Cutaneous Toxicity

Editors

Victor A. Drill · Paul Lazar

TARGET ORGAN TOXICOLOGY SERIES

Editor-in-Chief
Robert L. Dixon

Raven Press

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Raven Press ■ New York

Raven Press, 1140 Avenue of the Americas, New York, New York 10036

Made in the United States of America

Library of Congress Cataloging in Publication Data
Main entry under title:

Cutaneous toxicity.

(Target organ toxicology series)
Includes bibliographical references and index.
1. Dermatotoxicology—Addresses, essays, lectures.
I. Drill, Victor Alexander, 1916– II. Lazar, Paul.
III. Series. [DNLM: 1. Dermatitis, Contact—Congresses.
2. Dermatology—Congresses. 3. Skin diseases—Chemically induced—Congresses. W3 C587M 5th 1982c / WR 175 C9879 1982]
RL803.C88 1983 616.5 83-21215
ISBN 0-89004-935-5

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Target Organ Toxicology Series

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Editor-in-Chief: Robert L. Dixon
National Institute of Environmental Health Sciences
Research Triangle Park, North Carolina

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Foreword

The *Target Organ Toxicology* monographs have evolved from the need for periodic review of the methods used to assess chemically induced toxicity. In each monograph, experts focus upon the following areas of a particular organ system: (1) a review of the morphology, physiology, biochemistry, cellular biology, and developmental aspects of the system; (2) a description of the means routinely used to assess toxicity; (3) an evaluation of the feasibility of tests used in the assessment of hazards; (4) proposals for applying recent advances in the basic sciences to the development and validation of new test procedures; (5) a description of the incidence of chemically induced human disease; and (6) an assessment of the reliability of laboratory test data extrapolation to humans and of the methods currently used to estimate human risk.

Thus, these monographs should be useful to both students and professionals of toxicology. Each provides a concise description of organ toxicity, including an up-to-date review of the biological processes represented by the target organ, a summary of how chemicals perturb these processes and alter function, and a description of methods by which such toxicity is detected in laboratory animals and humans. Attention is also directed to the identification of probable toxic chemicals and the establishment of exposure standards which are both economically and scientifically feasible, while adequately protecting human health and the environment.

Robert L. Dixon
Editor-in-Chief

Preface

The skin is the largest organ of the body, serving to surround and insulate other organs from the environment. While providing important thermoregulatory and water-balance controls, the skin also is the first line of defense against noxious elements in the environment.

Not long ago studies in cutaneous toxicity were directed chiefly toward methods of producing and assessing skin irritation and allergic phenomena in animals and humans. This relatively limited horizon has expanded enormously; the advances made in general biology and toxicology, involving toxicokinetic principles, noninvasive techniques for measuring skin function, DNA, monoclonal antibodies, serum factors associated with inflammation, and other cellular biological phenomena, have led to a better understanding of the mechanisms involved in cutaneous toxicity.

The subjects presented in the text parallel the advances in technology and the basic sciences. Yet, the standard value of patch testing and other well-established avenues of study are still productive and also require discussion; these subjects are reviewed both from the experimental and clinical points of view. Other areas of importance include phototoxicity, photoallergy, teratological effects of topically applied materials, and dermatitis from cosmetics, plant materials and occupational exposures.

It is expected that the continuation of this series will attract researchers who will provide new information to aid us in dealing with the problems of cutaneous toxicology. It is the blending of old and new, the ability to adapt and use new technology, and the understanding of biochemical changes that maintain cutaneous toxicity as an exciting and changing focus of study. The addition of new areas brings the expertise, enthusiasm, and help of new investigators and their disciplines, and it is this cross-fertilization that is reflected in the text which, we believe, will be of value to students, practitioners, and researchers.

Victor A. Drill
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Acknowledgments

This text is based on the review of cutaneous toxicity provided by the Fifth Conference on Cutaneous Toxicity recently held under the auspices of the American Medical Association and the Society of Toxicology. These conferences have brought new faces, new ideas, new information, and new enthusiasm to the realm of cutaneous toxicity.

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Cutaneous Toxicity, edited by V. A. Drill and
P. Lazar. Raven Press, New York © 1984.

The Challenge for Toxicology

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Those who would be called toxicologists must be willing to accept challenge. Webster defines the word *challenge* as "a demand for identification; a calling into question; a demanding of proof; a task that calls for special effort or dedication." How better can the profession of toxicology be characterized than by this single word challenge? Its demand for identification should never diminish, its questions never ending, and sufficient proof its dedicated goal.

