Leachables and Extractables Handbook

Safety Evaluation, Qualification, and Best Practices Applied to Inhalation Drug Products
This book is dedicated to the memory of Professor Robert Kroes whose scientific contributions played a vital role in developing the concept of the threshold of toxicological concern and the application of that concept to important societal issues including the safety evaluation of inhalable pharmaceutical products.

Robert Kroes, known as Bobby to his friends and colleagues around the world, was a native of The Netherlands. He received his Doctor of Veterinary Medicine in 1964. His training in Veterinary Medicine provided him with a solid scientific basis for a career grounded in comparative medicine, toxicology, and risk assessment, with a focus on the promotion of human health. In 1964, he was appointed Research Scientist at the National Institute of Public Health, which later became the National Institute of Public Health and Environment (known by the Dutch acronym, RIVM) in Bilthoven, The Netherlands. In 1970, he received a PhD in experimental pathology. He became a certified toxicologist in 1988 and a certified laboratory animal pathologist in 1989.

In 1972, he became Head of the Department of Oncology in the National Institute of Public Health. During this time in his career, he made important scientific contributions to understanding carcinogenicity. Moreover, he soon became a key contributor to major scientific committees within The Netherlands and on the international scene including the Benelux, the European Community, the Food and Agricultural Organization of the United Nations, and the World Health Organization. He was a member and, ultimately, Chair of the Dutch Scientific Council on Cancer Research of The Netherlands Academy of Science. He was a key contributor in the development of the first cancer research policy plan (1980–1984) of the Dutch Organization for Cancer Research.

In 1977, he was appointed Deputy Director of the Central Institute for Food and Nutrition Research (CIVO-TNO). In that position, he provided critical leadership for stimulating research in carcinogenesis, toxicology, biochemistry, and nutrition. In 1980, he became Director of the CIVO-TNO Institute for Toxicology and Nutrition. In 1983, he was appointed as a Director of RIVM with responsibility for managing the Institute’s toxicology and pharmacology programs. He was also responsible for guiding the institute’s advisory mission to the government with respect to the safety of chemicals. In 1988, he developed the Center for Epidemiology, further broadening the scope of RIVM’s activities. In 1988, he began a part-time association as a Professor of Biological Toxicology in the Research Institute for Toxicology of the University of Utrecht. In 1989, he became Deputy Director-General of RIVM. In 1995, he retired from his leadership roles at RIVM. In that year, he became the Scientific Director of the Institute for Risk Assessment Sciences (IRAS) of the University of Utrecht. He retired from IRAS in 2005.
The use of the word “retired” certainly did not apply to Bobby’s scientific activities. He continued to play a prominent role in many scientific advisory groups in The Netherlands and on the international scene. He had a key role in the National Institute of Toxicology. Of special note are the key roles he played in the International Life Sciences Institute (ILSI) and the related ILSI Risk Science Institute, as well as the International Union of Toxicology. He served the latter organization in multiple roles including service as president-elect and was scheduled to assume the position of president in 2007. Unfortunately, Bobby lost a courageous battle with cancer and died on December 28, 2006.

During his scientific career spanning over four decades, Bobby’s many important scientific contributions to the fields of oncology, toxicology, comparative medicine, and risk assessment are well documented in some 200 publications he authored or coauthored. As noteworthy as those contributions are, his most significant contributions came from his ability to rise above the scientific details and understand how to synthesize and integrate science and relate it to important societal health issues. He took a pragmatic view and focused on concepts and solutions to resolving complex issues. He was truly a problem solver.

