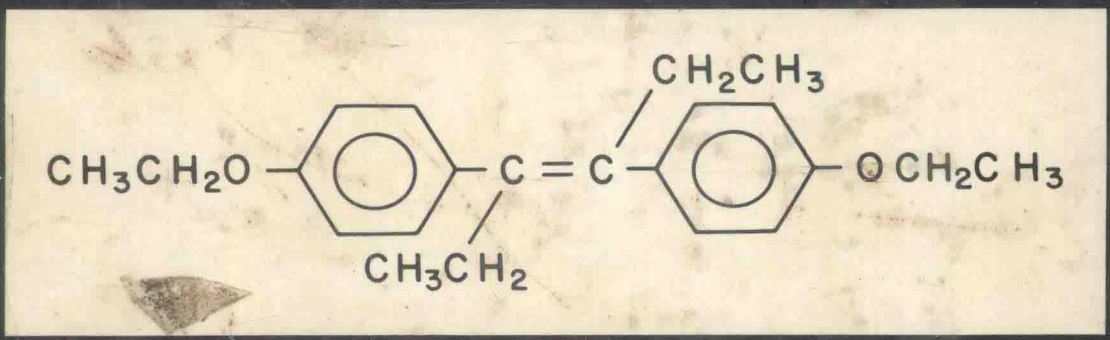
POLLUTION ENGINEERING AND TECHNOLOGY / 16

Carcinogens in Industry and the Environment



edited by James M. Sontag

CARCINOGENS IN INDUSTRY AND THE ENVIRONMENT

Edited by

James M. Sontag

National Cancer Institute
National Institutes of Health
Bethesda, Maryland

MARCEL DEKKER, INC. *New York and Basel*

Library of Congress Cataloging in Publication Data

Main entry under title:

1. Carcinogens. 2. Environmentally induced diseases.

(Pollution Engineering and Technology; 16)
Includes index.
1. Carcinogens. 2. Environmentally induced diseases.
3. Industrial hygiene. I. Sontag, James M. [date].
II. Series.
RC268.6.C37 363.1'79 81-5484
ISBN 0-8247-1021-5 AACR2

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Current printing (last digit):
10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

CARCINOGENS IN INDUSTRY AND THE ENVIRONMENT

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Associate Professor
of Environmental Engineering
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Foreword

Awareness that the environment plays a role in cancer development dates back to the early documented evidence of cancer of the scrotum among chimney sweeps, cancer of the face among sailors exposed to strong sunlight, urinary bladder cancer among workers exposed to certain intermediates in the synthetic dye industry, and so on. Yet little attention has been paid, until recently, to the possibility of extrapolating this evidence in a broader sense for the purpose of eradicating the disease by preventive measures. Even with the establishment of experimental carcinogenesis in animals—a relatively recent development—research had been devoted largely to mechanisms of action of carcinogens rather than to immediate practical application. The time, it seemed, was not yet ripe for substantial implementation of the available knowledge, except in a few specific areas, notably in relation to industrial occupations.

What was lacking was knowledge of the extent to which human cancer in general is attributable to environmental factors. And here epidemiological studies began to supply the relevant information, by bringing to light striking differences in tumor incidence among various populations, related to their habits and, more particularly, according to their geographical location. It thus became apparent that the environment plays a far more important role in human cancer development than had previously been supposed.

In consequence of this newly accumulated information, there has been a dramatic change in outlook in recent years, resulting in much greater emphasis on practical exploitation of the knowledge and on efforts to devise rapid methods of identifying carcinogens in our environment. This book reflects this new orientation in thinking, planning, and application.

If epidemiological studies revealed the scope of environmental carcinogenesis in human beings, the experimental studies in other animals provided most of the information about the complexity of carcinogenic action.

