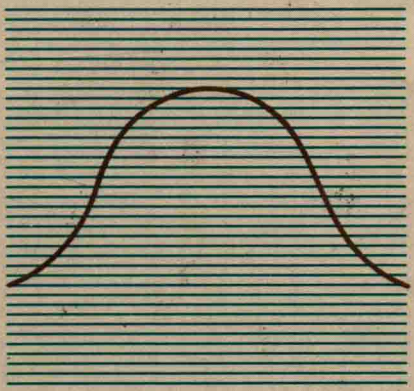
BIOTECHNOLOGY RISK ASSESSMENT

Issues and Methods for Environmental Introductions



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Pergamon Press

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National Science Foundation

Final Report to the Office of Science and Technology Policy
Executive Office of the President
Report No. NSF/PRA 8502286

PERGAMON PRESS
New York Oxford Beijing Frankfurt São Paulo Sydney Tokyo Toronto

Pergamon Press Offices:

U.S.A. Pergamon Press, Maxwell House, Fairview Park, Elmsford, New York 10523, U.S.A.

U.K. Pergamon Press, Headington Hill Hall, Oxford OX3 0BW, England

PEOPLE'S REPUBLIC OF CHINA Pergamon Press, Qianmen Hotel, Beijing, People's Republic of China

FEDERAL REPUBLIC OF GERMANY Pergamon Press, Hammerweg 6, D-6242 Kronberg, Federal Republic of Germany

BRAZIL Pergamon Editora, Rua Eça de Queiros, 346, CEP 04011, São Paulo, Brazil

AUSTRALIA Pergamon Press (Aust.) Pty., P.O. Box 544, Potts Point, NSW 2011, Australia

JAPAN Pergamon Press, 8th Floor, Matsuoka Central Building, 1-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 160, Japan

CANADA Pergamon Press Canada, Suite 104, 150 Consumers Road, Willowdale, Ontario M2J 1P9, Canada

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First printing 1986

Library of Congress Cataloging in Publication Data

Biotechnology risk assessment.

"Final report to the Office of Science and Technology Policy, Executive Office of the President."
"Report no. NSF/PRA 8502286."
Includes index.
1. Genetic engineering. 2. Microbial genetics. 3. Health risk assessment--Technique. I. Fiksel, Joseph R. II. Covello, Vincent T. III. United States. Office of Science and Technology Policy.
TP248.6.B56 1986 363.1 86-5061
ISBN 0-08-034213-2

Printed in the United States of America

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COMPREHENSIVE BIOTECHNOLOGY ABSTRACTS

Foreword

Since the publication by Professor Paul Berg and his colleagues calling for a moratorium on genetic engineering research appeared in *Nature* on July 19, 1974, a sweeping series of events have occurred. Advances in recombinant DNA research and molecular biology, and in genetic manipulation, have resulted in an impressive technology now being available for transfer of genetic material intra-, inter-, and supra-generically. Thus, in little more than ten years, a cascade of requests is flowing in to the regulatory agencies of the United States government for permission to release genetically engineered organisms to the environment for a variety of useful purposes.

Since 1974, the scientific, legal and policy issues associated with environmental applications of biotechnology have been addressed by several federal agencies. A cabinet council working group was appointed under the direction of the Office of Science and Technology Policy (OSTP), which included representatives of the U.S. Environmental Protection Agency (EPA), National Institutes of Health (NIH), U.S. Department of Agriculture (USDA), and other agencies. A proposal for a coordinated approach to the regulation of biotechnology applications was published in December 1984. Since then, a framework for federal regulation of biotechnology has been formulated that is directed at the product and not the process of recombinant DNA. The White House Biotechnology Science Coordinating Committee, chaired by Dr. David Kingsbury, Assistant Director of the National Science Foundation, has provided this framework, a refinement of the proposal published in December 1984, with the advantage that it provides a measure of regulatory certainty for industry, permitting U.S. industry to deal effectively with commercialization and to promote increased competitiveness internationally.

The issue of regulation of biotechnology is far from being closed, however, because the public will have an opportunity to comment on several proposed key definitions before the decisions become final. Public hearings will be held at the National Academy of Sciences. Additionally, three subcommittees of the House Science and Technology Committee of the U.S. Congress will hold joint hearings to review the program. As it now stands, four regulatory agencies will share responsibility for controlling organisms now covered by existing laws, including USDA, EPA, FDA and the Occupational Safety and Health Administration (OSHA). Three of the agencies, USDA, NIH and NSF, will be principally involved in overseeing research activities.

