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Chemical Analysis of Non-antimicrobial Veterinary Drug Residues in Food

Edited by

Jack F. Kay • James D. MacNeil • Jian Wang

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This book is dedicated to the memory of Dr. John J. O'Rangers Jr., 11 June 1936–20 January 2013.

John was internationally well known and respected in the field of veterinary drug residue chemistry and international regulations. Both Dr. James MacNeil and Dr. Jack Kay were honored to have known and worked with him over many years and also to call him a friend. Developing international cooperation and understanding was a cornerstone of John's view of life and work ethic, regardless of the more politically opinionated views held by some. Many international developments in this field and friendships are the result of the work John conducted behind the scenes to break down barriers. He truly was one of a kind and his passing leaves us all impoverished.

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Preface

Food safety continues to be a topic of great interest to consumers and is frequently a topic for media discussion. However, what is not routinely reported is the vast effort by many national, regional, and international bodies and scientists – both governmental and independent – to ensure that food production and trade do not place consumers at risk while ensuring a continuous supply of wholesome food.

A key aim of regulating the use of veterinary drugs is to ensure that authorized products are used responsibly in animals and that their residues in food of animal origin do not pose unacceptable health risks to consumers. To assist in this process, robust and validated analytical methods to detect a wide range of potential residues in food matrices are required.

The earlier volume in this series, *Chemical Analysis of Antibiotic Residues in Food*, was published in 2012 and set out in detail how drug safety is considered and limits are set for their residues in foods. It also described how residue monitoring programs are established and checked to ensure sound results are generated to inform necessary regulatory actions to protect consumers. These topics are generic and apply equally to antibiotics and other veterinary drug classes. The companion volume to this current book also provided detailed information on analytical methods for antibiotic residues.

The purpose of this current book, *Chemical Analysis of Non-antimicrobial Veterinary Drug Residues*, is to update readers on developments in technology and approaches since the publication of the earlier volume. It also seeks to expand the coverage of veterinary drug residues to all other key areas of veterinary drug treatments, thus providing a comprehensive two-volume set for reference and training purposes.

The main themes of the book include detailed discussions on emerging technologies (Chapter 2); high resolution mass spectrometry and related techniques (Chapter 3); hormones and β-agonists (Chapter 4); anthelmintics (Chapter 5); sedatives and tranquilizers (Chapter 6); pyrethroids, carbamates, organophosphates, and other pesticides used in veterinary medicines (Chapter 7); non-steroidal anti-inflammatories (Chapter 8); dyes (Chapter 9); and developments in the validation of multi-class multi-residue methods and related quality control/quality assurance issues (Chapter 10).

The editors and authors of this book are internationally recognized experts and leading scientists with extensive personal experience in preparing food safety regulations and/or in the chemical analyses of veterinary drug residues in food of animal origin. This book offers a valuable and up to date view of the science in this area. It has been deliberately written and organized to complement and update where necessary the information contained in the earlier companion volume. The editors hope that this volume completes and addresses the need for readers from regulatory backgrounds and analytical laboratory staff to have a cutting-edge reference and training resource for the residues of all veterinary drug residues in food of animal origin.

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About the Editors

Dr. Jack F. Kay received his Ph.D. from the University of Strathclyde, Glasgow, Scotland in 1980 and has been involved with veterinary drug residue analyses since 1991. He worked for the UK Veterinary Medicines Directorate to provide scientific advice on residue monitoring programs and managed the R&D program until his early retirement in September 2014. He helped draft Commission Decision 2002/657/EC and is an ISO trained assessor for audits to ISO 17025. He was co-chair of the CCRVDF ad hoc Working Group on Methods of Sampling and Analysis and steered Codex Guideline CAC/GL 71-2009 to completion after Dr. MacNeil retired. He co-chaired work extending this to cover multi-residue method performance criteria. He assisted JECFA in preparing an initial consideration of setting MRLs in honey and then took this forward for the CCRVDF. He also holds an Honorary Senior Research Fellowship in the Department of Mathematics and Statistics at the University of Strathclyde.

Dr. James D. MacNeil received his Ph.D. from Dalhousie University, Halifax, NS, Canada in 1972 and worked as a government scientist until his retirement in 2007. From 1982 to 2007 he was Head, Centre for Veterinary Drug Residues, now part of the Canadian Food Inspection Agency. He has served as a member of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), co-chair of the working group on methods of Analysis and Sampling, Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF), is the former scientific editor for "Drugs, Cosmetics & Forensics" of J. AOAC Int., worked on IUPAC projects, has participated in various consultations on method validation, and is the author of numerous publications on veterinary drug residue analysis. He is a former General Referee for methods for veterinary drug residues for AOAC International and was appointed scientist emeritus by CFIA in 2008. He holds an appointment as an adjunct professor in the Department of Chemistry, St. Mary's University, Halifax, Canada, and has served as a part-time consultant to the JECFA Secretariat of the Food and Agriculture Organization of the United Nations since 2012.

