

WORLD HEALTH ORGANIZATION



INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

STATISTICAL METHODS
IN
CANCER RESEARCH

VOLUME III – The design and analysis
of long-term animal experiments

by

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CONTENTS

Foreword	vii
Preface	ix
1. General Introduction and Outline	2
2. General Considerations on the Evaluation of Animal Carcinogenesis	
Experiments	5
2.1 Introduction	6
2.2 Determination of relevant biological events	6
2.3 Non-neoplastic precursors of a neoplasm	8
2.4 Adjustment for intercurrent mortality	8
2.5 Combining analyses as opposed to pooling data	10
2.6 Considerations related to sex and species	10
2.7 Consideration of tumour dose-response	11
2.8 Observable tumours	11
2.9 Problems with occult tumour data	12
2.10 Context of observation for occult tumours	12
2.11 Potential for bias in the analysis of fatal tumours	13
2.12 Potential for bias in the analysis of incidental tumours	14
2.13 Combining analyses of fatal and incidental tumour data	15
2.14 Context of observation unavailable	16
2.15 Analysis of crude tumour rates	17
2.16 Concomitant information	19
2.17 Need for interdisciplinary decision process	19
2.18 Overall evaluation of carcinogenicity	19
3. Experimental Design	21
3.1 Introduction	22
3.2 Principles of experimental design	28
3.3 Designs for screening studies	36
3.4 Designs for dose-response studies	43
3.5 Designs for studies of mechanism	47
3.6 Histopathological analysis	50
3.7 Recording of experimental data	51
3.8 Summary and recommendations	53

4. Some Illustrative Data Sets	57
4.1 Bioassay of 1,2-dichloroethane	58
4.2 Skin painting experiment with cigarette- and cigar-smoke condensates	58
4.3 Pituitary tumours in rats with various doses of <i>N</i> -nitrosodimethylamine (NDMA)	58
4.4 An artificial teaching example	66
5. Nonparametric Methods for Animal Carcinogenesis Experiments	69
5.1 Introduction	70
5.2 Computation of nonparametric test statistics	70
5.3 Nonparametric analysis of survival curves	73
5.4 Analysis of crude proportions	75
5.5 Prevalence analysis for nonlethal occult tumours	87
5.6 Analysis of rapidly lethal occult tumours and of observable tumours	94
5.7 Analysis of occult tumour data when contexts of observation are known	101
6. Model Fitting	107
6.1 Introduction	108
6.2 Dose-response models	109
6.3 Time-to-tumour models	122
6.4 Summary	143
7. Special Topics	147
7.1 Introduction	148
7.2 Statistical inference at multiple sites	148
7.3 Multiplicity of tumours	150
7.4 Graded responses	153
7.5 Multifactorial designs: combining results	155
7.6 Litter effects	160
7.7 Association among tumour types	165
7.8 Historical control tumour rates	167
8. Analysis of Auxiliary Data	169
8.1 Introduction	170
8.2 Analysis of survival data	170
8.3 Analysis of variance	171
8.4 Repeated measures and growth curves	180
9. References	185
Appendix I: Solution to teaching example	210
Appendix II: Computer programs	212

FOREWORD

In 1980, the Agency started a series on 'Statistical Methods in Cancer Research' within its programme of scientific publications. The first volume was devoted to the analysis of case-control studies and received wide attention as the first comprehensive textbook on this subject. It demonstrated clearly the need for authoritative texts in the field of cancer biostatistics, in which there have been considerable methodological developments in the last few decades.

The present volume, on the design and analysis of long-term animal experiments, addresses an area of cancer research that is of great importance to the understanding of carcinogenic risk factors. Long-term animal experiments play a major role in assessment of the carcinogenicity of chemicals in the light of the methodological difficulties of some epidemiological studies and the biological limitations of short-term assays. An effort to standardize methods for long-term tests has been made in recent years, and a thorough treatment of the statistical issues involved was therefore very necessary. The publication of this volume is in concordance with the Agency's aim to promote all facets of cancer research by disseminating information and providing methodological support.

It is a pleasure to commend the five authors on this book, which should prove to be of value for biostatisticians working in the field of long-term animal experiments as well as for experimentalists who want to learn about the statistical concepts involved and all those who have to interpret findings from such studies for regulatory purposes. Last but not least, it may also serve as a textbook for students in biostatistics and related fields.

The Agency is, at the same time, actively pursuing research into developing tests that can be used to make valid predictions of carcinogenic risk factors but which do not necessitate the use of experimental animals.

L. Tomatis, MD
Director, IARC

PREFACE

The roots of this monograph on the design and analysis of long-term animal experiments can be found in the programme of the *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, which started in 1971. Since adequate data for humans were often not available, this programme had to base its evaluations predominantly on data from long-term carcinogenicity studies in animals. In the event that there was sufficient evidence for a chemical to be considered carcinogenic in animals, it was noted that this compound should be regarded, for practical purposes, as if it represented a carcinogenic risk to humans. Also, when human data were available, animal studies provided, and continue to provide, valuable additional information for a chemical's evaluation. The Agency recognized that long-term, and, indeed, also short-term assays, could play their role in screening for carcinogens most effectively only if the methodology was thoroughly understood and standardized. Therefore, a meeting was organized in 1979 which resulted in the publication of a critical appraisal of the methodological aspects of long-term and short-term assays (IARC, 1980). During this meeting it became apparent that statistical issues play an important role in assessing the results of long-term carcinogenicity studies.

In order to convey the essential aspects of the statistical analysis of long-term carcinogenicity studies, Richard Peto initiated the writing of an Annex giving guidelines for simple, sensitive significance tests for carcinogenic effects in long-term animal experiments (Peto *et al.*, 1980). This Annex proved to be a very valuable text not only for experimentalists but also for statisticians who had to apply these methods or were developing the methodology further.

Statistical methods for long-term animal experiments have to account for the unique biological and toxicological problems encountered in animal tests and the development of such methods has become an active area of research. To summarize the recent research in a monograph was therefore felt to be a very natural consequence of the publication of the Annex and to fit very well in the Agency's series of monographs on *Statistical Methods in Cancer Research*.

At a first meeting held in Lyon in 1981, we outlined the structure of this book and organized its production; drafts were subsequently prepared and circulated, comments from colleagues were obtained, and further meetings and revisions followed before the final product became available.

The book is intended to be of interest not only for biostatisticians but also for other

scientists involved in the design, conduct and interpretation of long-term animal experiments. The first three chapters are written in a completely nontechnical fashion in order to introduce clearly the fundamental aspects of long-term animal experiments and to identify the issues involved in the design of such studies. The statistical methods presented in the later chapters are illustrated using data from real experiments. For teaching purposes, we also give a shorter, constructed example for which the relevant calculations can be done easily with a pocket calculator in the classroom. A detailed outline of the monograph is given at the end of the first chapter.

The book has profited considerably from the stimulating background provided by the *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*. Many colleagues have given valuable comments to improve earlier drafts and assisted in a careful final reading; we gratefully acknowledge the contributions of: N.E. Breslow, C.C. Brown, J.R.P. Cabral, D. Colin, N.E. Day, A. Dewanji, G.E. Dinse, L. Edler, R.A. Griesemer, J.K. Haseman, W. Lehmacher, B. McKnight, D. Murdoch, C. Portier, M. Schumacher, J.D. Wilbourn and T. Yanagimoto.

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Finally, we decided to arrange the authors' names in alphabetical order.

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