This pragmatic, science-based approach was exemplified by Professor Kroes championing the use of the concept of “threshold of toxicological concern” (TTC) and its application to the safety of food and pharmaceuticals. The TTC concept refers to the establishment of a generic human exposure threshold for groups of chemicals below which there would be no appreciable risk to human health. He recognized that such a value could be identified for many chemicals, including those of unknown toxicity, by considering their chemical structure and drawing analogies from the known toxicity and modes of action of many chemicals that have been extensively studied. In December 2005, the Product Quality Research Institute organized a workshop to address the use of the TTC concept in evaluating the safety of inhalable pharmaceuticals. The organizers were unanimous in deciding that Professor Kroes should be invited to give an opening presentation to set the stage for the workshop. He gave a marvelous review of the developing field. His presentation served to energize activities that culminated in preparation of this volume. Therefore, it is indeed fitting that this volume be dedicated to the memory of Professor Robert Kroes. In using the science-based concepts championed by Professor Kroes, we celebrate the value of his contributions as a scientist and, for many of us, also have the opportunity to recall a wonderful friend who lived life to its fullest.

Roger O. McClellan, DVM, DSc (Honorary), DABVT, DABT, FATS
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The establishment of data-based safety thresholds for leachables and extractables in orally inhaled and nasal drug products (OINDPs) is an important scientific advancement that helps OINDP manufacturers make knowledge-based safety and risk assessments for extractables and leachables and ensure the safety of their products for patient use. This book describes the development and application of these safety thresholds for OINDP and best practices for the chemical evaluation and management of extractables and leachables throughout the pharmaceutical product life cycle. Although the book addresses OINDP-specific thresholds and best practices, many of the general concepts presented can be applied to extractables and leachables assessments for other drug product types and dosage forms. The purpose of this book is to provide the reader with practical knowledge regarding how and why the thresholds were developed and how they can be applied, as well as practical approaches to management of extractables and leachables. This book is useful to analytical chemists, packaging and device engineers, formulation development scientists, component suppliers, regulatory affairs specialists, and toxicologists, all of whom must work together in the pharmaceutical development process to identify, qualify, and manage extractables and leachables.

Management of extractables and leachables in OINDP is a critical part of the OINDP life cycle. By “management” we mean a thorough understanding of (1) potential and actual extractables from a given container closure system or device material for the purposes of eliminating or limiting the levels of leachables from such materials and (2) potential safety concerns associated with these extractables and/or leachables. These issues highlight the key regulatory and industrial concern regarding leachables in OINDPs as well as other drug products—that of patient safety. Regulatory guidance identifies patient exposure to leachables via OINDPs as an area of high importance in risk assessments for these products. Over the last 30 years, scientific and regulatory thought has evolved on the best ways to approach both chemical and safety assessments of extractables and leachables in the OINDP pharmaceutical development process. A vexing challenge in these assessments has been knowing “how low to go” in determining what concentrations of extractables and leachables should be evaluated for safety assessments; that is, is there a threshold of safety that can be established for the majority of compounds that could be found as leachables or extractables in OINDPs, such that compounds existing at levels below the threshold need not undergo safety evaluation? This question has become increasingly important with the continuous advancement of chemical analysis techniques, which have been, for the past four decades, able to detect chemical compounds at picogram levels and below.
In 2006, the Product Quality Research Institute’s (PQRI) Leachables and Extractables Working Group, consisting of scientists from the United States Food and Drug Administration (FDA), academia, and industry, answered this question by developing data-based safety and analytical thresholds for OINDP extractables and leachables, and corresponding best practices for analytical evaluation of these compounds. This book is based on the information contained in the Working Group’s recommendations (publicly available through PQRI); but it provides further, more in-depth context and background, case studies, and specific regulatory perspectives and extends the concepts to practices that may be implemented across the industry.

Douglas J. Ball
Daniel L. Norwood
Cheryl L.M. Stults
Lee M. Nagao
We thank the Product Quality Research Institute (PQRI) for supporting the development of this book, and the members of the PQRI Leachables and Extractables (L&E) Working Group, whose efforts formed the basis for this volume. We also thank the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) for initiating the process to develop safety thresholds for inhalation and nasal drug products, for providing the impetus to form the PQRI L&E Working Group, and for giving its ongoing support of collaborative efforts addressing the most challenging aspects of leachables and extractables in inhalation and nasal drug products.

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D.J.B.
D.L.N.
C.L.M.S.
L.M.N.