ALTERNATIVE METHODS IN TOXICOLOGY 2

ACUTE TOXICITY TESTING: ALTERNATIVE APPROACHES

EDITOR
ALAN M. GOLDBERG

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ALTERNATIVE METHODS IN TOXICOLOGY
VOLUME 2

Acute Toxicity Testing: Alternative Approaches

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Alan M. Goldberg

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ALTERNATIVE METHODS IN TOXICOLOGY SERIES

Volume 1

PRODUCT SAFETY EVALUATION

Volume 2

ACUTE TOXICITY TESTING: ALTERNATIVE APPROACHES

Volume 3

IN VITRO METHODS IN TOXICOLOGY

ACUTE TOXICITY TESTING: ALTERNATIVE APPROACHES

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Preface

The proceedings of the 2nd symposium of The Johns Hopkins Center for Alternatives to Animal Testing, held in May of 1983, are published in this volume. The meeting was historic in that all segments of our society dealing with acute toxicity and the issue of the use of animals in testing were represented. We were fortunate to have a group of outstanding and well-recognized experts to speak to the important issues of Acute Toxicity Testing—Are There Alternative Approaches? The outcome of the meeting resulted in and provided the scientific basis for a multi-branch governmental meeting to examine their policies regarding the LD_{50}.

The program for the second symposium of The Johns Hopkins Center for Alternatives to Animal Testing was developed about a year prior to the actual meeting. The Advisory Board of the Center examined the broad issues of topics that might be appropriate for such a symposium. They suggested that the topic be timely, highly focused, and offer the opportunity for a thorough evaluation of a defined and important question. A subcommittee of the Advisory Board, consisting of Gareth Green, Leon Golberg, and Thomas Hickey, met with me on several occasions to work out the concept and the program. The final program was re-evaluated by the entire Advisory Board at a meeting that took place in November 1982 and the symposium took place five months later. The end result of the symposium—although predictable from the scientific standpoint, but unexpected—was a concensus of all present that the LD_{50}, *in the classical sense, could be replaced by approaches using considerably less animals. The participation encompassed academic, industrial, regulatory and advocate groups. There was a full airing of the issues; and the fact that a consensus was reached attests to the quality of the presentations, workshops, posters and discussions.*

The first day, and part I of this volume, focuses on prepared presentations which address the why, the how, and the what of acute toxicity testing. Part II presents several posters which address additional specific issues. These presentations and posters provided the background information for the workshops. Part III, the workshops, deals with the difficult scientific issues associated with the development of in vitro *methodology. A review of each workshop is provided. This is an almost verbatim transcript of what was reported to the entire conference. Part IV examines these discussions from a regulatory standpoint.*

As part of the audience, I was treated to well-developed rationales examining the purposes and practices of acute toxicity testing. Clearly, as the conference and workshops became completed, our biases, outlooks and approaches were modified. We defined what can and what cannot be accomplished in the development of in vitro *toxicological methods for acute toxicity testing in general and for the* LD_{50} *specifically.*

I would like to most sincerely thank the Cosmetic, Toiletry and Fragrance Association and its member companies for establishing the Center. I am very grateful to the Bristol-Myers Company for sponsoring this symposium. Not only have they given financially but their encouragement, shared thinking, and enthusiasm is truly appreciated. I am most thankful.

Alan M. Goldberg
January 1984

CONTRIBUTORS

Michael Balls, M.A., D. Phil.
FRAME, 5b The Poultry, Bank Place, St. Peter's Gate, Nottingham, England

Rolf Bass, M.D.
Bundesgesundheitsamt (Federal Health Office), Berlin, FRG

David A. Blake, Ph.D.
Department of Pharmacology, The Johns Hopkins University, School of Medicine, 720 Rutland Avenue, Baltimore, MD 21205

Ellen Borenfreund, Ph.D.
Laboratory Animal Research Center, The Rockefeller University, 1230 York Avenue, Box 2, New York, NY 10021

James Bridges, Ph.D.
Department of Toxicology, Robens Institute of Industrial and Environmental Health and Safety, University of Surrey, Guildford, Surrey, England

Robert D. Bruce
The Procter & Gamble Company, P.O. Box 39175, Cincinnati, OH 45247

Paul Craig
Health Designs, Inc., 183 Main Street East, Rochester, NY 14604

L.R. DePass, Ph.D.
Bushy Run Research Center, Mellon Institute—Union Carbide Corporation, Export, PA 15632

M.C. DiBlasi
Department of Gynecology and Obstetrics, The Johns Hopkins University, School of Medicine, 720 Rutland Avenue, Baltimore, MD 21205

Norman H. Dubin, Ph.D.
Department of Gynecology and Obstetrics, The Johns Hopkins University, School of Medicine, 720 Rutland Avenue, Baltimore, MD 21205

