

TOPICS IN ENVIRONMENTAL PHYSIOLOGY AND MEDICINE

H.F. Stich and R.H.C. San

Short-Term Tests for Chemical Carcinogens



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Edited by

H.F. Stich

Head, Environmental Carcinogenesis Unit
British Columbia Cancer Research Centre

R.H.C. San

Chief, Carcinogen Testing Laboratory
British Columbia Cancer Research Centre

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H.F. Stich

Head, Environmental Carcinogenesis Unit
British Columbia Cancer Research Centre
Vancouver, British Columbia
Canada

R.H.C. San

Carcinogen Testing Laboratory
British Columbia Cancer Research Centre
Vancouver, British Columbia
Canada

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Edited by Karl E. Schaefer

Preface

The recent surge of interest in designing, validating, and implementing short-term tests for carcinogens has been spurred by the fairly convincing correlation between the carcinogenicity and mutagenicity of chemicals and physical agents and by the assumption that DNA alteration, mutations, and chromosome aberrations are somehow involved in neoplastic transformation. Moreover, it has been tacitly assumed that the mutagenic capacity alone of compounds would induce regulatory agencies to pass rules for their removal from the environment and would lead the public to avoid them. The actual response, however, is quite different.

Governmental departments shy away from making any decisions on the basis of *in vitro* test systems. The public at large is becoming irritated by daily announcements that many of their cherished habits could adversely affect their health. Industry appears to feel threatened and may reduce its search for new beneficial chemicals. The reluctance to accept wholeheartedly the mutagenicity tests for the detection of carcinogens is partly due to uncertainty about the involvement of mutations in neoplastic transformation, partly due to the present difficulty of extrapolating results from various endpoints obtained on numerous organisms to man, and partly due to a multitude of complex events that lead *in vivo* to the evolution of benign or malignant tumors.

Following the initial rapid advances in the detection of environmental chemicals with carcinogenic and mutagenic properties, we seem to have arrived at a crossroads: We must now set new priorities for future research and must make an unbiased assessment of the *actual* hazard of a compound to man and the human population.

Forty-three experts were invited to assess the pros and cons of using short-term tests to detect the genotoxic and by implication carcinogenic potency of environmental chemicals and complex mixtures of compounds. It has become evident that no single bioassay can uncover all genotoxic agents. Thus this book covers a spectrum of tests that use a great variety of organisms and endpoints.

The possibility of using viral test systems is discussed in three papers. In the past, viruses, with their well-defined genomes and ease of handling, have not received the attention they seem to warrant. Seven papers focus on methods based on the interaction of genotoxic agents and carcinogens with the DNA of

the target cells. Recent advances in microbial tests for mutagenicity were reviewed in seven papers. With the development of new tester strains that provide metabolic activation and improved handling procedures, microbes will undoubtedly find an even broader use in mutagenicity testing. A single paper defends the use of higher plants. The recent successful introduction of *Tradescantia* staminal hairs as a sensitive bioassay to detect airborne mutagens and carcinogens may lead to a wider recognition and application of various plant tests.

Chromosome aberrations, sister-chromatid exchanges, the micronucleus test, and the automation of cytogenic alterations are discussed in five papers. Anomalies of chromosome complements were found at high frequencies among congenital anomalies, stillbirth, and spontaneous or induced tumors. These chromosome anomalies may represent an endpoint which appears to be an integral part of several genetic disorders affecting human populations.

The most important aspect of mammalian tests including the use of cultured human cells are covered in four papers. The greatest contributions of these tests are in the area of metabolic activation of precarcinogens and the inactivation of ultimate carcinogens. Since human cells of various cancer-prone individuals can be used, it is possible to estimate the variations in response towards carcinogens and mutagens within human population groups. Neoplastic transformation *in vitro* is reviewed in five papers. There should be no question about the high relevance of these bioassays.

Scientists as well as regulators would like to see the introduction of an endpoint that is a definite part of tumor formation in mammals, including human populations. With the issue of relevance in mind, attempts are being made to design short-term tests in entire animals. Several of the newly developed *in vivo* assays incorporate the advantages of *in vitro* short-term tests with the completeness of bioassays using whole animals. These issues are summarized in four papers.

