine. His specialty is environmental and occupational toxicology.

Ritz, Vera Dr. Vera Ritz has worked at the German Federal Institute for Risk Assessment since 2006 and heads the Steering and Overall Assessment Biocides unit in the Department of Safety of Pesticides. Her expertise is the toxicological evaluation of biocides and plant protection products as a European Registered Toxicologist. Her background is a diploma in biology and a PhD in toxicology and genetics.

Rozman, Karl Karl Rozman (1945–2017) studied organic and pharmaceutical chemistry at the University of Innsbruck and received his PhD in 1973. He then worked in the Institutes of Ecological Chemistry and of Toxicology of the former Gesellschaft für Strahlen- und Umweltforschung,

first in Munich and since 1974 in the branch at the Albany Medical College in Alamogordo, New Mexico. In 1981 he joined the Department of Pharmacology, Toxicology and Therapeutics of Kansas Medical Center in Kansas City, where he was appointed professor in 1986. His main field of work was the toxicology of halogenated hydrocarbons such as TCDD.

Schlossmann, Jens Jens Schlossmann studied chemistry at the Universities of Tübingen and Munich. For his diploma thesis he worked at the Max-Planck-Institute for Biochemistry (Martinsried) in the Department of Cell Biology. In 1990 he joined the Institute of Physiological Chemistry of Munich University and between 1995 and 2007 worked at the Institute of Pharmacology and Toxicology of the Technical University of Munich investigating substrate proteins of cGMP-dependent protein kinase. In 2007 he was appointed Professor for Pharmacology and Toxicology at the Institute of Pharmacy of the Regensburg University, Germany. His research fields comprise NO/cGMP signaling mechanisms in cardiovascular, renal and immunological functions, and he also studies the role of cyclic pyrimidinic nucleotides. He is editor and reviewer of several scientific journals.

Schriever-Schwemmer, Gerlinde Gerlinde Schriever-Schwemmer studied biology and mathematics with a focus on human genetics and did her PhD thesis in the field of immunology and carcinogenicity at the DKFZ, German Cancer Research Center, Heidelberg. Thereafter she worked in the field of mammalian mutation research in the group of Ilse-Dore Adler at the Helmholtz Center, Munich, the German research center for environmental health. Since 2000 she has been a member of the scientific secretariat of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (German MAK Commission).

Schulz, Florian Dr. Florian Schulz holds a PhD in biochemistry. During his doctoral thesis in the Institute of Toxicology at Hannover Medical School he was engaged with the cellular mode of action of bacterial toxins. Afterwards Dr. Florian Schulz joined the Department of Chemical Risk Assessment at the Fraunhofer Institute for Toxicology and Experimental Medicine in Hannover, Germany. Since then he has worked as a scientist in the field of inhalation toxicology, including the derivation of occupational exposure limit values for particles and fibers.

Schwenk, Michael Michael Schwenk studied biochemistry and medicine at the University of Tübingen, Germany. He specializes in pharmacology, toxicology and environmental medicine, and is Member of IUPAC Division on Chemistry and Human Health.

Snyder, Robert Robert Snyder is a trained chemist and biochemist and received his PhD at the College of Medicine, Syracuse, NY. After a postdoctoral fellowship in the Department of Pharmacology, University of Illinois College of Medicine he joined the Department of Pharmacology at the Jefferson Medical College, Philadelphia, being finally promoted to Professor of Pharmacology. Between 1981 and 2010 he held the Professorship of Toxicology at Rutgers, State University of New Jersey. During this time he served as Professor and Chairman of Pharmacology and Toxicology, Director of the Health Effects Assessment Division at the New Jersey Institute of Technology, and Director of the Division of Toxicology of the Environmental and Occupational Health Institute. Dr. Snyder's main research interest is the metabolism and toxic mechanism of benzene. He has been the chief organizer of the International Symposia on Benzene 1995 in Piscataway, NJ, 1998 in Ottawa, 2005 and 2009 in Munich, Germany, and at the New York Academy of Sciences in 2012. He served as member of several national advisory committees (USEPA, FDA, NAS/NRC) and was President of the American College of Toxicology.