Dr. Jian Wang received his Ph.D. at the University of Alberta in Canada in 2000, and then worked as a Postdoctoral Fellow at the Agriculture and Agri-Food Canada in 2001. He has been working as a leading research scientist at the Calgary Laboratory with the Canadian Food Inspection Agency since 2002. His scientific focus is on method development and validation using LC-MS/MS, UHPLC-QTOF, and UHPLC-Q Orbitrap for analyses of chemical residues including antibiotics, pesticides, and other chemical contaminants in foods. He also develops statistical approaches to estimating the measurement uncertainty based on method validation and quality control data using SAS program.

1

Basic Considerations for the Analyst for Veterinary Drug Residue Analysis in Animal Tissues

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1.1 Introduction

It is not sufficient to be expert in the techniques applied in an analytical method to produce a meaningful result when applying a method for the analysis of veterinary drug residues, as is the reality in many other types of chemical analysis. The analyst must also have a sufficient understanding of the nature of the targeted veterinary drug residues to ensure that the method used is fit for the purpose. That is, the method used should be developed and validated for an appropriate concentration range for the right analyte and should be directed at a matrix where residues are likely to be found. In addition, the analyst might reasonably be expected to provide advice on the significance of the results generated with respect to regulatory limits to clients with limited scientific knowledge.

In this chapter, we discuss some of the terminology that is commonly applied in veterinary drug residue analysis, as well as some of the basic information on pharmacokinetics, metabolism, and distribution that help with direct choices of analyte and matrix and that also inform the interpretation of analytical results. We also briefly review the common national and international approaches to the regulation of veterinary drug residues in foods and the establishment of maximum residue limits (MRLs).

1.2 Pharmacokinetics

The term pharmacokinetics is used to describe studies related to quantitative changes in the concentrations of an administered drug in a body over time. Basic parameters associated with a dose are C_{max}, the maximum concentration attained

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following the receipt of a dose of a drug, and $t_{1/2}$, the half-life of the drug in the body. These may be determined in the blood or in specific tissues. For the residue analyst, some knowledge of these factors is required to help target analysis at a matrix where residues are likely to be found and to interpret the significance of a residue finding. If the half-life ($t_{1/2}$) of a drug in a body fluid or a tissue is measured in minutes or a few hours, there is very probably little to be gained by testing that matrix for residues in an animal slaughtered days or weeks after the drug administration.

The means by which a drug is administered may influence the pharmacokinetics. Veterinary drugs may be available in a variety of formulations, which include injectables, feed additives, sprays, pour-ons, and dips. Injections may be via routes which included intravenous, intramuscular (i.m.), subcutaneous (s.c.), and intramammary. In some cases, the injection may lead to the occurrence of a depot at the injection site, with a low rate of absorption, leading to the presence of significant residues at the injection site for an extended period. The residues at the injection site will not be representative of residues found in muscle tissue away from the site of injection. Thus, a finding of high residue concentrations in muscle tissue, for example, should lead the analyst to suspect that the tissue analyzed may be from an injection site, and therefore additional analyses should be conducted on muscle samples from other parts of the carcass or lot before concluding that the initial results are truly representative.

For example, the 47th Meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) recommended MRLs of 10 μg/kg for doramectin residues in beef muscle.[1] It also noted that residues were slightly higher in the muscle from cattle given an s.c. dose when compared to cattle which received treatment by i.m. injection. In addition, after 35 days withdrawal, residues in muscle were < 3 and < 2 μg/kg from the s.c. and i.m. treatment groups, respectively. However, injection site muscle from these animals contained 930 μg/kg (s.c. group) and 177 μg/kg (i.m. group) at 35 days post-treatment. The committee in recommending MRLs for doramectin in cattle noted that high concentrations of residues may remain at the injection site after treatment according to approved uses. In adopting the MRL recommendations, the Codex Alimentarius Commission (CAC) included a note with the MRLs for beef muscle and fat that there was a potential that residues of doramectin in excess of the MRLs could persist at injection sites following recommended treatment.[2]

Subsequently, in reviewing data for the use of doramectin in the treatment of pigs, the 52nd Meeting of the JECFA recommended an MRL of 5 μg/kg in pork muscle, based on twice the limit of quantification (LOQ) of a method judged to be suitable for routine regulatory use.[3] In a depletion study reviewed by the 52nd Meeting of the JECFA, pigs were treated by i.m. injection at 1.25 times the recommended dose and subjected to a 28-day withdrawal period, as per the approved use from a Codex Alimentarius member state.[3] No quantifiable residues were detected in "normal" muscle tissue, meaning that residues in the muscle tissue should be below this limit if the drug is used according to the