The emphasis on mutagens and carcinogens should not detract from the importance of modulating agents including anticarcinogens, desmutagens, cocarcinogens, promoters, antipromoters, sensitizers, electron scavengers, and DNA-repair inhibitors. Four papers deal with this important field. The final four papers are dedicated to the discussion of quantitative measurements of mutagenesis, the problem of application of short-term tests, and a host of unresolved issues.

This comprehensive review of short-term tests for genotoxicity should appeal to all interested in environmental carcinogenicity and mutagenicity. It will be helpful to all who actively work in this field as well as to regulators and administrators who must choose test systems that will provide reliable and relevant results for regulatory decisions.

H.F. Stich

Contributors

B.N. Ames *Chapter 11*
Department of Biochemistry
University of California
Berkeley, California 94720, U.S.A.

F. Anders *Chapter 35*
Genetisches Institut der Justus Liebig-
Universität
Heinrich-Buff-Ring 58-62
6300 Giessen, Federal Republic of Ger-
many

J. Ashby *Chapter 42*
Genetic Toxicology Section
Central Toxicology Laboratory
Imperial Chemical Industries Ltd
Alderley Park
Nr Macclesfield
Cheshire SK10 4TJ, England

W.W. Au *Chapter 19*
Section of Cell Biology
The University of Texas System Cancer
Center

M.D. Anderson Hospital and Tumor Insti-
tute
Texas Medical Center
Houston, Texas 77030, U.S.A.

A.L. Boynton *Chapter 32*
Animal and Cell Physiology Section
Division of Biological Sciences

National Research Council of Canada
Ottawa, Ontario, Canada K1A 0R6

J.W. Bridges *Chapter 27*
Institute of Industrial and Environmental
Health and Safety
University of Surrey
Guilford
Surrey GU2 5XU, England

K.R. Castleman *Chapter 23*
Jet Propulsion Laboratory
California Institute of Technology
Pasadena, California 94301, U.S.A.

B.C. Casto *Chapter 31*
Environmental Sciences Group
Northrop Services Inc.
P.O. Box 12313
Research Triangle Park, North Carolina
27709, U.S.A.

A. Chan *Chapter 8*
Mutagenesis Section
Environmental and Occupational Toxicol-
ogy Division
Department of National Health and Wel-
fare
Tunney's Pasture
Ottawa, Ontario, Canada K1A 0L2

C.-C. Chang *Chapter 37*

Department of Pediatrics and Human Development
College of Human Medicine
Michigan State University
East Lansing, Michigan 48824, U.S.A.

B. Dawson *Chapter 37*

Department of Pediatrics and Human Development
College of Human Medicine
Michigan State University
East Lansing, Michigan 48824, U.S.A.

F.J. de Serres *Chapter 16*

Associate Director for Genetics
Office of the Director
National Institute of Environmental Health Sciences
P.O. Box 12233
Research Triangle Park, North Carolina 27709, U.S.A.

J.A. DiPaolo *Chapter 28*

Laboratory of Biology, Division of Cancer Cause and Prevention
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20205, U.S.A.

G.R. Douglas *Chapter 8*

Mutagenesis Section
Environmental and Occupational Toxicology Division
Department of National Health and Welfare
Tunney's Pasture
Ottawa, Ontario, Canada K1A 0L2

F. Eckardt *Chapter 41*

Gesellschaft für Strahlen-und Umweltforschung
Abteilung Strahlenbiologie
8042 Neuherberg, Federal Republic of Germany

J. Edwards *Chapter 2*

Environmental Carcinogenesis Unit
British Columbia Cancer Research Centre
601 West 10th Avenue
Vancouver, B.C., Canada V5Z 1L3

R.K. Elespuru *Chapter 1*

Biological Carcinogenesis Program
Frederick Cancer Research Center
P.O. Box B
Frederick, Maryland 21701, U.S.A.

C.H. Evans *Chapter 28*

Tumor Biology Section
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20205, U.S.A.