Interestingly, exceptions to federal regulation include regulating genes and deleted genes in the new framework that has been put forward. Otherwise, each agency will continue its regulatory functions, without specific reference to whether or not recombinant DNA methods were employed. Thus, the FDA will regulate human and animal drugs, medical devices and biologics, and OSHA will oversee workplace hazards. The FDA will serve as the lead agency for foods and food additives, and the USDA for food use and exclusive control over animal biologicals. The EPA will serve as the lead agency for regulating microbial pesticides released to the environment, with USDA involved if the microorganism to be released is a plant pest, animal pathogen, or a regulated article requiring a permit.

A major issue on which there is continuing debate is whether combinations of genetic material from organisms that exchange DNA by known physiological processes should be excluded from the definition of inter-generic organisms. That is, it remains to be decided whether organisms should be excluded from regulation which contain inter-generic combinations of certain specified recombinant DNA molecules which consist entirely of DNA segments from different genera that may exchange DNA by known physiological processes. Clearly, debate on this and other aspects of the regulation and control of biotechnology will continue into the future.

The focus of this book is on risk assessment of introductions of genetically engineered microorganisms to the environment. The background and motivation for study of risk assessment for such organisms, an overview of existing risk assessment approaches, available methods that can be used to assess biotechnology applications, and the suitability of the methods and their strengths and limitations are covered.

The breadth of the book is extensive in coverage of the major issues involved in risk assessment of genetically engineered organisms released to the environment. Methods for evaluation of microorganism properties, human exposure and effects analysis for genetically modified bacteria, as well as risks of human exposure to viruses as a consequence of such exposure are discussed in detail. Ecological consequence assessment, including trans-

port and fate of bioengineered organisms in the environment, has been addressed. The value of this volume lies in the broad sweep in coverage and success in touching upon the major issues associated with release, including inter-generic genetic exchange in different ecosystems, properties contributing to environmental persistence of introduced genes and most importantly, a discussion of various risk assessment methods suitable and applicable to release of genetically engineered organisms to the environment.

Formation or creation of a genetically altered microorganism through deliberate or accidental means, deliberate release or accidental escape of these microorganisms to the environment including possible transfer of their genetic material to other microorganisms, establishment of these microorganisms within an ecosystem niche including possible colonization of humans or other biota, and subsequent occurrence of human or ecological effects arising from interaction of the organism with some host or environmental factor each require risk assessment methods. Therefore, available risk assessment methods for biotechnology applications are examined critically in this volume, with a useful model for organizing methods for risk assessment being offered.

The conclusion of the authors and of participants in the workshop is that, while methods such as ecosystem structural analysis may be useful in identifying potential risks, actual observation and testing will be essential in assuring the success and safety of environmental applications. Controlled testing and monitoring methods will be required, which include methods for detecting, identifying and enumerating specific microorganisms, methods for assessing the fate and effects of the microorganisms, and methods for assessing genetic stability of the microorganisms and the potential for genetic transfer.

Clearly, beneficiaries of attention being paid to the question of release of bioengineered organisms are the areas of microbial ecology and systematics, both disciplines having been neglected in the past mainly for not being "fashionable" or "relevant." It now appears that microbial ecology and systematics are both fashionable and relevant as well as badly needed, because of the lack of information in these disciplines to underpin decisions whether or not to release specific organisms. Fortunately, this volume will take us a significant step forward in dealing with and understanding risk and risk assessment of release of bioengineered organisms to the environment.

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and Professor of Microbiology
The University of Maryland

Preface

The potential applications of modern biotechnology include controlled introduction of genetically altered microorganisms into the environment for agricultural and other purposes. A number of existing scientific methods can be used to assess the risks hypothetically associated with such applications. In 1984, the National Science Foundation, at the request of the Office of Science and Technology Policy in the Executive Office of the President, initiated a study to evaluate the suitability and applicability of these scientific methods for risk assessment of environmental applications of biotechnology.

The hypothetical stages and conjectural events to be addressed in a risk assessment include:

- Formation of a genetically altered microorganism through recombinant DNA or other techniques.
- Planned release of a certain quantity of such microorganisms into the environment.
- Proliferation of the microorganism within the environment, including physical dispersal, genetic changes, or transfer of genetic material to or from other microorganisms.
- Establishment of the microorganism within an ecological niche, with or without colonization of other organisms.
- Adverse effects upon humans or the ecosystem arising from interactions of the microorganism with host or environmental factors.

Assessment of these five stages is not directly analogous to conventional risk assessment for chemical or physical agents, because microorganisms are capable of mutating, multiplying, and adapting to their environment. Microorganisms are also subject to natural barriers, competition from other species, and additional factors that tend to mitigate or prevent their proliferation and establishment. However, the capacity for proliferation and establishment is not per se problematic; in fact, it may intentionally be enhanced for beneficial purposes. Insight into these phenomena can be provided by existing methods that have been developed in molecular biology, microbial ecology, epidemiology and medicine. The major method catego-

ries addressed in this book are evaluation of microorganism properties, human exposure and effects analysis, ecosystem structural and functional analysis, environmental fate and transport analysis, ecological consequence assessment, and controlled testing and monitoring.