We now know that some carcinogens can operate on virtually any tissue in the body in most species of animals, that others have a more limited range of action with respect to organ or species response, and that still others are virtually single-organ carcinogens and effective in very few species. With some carcinogens repeated administrations of large doses for long periods are needed for tumor induction; with others a single exposure to a very small dose is sufficient. (This variation is partly explained by differences in metabolic activation among carcinogens, on the one hand, and detoxication differences among compounds on the other, with the relative proportion of the two competing processes determing the effective dose for carcinogenic action; and this proportion may vary according to species, strain, or individual.) Again, some carcinogens act fairly quickly, others very slowly. And finally, cocarcinogenic factors, and more specifically, promoting or "precipitating" action following a subeffective dose of carcinogen, or after the action of a pure initiator, can be decisive in determining whether a tumor will develop. These are but a few of the important variables that must be taken into account in assessing carcinogenic risks for humans.

The important role of cocarcinogenesis in human cancer development is only now beginning to be recognized. The implications are far reaching, and since existing methods of assay are only capable of detecting "complete" carcinogens, and in the case of the short-term Ames' test can only recognize the initiating phase of carcinogenesis, new testing procedures will have to be devised to cope with the important problem of "cofactors."

We turn next to the implementation of the knowledge about environmental carcinogenesis, in terms of potential and realizable cancer prevention in humans.

A policy of cancer prevention is most easily formulated for carcinogenic hazards in industry. The workers at risk can be more easily traced than people in the general population, and so can the various products to which they are exposed. Thus, carefully conducted statistical surveys of cancer incidences among the employees and systematic carcinogenicity testing of the suspected products enable one eventually to establish the causal association and to assess the degree of risk. The implementation of preventive measures is then the primary responsibility of the industry concerned, though often calling for governmental legislation for proper enforcement.

The situation is more complicated for carcinogens of occupational origin outside industrial establishments. The people at risk are more widely dispersed among the general population, and the suspected (or unsuspected) carcinogens to which they are exposed are less easily traced. Elaborate statistical surveys are, therefore, called for here, and possibly more extensive carcinogenicity testing, to establish a true association and to assess the degree of risk involved. Implementation of preventive measures is, in such cases, largely the responsibility of public health authorities, at both the regional and national levels.

By far the most difficult problem (and numerically perhaps the most important) is concerned with environmental carcinogens that are not industrial or occupational (or, as in the case of pollutants, indirect products of industrial or occupational processes). The difficulties here involve not only procedure—discovering who are the people at risk, identifying the incriminating substances, and recognizing cocarcinogenic, promoting, and other "associated" factors—but also the means of implementing preventive measures, because cancer prevention, in such cases, is to a large extent in everyone's hands and public education on the subject is therefore critical.

This problem further poses a number of conflicting problems which have not yet been properly resolved, and to which serious attention must be paid.

Public education on the subject of potential carcinogenic risks—in relation to certain habits, such as cigarette smoking, and to pollution, food additives, contaminants, and other elements in our environment, whether naturally occurring or caused by people—is likely to be counterproductive if one fails to discriminate between serious hazards and those of marginal risks. People are already heard to say that if almost everything is potentially dangerous, why bother to take any precautions? (This also applies, incidentally, to the more technical debates about, and preoccupation with, "safe" (minimal) doses of carcinogenic exposure, often overlooking the fact that the real dangers lie at the other extreme. Note, in this connection, the sobering comment by A. C. Kolbye, Jr. [1976, Oncology 33:90] that a precipitous rush to "zero tolerance" for all animal carcinogens may impair our efforts to prevent the worst "causes" of cancer induction in humans.) On the other hand, to withhold or limit information to the public about potential carcinogenic hazards would be inexcusable.

A properly balanced program of public education about carcinogenic risks has not yet been devised (e.g., the poor results so far obtained from intensive efforts in public education to wean the public from cigarette smoking!). Related to the problem of public education is the need to provide authoritative responses to recurrent scares in the lay press about causes of cancer, some of which may be justified, others grossly exaggerated, and still others completely without foundation. The public should be kept properly informed and be spared unnecessary anguish and, at the same time, encouraged to exercise reasonable vigilance when it is appropriate.