Solecki, Roland Alfred Dr. Roland Alfred Solecki is a biologist and toxicologist by training and Head of Department of Pesticide Safety in the German Federal Institute for Risk Assessment. He is involved in the toxicological testing and human health risk assessment of pesticides. Dr. Solecki was a World Health Organization panel member in the JMPR and is currently a member of the Scientific Committee of EFSA.

Spielmann, Horst Horst Spielmann is Professor for Regulatory Toxicology at the Freie Universität Berlin, Germany. His book *Drugs in Pregnancy and Lactation*, with various co-authors, was first published in 1987 in German and has now appeared in seven German editions, three English editions, one edition each in Russian and Chinese. He is one of the international promoters of alternative test methods in toxicology and an Honorary Member of the following societies: Japanese Society for Alternatives to Animal Experiments (2007), European Society for Toxicology In Vitro (2012), Society for Dermopharmacy (2013) and the Chinese In Vitro Science Academic Committee (2017).

Stanley, Lesley Dr. Lesley Stanley is a toxicologist with over 30 years' experience in assessing the effects of chemicals on human health. Since May 2005 she has been a freelance consultant in investigative toxicology, advising clients in academia, government and industry on experimental strategy and assisting with literature reviews, grant applications and report/manuscript preparation. Her previous experience includes six years as a Senior (latterly Principal) Lecturer in Biomedical Science at De Montfort University, Leicester, UK as well as at the University of Oxford, the Medical Research Council Toxicology Unit and the National Institute of Environmental Health Sciences, North Carolina, USA.

Strauss, Volker Volker Strauss is certified specialist of clinical pathology. He has 15 years of toxicology expertise in the pharmaceutical and chemical industry. Presently he is Senior Scientist in the Department of Experimental Toxicology and Ecology, BASF SE, Ludwigshafen, Germany.

Suter-Dick, Laura Laura Suter-Dick is European Registered Toxicologist and Professor for Molecular Toxicology in the School of Life Sciences at the University of Applied Sciences Northwestern Switzerland. She acquired more than 20 years of research experience in the pharmaceutical industry before moving to academia in 2012. Her research included the fields of toxicogenomics and molecular toxicology, applying *in vivo* assays, new technologies, and alternative *in vitro* methods.

Thiermann, Horst Colonel (MC) Professor Dr. Horst Thiermann studied medicine. He started his career in the Bundeswehr Hospital, Munich, Germany in the departments of anaesthesiology and surgery. Thereafter, he moved to the Bundeswehr Institute of Pharmacology and Toxicology. He specialized in Pharmacology and Toxicology at the Walther-Straub-Institute of Pharmacology and Toxicology, Ludwig Maximilians-University, Munich in 1996. In 2002, he completed his advanced studies of clinical pharmacology at MDS Pharma Services, Höhenkirchen-Siegersbrunn. Since November 2006 he has been director of the Bundeswehr Institute of Pharmacology and Toxicology. In January 2012 he was appointed Professor at the Technical University of Munich.

Timm, Jürgen Jürgen Timm is Professor for Mathematics and Applied Statistics at the University of Bremen, where he founded the Centre of Competence for Clinical Trials and the masters program Medical Biometry/Biostatistics. He has served as leading biostatistician in hundreds of biomedical projects, as a biometrical expert for the federal and state government, and as a temporary WHO advisor. For 20 years he managed the University of Bremen as Rektor (President).

Ulm, Kurt After studying mathematics and information science at the Technical University of Munich Kurt Ulm received a PhD in statistics and later on became Professor at the Institute of Medical Statistics and Informatics. He spent about a year at the University of Washington at Seattle, USA. Dr. Ulm serves as member of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (German MAK Commission).

