FUNDAMENTALS OF ANALYTICAL TOXICOLOGY

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Clinical and Forensic

Second Edition

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Preface

The analytical toxicologist may be required to detect, identify, and in many cases measure a wide variety of compounds in samples from almost any component of the body or in related materials such as residues in syringes or in soil. Many difficulties may be encountered. The analytes may include gases such as carbon monoxide, drugs, solvents, pesticides, metal salts, and naturally-occurring toxins. Some poisons may be individual chemicals and others complex mixtures. New drugs, pesticides, and other substances continually present novel challenges in analysis and in the interpretation of the results of the analysis. The analyte might be an endogenous compound such as acetone, or an exogenous compound such as a drug and/or metabolite(s) of the drug, whilst the sample matrix may range from urine to bone.

Many biological samples contain muscle, connective tissue, and so forth, which may have to be separated or degraded prior to an analysis, as well as a multitude of small and large molecular weight compounds. The concentration of the analyte to be measured can range from g L^{-1} (parts per thousand) in the case of blood ethanol to μg L^{-1} (parts per thousand million) in the case of plasma digoxin, and even ng L^{-1} (parts per million million) in the case of the potent opioid carfentanil. The stability of the analytes in biological samples also varies considerably, ranging from a few minutes for protease sensitive peptides and esters such as aspirin and diamorphine, to several years for some other drugs and pesticides.

This book aims to give principles and practical information on the analysis of drugs, poisons and other relevant analytes in biological and related specimens, particularly clinical and forensic specimens, i.e. it is a 'toolkit' in modern parlance. As such, this volume extends the scope of the World Health Organization (WHO) basic analytical toxicology manual[1] and builds on the success of the first edition of this work that appeared in 2007.[2] Moreover, it is intended to complement Dr Randall Baselt's *Disposition of Toxic Drugs and Chemicals in Man* (Edition 12. Seal Beach: Biomedical Publications, 2020), which remains the seminal reference work as regards the interpretation of analytical toxicology data.

A major difficulty in writing any textbook is deciding on the order of presentation. Having taken account not only of reviewer comments on the first edition, but also of the advances in analytical methods on the one hand, and the range of analyses that may now be required on the other, the material has been updated, expanded and presented in a new order. However, much of the discussion of the historical development of analytical toxicology present in the first edition has been removed to save space. On the other hand, some discussion of more traditional methods such as thin-layer chromatography has been retained for the simple reason that such methods are still used in many parts of the world.

After providing some background information, Section A outlines basic laboratory operations (aspects of sample collection, transport, storage, and disposal, use of internal standards, method implementation/validation, quality control and quality assessment, staff training, laboratory

[1] Flanagan RJ, Braithwaite R, Brown SS, Widdop B, De Wolff FA. *Basic Analytical Toxicology*. Geneva: WHO, 1995; available at www.who.int/ipcs/publications/training_poisons/analytical_toxicology.pdf

[2] Flanagan RJ, Taylor A, Watson ID, Whelpton R. *Fundamentals of Analytical Toxicology*. Chichester: Wiley, 2007

accreditation, etc.) and basic methodology ranging from simple colour tests through spectrophotometry to immunoassay and enzyme-based assays. Section B discusses separation science in detail (chromatography and electrophoresis, mass spectrometry, and ion mobility spectrometry). Section C reviews xenobiotic absorption, distribution and metabolism, and pharmacokinetics. Section D aims to unify this material and discusses point-of-contact testing, laboratory-based substance misuse and general toxicology screening, therapeutic drug monitoring, and trace elements and toxic metals analysis. The section concludes with a general discussion on the interpretation of analytical toxicology results.

Health and Safety

This book is intended for use by scientists trained appropriately in laboratory work. Care should be taken to ensure the safe handling of all chemical and biological materials, and particular attention should be given to the possible occurrence of allergy, infection, fire, explosion, or poisoning (including transdermal absorption or inhalation of toxic vapours). Readers are expected to consult current local health and safety regulations and to adhere to them.

Nomenclature, Symbols, and Conventions

We have followed IUPAC nomenclature for chemical names except when Chemical Abstracts nomenclature or trivial names are more readily understood. With regard to symbols, we have adopted the convention that variables and constants are italicized, but labels and mathematical operators are not. Thus, for example, the acid dissociation constant is written K_a, K being the variable, a being a label to denote that it is an acid dissociation constant. The notation for the negative logarithm of K_a is pK_a – p is a mathematical symbol and is not italicized. Where the subscript is a variable then it is italicized, so the concentration at time t, is C_t, but the concentration at time 0 is C_0. Note especially that relative molecular mass (molecular weight, relative molar mass), the ratio of the mass of an atom or molecule to the unified atomic mass unit (u), is referred to throughout as M_r. The unified atomic mass unit, sometimes referred to as the dalton (Da), is defined as one twelfth of the mass of one atom of ^{12}C. The symbol amu for atomic mass unit can sometimes be found, particularly in older works. The unified atomic mass unit is not a Système International (SI) unit of mass, although it is (only by that name, and only with the symbol u) accepted for use with SI.

As to drugs and pesticides, we have used recommended International Non-proprietary Name (rINN) or proposed International Non-proprietary Name (pINN) whenever possible. For misused drugs, the most common chemical names or abbreviations have been used. It is worth noting that for rINNs and chemical nomenclature, it is now general policy to use 'f' for 'ph' (e.g. sulfate not sulphate), 't' for 'th' (e.g. chlortalidone not chlorthalidone) and 'i' for 'y' (mesilate not mesylate for methanesulfonate, for example). However, so many subtle changes have been introduced that it is difficult to ensure compliance with all such changes. Names that may be encountered include the British Approved Name (BAN), the British Pharmacopoeia (BP) name, the United States Adopted Name (USAN), the United States National Formulary (USNF) name, and the United States Pharmacopoeia (USP) name. Where the rINN is markedly different from common US usage, for example acetaminophen rather than paracetamol, meperidine instead of pethidine, the alternative is given in parentheses at first use and in the index.

Isotopically-labelled compounds are indicated using the usual convention of square brackets to denote the substituted atoms, and site of substitution where known. For example, [$^2H_3$-*N*-methyl]-hyoscine indicates that the hydrogen atoms in the *N*-methyl group have been substituted by deuterium – this should not be confused with *N*-methylhyoscine (methscopolamine).

A useful source of information on drug and poison nomenclature is the *Merck Index Online* (www.rsc.org/Merck-Index/). Chemical Abstracts Service (CAS) Registry Numbers (RN) provide a unique identifier for individual compounds, but it is important to note that salts, hydrates, racemates, etc., each have their own RNs. Similarly, when discussing dosages we have tried to be clear when referring to salts, and when to free acids, bases, or quaternary ammonium compounds.

The oxidation number of metal ions is given by, for example, iron(II), but older terminology such as ferrous and ferric iron for Fe^{2+} and Fe^{3+}, respectively, will be encountered in the literature.

We emphasize that cross-referral to an appropriate local or national formulary is mandatory before any patient treatment is initiated or altered. Proprietary names must be approached with caution – the same name is sometimes used for different products in different countries.