



Book Review

TOXICOLOGY AND RISK ASSESSMENT

A Comprehensive Introduction

Helmut Greim and Robert Snyder (Editors)

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Toxicology is concerned with the health risks human exposure to chemicals, and it describes the adverse effects of chemicals in a qualitative sense and how to evaluate them quantitatively to determine how much of a chemical is required to produce given response.

The book *Toxicology and Risk Assessment: A Comprehensive Introduction* is dedicated to Professor Herbert Remmer (1919-2003), 1st Director of the Institute of Toxicology of the University of Tübingen, who was a pathfinder in the biomedical sciences, a dedicated teacher which work established a standard of excellence for generations of scientists to come. The editors, Helmut Greim from Institute for Toxicology and Hygiene, Technical University of Munich (Germany), and Robert Snyder from Environmental and Occupational Health, Science Institute, The State University of New Jersey (USA) decided to prepare a completely new book to ensure that recent achievements in toxicology are covered and each chapter produced contains essential knowledge for a toxicologist, so that they have a great contribution in editing this book, structured in six chapters and index, 677 pages, written by 53 scientists from academia or government agencies from USA, Germany, The Netherlands, Denmark, Switzerland and Scotland.

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 allow the reader to go beyond this book, into the toxicological literature. Furthermore, coverage extends into areas such as the biomarkers, molecular and cell biology, and newer approaches to risk assessment. It stresses the important need for overlap between mechanistic studies and safety assessment.

Topics covered by this book are: *Principles in toxicology* (refers to toxicokinetics including absorption distribution, metabolism and excretion; the mechanism that lead to cytotoxicity, carcinogenicity, and effects on reproduction; and the toxic effects of mixtures of chemicals), *Organ toxicology* (refers to information on anatomy and physiology of the major organs; why they are specific targets; and the mechanisms of specific chemicals affecting these organs), *Methods in toxicology* that refers to the commonly used methods for toxicity tests, both *in vivo* and *in vitro*. Next topics covered by this book are *risk assessment* (concepts comprising hazard identification, dose-response, and exposure assessment and the different approaches for threshold and non-threshold effects; recent molecular-biological results on cellular responses to genotoxic agents such as DNA repair, halt of proliferation, and apoptosis that allow assumption of threshold genotoxic effects are also described), *risk management* (USA and European regulations for chemicals), and, the last topic is *toxicity of chemicals* that refers to the toxic mechanisms and effects of major groups of chemicals.

First chapter, *Introduction to the discipline of toxicology*, written by Helmut Greim and Robert Snyder, underlies the risk assessment as a process for describing the adverse effects of chemicals in a qualitative sense, and evaluating them quantitatively by determining how much of a chemical is required to produce a given response, so that the intrinsic properties of an agent (hazard identification) can be described, and the amount of chemical required to produce these properties (risk characterization) can be estimated.

Toxicological evaluation of new and existing chemicals and the various toxic effects which chemicals may exert and the different applications for

which chemicals are designed to require in-depth understanding of the cause and effect relation, i.e. knowledge of the chemical and the specific organs upon which it impacts. As a result, toxicologists tend to focus on specific organs, specific applications (such as pesticides or drugs), specific compounds like metals or solvents or specific effects of compounds such as carcinogenicity and mutagenicity. Toxicological evaluation of chemicals requires knowledge on health consequences of acute, subchronic, and chronic exposure via routes relevant to the common use of chemicals. Therefore, all elements of risk assessment: hazard identification, dose-response, exposure, and risk have to be evaluated.

So that, in this chapter the authors are presenting the general requirements and approaches for hazard identification, toxicological issues related to specific chemical classes, the existing chemicals and the classification of carcinogens.

Principles, the second chapter, written by Johannes G. Filser, Jeroen T.M. Buters, Leslie Schwarz, John B. Watkins, Lesley Stanley, Jens Schlossmann, Franz Hoffman, Victor J. Feron, Diana Jonker, Thomas Efferth, Bernd Kaina, Horst Spielmann, Peter Calow, Valery E. Forbes, describes the toxicokinetics – definition and purpose, absorption, distribution and elimination, toxicokinetics models, phase I metabolism, phase III metabolism, drug metabolism (conjugation and hydrolysis), toxicogenetics, cytotoxicity, receptor-mediated mechanism, mixture and combinations of chemicals, chemicals carcinogenesis (genotoxic and non-genotoxic mechanism) and reproductive toxicology, ecotoxicology (not just for wildlife toxicology).