E. Farber *Chapter 33*

Department of Pathology
University of Toronto
Banting Institute
100 College Street
Toronto, Ontario, Canada M5G 1L5

H.J. Freeman *Chapter 7*

Environmental Carcinogenesis Unit
British Columbia Cancer Research Centre
601 West 10th Avenue
Vancouver, B.C., Canada V5Z 1L3

C.E. Grant *Chapter 8*

Mutagenesis Section
Environmental and Occupational Toxicology Division
Department of National Health and Welfare
Tunney's Pasture
Ottawa, Ontario, Canada K1A 0L2

W.F. Grant *Chapter 18*

Genetics Laboratory, Department of Plant Sciences, Faculty of Agriculture
Macdonald Campus of McGill University
Ste Anne de Bellevue, P.Q., Canada H9X 1C0

M.H.L. Green *Chapters 26, 27*

MRC Cell Mutation Unit
University of Sussex
Falmer
Brighton BN1 9QG, England

A.J.F. Griffiths *Chapter 17*

Department of Botany
Biological Sciences 2125a

University of British Columbia
Vancouver, B.C., Canada V6T 1W5

L. Haroun *Chapter 11*
International Agency for Research on Cancer
150 Cours Albert Thomas
69372 Lyon Cedex 2, France

R.H. Haynes *Chapter 41*
Department of Biology
Faculty of Science
York University
4700 Keele Street
Downsview, Ontario, Canada M3J 1P3

J.A. Heddle *Chapters 21, 22*
Department of Biology
Faculty of Science
York University
4700 Keele Street
Downsview, Ontario, Canada M3J 1P3

T.C. Hsu *Chapter 19*
Section of Cell Biology
The University of Texas System Cancer
Center
M.D. Anderson Hospital and Tumor Insti-
tute
Texas Medical Center
Houston, Texas 77030, U.S.A.

S.A. Hubbard *Chapter 27*
MRC Cell Mutation Unit
University of Sussex
Falmer
Brighton BN1 9QG, England

J. Hyman *Chapter 13*
Department of Microbiology
New York Medical College, Basic Sci-
ences Building
Valhalla, New York 10595, U.S.A.

D.A. Johnston *Chapter 19*
Department of Biomathematics
The University of Texas System Cancer
Center
M.D. Anderson Hospital and Tumor Insti-
tute
Texas Medical Center
Houston, Texas 77030, U.S.A.

T. Kakunaga *Chapter 30*
Cell Genetics Section
Laboratory of Molecular Carcinogenesis
Chemistry Branch
Building 37, Room 3E08
National Cancer Institute
Bethesda, Maryland 20205, U.S.A.

A.B. Krepinisky *Chapter 22*
Department of Biology
Faculty of Science
York University
4700 Keele Street
Downsview, Ontario, Canada M3J 1P3

U. Kuhnlein *Chapter 2*
Environmental Carcinogenesis Unit
British Columbia Cancer Research Centre
601 West 10th Avenue
Vancouver, B.C., Canada V5Z 1L3

W.B. Leebherz, III *Chapter 29*
Chemical Carcinogenesis Program
Frederick Cancer Research Center
P.O. Box B
Frederick, Maryland 21701, U.S.A.

M.S. Legator *Chapter 43*
Division of Environmental Toxicology
Department of Preventive Medicine and
Community Health
The University of Texas Medical Branch
Galveston, Texas 77550, U.S.A.

Z. Leifer *Chapter 13*
Department of Microbiology
New York Medical College, Basic Sci-
ences Building
Valhalla, New York 10595, U.S.A.

V.M. Maher *Chapter 24*
Carcinogenesis Laboratory—Fee Hall
Department of Microbiology and Depart-
ment of Biochemistry
Michigan State University
East Lansing, Michigan 48824, U.S.A.

D.R. McCalla *Chapter 4*
Department of Biochemistry
McMaster University
Health Sciences Center

1200 Main Street West
Hamilton, Ontario, Canada L8S 4J9

J.J. McCormick *Chapter 24*
Carcinogenesis Laboratory—Fee Hall
Department of Microbiology and Department of Biochemistry
Michigan State University
East Lansing, Michigan 48824, U.S.A.