Isaac Berenblum
The Weizmann Institute of Science
Rehovot, Israel

Preface

An increasing number of carcinogens are being identified in our environment. Frequently, it is difficult to understand the human significance of these carcinogens because their relationship to humans may be obscure. A major objective of this book is to clarify this relationship by sorting out carcinogens according to where they are found and how they are used. In addition, the book attempts to address some of the critical social and scientific issues associated with environmental carcinogens.

The book's early chapters deal with the cost and social implications of cancer, as well as with the identification and evaluation of carcinogens. Subsequent chapters address specific categories of carcinogens found in industry and the environment. The chapter on the research chemical N-2-fluorenylacetamide (Chapter 14) is included to show the tremendous effort and variety of scientific disciplines required to understand how carcinogens produce their effects. The last chapter is on ionizing radiation, a physical carcinogen of concern to all sectors and at all levels of society.

This compilation by authorities in the field presents a detailed, up-to-date account of carcinogens in the environment. It is hoped that the information provided will be useful to researchers and other workers in areas of public health and will serve as a basis for actions directed toward cancer prevention in humans.

James M. Sontag

Contributors

JOSEPH C. ARCOS* Professor, Department of Medicine, Tulane University School of Medicine; Biochemistry Section, Seamen's Memorial Research Laboratory, U.S. Public Health Service Hospital, New Orleans, Louisiana

NICHOLAS A. ASHFORD Assistant Director, Center for Policy Alternatives, and Associate Professor, Department of Technology and Policy, Massachusetts Institute of Technology, Cambridge, Massachusetts

GEORGE W. CASARETT Professor, Department of Radiation Biology and Biophysics, University of Rochester School of Medicine, Rochester, New York

DAVID BARRINGER CLAYSON Deputy Director, Eppley Institute for Research in Cancer and Allied Diseases, University of Nebraska Medical Center, Omaha, Nebraska

DAVID J. CLEGG Head, Bureau of Chemical Safety, Food Directorate, Pesticide Section, Toxicological Evaluation Division, Health and Welfare Canada, Ottawa, Ontario, Canada

D. EARLE COFFIN Director, Bureau of Nutritional Sciences, Food Directorate, Health Protection Branch, Health and Welfare Canada, Ottawa, Ontario, Canada

PAUL B. FISHER Associate Professor, Department of Biology, Bronx Community College of the City University of New York, New York; Department of Microbiology Cancer Center, Institute of Cancer Research, Columbia University College of Physicians and Surgeons, New York, New York

DAVID W. GAYLOR Director, Division of Biometry, National Center for Toxicological Research, Jefferson, Arkansas

BERNARD M. GOLDSCHMIDT Associate Professor, Institute of Environmental Medicine, New York University Medical Center, New York, New York

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Present affiliations:
*Senior Environmental Health Scientist, Chemical Hazard Identification Branch (TS-792), Assessment Division, Office of Toxic Substances, Environmental Protection Agency, Washington, D.C.

HAROLD C. GRICE* Director, Bureau of Chemical Safety, Health Protection Branch, Health and Welfare Canada, Ottawa, Ontario, Canada

THOMAS A. HODGSON Economist, Office of Health Research, Statistics, and Technology, National Center for Health Statistics, Department of Health and Human Services, Hyattsville, Maryland

DAVID G. HOEL Chief, Biometry Branch, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina

NEIL B. JURINSKI† Industrial Hygiene Consultant, Tracor Jitco, Inc., Rockville, Maryland

DONALD V. LASSITER‡ Environmental Health Scientist, Environmental Health Associates, Inc., Berkeley, California

MEI-TEIN LO Toxicologist, Toxicological Evaluation Division, Food Directorate, Health Protection Branch, Health and Welfare Canada, Ottawa, Ontario, Canada

PRABHAKAR D. LOTLIKAR Associate Professor, Department of Biochemistry, Fels Research Institute, Temple University Medical School, Philadelphia, Pennsylvania

FRANCIS N. MARZULLI** Senior Scientist, Toxicology Division, Bureau of Foods, Food and Drug Association, Washington, D.C.