Subchapter *Toxicogenetics* refers to genotyping and phenotyping, the correlation between, to the role of polymorphisms in influencing susceptibility to toxic agents, to acute toxicity, polymorphic drug transporters and polymorphic xenobiotic receptors. The strength of toxicogenetics approach is that it makes possible to examine susceptibility to xenobiotics in human populations, thus answering concerns relating to differences in susceptibility between humans and animals. However, the nature of toxicogenetic analysis, including the fact that, for ethical reasons, chemicals may not be administered to humans at known toxic doses and invasive methods may not be used to obtain relevant tissue samples, means that a degree of variability and uncertainty will always be present.

Cytotoxicity refers to all cell structures and functions that may be targets of cytotoxic chemicals. Damage may be due to covalent or non-covalent interaction with the xenobiotic. The consequences of the damage depend on the structure and function of the affected cellular component and the cell's ability to repair the damage. Important cellular targets of toxic chemicals are membrane systems, the generation of metabolic energy, the synthesis of

critical macromolecules, and the control of redox homeostasis.

Receptor-mediated mechanisms, this chapter presents the ligand-receptor interactions and receptor – signal transduction. *Mixture and combinations of chemicals* in this chapter various types of mixed exposures and joint action are defined, designs for mixture toxicity studies are briefly described and methods for the safety evaluation of mixed exposure are discussed. The chapter *Chemical carcinogenesis: genotoxic and non-genotoxic mechanism* describes the main mechanisms of DNA damage, repair and carcinogenesis, cancer development, non-genotoxic mechanism of carcinogenesis, implications of initiation and promotion for risk assessment. *Reproductive toxicology* covers a wide spectrum of effects on all segments of the reproductive cycle, starting with female and male fertility, pre- and post-natal effects, and, also, late manifestations that can only be detected in the next generation. Thus, reversible and irreversible effects of exposure to toxicants may occur not only in the individuals who were exposed but also in their offspring. Chemicals that are specifically toxic during human pregnancy and lactation were described, as well as international test methods applied in reproductive toxicology.

Ecotoxicology: not just wildlife toxicology has been refined to the description and understanding of impacts of industrial and agricultural chemicals on ecological systems. This includes the study of natural chemicals used in industrial processes, such as metals and oils, and synthetically produced chemicals that do not occur naturally in the environment, such as PCBs, detergents, most pesticides, and most pharmaceuticals. Ecotoxicology has its roots in toxicology, but the targets of interests are different: toxicology is concerned with impacts on individual human beings, and ecotoxicology on ecological systems. So, ecotoxicology is not just toxicology applied to wildlife.

Ecotoxicology aims to describe and understand how the structures and processes of ecological systems are affected by exposure to chemicals as a result of human activities. The responses of individual organisms are less interesting in this context than the responses of populations, communities, and ecosystems. However, it is easier to make observations on individuals in test systems than on populations, communities and ecosystems. Extrapolations from one level to another involve a number of uncertainties that are most often brought into consideration through use of uncertainty factors. Owing to the inherent complexity of ecological systems, methods promising short-cuts in assessments should be treated with caution.

Organ toxicology, chapter 3, written by Michael Schwenk, Leslie Schwarz, John B. Watkins, Jurgen Pauluhn, Gunter P. Eckert, Walter E. Muller, Andreas Seeber, Tibor A. Rozman, Myriam Straube, Karl K. Rozman, Helmut Greim, Robert Snyder, Carol R. Gardner, Debra L. Laskin, and Ines M. Lanzl, is structured in eleven subchapters: The Gastrointestinal

Tract, The Liver, The Respiratory System, The Nervous System, Behavioral Neurotoxicology, The Skin, The Kidney and Urinary Tract, Toxicology of the Blood and Bone Marrow, Immunotoxicology, The Eye, and The Cardiovascular System, and describes the structures and functions of main organs, their role in organism and toxicological aspects.

Chapter 4, *Methods in toxicology* has 12 contributors (Rudiger Bartsch, Ilse-Dore Adler, Ulrich Andrae, Gunter Speit, Stephan Madle, Peter Kasper, Ulrike Pabel, Michael G. Bird, Kurt Ulm, Laura Suter-Dick, Thomas Singer, and Gyorgy Csanady) and it is structured in 6 subchapters.

