ACUTE TOXICITY TESTING: ALTERNATIVE APPROACHES

ALAN M. GOLDBERG

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Acute Toxicity Testing: Alternative Approaches

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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 LD₅₀.

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 LD₅₀, 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

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Contents

Part Or	re. Acute	Toxicity	Testing
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1.	Acute Toxicity Testing, Purpose Gerhard Zbinden	3
2.	Acute Toxicity Testing, Practice	23
	Thomas E. Hickey	
3.	Regulatory Uses of Acute Toxicity Data	47
	Paul H. LaFlamme	
4.	The FRAME Research Programme on In Vitro Cytotoxicology	61
	Michael Balls and James W. Bridges	
5.	Hazard Identification with Small Numbers of Animals:	
	Implications for Risk Assessment	81
	Victor G. Laties and Ronald W. Wood	
Part	Two. Poster Presentations	
6.	In Vitro Cytotoxicity Assays as Potential Alternatives to the	
0.	Draize Ocular Irritancy Test	101
	C. Shopsis, E. Borenfreund, J. Walberg, and D. Star	101
7.	The Toxicity of Sixteen Metallic Compounds in Chinese Hamster	
	Ovary Cells: A Comparison with Mice and Drosophila	115
	A. W. Hsie, R.L. Schenley, EL. Tan, S.W. Perdue, M.W. Williams,	115
	T.L. Hayden and J.E. Turner	
8.	Development of an In Vitro Test for Cytotoxicity in Vaginal Tissue:	
	Effect of Ethanol on Prostanoid Release	127
	N.H. Dubin, M.C. DiBlasi, C.L. Thomas and M.C. Wolff	
9.	An Assessment of the Importance of Number of Dosage Levels, Number	
	of Animals per Dosage Level, Sex and Method of LD ₅₀ and	
	Slope Calculation in Acute Toxicity Studies	139
	L.R. DePass, R.C. Myers, E.V. Weaver and C.S. Weil	
0.	An In Vitro Novel Technique for Screening Antidote Potentiality of Drugs	155
	K.S. Swami and K.S. Jagannatha Rao	
	0.0	

11.	Methodology Updating of Acute Toxicity Testing R. Bass, H.P. Gelbke, C. Gloxhuber, H. Greim, P. Gunzel, D. Henschler, A. Hildebrandt, D. Kayser, J. Konig, D. Lorke, D. Neubert, E. Schutz, D. Schuppan, G. Zbinden	173
Poste	er Abstracts	
12.	Validation of a Structure-Activity Model of Rat Oral LD50	183
13.	T. Lander, K. Enslein, P. Craig and M. Tomb An Up-and-Down Procedure for Acute Toxicity Testing	
15.	Robert D. Bruce	184
Part	Three. Workshops	
14.	Charge to Workshops: Definitions and Goals	187
15.	Alan M. Goldberg Opening Statement of Workshops:	
	A. Statistical Considerations and Protocols Using Small Numbers	
	of Animals. Introductory Remarks Gerard Zbinden	195
	B. Species and Host Factors in Safety Evaluation	207
	Gareth M. Green C. The Preselection or Establishment of a Hierarchy of Chemicals	
	in Safety Evaluation	215
	Warren Muir D. Protocol Development and the Scientific and Clinical Uses of	
	D. Protocol Development and the Scientific and Clinical Uses of Acute Toxicity Data	223
	David A. Blake	
16.	Summaries of Workshops: A. Statistical Considerations and Protocols Using Small Numbers	
	of Animals	227
	Charles Rohde B. Species and Host Factors in Safety Evaluation	237
	John A. Moore	237
	C. The Preselection or Establishment of a Hierarchy of Chemicals	0.47
	in Safety Evaluation Robert Squire	247
	D. Protocol Development and the Scientific and Clinical Uses of	
	Acute Toxicity Data Paul Kotin	257
Part	Four. Regulatory Implications	
17.	Summary: Regulatory Implications W. Gary Flamm	281
	ii. Oury i winin	

Part One

Acute Toxicity Testing

Acute Toxicity Testing, Purpose

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Alternative Methods in Toxicology

Volume 2: Acute Toxicity Testing: Alternative Approaches

Teratogenesis

PHASE

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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

POTENTIAL TOXIC EFFECTS

I and	Acute Cardiovascular Reactions: Orthostatic
early	Hypotension, Collapse, Arrhythmia, Myocardial
II	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	Cumulative Organ Toxicity: Liver, Kidney, Nervous
III	System, Sensory Organs, Bone Marrow, Reproductive
	Organs
	Hypersensitivity Reactions, Endocrine Disturbances,

Idiosyncratic Reactions in Selected Populations

Effects, Tolerance, Drug Dependence, Abuse,

Suicide, Accidental Poisoning

Carcinogenesis, Mutagenesis, Drug Interactions, Rebound

6 ZBINDEN

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.