structure-activity correlation as a predictive tool in toxicology

fundamentals, methods, and applications

Leon Golberg

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Preface

This volume is based on a symposium held in Raleigh, North Carolina, February 10-12, 1981. The symposium was cosponsored by the Chemical Industry Institute of Toxicology (CIIT), the United States Environmental Protection Agency (EPA), the National Institute of Environmental Health Sciences (NIEHS), and the Burroughs Wellcome Company (BW). It broke new ground as a joint endeavor by four neighboring organizations located in Research Triangle Park, North Carolina sharing a common interest in toxicology.

It is thus appropriate to acknowledge with deep appreciation the contributions made by the following scientific colleagues to the planning of the meeting: Dr. Michael Cory, BW; Dr. James E. Gibson, CIIT; Dr. Peter C. Jurs, The Pennsylvania State University; Dr. Stephen C. Nesnow, EPA; and Dr. Michael D. Waters, EPA.

The organization of the meeting was in the capable hands of the following members of the CIIT administrative staff, to whom we are all most grateful: Ms. Willanna Griffin, Mrs. Elizabeth Barnhill, Mrs. Edna Mangum, Ms. Sena Taylor, Dr. Donald A. Hart, Mr. Lanny Bynum, Mr. Charles Overton,

and Mr. Sterling Isom. In addition, Ms. Willanna Griffin worked tirelessly and effectively to organize the manuscript for publication. Ms. Linda Smith and Ms. Joanne Quate were responsible for word processing.

Leon Golberg

Introduction

The subject of structure-activity relationships is seldom far from the toxicologist's consciousness when exploring the biological properties of new compounds or examining those of existing materials whose potential hazards are under further investigation. The attributes observed in the test materials inevitably invite an intuitive comparison with the structures of compounds sharing the same, or similar, toxicological properties. The volume of literature on which these comparisons are based has grown to such an extent as to defy the ability of any individual to recall an adequate expanse of data. Simultaneously, the toxicologist is called on to deal with more and more complex mixtures of environmental or industrial origin. Thus, for instance, in the development of synthetic fuels, the old, familiar, and seemingly innocuous materials like shale or coal are transformed into liquids containing hundreds of characterized or identifiable mutagens and carcinogens. It is time for new approaches.

The correlation of biological properties with chemical structure has its roots in the study of pharmacological action in animals and therapeutic efficacy in humans. Such comparisons were drawn early in the nineteenth

century, even before chemical structures could be accurately assigned to many of the medicinal agents under investigation (1). Early enthusiasm for the predictive power of such correlations, and the possibility of beneficial practical applications for clinical purposes, is illustrated by Thomas Huxley's forecast—a century ago—of a radiant future:

> . . . there surely can be no ground for doubting that, sooner or later, the pharmacologist will supply the physician with the means of affecting, in any desired sense, the functions of any physiological element of the body. It will, in short, become possible to introduce into the economy a molecular mechanism which, like a cunningly contrived torpedo, shall find its way to some particular group of living elements, and cause an explosion among them, leaving the rest untouched [2].

All this has a familiar ring, especially when applied to the advances and achievements in chemotherapy and other branches of therapeutics. At the time, however, the passing years brought initial disillusion that the brave new world promised by Huxley had not materialized (3). Nevertheless, belief in the importance of structure-activity correlation remained strong. Spurred on by the work of Hansch (4) and others, drug development began to utilize the new techniques involving quantitative structure-activity relationships (QSAR). Toxicology entered the picture with the application of quantum chemistry by the Pullmans (5) to account for carcinogenic activity of polycyclic aromatic hydrocarbons. The advent of the computer has transformed the situation in the field of QSAR, making possible applications of a wide variety of techniques to an ever-widening range of biological properties, from psychotropic agents to olfactory stimulants (6).

In the belief that QSAR is a powerful instrument with whose vast potentialities toxicologists should become familiar, a symposium was convened that forms the basis of this book. Its purpose was twofold: to develop tools to be used in setting priorities for toxicological testing of chemicals and to foster discussions and collaborative interactions in this important area of research between those in a position to develop and perfect the methods and those seeking to utilize them.

The term "predictive tool" was introduced into the title of the symposium to stress the distinction between judgment and computation. The toxicologist's experience, perspective, understanding of, and intuitive feeling for biological phenomena are essential parts of the judgment that he or she brings to bear on findings labeled as statistically significant. There is a parallel with clinical judgment and the breadth of comprehension that it requires, *vis à vis* the role of computers as adjuncts to decision-making in the handling of clinical laboratory and dosage data (7).

Enthusiasm for the application of QSAR methodologies needs to be tempered by a realization of the weaknesses of existing biological data bases. Equally, one should take note of the multitude of variables that influence the toxicological end-results–animal species, strains, experimental conditions, and other factors. For this reason, care should be exercised in selecting data that may be considered valid. Even when this is done, one is faced with the complexities, not to say the vagaries, of metabolic transformation and the multitude of modulating factors that help to determine the biological outcome in any given situation. Two further confounding factors are the often unique susceptibilities of individuals in animal, and especially human populations, dependent on complex genetic, environmental, and lifestyle factors; also, the effects of simultaneous exposures to a variety of toxicants such as alcohol and tobacco smoke can exercise a striking influence on the toxic manifestations of a test material (8).

These considerations need to be borne in mind lest we be carried away by an excess of euphoria as great as Huxley's. Until an Einstein appears on the scene to rationalize the present state of confusion and provide some standard criteria by which to foretell the range of individual human responses to various types of chemical exposure, the role of QSAR is to warn and to predict. "Double, double toil and trouble" (9) surely continues ahead for toxicologists; but we should learn from Macbeth's experience and not take predictions too literally, even when they come from a computer rather than a Witch.

REFERENCES

1 Bynum, W. F. Chemical structure and pharmacological action: A chapter in the history of 19th century molecular pharmacology. *Bull. Hist. Med.* 44:518 (1970).

2 Huxley, T. The connection of the biological sciences with medicine. *Nature* 24:346 (1881). [Cited by Parascandola, J. Structure-activity relationships–the early mirage. *Pharmacy in History* 13:3 (1971).]

3 Parascandola, J. Early efforts to relate structure and activity. *Trends Pharmacol. Sci.* 1:417 (1980).

4 Hansch, C., and S. M. Anderson. The structure-activity relationship in barbiturates and its similarity to that in other narcotics. *J. Med. Chem.* 10:745 (1967).

5 Pullman, A., and B. Pullman. Electronic structure and carcinogenic activity of aromatic molecules. *Adv. Cancer Res.* 3:117 (1955).

6 Stuper, A. J., W. E. Brügger, and P. C. Jurs. *Computer Assisted Studies of Chemical Structure and Biological Function.* New York: Wiley (1979).

7 Blois, M. S. Clinical judgment and computers. *N. Engl. J. Med.* 303:192 (1980).

8 Golberg, L. Toxicology: Has a new era dawned? *Pharmacol. Rev.* 30:351 (1979).

9 Shakespeare, W. Macbeth, act iv, scene I. In *The Complete Works of William Shakespeare.* New York: Avenel Books (1975).

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