R.D. Mehta *Appendix I*
Department of Genetics
The University of Alberta
Edmonton, Alberta
Canada T6G 2E9

J. Melnyk *Chapter 23*
Department of Developmental Cytogenetics
City of Hope National Medical Center
1500 East Duarte Road
Duarte, California 91010, U.S.A.

M.L. Mendelsohn *Chapter 44*
Biomedical Sciences Division
Lawrence Livermore Laboratory
University of California
P.O. Box 5507
Livermore, California 94550, U.S.A.

R.B. Painter *Chapter 6*
Laboratory of Radiobiology, School of Medicine
University of California
San Francisco, California 94143, U.S.A.

B. Palcic *Chapter 9*
Medical Biophysics Unit
British Columbia Cancer Research Centre
601 West 10th Avenue
Vancouver, B.C., Canada V5Z 1L3

G.W. Persinger *Chapter 23*
Department of Developmental Cytogenetics
City of Hope National Medical Center
1500 East Duarte Road
Duarte, California 91010, U.S.A.

R.J. Pienta *Chapter 29*
Chemical Carcinogenesis Program
Frederick Cancer Research Center
P.O. Box B
Frederick, Maryland 21701, U.S.A.

A.J. Rainbow *Chapter 3*
Department of Biology
McMaster University
1280 Main Street West
Hamilton, Ontario, Canada L8S 4K1

A.S. Raj *Chapter 22*
Department of Biology
Faculty of Science
York University
4700 Keele Street
Downsview, Ontario, Canada M3J 1P3

S.J. Rinkus *Chapter 43*
Division of Environmental Toxicology
Department of Preventive Medicine and Community Health
The University of Texas Medical Branch
Galveston, Texas 77550, U.S.A.

H.S. Rosenkranz *Chapter 13*
Department of Microbiology
New York Medical College, Basic Sciences Building
Valhalla, New York 10595, U.S.A.

M.P. Rosin *Chapter 40*
Environmental Carcinogenesis Unit
British Columbia Cancer Research Centre
601 West 10th Avenue
Vancouver, B.C., Canada V5Z 1L3

M.F. Salamone *Chapter 21*
Department of Biology
Faculty of Science
York University
4700 Keele Street
Downsview, Ontario, Canada M3J 1P3

R.H.C. San *Chapter 7*
Carcinogen Testing Laboratory
British Columbia Cancer Research Centre
601 West 10th Avenue
Vancouver, B.C., Canada V5Z 1L3

E. Scholl *Chapter 35*
 Genetisches Institut der Justus Liebig-
 Universität
 Heinrich-Buff-Ring 58-62
 6300 Giessen, Federal Republic of Ger-
 many

R.F. Schuman *Chapter 29*
 Chemical Carcinogenesis Program
 Frederick Cancer Research Center
 P.O. Box B
 Frederick, Maryland 21701, U.S.A.

M. Schwab *Chapter 35*
 Genetisches Institut der Justus Liebig-
 Universität
 Heinrich-Buff-Ring 58-62
 6300 Giessen, Federal Republic of Ger-
 many

J.P. Seiler *Chapter 10*
 Swiss Federal Research Station for Fruit-
 Growing, Viticulture, and Horticulture
 8820 Waedenswil, Switzerland

M.M. Shahin *Appendix 1*
 Department of Genetics
 The University of Alberta
 Edmonton, Alberta, Canada T6G 2E9

V.F. Simmon *Chapter 12*
 Genex Corporation
 6110 Executive Boulevard
 Rockville, Maryland 20852, U.S.A.

L.D. Skarsgard *Chapter 9*
 Medical Biophysics Unit
 British Columbia Cancer Research Centre
 601 West 10th Avenue
 Vancouver, B.C., Canada V5Z 1L3

H.F. Stich *Chapters 7, 38*
 Environmental Carcinogenesis Unit
 British Columbia Cancer Research Centre
 601 West 10th Avenue
 Vancouver, B.C., Canada V5Z 1L3

D.R. Stoltz *Chapter 39*
 Toxicology Research Division

Food Directorate
 Health Protection Branch
 Health and Welfare Canada
 Tunney's Pasture
 Ottawa, Ontario, Canada K1A 0L2

L.C. Strong *Chapter 19*
 Section of Cell Biology
 The University of Texas System Cancer
 Center
 M.D. Anderson Hospital and Tumor Insti-
 tute
 Texas Medical Center
 Houston, Texas 77030, U.S.A.

