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QUANTITATIVE TOXICOLOGY

Selected Topics

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(Kolichestvennaya Toksikologiya)

Selected Topics

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To the Memory of our Teacher, Professor Nikolai V. Lazarev

SERIES PREFACE

Environmental Science and Technology

The Environmental Science and Technology Series of Monographs, Textbooks, and Advances is devoted to the study of the quality of the environment and to the technology of its conservation. Environmental science therefore relates to the chemical, physical, and biological changes in the environment through contamination or modification, to the physical nature and biological behavior of air, water, soil, food, and waste as they are affected by man's agricultural, industrial, and social activities, and to the application of science and technology to the control and improvement of environmental quality.

The deterioration of environmental quality, which began when man first collected into villages and utilized fire, has existed as a serious problem under the ever-increasing impacts of exponentially increasing population and of industrializing society. Environmental contamination of air, water, soil, and food has become a threat to the continued existence of many plant and animal communities of the ecosystem and may ultimately threaten the very survival of the human race.

It seems clear that if we are to preserve for future generations some semblance of the biological order of the world of the past and hope to improve on the deteriorating standards of urban public health, environmental science and technology must quickly come to play a dominant role in designing our social and industrial structure for tomorrow. Scientifically rigorous criteria of environmental quality must be developed. Based in part on these criteria, realistic standards must be established and our technological progress must be tailored to meet them. It is obvious that civilization will continue to require increasing amounts of fuel, transportation, industrial chemicals, fertilizers, pesticides, and countless other products; and that it will continue to produce waste products of all descriptions.

What is urgently needed is a total systems approach to modern civilization through which the pooled talents of scientists and engineers, in cooperation with social scientists and the medical profession, can be focused on the development of order and equilibrium in the presently disparate segments of the human environment. Most of the skills and tools that are needed are already in existence. We surely have a right to hope a technology that has created such manifold environmental problems is also capable of solving them. It is our hope that this Series in Environmental Sciences and Technology will not only serve to make this challenge more explicit to the established professionals, but that it also will help to stimulate the student toward the career opportunities in this vital area.

Robert L. Metcalf
James N. Pitts, Jr.
Werner Stumm

PREFACE TO THE 1973 RUSSIAN EDITION

Toxicology as a science is now more than a century old. At first it was of necessity a purely descriptive discipline; but as more and more facts accumulated, there arose an urgent need to make generalizations, and this required an increasing use of various quantitative methods. It is precisely the wide application of these methods, which in recent years have been penetrating into many other biological disciplines, that has imparted to toxicology a truly scientific character by making it possible to derive many important and orderly relationships from an abundance of scattered factual data. It is gratifying to realize that many of these relationships have found practical applicability. Of great importance for the various branches of toxicology, including industrial toxicology, is the growing possibility of predicting the pattern and magnitude of toxic action of chemical agents from the results of simple and rapid tests or even without resorting to experiment at all. Physical and mathematical modeling of the complex interactions between poisons and living organisms is also becoming a reality.

R. P. Feynman, an outstanding physicist and Nobel Laureate, has said, "Science is only useful if it tells you about some experiment that has not been done" (*The Character of Physical Law*, The M.I.T. Press, Cambridge, Mass., 1967, p. 164). It may be stated that quantitative methods are making toxicology such a science to a large extent.

Although the various individual aspects of quantitative toxicology have for a relatively long time been dealt with in journal articles, conference papers and abstracts, contributions to nonperiodical publications, and so on, the relevant information remains widely scattered in the literature. The time seems ripe for an attempt to sum up the results of work accomplished by various authors, to arrange systematically the information amassed, and to demonstrate its possible practical applications. This monograph represents such an attempt.