Kurt Enslein
Health Designs, Inc., 183 Main Street East, Rochester, NY 14604

W. Gary Flamm, Ph.D.
Bureau of Foods, Food and Drug Administration, 200 C Street, S.W., Washington, DC 20204

H.P. Gelbke, M.D.
BASF Aktiengesellschaft, Ludwigshafen, FRG

C. Gloxhuber, M.D.
Henkel KG, Dusseldorf, FRG

Gareth M. Green, M.D.
Department of Environmental Health Sciences, The Johns Hopkins University, School of Hygiene and Public Health, 615 N. Wolfe Street, Baltimore, MD 21205

H. Greim, M.D.
Gesellschaft fur Strahlen- und Umweltforschung, Neuherberg, Munich, FRG

Alan M. Goldberg, Ph.D.
Department of Environmental Health Sciences, Center for Alternatives to Animal Testing, The Johns Hopkins University School of Hygiene and Public Health, 615 N. Wolfe Street, Baltimore, MD 21205

P. Gunzel, D.V.M.
Schering AG, Berlin FRG

T.L. Hayden, Ph.D.
Health and Safety Research Division, Oak Ridge National Laboratory, Oak Ridge, TN 37830

D. Henschler, M.D.
Institut fur Pharmakologie und Toxikologie der Universitat, Wurzberg, FRG

Thomas E. Hickey, D.V.M.
Bistol-Myers Company, Pharmaceutical Research and Development Division, Evansville, IN 47721

A. Hildebrandt, M.D.
Bundesgesundheitsamt (Federal Health Office), Berlin, FRG

A.W. Hsie, Ph.D.
Biology Division, Oak Ridge National Laboratory, Oak Ridge, TN 37830

D. Kayser, Ph.D.
Bundesgesundheitsamt (Federal Health Office), Berlin, FRG

J. Konig, M.D.
Byk-Gulden Pharmazeutika, Hamburg-Rahlstedt, FRG

Paul Kotin
Adjunct Professor of Pathology, University of Colorado, School of Medicine, Denver, CO

Paul H. LaFlamme, B.S., M.A.T.
Springborn Regulatory Services, Inc., 30 Springborn Center, Enfield, CT 06082

Thomas Lander
Health Designs, Inc., 183 Main Street East, Rochester, NY 14604

Victor G. Laties, Ph.D.
Division of Toxicology and Environmental Health Sciences Center, Department of Radiation Biology and Biophysics, University of Rochester, School of Medicine and Dentistry, Rochester, NY 14642

D. Lorke, M.D.
Bayer AG, Institut fur Toxikologie, Wuppertal, FRG

James McCulley, M.D.
Department of Ophthalmology, University of Texas, Dallas, TX 75235

John A. Moore, D.V.M.
National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709

Warren Muir, Ph.D.
Division of Environmental Engineering, Department of Environmental Health Sciences, The Johns Hopkins University, School of Hygiene and Public Health, 615 N. Wolfe Street, Baltimore, MD 21205

R.C. Myers
Bushy Run Research Center, Mellon Institute—Union Carbide Corporation, Export, PA 15632

D. Neubert, M.D.
Institut fur Toxikologie und Embryonalpharmakologie der Freien Universitat, Berlin, FRG

S.W. Perdue, M.S.
Biology Division, Oak Ridge National Laboratory, Oak Ridge, TN 37830

K.S. Jagannatha Rao
Division of Molecular Physiology, Department of Zoology, SRI Venkateswara University, Tirupati-517 502. A.P., India

Charles Rohde, Ph.D.
Department of Biostatistics, The Johns Hopkins University, School of Hygiene and Public Health, 615 N. Wolfe Street, Baltimore, MD 21205

R.L. Schenley, M.S.
Biology Division, Oak Ridge National Laboratory, Oak Ridge, TN 37830

D. Schuppan, Ph.D.
Bundesverband der Pharmazeutischen Industrie (BPI), Frankfurt, FRG

E. Schutz, M.D.
Hoechst AG, Frankfurt, FRG

Charles Shopsis, Ph.D.
Laboratory Animal Research Center, The Rockefeller University, 1230 York Avenue, Box 2, New York, NY 10021

Robert Squire, D.V.M., Ph.D.
Department of Comparative Medicine and Pathology, The Johns Hopkins University, School of Medicine, 720 Rutland Avenue, Baltimore, MD 21205

Dennis M. Stark, D.V.M., Ph.D.
Laboratory Animal Research Center, The Rockefeller University, 1230 York Avenue, Box 2, New York, NY 10021

K.S. Swami, M.A., Ph.D.
Division of Molecular Physiology, Department of Zoology, SRI Venkateswara University, Tirupati-517 502. A.P., India