OECD test Guidelines for toxicity tests in vivo presents that *in vivo* tests are required to discover possible adverse effects of chemical substances and pharmaceuticals to humans. They must be carried out according to internationally recognized test guidelines and under the principles of Good Laboratory Practice to ensure validity of the data. Although *in vitro* tests offer a great deal of information on the actions of a substance, *in vivo* tests cannot be replaced, due to the complexity of the cell surface, within cells, and in sub cellular structures. For each of these tests, their most important principles and requirements according to the latest OECD test guidelines are described in this chapter.

Mutagenicity tests in vivo chapter outlines the chromosomal and gene mutations in somatic cells, and chromosomal and gene mutations in germ cells. The chapter *In vitro tests for genotoxicity* describe the xenobiotic metabolism *in vitro*, tests systems employing bacteria and mammalian cells, and cell transformation assays. In subchapter *Strategies for the evaluation of Genotoxicity* are presented the basics of genotoxicity testing and current approaches for assessing genotoxicity. *Biomonitoring* chapter refers to biomonitoring programs, study design and some case study examples are presented too. Biomonitoring is a powerful and versatile surveillance tool with demonstrated benefit in identifying health risk and unsuspected exposure sources. However, the ability to properly interpret new biomonitoring data, which are generated using increasingly sensitive analytical methods, is often outpaced by the technology. This challenge can only be met by integrating valid biomonitoring data, together with accompanying relevant information, into an appropriate risk assessment process.

Epidemiology chapter presents the main measures to describe the risk, standardization, types of epidemiological studies, statistics, causality, bias, confounding, and chance. The goal of epidemiology is to identify risk factors for certain diseases. Several types of epidemiological studies are available, but the most well known are the cohort study and the case-control study. The association between a factor and a disease is described by the relative risks or the odds-ratio. A variety of criteria are mentioned, not all of them have to be fulfilled in order to establish the

causality, but, before doing so, the influence of bias, confounding or chance has to be ruled on.

Concepts of toxicogenomics, technology platforms, bioinformatics and biostatistics, and applications of toxicogenomics are presented in chapter entitle *Omics in toxicology*. The results obtained from different technology platforms are expected to lead to the identification of novel safety biomarkers, which in due time will need to be validated and might have a strong impact in how toxicology is performed. Hence the promise of toxicogenomics is well on the way to implementation and additional news in the near future is expected. In the last part of chapter 4 are shown the descriptive statistics, error propagation, probability distribution, inferential statistics, regression analysis, probit analysis, experimental designs and statistical software.

Chapter 5, *Risk assessment*, written by Jurgen Timm, Dennis J. Paustenbach and Pearl Moy outlines the mathematical models for risk extrapolation, regulations regarding chemicals and radionuclide in the environment, workplace, consumer products, food, and pharmaceuticals. The risk resulting from exposure to toxic substances can be evaluated by epidemiological studies or animal experiments. The human risk can be derived directly in epidemiological studies. Epidemiological studies, as well as the knowledge resulting from animal research mainly cover the risks resulting from comparably high exposure conditions. Therefore one has to extrapolate to the considerably lower concentrations found at work or in the environment by mathematical models. With details about the risk at a certain exposure (unit risk) or the dose needed to induce a specific effect, one may compare the carcinogenic power of various harmful substances, independently to the contamination situation. Carcinogens with high unit risk are more dangerous at a very low concentration compared with those of a very low unit risk and a very flat course in the environmental interval of the dose-effect curve. For this reason the unit risk concept was originally developed in this chapter. For a specific evaluation of the risk different methods have been developed. A decision between them is difficult, as they have different advantages and disadvantages. The EPA (Environmental Protection Agency) Model, for example, is much more complex and allows a consideration of important details of the empirical findings, which with the WHO method will inevitably not be considered. The method gives better results, which are also relative close to the real danger, if it is properly validated. The uncertainty of specifying this linear approximation is rather significant when data base is poor. As the EPA estimation depends on the confidence interval of the ascent, it tends to overestimate the risk considerably. If in this case the deviation is non-significant from the straight line trough the origin, the WHO estimation should be preferred, because of its simple arrangement and its mostly smaller overestimation of

the risk. In case only one record of a summarized evaluation of contamination and relative risk is available, which regretfully happens to be the case with many epidemiological studies, the direct linear method has to be used. In either case a biological based cancer risk assessment should be the goal of further research and results within the frame of this research program will provide a better fit of mathematical models (some of them newly derived) and practical use of more sophisticated procedures based on such models. The regulation of chemicals and chemical exposures has increased significantly over the years. This chapter presents a brief overview of major environmental, human health, and occupational safety regulations in USA and European Union. The development of new technologies and scientific knowledge plays an important role in how these regulations are created and evaluated. By knowledge and experiences transfer about the implementation of such regulations, governments can anticipate that their overall effectiveness in protecting human health and the environment will continue to improve in the years to come.