A book of this size cannot be expected to encompass all the facets of quantitative toxicology that have been worked out in more or less detail. The presentation is therefore confined to selected topics covering what appear to be the more important, though by no means all, developments in quantitative toxicology. Also discussed are some theoretical aspects of toxicology that as yet cannot be dealt with in quantitative terms but are deemed worthy of consideration either because they have served as a basis for revealing sustained quantitative relationships in the action of poisons on the living organism or because they point out some of the paths to be followed by quantitative toxicology.

Chapters 1, 2, and 6 were written by N. A. Tolokontsev; Chapters 3 and 4 by V. A. Filov; Chapter 5 by E. I. Liublina; Chapter 7 by A. A. Golubev, V. A. Filov, and E. I. Liublina; and Chapter 8 by E. I. Liublina and A. A. Golubev.

The authors will welcome any suggestions and criticisms regarding the choice and treatment of the topics included in the book.

PREFACE TO THE ENGLISH-LANGUAGE EDITION

This book appears to have been the first attempt to present a systematic account of the more important quantitative aspects of toxicology, mainly industrial toxicology. It has been well received in the USSR and some East European countries. We were gratified to be requested to prepare the book for publication in the United States.

The substantial progress made in quantitative toxicology since the book was first published in Russian in 1973 has necessitated its revision and considerable expansion. Since most of the material contained in the original edition has not grown obsolete, the structure of the book has been retained, and the revision has mainly involved corrections, deletions, and short additions, as well as updating of the text where necessary. The bulk of new material is contained in the addenda to the various chapters, where most of the topics discussed in the main text are elaborated on and other aspects not covered there are included. The main text of the book is therefore independent of the addenda and may be read separately.

Addenda have been prepared to all chapters except Chapter 3; the subject discussed therein appears to have been exhausted, and no further developments have occurred. The addendum to Chapter 6 consists of two parts, concerned, respectively, with combined and complex exposures to poisons.

In addition to toxicologists as such, the book is intended for environmental specialists and hygienists and, we hope, may be found useful by pharmacologists, sanitary chemists, biochemists, and indeed by all those interested in the problems of interaction between xenobiotics and the living organism or between pollutants and the biosphere. The latter aspect deserves a few words of special mention.

In the face of the ever-growing pollution of the biosphere with a multitude of chemicals, many of which are detrimental to human health and deteriorate the natural environment, it is inevitable that problems of toxicology draw the

attention of many specialists from allied fields of science. A consequence of this "movement into toxicology" has been its mathematization, an increasing reliance on quantitative methods for the tackling of both traditional (dose-time-response relationships, joint action of poisons, etc.) and relatively new problems of toxicology relating to toxicokinetics, cumulation and adaptation, migration of substances in the various components of the environment, evaluation of multiple and complex exposures, determination of permissible burdens on the environment and on man, and many other aspects, including the creation of mathematical models of the environment on which to base scientifically sound strategies of environmental monitoring and quality control. A good illustration of the introduction of quantitative methods into toxicology and of its conversion into a global discipline can be seen in the proceedings of the Soviet-American Symposia on the Comprehensive Analysis of the Environment held in 1974 (Tbilisi, USSR) and 1975 (Honolulu, Hawaii).

One final remark is in order. This book cannot be regarded as an all-embracing account of current theoretic concepts, methods, or results in quantitative toxicology. Also, along with quantitative aspects, it contains some of a qualitative nature, but these have been included solely for the purpose of showing that a given property, mechanism, or condition has to be taken into account in the quantitative study of toxic effect.

Throughout the process of revising the book and preparing the addenda we have constantly missed the logical thinking and expertise of Alexander A. Golubev, one of the authors of the original edition, who died in 1972.

We will consider our objective fulfilled if those wishing to become acquainted with the quantitative aspects of toxicology find the book useful and, perhaps more important, if it provides a stimulus to the advancement of this important and exciting field of study.

The authors wish to express their gratitude to V. E. Tatarchenko for his technical assistance in preparation of the Russian text and for his translation of it into English.