J.A. Swenberg *Chapter 5*
 Department of Pathology
 Chemical Industry Institute of Toxicology
 P.O. Box 12137
 Research Triangle Park, North Carolina
 27709, U.S.A.

S.H.H. Swierenga *Chapter 32*
 Division of Drug Toxicology
 Health and Welfare Canada
 Tunney's Pasture
 Ottawa, Ontario, Canada K1A 0L2

H.W. Thielmann *Chapter 14*
 Institut für Biochemie
 Deutsches Krebsforschungszentrum
 Im Neuenheimer Feld 280
 6900 Heidelberg 1, Federal Republic of
 Germany

J.E. Trosko *Chapter 37*
 Department of Pediatrics and Human
 Development
 College of Human Medicine
 Michigan State University
 East Lansing, Michigan 48824, U.S.A.

S.S. Tsang *Chapter 2*
 Environmental Carcinogenesis Unit
 British Columbia Cancer Research Centre
 601 West 10th Avenue
 Vancouver, B.C., Canada V5Z 1L3

H. Tsuda *Chapter 33*
Department of Pathology
University of Toronto
Banting Institute
100 College Street
Toronto, Ontario, Canada M5G 1L5

D.J. Tweats *Chapter 26*
Glaxo Group Research
Harefield
Uxbridge
Middlesex UB9 6IS, England

E. Vogel *Chapter 34*
Department of Radiation Genetics and
Chemical Mutagenesis
State University of Leiden
Wassenaarseweg 72
2333 AL Leiden,
The Netherlands

R.C. von Borstel *Chapter 15, Appendix 1*
Department of Genetics
The University of Alberta
Edmonton, Alberta, Canada T6G 2E9

L. Wei *Chapter 38*
Environmental Carcinogenesis Unit
British Columbia Cancer Research Centre
601 West 10th Avenue
Vancouver, B.C., Canada V5Z 1L3

J.F. Whitfield *Chapter 32*
Animal and Cell Physiology Section
Division of Biological Sciences
National Research Council of Canada
Ottawa, Ontario, Canada K1A 0R6

R.F. Whiting *Chapter 38*
Canadian Centre for Occupational Health
and Safety
McMaster University
1200 Main Street West
Hamilton, Ontario, Canada L8N 3Z5

G.M. Williams *Chapter 25*
Division of Experimental Pathology

Naylor Dana Institute for Disease Preven-
tion
American Health Foundation
1 Dana Road
Valhalla, New York 10595, U.S.A.

S. Wolff *Chapter 20*
Laboratory of Radiobiology, School of
Medicine
University of California
San Francisco, California 94143, U.S.A.

A.J. Wyrobek *Chapter 36*
Biomedical Sciences Division
Lawrence Livermore Laboratory
University of California
P.O. Box 5507
Livermore, California 94550, U.S.A.

J.M. Wytsma *Chapter 8*
Mutagenesis Section
Environmental and Occupational Toxicol-
ogy Division
Department of National Health and Wel-
fare
Tunney's Pasture
Ottawa, Ontario, Canada K1A 0L2

L.P. Yotti *Chapter 37*
Department of Pediatrics and Human
Development
College of Human Medicine
Michigan State University
East Lansing, Michigan 48824, U.S.A.

A.E. Zinov'eva-Stahevitch *Chapter 18*
Genetics Laboratory, Department of Plant
Sciences, Faculty of Agriculture
Macdonald Campus of McGill University
Ste Anne de Bellevue, P.Q., Canada H9X
1C0

K.D. Zura *Chapter 18*
Genetics Laboratory, Department of Plant
Sciences, Faculty of Agriculture
Macdonald Campus of McGill University
Ste Anne de Bellevue, P.Q., Canada H9X
1C0

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