E.-L. Tan, Ph.D.
Biology Division, Oak Ridge National Laboratory, Oak Ridge, TN 37830

C.L. Thomas
Department of Gynecology and Obstetrics, The Johns Hopkins University, School of Medicine, 720 Rutland Avenue, Baltimore, MD 21205

Michael Tomb
Health Designs, Inc., 183 Main Street East, Rochester, NY 14604

J.E. Turner, Ph.D.
Health and Safety Research Division, Oak Ridge National Laboratory, Oak Ridge, TN 37830

James Walberg, D.V.M.
Laboratory Animal Research Center, The Rockefeller University, 1230 York Avenue, Box 2, New York, NY 10021

E.V. Weaver
Bushy Run Research Center, Mellon Institute—Union Carbide Corporation, Export, PA 15632

C.S. Weil
Bushy Run Research Center, Mellon Institute—Union Carbide Corporation, Export, PA 15632

M.W. Williams, Ph.D.
Health and Safety Research Division, Oak Ridge National Laboratory, Oak Ridge, TN 37830

Mark C. Wolff, Ph.D.
Department of International Health, The Johns Hopkins University, School of Hygiene and Public Health, 615 N. Wolfe Street, Baltimore, MD 21205

Ronald W. Wood, Ph.D.
Division of Toxicology and Environmental Health Sciences Center, Department of Radiation Biology and Biophysics, University of Rochester, School of Medicine and Dentistry, Rochester, NY 14642

Gerhard Zbinden, M.D., FRC Path.
Institute of Toxicology, Swiss Federal Institute of Technology, University of Zurich, Schwerzenbach, Switzerland

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Acute Toxicity Testing

Acute Toxicity Testing, Purpose

GERHARD ZBINDEN

Institute of Toxicology, Swiss Federal Institute of Technology and University of Zurich, Schwerzenbach, Switzerland

Alternative Methods in Toxicology

Volume 2: Acute Toxicity Testing: Alternative Approaches

IMPORTANCE FOR TOXICOLOGY - RELEVANCE IN PRACTICE

Toxicologist often have a tendency to regard the world solely from their point of view. This may explain their preoccupation with acute toxicity testing which captures an inordinately large part of their attention.

TABLE I

MAJOR CONCERNS IN CLINICAL USES OF NEW DRUGS

PHASE	POTENTIAL TOXIC EFFECTS
I and early II	Acute Cardiovascular Reactions: Orthostatic Hypotension, Collapse, Arrhythmia, Myocardial Infarction Gastrointestinal Disturbances: Hemorrhage, G.I. Paralysis, Vomiting CNS Disturbances: Seizures, Psychotic Reactions, Hallucinations, Somnolence, Depression Bronchopulmonary Reactions: Asthma, Bronchospasm Anaphylactic Reactions: Shock, Hemorraghes, Edema Miscellaneous Reactions: Hemolysis, Thrombosis, Local Irritation, Disulfiram-Like Effect
II and III	Cumulative Organ Toxicity: Liver, Kidney, Nervous System, Sensory Organs, Bone Marrow, Reproductive Organs Hypersensitivity Reactions, Endocrine Disturbances, Teratogenesis
Post-marketing	Idiosyncratic Reactions in Selected Populations Carcinogenesis, Mutagenesis, Drug Interactions, Rebound Effects, Tolerance, Drug Dependence, Abuse, Suicide, Accidental Poisoning

In fact, the acute toxicity test is the first biological experiment done with the majority of compounds synthetized by the chemists or discovered in the environment. It often provides a wealth of information which can greatly influence the fate of a new chemical. The results of acute toxicity tests are used as guidance for dose selection and design of further toxicologic experiments, they signal the presence of special hazards requiring immediate preventive measures, and they are sure to figure prominently in a data sheet or dossier, should the compound ever be registered with a regulatory agency.

For the people who have to deal with the chemicals outside toxicology acute toxicity testing has a different meaning. Let us consider the clinical pharmacologist who supervises the investigation of a potential new drug in volunteers and patients. His concerns with toxicity are summarized in Table I. In the early phases of the clinical trial the major hazards are functional disturbances, particularly of the cardiovascular, gastrointestinal and nervous systems and anaphylactic reactions. In order to prepare for these problems, the clinician consults the pharmacology section of the data sheet and not the information on acute toxicity. Acute toxicity tests are also of little use for the prediction of cumulative organ toxicity which is the major concern during extended clinical studies (Phase III). Only when the new drug reaches a wider distribution and gets in the hands of patients not closely supervised by the physician, does the problem of intentional or accidental overdosage reach significant proportions. It is at this time that the results of acute toxicity tests become of practical importance.