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Leningrad, USSR
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CONTENTS

1

THE TOXIC EFFECT AS A RESULT OF INTERACTION BETWEEN THE POISON AND THE LIVING ORGANISM

The title of this chapter serves to emphasize that any reaction of a living organism in response to any harmful substance results from an interaction of the organism and the substance—a fact which is not always fully appreciated. This means that in any study of the toxicity of particular substances, in designing and conducting any toxicological experiment, and in interpreting its results the fullest possible consideration must be given to the properties and features of both the organism and the chemical agent concerned. Moreover, the toxic effect produced by a poison may be strongly affected by various environmental variables such as temperature, humidity, and pressure. Therefore a toxic effect, strictly speaking, is the result of interaction of three distinct entities, namely, the poison, the organism, and the environment.

It should be stated at the outset that no attempt will be made here to present a review or summary of the literature dealing with each particular aspect of the subject discussed in this introductory chapter. Rather, only a few examples will be given, for the main purpose of illustrating the need to take into proper account the aspect or variable under consideration when studying the toxicity of substances.

SPECIES DIFFERENCES IN SENSITIVITY TO POISONS

It has long been known that different species of animals vary in their sensitivity to poisons. A knowledge of the origin, development, and course of intoxications in particular animal species is very important for toxicologists because toxicity data obtained in animal experiments are in most cases to be transferred to man. A reliable extrapolation is not possible unless the qualitative and quantitative characteristics underlying species differences in sensitivity to

the poisons concerned are well known. In the USSR the first (and still relevant) summary of the problem of interspecies differences in sensitivity to poisons appears to be the one contained in Lazarev's book, *General Principles of Industrial Toxicology*, published in 1938. Of the more recent works mention may be made, for example, of those by Krasovsky (1967, 1973), Krasovsky et al. (1969, 1970a,b), and Ulanova (1970), wherein a large body of evidence on quantitative interspecific differences is presented.

The mere accumulation of quantitative data, important as they are, is of course insufficient, and attempts have been made to disclose the mechanisms underlying species differences in sensitivity to poisons. Of the studies along this line those of L. A. Tiunov and his associates deserve first mention (e.g., Tiunov, 1967; Tiunov and Keizer; 1966; Tiunov et al., 1969; Liniucheva and Tiunov, 1966; Liniucheva et al., 1969). Among other things these studies have clearly demonstrated that species differences in responses to poisons depend primarily on the way in which the poisons are metabolized. It has been found, for instance, that dogs cannot be used to study poisons capable of acetylation, such as meta- and para-aminobenzoic acids, if the data are to be transferred to man: these substances do not acetylate in dogs, in contrast to man. On the other hand, their fates in man and rabbits are similar. One example illustrating the importance of knowing the qualitative features of the particular biological systems involved in the metabolism of the poison under consideration and responsible for the observed species differences in responsiveness to that poison is provided by a study of liver catalase activities in white mice and rats (Tiunov, 1967). Although the catalase level in mice is normally similar to that in rats, a 2-hr exposure to benzene by inhalation resulted in a noticeable reduction of catalase activity in rats (from 20.0 ± 1.5 to 13.1 ± 1.2 units), whereas in mice the activity remained virtually unchanged (17.6 ± 0.5 before and 17.7 ± 0.5 after exposure).

Among many other important factors contributing to species sensitivity are degree of complexity and differentiation of the central nervous system; level of development of the mechanisms regulating various body functions; characteristics of the skin; body size and weight; and life span. Of these factors let us consider life span, which appears to be of considerable importance in toxicological experiments on animals, especially when the experiment is aimed at arriving at an estimate of the maximum permissible concentration of a poison in the human environment. It is desirable that the duration of such an experiment be determined on the basis of the ratio of the fraction of life span during which man is likely to be exposed to the poison in question, to the whole life span. That life span is indeed an important consideration can be seen from the following.

As shown by Sacher (1960) and other authors, life span correlates well with, and has a significant regression on, a number of important species-