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Wollin, Klaus-Michael Klaus-Michael Wollin studied chemistry at the Technical University of Dresden and the University of Rostock. In 1980 he received his doctorate from the University of Rostock, where he worked at the Institute of Public Health from 1979 to 1989. From 1990 to 2004 he headed the Department for Risk Assessment of Contaminated Sites at the State Agency of Ecology Hildesheim-Hannover and 2006 moved to the Centre of Health and Infection Control at the Lower Saxony Agency of Public Health Hannover, Germany. He is a certified toxicologist (DGPT, ERT). He is a member of the German federal advisory bodies Committee on Hazardous Substances (AGS) and Human Biomonitoring Commission, and of the pool of experts on Rapid Risk Assessment at the EU's SCHER. His research focuses on health effects from environmental pollution.

Zilker, Thomas Thomas Zilker studied medicine at the University of Munich, where he received his MD. He specialized in internal medicine, endocrinology, and environmental medicine. After serving as Assistant Medical Director of the Department of Clinical Toxicology at the Technical University of Munich he directed this institution for almost 20 years.

Preface

About 40 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 “Fachtoxikologe” and initiated a broad training program to provide the information required. Later on the criteria to become a “Certified Toxicologist” were developed by the European Society of Toxicology. It became obvious that a textbook was needed to accompany the classroom work to meet the needs of the students. The first 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 were covered and each chapter produced by the faculty contained essential knowledge for a toxicologist or anyone interested in understanding the basics of our discipline. In the meantime the German book was updated and published in 2017.*** We now present the second edition of the English textbook. Apart from two, all chapters have been rewritten, mostly by new authors, and chapters have been added to cover new areas of toxicological relevance, including general concepts of human health risk assessment, threshold effects for genotoxic carcinogens, the endocrine system, principles of nanomaterial toxicology, pesticides, fragrances, and diesel engine emissions. Since an understanding of the regulations of dangerous materials has become increasingly important, in addition to the US regulations the corresponding EU regulations and the concept of REACH are covered.

This book is intended for people with a broad range of toxicological interests, including both practical and science-based subjects. References at the end of each chapter allow the reader to go beyond this book into more detailed information.

The authors and editors hope that the book proves useful to all users and provides information at a level that will enable them to understand the basic principles of toxicology and to successfully study our discipline.

There are two famous admonitions in toxicology. The first, by Paracelsus, “the dose makes a poison”, appears in the introduction. The second has been credited to any of several of our colleagues: “Toxicology can be learned in two lessons, each 10 years long.”

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

** Tossicologia, H. Greim and E. Deml (eds), Zanichelli, Bologna, 2000.

*** Das Toxikologiebuch: Grundlagen, Verfahren, Bewertung, Wiley-VCH, Weinheim 2017.

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Dedication

This book is dedicated to Herbert Remmer (1919–2003) and John Doull (1922–2017). Herbert Remmer was Professor and Director of the Institute of Toxicology at the University of Tübingen. In Germany, together with Dietrich Henschler in Würzburg he converted toxicology from a mere observational discipline to a research-based branch of medicine and sciences.

John Doull was Professor of Pharmacology and Toxicology at the University of Kansas. In 1981 in his article “The Discipline of Toxicology” in *Fundamental and Applied Toxicology* he questioned “Is it desirable for toxicology to be viewed as a scientifically rigorous discipline? The answer is clearly yes. One of the most important reasons is that if we expect to recruit the bright students to the discipline of toxicology we must strive to be scientifically rigorous and objective.”

The contributions of both these men as educators, authors, and editors served to build a solid and stable base for the discipline of toxicology. Their work established a standard of excellence for generations of scientists to come. They are sorely missed.

