RADIOTRACER TECHNIQUES AND APPLICATIONS

VOLUME 1

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PREFACE

This book is aimed at identifying problems and their solutions in the numerous applications of radiotracer techniques in chemical and biological research. Contributors were selected who are expert in the various scientific disciplines, and who are very familiar with the problems pertaining to radiotracer methodology. Much of the information contained within these two volumes provides a basic understanding of the problems and knowledge in the applications of radiotracer techniques.

The book is divided into two volumes, with twenty-three chapters covering three principal sections of scientific interest. The fundamental techniques in the design of tracer experiments are discussed in chapters 1 through 7 of this volume. These include the selection of radionuclides, handling and health physics aspects of radiotracer uses, measurements of radioactivity, with special emphasis on biological samples, the philosophy of selecting methods for the preparation of radiotracer compounds, the essential factors to consider and methods for the analysis and quality control of radiotracers, and the difficulties in controlling self-decomposition of radiochemicals in storage.

Chapters 8 through 14, also in this volume, discuss problems in the application of radiotracer techniques for studies familiar to chemists, namely the special behavior of radionuclides at maximum isotopic abundance, isotope effects, exchange processes, solution properties, diffusion and interfacial phenomena, and important environmental studies with radiotracers.

Volume 2, chapters 15 through 23, will survey problems and pitfalls in many applications of radiotracer techniques to

biological research. These include applications to studies of biosynthesis, and radiotracer techniques in drug metabolism and in cytology. The assay of enzymes and enzymatic assays using the high sensitivity of radiotracer techniques can often lead to a better understanding of mechanisms in the biochemistry of man, and subsequently to new methods of diagnosis, prognosis, and treatment of diseases. An understanding of the metabolism of chemicals used in agriculture is very important, especially for the safe protection of our food supplies and of our environment, areas which are readily investigated with radiotracers. Similarly, radiotracers help to further our understanding of marine biology. Biological research with radiotracers helps to set down the foundations upon which to build procedures for routine clinical diagnosis for disease control, and the final three chapters are of special interest to clinical investigators. These chapters deal with the assay of drugs and hormones by competitive protein binding (radioimmunoassay), the uses of not only inorganic ions of radionuclides but also of radiochemicals in diagnostic medicine, and a discussion of the philosophy and difficulties in developing radioactive drugs for the radiotherapeutic treatment of cancer.

The nomenclature which has been adopted for this text is referred to as the "square-brackets-preceding" system recommended by the American and British Chemical Societies and by most biochemical journals. The symbol for the isotope is placed in square brackets directly attached to the front of the chemical name, or to that part of the chemical name to which the label refers.

Some readers will already be aware that the familiar units of radioactivity and radiation dose, namely the *curie* and the *rad*, respectively, may well disappear in time as the intention is to introduce the International System of Units (SI units) of the becquerel (Bq) and the gray (Gy) for activity and for absorbed dose, respectively, as agreed by the General Conference on Weights and Measures and ratified by the Council of the European Community

in 1972. The becquerel is equal to 1 sec^{-1} and the gray to 1 J kg^{-1}. The use of these units is already legally approved in several countries. However, as there is a large international trade in radioactive materials, and also a well familiarized use of the curie units in medical practice for applications of radiopharmaceuticals, it is clearly most desirable that all countries should agree to change to SI units at the same time. With these problems in mind therefore, one suspects that it will be many years before the "old" familiar units finally disappear from use. (See p. xiii for the SI Units for radioactivity.)

We trust that many scientists will find the wealth of knowledge discussed in this text useful in helping them to develop further valid applications of radiotracer techniques. Finally, we should like to express our appreciation for the excellent cooperation of the scientists whose contributions to this book have made its publication possible.

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INTERNATIONAL SYSTEM OF UNITS (SI UNITS) FOR RADIOACTIVITY

The SI unit for radioactivity is the becquerel (Bq) equal to 1 disintegration per second. The table below gives the conversion values for becquerels to curies.