EDWARD J. MIDDLETON Head, Food Additives, Bureau of Health, Food Directorate, Toxicological Evaluation Division, Health Protection Branch, Health and Welfare Canada, Ottawa, Ontario, Canada

DOROTHY P. RICE Director, National Center for Health Statistics, U.S. Department of Health and Human Services, Hyattsville, Maryland

ADRIANNE E. ROGERS Senior Research Scientist, Department of Nutrition and Food Science, Massachusetts Institute of Technology, Cambridge, Massachusetts

EMIL SANDI Head, Food Contaminants Section, Toxicological Evaluation Division, Food Directorate, Health and Welfare Canada, Ottawa, Ontario, Canada

PETER M. SCOTT Research Scientist, Health Protection Branch, Health and Welfare Canada, Ottawa, Ontario, Canada

NRISINHA P. SEN Research Scientist, Bureau of Chemical Safety, Food Directorate, Health Protection Branch, Health and Welfare Canada, Ottawa, Ontario, Canada

BARRY L. SMITH Adviser, Legislative Policy, Food Directorate, Health Protection Branch, Health and Welfare Canada, Ottawa, Ontario, Canada

JAMES M. SONTAG Assistant Director, Interagency Affairs, Office of the Director, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

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Present affiliations:
*Toxicology Consultant, F.D.C. Consultants, Inc., Nepean, Ontario, Canada
†President, NuChemCo, Inc., Burke, Virginia
‡Consultant, Environmental/Occupational Health, San Jose, California
**Senior Toxicologist, National Academy of Sciences, Washington, D.C.

I. BERNARD WEINSTEIN Professor, Department of Medicine and Environmental Science, Division of Environmental Sciences and Cancer Center, Institute of Cancer Research, Columbia University College of Physicians and Surgeons, New York, New York

ELIZABETH K. WEISBURGER Chief, Laboratory of Carcinogen Metabolism, Division of Cancer Cause and Prevention, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

JAMES R. WITHEY Research Scientist, Health Protection Branch, Health and Welfare Canada, Ottawa, Ontario, Canada

YIN-TAK WOO* Instructor, Department of Medicine, Tulane University Medical Center; Biochemistry Section, Seamen's Memorial Research Laboratory, U.S. Public Health Service Hospital, New Orleans, Louisiana

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Present affiliation:
*Senior Toxicologist, Health Hazard Assessment Group, JRB Associates, Inc., McLean, Virginia

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Introduction

JAMES M. SONTAG / National Cancer Institute, Bethesda, Maryland

It is now commonplace to hear or read that up to 90% of all human cancers are attributable to environmental factors (Boyland, 1969; Higginson, 1972; Doll, 1977). The basis for the claim is founded on worldwide epidemiologic studies showing different incidences for the same types of cancer. After considering genetic and other factors that might account for the differences, it has become clear that variations in cancer incidence are inextricably linked to the environments in which the populations live. The identification of the major environmental factors linked to human cancer is important for prevention and intervention efforts.

In speaking of environmental factors, it is important to understand the frame of reference. Frequently, environmental factors have been thought of simply as synthetic industrial chemicals. Besides man-made chemicals (e.g., industrial intermediates, agricultural chemicals, drugs, food additives, and other societally important chemicals), environmental factors include sunlight, alcoholic beverages, tobacco products, medical treatments, dietary components, and any other component of the human environment. It is thus important to have a holistic perspective in understanding the significance of the statement that up to 90% of all cancers have an environmental association.