A case can be made that toxicology describes man's first intellectual response to the challenge for survival which he faced daily. He was a captive subject in a continuing protocol of nature in which the toxic properties of plants and venoms were randomly examined. He soon recognized that certain things were unsuitable for food and that the sting of certain creatures was worse than mere annoyance. He learned by serendipity to frustrate the gaussian probability curve for survival versus careless sampling of things for food. Animals and vegetables were recognized as being safe to eat or were rejected as being hazardous. No provision was made in his classification for a gray area in between. When the value of this painfully acquired data to dictate his diet and the power the rejected hazards had as weapons were appreciated, they were incorporated into his life-style and future plans. The science of toxicology had a beginning. No longer were toxic materials simply avoided, but, rather, they were evaluated and the most potent of them exploited. When a sufficient number of people or animals became ill or died after consuming an amount of an unclassified substance, it became known as a bane. The statistical evaluation was made by observation, not mathematical manipulation. Before the nineteenth century A.D., most of the toxicity information was obtained from human subject trials.

From accidental human exposure, it was an easy, logical step to arrange for such a test so it could be closely studied. Subjugated victims were plentiful. That this took place before written records could be made is quite likely. That it did afterward has been documented.

Locusta was the Roman, female slave of Aggripina, the mother of Nero. She was an early, experimental toxicologist who is said to have tested her concoctions on other, less valuable servants who were denied the opportunity to provide informed consent. A brew, proved in such a clinical trial, was used to dispatch Britanicus, Nero's half-brother, thus paving the way for Nero to become emperor. Such poison episodes are replete in the political history of early governments.

Toxicology began as a weapons discovery occupation and progressed to a methodical, innovative discipline by which the weak could effect revenge, political aspirants could gain office, and anyone could conquer an enemy, inactivate a rival, or kill for food.

Because of the limited knowledge about poison, misadventures must have occurred. Occasionally an ill or infirm individual ignorantly or inadvertently exposed himself to a known toxic plant and thought his symptoms were improved by the exposure. Gradually the search among noxious plants, animal parts, and minerals for poisons to kill was enlarged to include an interest in medicaments. The science divided, and the field of therapeutic adventuring split off.

The new specialty became part of the then classical medicine. One must speculate over the probable failures and occasional successes which resulted from such experimenting. Dioscorides (1) described colchicine, a deadly poison, as useful in gout without any knowledge or concern about its mechanism of action. Curare-like compounds were used for centuries to kill animals before they were found to be useful as adjuncts to anesthesia. Paracelsus (1493–1541) said it best: "all substances are poison . . . the right dose differentiates a poison and a remedy" (2). The science became either forensic or clinical toxicology.

Toxicologists were first known as poisoners and were highly successful in this profession. The first laws to regulate the sale of toxic chemicals were passed to restrict the sale of poisons. Physicians were given the right to authorize this use by prescription. Louis the XIV outlawed the then legal profession of toxicologist, or poisoner, as a prophylactic measure for his own welfare.

From this point, emphasis in toxicology began to shift from the pursuit of poisons as weapons to their classification by properties. No one individual was responsible for this advance, but Mathieu Joseph Bonaventura Orfila (1787–1853) has been given the credit (3). He published reliable data on the toxicity of many of the poisons known to him based on his experiments with some 4,000 dogs. He preached the necessity for chemical analysis to prove lethal intoxication and classified poisons by their potency to kill dogs. He pioneered treatment of intoxication based on what he learned in his animal experiments, and he rejected some ineffective, even dangerous, antidotes of the day. He helped create the foundation of experimental toxicology and live animal research. His views were not new in his day. The *Antidotarium of Nicholous* was published in Venice in 1481 while he was head of the Salerno medical school. He expressed the philosophy that disease was caused by poison, and successful treatment depended on proper antidotes.

Early proof of a specific biochemical lesion produced by a poison was presented by Peters in 1945 (4). It was based on data obtained from experiments with keratin, the only accessible, living protein he knew about that had a high thiol content. His experiments followed a hypothesis that arsenic toxicity is caused by its ability to combine with essential thiols. The preparation of a new specific antidote for arsenic which followed was derived using these data and supported the view that a biochemical lesion made by blocking an enzyme system can cause pathological damage.

The interest to understand mechanisms of toxicity grew with the acquisition of each successive information bit and in turn increased the investigators demand for more sensitive, analytical techniques. Those with a need to know exercised scientific curiosity and conditioned the lay public to inflate its concern for safety without defining, in reasonable terms, what it meant by it.