List of Abbreviations

- 5-CSRTT** 5-choice serial reaction time task
- 2,4-D** 2,4-dichlorophenoxyacetic acid
- 2,4-DB** 4-(2,4-dichlorophenoxy)butyric acid
- 2,4,5-T** 2,4,5-Trichlorophenoxyacetic acid
- AAF, 2-AAF** 2-acetaminofluorene
- AAS** Atomic absorption spectrometry
- ACD** Allergic contact dermatitis
- ADH** Alcohol dehydrogenase
- ADI** Acceptable (allowable) daily intake
- ADME** Absorption, distribution, metabolism, excretion
- ADP** Adenosine phosphate
- Ah** Aryl hydrocarbon
- AHH** Aryl hydrocarbon hydroxylase
- AhR, AHR** Ah receptor
- ALARA** As low as reasonably achievable
- ALDH** Aldehyde dehydrogenase
- AMH** Anti-Muellerian hormone
- AML** Acute myelogenous leukemia
- ANFT** 2-amino-4-(5-nitro-2-furyl)thiazole
- AOEL** Acceptable operator exposure level (for applicators of pesticides)
- AP** Apurin
- AP-1** Activator protein 1
- Apaf-1** Apoptosis protease activating factor-1

- APC** Antigen-presenting cells
- APS** Adenosine-5-phosphosulfate
- AR** Androgen receptor
- ARE** Antioxidant/electrophile response element
- ARfD** Acute reference dose
- ARNT** Aryl hydrocarbon receptor response element
- AT** Acetyl transferase
- ATE** Acute toxicity estimates
- ATM** Ataxia-telangiectasia mutated (kinase)
- ATP** Adenosine triphosphate
- ATR** Ataxia telangiectasia and Rad3-related (kinase)
- ATRIP** ATR-interacting protein
- AUC** Area under the curve
- BALF** Bronchoalveolar lavage fluid
- B[a]P** Benzo[a]pyrene
- BARS** Behavioral assessment and research system
- Bax** bcl-2-associated X protein (expressed by p53)
- BBN** *N*-butyl-*N*-(4-hydroxybutyl) nitrosamine
- BER** Base excision repair
- BMD** Benchmark dose
- BMDL** Benchmark dose level
- BPA** Bisphenol A
- BrdUrd, BrdU** Bromodesoxyuridine
- BSEP** Bile salt export pump
- BUN** Blood urea nitrogen
- CA** Carboanhydrase
- CAD** Caspase activated DNase
- cAMP** Cyclic adenosine monophosphate
- CAR** Constitutive androstane receptor
- CASE** Computer automated structure evaluation
- CAT** Catalase

- CANTAB** Cambridge neurophysiological test automated battery
- CDK** Cyclin-dependent kinase
- CEO** Cyano ethylene oxide
- cGMP** Cyclic guanosine monophosphate
- CHK, Chk** Checkpoint kinase
- CHMP** Committee for Medicinal Products for Human USE (of EMA)
- CK** Creatine kinase
- CKMB** Creatine kinase primarily in myocardial cells
- CLP** 1. Classification, Labelling and Packaging (of Substances and Mixtures); 2. Common lymphoid progenitor
- CLRTAP** Convention on long-range transboundary air pollution
- CMP** Common myeloid progenitor
- CPT** Continuous performance test
- CRP** C-reactive protein (parameter for systemic inflammatory processes)
- CSE** Chronic solvent-induced encephalopathy
- cSNP** Coding SNP (single nucleotide polymorphism)
- CTBP** Cytosolic T3-binding protein
- CTL** Cytotoxic T-lymphocytes
- CYP** Cytochrome P450
- Cys** Cysteine
- DAG** Diacylglycerol
- DDE** *p,p'*-dichlorodiphenyl dichloroethene
- DDR** DNA-damage response
- DDT** 2,2-bis(chlorophenyl)-1,1,1-trichloroethane
- DEHP** Di(2-ethylhexyl)phthalate
- DES** Diethylstilbestrol
- DHT** Dihydrotestosterone
- DIGE** Difference gel electrophoresis
- DISC** Death-inducing signalling complex
- DMAP** Dimethylaminophenole
- DMSO** Dimethylsulfoxide
- DMT-1** Divalent metal transporter-1