Toxicity of selected chemicals, last chapter, written by Kristian W. Fried, Karl K. Rozman, Karl-Heinz Summer, Stefan Halbach, Herrmann Kappus, Helmut Greim, Paul J.A. Borm, Gisela H. Degen, J. William Owens, Wolfgang Dekant, Marion W. Anders, Ladislaus Szinicz and Thomas Zilker is structured in seven parts that are related to *Persistent Polyhalogenated Aromatic Hydrocarbons*, *Metals*, *Toxicology of Fibers and Particles*, *Xenoestrogens and Xenoantiandrogens*, *Toxicology of solvents*, *Noxious gases*, and *Animal and Plant Toxins*.

The production, emission and use of persistent PHAHs peaked in the middle of the last century with an increase in synthetic chemistry and an upswing in agriculture and technology. Today, most of these materials are being phased out or have already been banned. Unintentional emissions have been reduced and clean-up of heavily contaminated sites is underway in developed countries. These facts could lead to the wrong assumption that these substances belong to our past and merit little further attention. However, these compounds are highly persistent and are present in the environment and the human food chain both at the present time and in the foreseeable future. The effects of PHAHs on humans, animals, and the environment have been studied for decades, and the investigations of the toxicity of these compounds, applying classical and modern technologies, still yield new findings, providing new and improved bases for risk assessment and for the improvement of directives in regulatory agencies worldwide. PHAHs serve also as model compounds to study mechanisms of toxicity, which might facilitate the development of new drugs.

Metals are as well as the PHAHs present in the environment, but in contrast with organic compounds they cannot be degraded, which means that their anthropogenic use leads to redistribution and

accumulation in ecological systems. Acute exposure to metals can induce local irritations of skin and mucosa. Chronic toxicity of metals is reflected by specific effects related to organs and tissues and is frequently mediated by metal-binding proteins. Another general mechanism of action consists in the replacement of essential metal atoms bound to functionally important sites by toxic metals, which disrupts metal-dependent biological functions.

Massive exposure to respirable particles over a period of years at more than 5 mg/m³ is known to cause both chronic obstructive pulmonary diseases including bronchitis, emphysema, fibrosis, pneumoconiosis, and lung cancers. Differences in particle toxicity can be related to their surface reactivity, their ability to adsorb various chemicals. Most toxic mechanism of nanoparticles is probably qualitatively not different from cell particle interactions for fibers and fine particles. Other mechanisms such as translocation to the brain or the vascular system are substantially different from their fine analogues.

Xenoestrogens and Xenoantiandrogens chapter describes their toxicity, modes of action and testing, and compound assessment. Toxicology of selected solvent are also described, considering the fact that many solvents, upon acute exposure at high dose can cause anesthesia, but after repeated exposures, solvents may induce a wide variety of toxic effects. Acute poisoning by airborne toxicants is based either on systemic effects or on local damage or airway epithelia. Systemic poisoning is caused by gases such as carbon monoxide, hydrogen cyanide, or hydrogen sulfide. These compounds interfere with oxygen availability or its utilization in the tissues, thereby reducing oxidative metabolism in the mitochondria and the availability of energy for metabolic process. So that, airborne systemic poisons, respiratory tract irritants and irritants gasses are outline herein.

The last part of chapter 6, *Animal and Plant Toxins* describes the variety of naturally occurring toxins. The chemicals structure of these toxins ranges from simple organic compounds to very complex proteins. Animal toxins mostly consist in mixture of polypeptides and different digestive enzymes. In plants alkaloids and glycosides are responsible for the toxic effects.

Toxicology and Risk Assessment: A Comprehensive Introduction describes the basic concepts of toxicology, and aims, and successful achieve to equip the reader with the skills needed to evaluate risks at given exposures. Toxicology and risk assessment is an essential book for scientists in academia, industry and government agencies who want to understand how our bodies respond to toxicants, and the principles used to assess the health risks of specific exposure scenarios.

Brinđușa Robu

*Department of Environmental Engineering
and Management
Technical University of Iasi*