Chapters that describe these methods were prepared by selected experts in various disciplines. The National Science Foundation sponsored a workshop to discuss methods and to review the current state of the art of risk assessment for environmental applications of biotechnology. The principal conclusions that emerged are:

- Environmental applications of biotechnology are not a new endeavor. Microorganisms have frequently been modified in the past by methods other than recombinant DNA and have been successfully and safely introduced into the environment.
- Development of a generic approach to risk assessment for environmental applications of biotechnology is both feasible and desirable.
- The application of risk assessment methods to biotechnological products presents scientific challenges, but available methods provide a useful foundation. At the present time only a qualitative approach is feasible, since the state of the art does not permit quantitative risk assessment.
- An important requirement in the risk assessment process is detailed knowledge of the microorganism that is to be modified. One of the criteria for the selection of a candidate microorganism should be sufficiency of knowledge regarding its environmental and pathogenic characteristics.
- Microbial ecology is important to risk assessment for most microorganism introductions, and further development of this field is required. Predictive ecosystem modeling also is needed to guide and support empirical methods of risk assessment.
- Risk assessment of environmental applications of genetically engineered microorganisms should include analyses of both expected impacts and scientifically plausible, low-probability outcomes.
- Several alternative risk assessment approaches are possible, including deterministic consequence analysis with confidence bounds, qualitative screening, and probabilistic risk assessment. The choice of an appropriate risk assessment approach depends on the degree of knowledge about the microorganism and corresponding uncertainties about its characteristics under specific environmental conditions.
- At present, empirical methods such as microcosm testing are indispensable for purposes of risk assessment, but must be supplemented by predictive modeling methods.

Although risk assessment remains an inexact process, it provides a systematic means of organizing and interpreting a variety of relevant knowledge about the behavior of microorganisms in the environment.

Acknowledgments

This study was prepared by the National Science Foundation at the request of the Office of Science and Technology Policy in the Executive Office of the President. The authors gratefully acknowledge the assistance and participation of the following individuals, without whom the study could not have been completed:

Rita Colwell and John Cantlon, who served on the Steering Committee for the project.

John Cohrssen, who served as the principal coordinator on behalf of the Council on Environmental Quality and the Office of Science and Technology Policy.

David Sakura, Mildred Broome, Robert Bondaryk, Louis Anthony Cox, Patricia Deese, and John Ehrenfeld, who formed the Arthur D. Little, Inc., project team.

Sidney Draggan, who was instrumental in the conception and organization of this study.

Grant Brewen, Clint Kawanishi, Robert Rabin, Carol Scott, Sue Tolin, and Curtis Travis, who participated in an expert workshop providing many important insights contained in the book.

Joshua Menkes, who provided overall policy guidance for the project.

James Callahan, Mary Clutter, Robert Colwell, Patrick Flanagan, Robert Friedman, John Gosz, Carol Gronbeck, Frank Harris, Mark Harwell, Herman Lewis, Jonathan Plaut, Guenther Stotzky, and Peter Vitousek, who reviewed the contributed chapters.

Gloria Taylor of Arthur D. Little, Inc., who supervised preparation of the manuscript and the workshop communications.

Coordination and preparation of the contributed chapters were performed by Arthur D. Little, Inc., under Contract No. PRA-8400692 with the Division of Policy Research and Analysis, National Science Foundation, Washington, D.C.

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The Suitability and Applicability of Risk Assessment Methods for Environmental Applications of Biotechnology

Joseph R. Fiksel and Vincent T. Covello

This chapter evaluates the suitability and applicability of existing methods for the assessment of conjectural risks that may be associated with environmental applications of biotechnology. The specific goals of the chapter are

- to describe and evaluate the state of the art of risk assessment for conjectural risks that may be associated with environmental releases of genetically engineered microorganisms;
- to determine the extent to which existing methods fulfill risk assessment needs, and to identify significant methodological gaps; and
- to provide a foundation and set of principles for guiding future methodological research and development.

A number of fundamental risk assessment issues are addressed:

- Does the existing risk assessment framework need to be modified to account for novel aspects of future biotechnology applications?
- What are the prospects for development of a generic risk assessment methodology for microorganisms as a complement to the case-by-case approach?
- What is the range of environmental end points that need to be considered in a comprehensive risk assessment of biotechnology applications?
- Will it be feasible in the foreseeable future to develop a capability for