- DNA** Desoxyribonucleic acid
- DNEL** Derived no effect level
- DPRA** Direct peptide reactivity assay
- DRE** Dioxin responsive element
- DROSHA** Double-stranded RNA-specific endoribonuclease
- DSB** Double-strand break
- DTH** Delayed type hypersensitivity
- EAA** Excitatoric amino acid
- EAC** Endocrine-active compound
- EBV** Epstein–Barr virus
- EC** European Commission
- ECG** Electrocardiography
- ECHA** European Chemicals Agency
- ED** Endocrine disrupter
- ED₅₀** Effective dose causing the expected effect in 50% of exposed individuals
- EE** Ethinylestradiol
- EFSA** European Food Safety Authority
- EGF** Epidermal growth factor
- ELISA** Enzyme-linked immunosorbent assay
- EMA, EMEA** European Medicines Agency
- EMP** Erythromyeloic progenitor
- EMS** Ethyl methanesulfonate
- ENTIS** European Network of Teratology Information Service
- EoBP** Eosinophil/basophil progenitor
- EOGRTS** Extended one-generation reproductive toxicity study
- EPA** Environmental Protection Agency (USA)
- ER** Estrogen receptor, endoplasmic reticulum, excess risk
- ESTR** Expanded single tandem repeat (assay)
- EU** European Union
- EURATOM** European Atomic Energy Community
- FAD** Flavin adenine dinucleotide

- FADD** Fas-associated protein with death domain
- FANFT** *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide
- FAO** Food and Agriculture Organization
- Fapy** Formamidopyridimidine
- FasR** Fas-receptor (CD95)
- FDA** Food and Drug Administration (USA)
- FELS** Fish early life stage
- FISH** Fluorescence *in situ* hybridization
- FMN** Flavin mononucleotide
- FMO** Flavin-dependent monooxygenase
- FNT** 2-(4-(5-nitro-2-furyl)-2-thiazolyl)hydrazin
- FOB** Functional observation battery
- FPG** Formamidopyrimidine DNA glycosylase
- FSH** Follicle-stimulating hormone
- FS-OOH** Fatty acid hydroperoxides
- G6PD** Glucose-6-phosphate dehydrogenase
- GABA receptor** Gamma-aminobutyric acid receptor
- GALT** Gut-associated lymphoid tissue
- GAP** GTPase-activating protein
- GBP** Granular biopersistent particles
- GC** Guanylyl cyclase
- GCP** Good clinical practice
- GD** Gestation day
- GDP** Guanosindiphosphate
- GEF** Guanine nucleotide exchange factor
- GGR** Global genomic repair
- GHS** Globally Harmonized System for classification and labelling of chemicals
- GI** Gastrointestinal
- GLP** Good laboratory practice
- Glu** Glutamic acid
- Gly** Glycine

GMP	Granulocyte-macrophage progenitor, good manufacturing practice
GnRH	Gonadotropin-releasing hormone
GPCR	G-protein-coupled receptor
GPMT	Guinea pig maximization test
GPT	Glutamate pyruvate transaminase
GSEC	Genetic susceptibility to environmental carcinogens
GSH	Glutathione (reduced)
GSSG	Glutathione (oxidized)
GST	Glutathione-S transferase
GTP	Guanosine triphosphate
GW	Gestation week
GWAS	Genome wide association studies
Hb	Hemoglobin
HC5	Hazardous concentration 5%
HCB	Hexachlorobenzene
HCBD	Hexachloro-1,3-butadiene
hCG	Human choriogonadotropin
HDI	Hexamethylene-diisocyanate
HGF	Hepatocyte growth factor
HGPRT	Hypoxanthine-guanine phosphoribosyl transferase
HL	Half-life (time)
HLA	Human leukocyte antigen
HNPC	Hereditary non-polyposis colon cancer
hOGG	Human 8-oxoguanine-DNA-glycosilase
HPG axis	Hypothalamus–pituitary–gonades axis
HPRT	Hypoxanthine-phosphoribosyl transferase
HPT	Hypothalamus–pituitary–thyroid axis
HR	Homologous recombination
HRE	Hormone-responsive element
HRIPT	Human repeated insult patch test
HPTE	2,2-bis(<i>p</i> -hydroxyphenyl)-1,1,1-trichloroethane
IARC	International Agency for Research on Cancer