A flourishing industrial revolution, stimulated by the availability of new chemicals and thus new products, confronted the workers and consumers with health problems whose frequency in the past had been too low for either recognition or concern. The laissez-faire position toward management did not really change until the increasing magnitude of the problem dispelled public apathy. Public concern grew into active movements calculated to reform working conditions and protect the environment. The responsibility for current and future medical ills was assigned to chemical exposure. The explanation of "toxic syndrome" was applied to ailments otherwise unexplained and became popular. This general anxiety was in no way minimized by the legal profession, which recognized an opportunity for fruitful litigation, or regulatory agencies; those involved with the latter saw an opportunity to enlarge their responsibility for the health and general welfare of our citizens as well as having the security of an enlarged bureaucracy.

The hazard of chemical exposure does not require a college degree to recognize and appreciate. A concern for the quality of all life and the preservation of the environment is not exclusive to a vocal few who observe their biases under a microscope and disdain the exercise of understanding and problem solving. The concern is also not exclusive with toxicologists, but it is inherent in the profession.

A name does not make a science. To say you are a toxicologist may express an important commitment to the scientific discipline, but to be a toxicologist one must also accept the challenge the discipline is being relied on to meet. We live in a chemically dependent world. The presence of chemicals is ever increasing. This resulting environment will either persist with us or eliminate us, but we cannot survive without it. A no-risk chemical environment is beyond our power to create for anyone outside a laboratory. Toxicologists cannot dictate the attitudes of those who are able only to recognize hazards. We may not even modify the convictions of those who consider the sanctity of all life to be on a par and cannot accept the involuntary sacrifice of one for another.

If we believe in the social philosophy that promotes majority rule, that intends to secure the greatest good for the greatest number consistent with reasonable concern for all, it is implicit that there will be outliers among us who will not experience, to the same degree, the advantages of the majority. Variables in age, sex, physical and mental states, and so on will influence all responses to chemical exposure. The challenge, then, is to so understand the toxic properties of chemicals that the hazards associated with their use can be minimized, attainable, and acceptable as judged in a benefit-to-risk concept.

To set arbitrary, time-weighted limits for exposure to chemicals in order to ensure safety has some merit as an expedient measure. It must be understood, however, that safety should be defined in terms of an acceptable risk. Further, maximum allowable concentrations of chemicals in the environment must not be dictated by analytical chemists and geared to the sensitivity of their instrumental techniques. Analytical sophistication is invaluable for providing reproducible facts which are useful for interpreting experimental data and identifying standards arrived at by convincing observations in real or devised settings.

The question is, then, given that the environment as we make it may not be 100% safe for everyone in it, how safe do we need it to be? How many standard deviations from the apex of the risk-to-benefit curve will we, as a society, accept? The prevention of chemical toxicity responses in 100% of the population may deny us the use of most drugs, most pesticides, many comfort chemicals, etc. The decisions on chemical use are not amenable to a popular vote. Although the goal of maximum safety has universal appeal, the way to obtain an approximation of it will only be divined by those who are trained to accept the challenge to point it out and document the decision-making process in discovering it.

Prior to the ultimate exposure of man to a new chemical, an effort dictated by conscience, regulation, and legal threat will be made to anticipate the hazard and define the conditions for its use which will provide for maximum safety and reasonable benefit at the time of determination. The dedication of well-trained, skilled technicians will be required to follow established protocols and guidelines if reliable toxicity data, which are necessary, are to be generated. For this important mission, innovation is discouraged. This stereotyped approach to chemical toxicity determination will ensure that a classical interpretation for safety evaluation will be made. When this process follows the "state of the art" science and technology, judgments should then be criticized only by the same standards. The legal profession can drive society into an untenable position by trying to hold individuals or companies forever responsible for their actions taken in good faith at any given time. The public must always be convinced that the judgments of toxicologists are consistent with the best data available at the time such judgments are required. The assessment of the toxic properties of chemicals and the projections of the conditions for their safe use will be subjected continually to modification as new, better data are generated. There can be no unconditional guarantee for the reliability of a reported limit to risk. Such estimates must be considered to be best advice, not dictums. The toxicologist should not be distracted from his major challenge or, worse, concede that his efforts to advance the science are prompted by the urgency to defend current or past decisions.

The challenge for toxicologists is to advance the science, to better understand toxicity—its mechanisms and its short-term and long-range effects. It is generally assumed that we should be able to anticipate toxicity in human chemical use before humans are exposed. It is also well known that although animals and man have much in common as living, reproducing creatures they are also quite dissimilar in their response to many of the chemicals to which they may be exposed. Some of these are species differences. For example, the rat does not develop metabolic