It is likely that many, if not most, of the major environmental factors contributing to the overall cancer burden are not complete carcinogens in themselves (see Chapter 8). In other words, they must act together and/or in combination with other environmental factors before they produce their carcinogenic effect. Such factors may naturally occur together,

as in the diet, or may result from discrete but coincidental exposures, as with smoking and drinking alcoholic beverages. Individual genetic susceptibility also plays an important but as yet ill-defined role. Because of the complexity of these relationships, good model systems and methods still have not been developed which would lead to the identification and understanding of interactions of these environmental factors. Thus, efforts have been mainly focused on the identification of individual environmental substances that may pose carcinogenic hazards. Although these efforts may identify only a small fraction of environmental contributors to human cancer, the knowledge learned through them is adding to the science base which, together with other efforts in carcinogenesis research, ultimately should provide the clues and answers leading to cancer prevention.

I. IDENTIFICATION OF CARCINOGENS

Epidemiologic studies provide the most convincing evidence that a substance is a human carcinogen. Such studies, however, have severe limitations which restrict their usefulness. It is not until after the "body count" has been made that an effect can be identified by epidemiology. As a result, people may be exposed to a carcinogenic agent for decades before it is identified and control actions are instigated. Ideally, the potential hazard of a substance should be known before the occurrence of human exposure.

Epidemiologic studies are limited by the long latency periods (10-40 years) between first exposure to a substance and the appearance of cancer. By the time an effect is observed, it may be impossible to track down the etiologic agents in the cancer patient's past. Epidemiologic studies also may be confounded by the inability to find adequate control populations against which to compare exposed groups. Even when using an acceptable cohort, an increased cancer incidence may easily be missed when the increase is of a relatively common type of cancer, for example, lung, colon, or breast (in females). For these and other reasons, animal studies are the most desirable and feasible means of identifying potential human carcinogens.

Laboratory animals have been used since the early part of the century to identify chemical carcinogens. In 1918 Yamagiwa and Itchikawa induced skin tumors in rabbits after continued application of coal tar. Since that time, of the few thousand chemicals that have been adequately tested, several hundred entities have been reported to be carcinogenic (Maugh, 1978a). Small rodents have been the most widely used animal models to detect and identify carcinogens.

The validity of laboratory animals is confirmed by the fact that all human carcinogens identified epidemiologically, with the exception of only a few compounds, also induce cancer in animal models (Tomatis et al, 1978). In a number of instances, a substance was identified first as an animal carcinogen and only later found to be a human carcinogen as well. For the many carcinogens thus far identified only in animals, the possible untoward human effects are unknown. However, given the almost perfect correlation between known human carcinogens and their carcinogenicity in animal models, unless proven otherwise, it is prudent to treat all animal carcinogens as if they were confirmed human carcinogens.

II. EXPERIMENTAL CONSIDERATIONS

The choice of animal models, study size, conditions of test, and other experimental factors are often dictated by practical considerations. Details of experimental designs, study conduct, pathology protocols, and other aspects of carcinogenesis bioassay can be found in a number of publications (Berenblum, 1969; Sontag et al., 1976; Weisburger, 1976; Page, 1977; Sontag, 1977; Food Safety Council, 1978). The conceptual basis for certain bioassay practices is now given.

A. Animal Model

Rats, mice, and hamsters are the most commonly used and accepted animal models for carcinogenesis bioassay. Over the years they have proven to be reliable and sensitive models for detecting carcinogens representing a variety of chemical classes. In instances of human carcinogens, one or more of the species usually respond with the same tumor type as found in people. The historical data accumulated on each species, and strains within species, are important in defining the peculiar characteristics of each animal model, as well as in providing a baseline of spontaneous tumor incidence. The latter may be particularly important in evaluating rare tumors occurring in nonstatistically significant incidences among treated animals. Other considerations for using small rodents include their size, ease of handling, reproductivity, hardiness, longevity, sensitivity, and relatively cheap cost.