1 becquerel	1 Bq	27.03 picocuries
1 kilobecquerel (1 kBq)	10^3 Bq	27.03 nanocuries
1 megabecquerel (1 MBq)	10^6 Bq	27.03 microcuries
1 gigabecquerel (1 GBq)	10^9 Bq	27.03 millicuries
1 terabecquerel (1 TBq)	10^{12} Bq	27.03 curies
1 petabecquerel (1 PBq)	10^{15} Bq	27.03 kilocuries
1 exabecquerel (1 EBq)	10^{18} Bq	27.03 megacuries

1 microcurie = 37 kBq

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Chapter 1

THE DESIGN OF RADIOTRACER EXPERIMENTS

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It is an unrewarding exercise to apportion excessive credit to any single scientific study for its part in the progress of knowledge in the chemical and biological sciences. Nevertheless, certain aspects of scientific achievement are unequivocally indebted to radiotracer experiments for direct information about the fate of specified species -- atoms, molecules, ions, fragments, aggregates, etc. -- in terms of their mass, which is a primary measure for the extent of chemical and biological processes. Such information can, in principle, refute or definitively confirm knowledge previously established by conventional techniques. This is indeed the case when the radiotracer techniques appropriate to the experimental conditions under which the radioactivity R of a radionuclide is absolutely proportional to the mass or number n of the specified species thereby concerned. To establish the constancy of

$$\frac{R}{n} = k \qquad (1)$$

variously contradictory requirements from different aspects must be simultaneously satisfied. The constant k is conventionally defined as

$$k = \eta\lambda q\sigma \tag{2}$$

with

$$\eta = \frac{R}{-dN'/dt} \tag{3}$$

for the detection coefficient (or overall counting efficiency) of N' radioactive atoms at time t,

$$\lambda = \frac{-dN'/dt}{N'} \tag{4}$$

for their decay constant,

$$q = \frac{N'}{n'} \tag{5}$$

to specify the chemical form of n' molecules labeled with N' radioactive atoms, and

$$\sigma = \frac{n'}{n} \tag{6}$$

for the ratio of the number of radiolabeled, n', to that of the total (labeled plus unlabeled), n, molecules. The last term σ (moleculues/molecule or atoms/atom) or, more conveniently, the product of $\lambda q\sigma$ (atoms/time/molecule, dpm/mol, or Ci/mol) is called specific activity. This is an important factor in designing the radiotracer experiments.

In many cases, n for a chemically or biologically treated specimen is determined by comparing its R value with the radioactivity R_s for a known number n_s (or mass) of the same molecules in an untreated standard sample, so that the relationship

$$n = \frac{n_s R}{R_s} \tag{7}$$

holds. It must be borne in mind, however, that Eq. (7) can be rationalized only when k $(= \eta\lambda q\sigma)$ for the unknown specimen equals to that for the standard. For this purpose, we usually choose such conditions as

$$\frac{\eta}{\eta_s} = \frac{\lambda}{\lambda_s} = \frac{q}{q_s} = \frac{\sigma}{\sigma_s} = 1 \qquad (8)$$

where the subscript s refers to the standard sample.

Fulfillment of the first condition, $\eta = \eta_s$, depends primarily on the choice of radionuclide (Chap. 2) and the method used for measurement of radioactivity (Chap. 4). The former determines the type and energy of radiation to be detected, while the latter is concerned with how adequately and efficiently it is quantified. In general expression,

$$\eta = \eta_g \cdot \eta_a \cdot \eta_b \cdot \eta_{sa} \cdot \eta_{sc} \cdot \eta_c \qquad (9)$$

for the detection coefficient η as a function of the sample-geometric factor η_g, the attenuation factor η_a, the back-scattering factor η_b, the self-absorption and -scattering factors, η_{sa} and η_{sc}, respectively, and the counting efficiency η_c, each factor would be made equal between the two samples; otherwise appropriate correction must be made for the difference. The correction methods for differences in η between different samples are discussed in the cases of dose assessment in radiation monitoring (Chap. 3), liquid scintillation and other measurement techniques for various specimens (Chaps. 4 and 6), estimation of radioisotopes incorporated in human body for diagnosis (Chap. 22), and sample preparation for environmental studies (Chap. 14). Autoradiographic techniques (Chap. 4) are also applicable, especially in determining the distribution of radiolabeled compounds adsorbed heterogeneously at solid/solution interfaces (Chap. 13), as well as those incorporated in animal tissues and cells (Chaps. 16, 17, and 20).

The attenuation of radiation in matter is skillfully utilized for determination of diffusion constants (Chap. 12) and adsorbed amounts (Chap. 13) of various compounds labeled with soft β-emitters such as ^{14}C, ^{35}S, and ^{3}H. The radioactivity thereby observed is contributed mostly by the radiolabeled molecules within the relevant medium. In Chapter 23, which deals with