B. Dose Levels

Chemicals are frequently tested at dose levels several orders of magnitude higher than concentrations to which humans are exposed. Although attempts have been made to discredit this practice, there are sound and valid reasons to support it. First, it should be noted that most chemicals tested at the "maximum tolerated dose" have not been proven to be carcinogenic. Thus, the intrinsic carcinogenicity of chemicals is not linked to dosage, although the expression of carcinogenicity in animals is related. Second, a great deal more confidence can be placed in the safety of a substance if it is shown not to be carcinogenic when tested at high concentrations.

The major reason for testing at high dosages relates to the sensitivity of the test system. The probability of detecting a carcinogenic response is linked to the "potency" of a chemical; the less potent the chemical, the smaller the probability of detecting an effect in an animal group of constant size. The probability diminishes as the test population becomes smaller. In a typical bioassay, a group of 200-400 test animals serves as a surrogate for as many as 220 million Americans. If the animals are exposed to the low levels at which most human exposures occur, the probability of detecting the response in such a small test population becomes remote, even for relatively potent carcinogens. To increase the sensitivity of the test system, hence the probability of detection, "maximum tolerated doses" are administered. Results from studies, in which high dose levels are used to compensate for the relative insensitivity of test systems, are valid qualitative indicators of potential human risk.

C. Duration of Study

Typical bioassay studies are conducted over the majority of the test animals' life span. In the case of rats and mice, the chronic study period lasts for a minimum of 24 months and for hamsters, at least 18 months. Treatment of the animals continues over the entire study period. This practice maximizes the intake of the substance, thus adding to the sensitivity of the study. Also, greater confidence can be given to the validity of "negative" results, if no effect is found after the study is completed.

D. Route of Exposure

Questions have arisen regarding the inappropriateness of testing chemicals by routes other than those by which humans are exposed. The necessity to use alternative routes may result for a number of reasons. First, animals may not eat a substance normally ingested by humans because of its disagreeable odor or taste; it therefore must be force fed through a stomach tube. The instability of other substances requires that they be administered immediately after preparation, thereby influencing the route of exposure used. The cost of administering a substance by a particular route also is a factor in selecting which is to be employed. (Inhalation studies may cost almost twice as much as feeding studies.) A critical factor in

selecting an experimental route of exposure is evidence that it would not produce a different general effect from the one expected by the route comparable to the one by which humans are exposed. In this regard, data on qualitative and quantitative absorption patterns by the different routes are important in determining comparability.

Humans are often exposed to a substance by more than a single route. A colorant, for example, may be ingested in foods by the general public, inhaled by workers manufacturing or processing the substance, and contacted on the skin by others using it in vocational pursuits. In the final analysis, it may make no difference whether the route of exposure is inhalation, ingestion, or skin if systemic absorption occurs by all three routes.

E. Statistical Analysis

The basis for determining if a substance is carcinogenic often relies solely on the statistical analysis of results. Such an analysis must allow for a number of factors that may bias the conclusions one way or another. The importance of proper statistical analysis is so critical that Chapter 5 is devoted solely to this topic.

III. MAGNITUDE OF THE PROBLEM

The cost of cancer to society is enormous. Costs have implications not only to cancer victims, but also to federal, state, and local governments, industrial and worker communities, and the general public. These implications are discussed in Chapters 2-4.

The number of chemicals in common use has been estimated to be more than 60,000 (Maugh, 1978b). A 1978 inventory by the U.S. Environmental Protection Agency identified more than 44,000 chemicals with "significant" commercial production (U.S. Environmental Protection Agency, 1979). Using today's testing standards it is clearly impossible to study the carcinogenicity of all existing chemicals and those to be developed; the resource requirements would be overwhelming. Thus, there is a need to apply reliable, rapid, and inexpensive screening techniques to identify substances having the greatest likelihood of being carcinogenic; these then can be tested by traditional methods. The importance of screening techniques and progress in their development is described in Chapter 6.

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