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A. L. Young

Chemicals & Health

Report of the Panel on
Chemicals and Health of the
President's Science Advisory Committee
September 1973

Science and Technology Policy Office • National Science Foundation

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FOREWORD

A large and growing number of chemical substances are introduced into man's environment each year. To many of these substances man is involuntarily exposed. Some exposures represent identified and recognized hazards to his health and well being, but to a great extent our ability to understand the biological effects of chemical substances such as pesticides, food additives and therapeutic drugs has not kept pace with our technological ability to develop and use new substances.

In May 1970, a panel of the President's Science Advisory Committee was established to review a broad set of issues concerning chemical substances and human health. This panel was a reflection of the initiative and concern of two previous Science Advisers, Drs. Lee A. DuBridge and Edward E. David, Jr. It was their belief that the time had come to take stock of the scope of the intrusion of chemical substances into man's environment, of the known or implied threats to human health which they represented, and of the degree of protection which regulatory processes could be reasonably expected to provide. The report of the panel is the product of almost two years of deliberation and contains much useful information on the size and nature of both the risks and the benefits that are involved in the use of chemicals.

The report was prepared by an outside advisory group. It has been reviewed by the Federal agencies most concerned with these matters. Many of its recommendations deal with administrative, resource, organizational and procedural matters. Implementation of such recommendations involves a weighing of broad policy questions that a technical group cannot adequately undertake. Several of the report's recommendations, however, have already been implemented. Others will quite likely be the source of continuing debate and study. I am releasing the report, therefore, in order that it may contribute to the state of public knowledge and deliberation on this difficult and complex subject.

H. Guyford Stever
Director
and
The Science Adviser

President's Science Advisory Committee (1972)

Edward E. David, Jr., *Chairman*
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Berkeley, California

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Bell Telephone Laboratories
Holmdel, New Jersey

Theodore L. Cairns
Director
Central Research Department
E. I. du Pont de Nemours and Company
Wilmington, Delaware

James S. Coleman
Department of Sociology
University of Chicago
Chicago, Illinois

Lee A. DuBridge
Laguna Hills, California

Val L. Fitch
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Princeton University
Princeton, New Jersey

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Space Research
U. S. Naval Research Laboratory
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James B. Wyngaarden
Chairman
Department of Medicine
Duke University Medical Center
Durham, North Carolina

Panel on Chemicals and Health

John W. Tukey, *Chairman*
Professor of Statistics
Princeton University
Princeton, New Jersey

Edward J. Burger, Jr.
Office of Science and Technology
Executive Office of the President
Washington, D. C.

James E. Baldwin
Department of Chemistry
University of Oregon
Eugene, Oregon

Nyle C. Brady
Director
International Rice Research Institute
Manila, Philippines

John J. Burns
Vice President for Research
Hoffmann-LaRoche Company
Nutley, New Jersey

Theodore L. Cairns
Director
Central Research Department
E. I. du Pont de Nemours & Company
Wilmington, Delaware

Alfred Gilman
Department of Pharmacology
Albert Einstein College of Medicine
Bronx, New York

Richard L. Hall
Vice President
Research and Development
McCormick and Company, Inc.
Hunt Valley, Maryland

Stanley Lebergott*
John E. Andrus Center for
Public Affairs
Department of Economics
Wesleyan University
Middletown, Connecticut

*Starting September 1971

Roland H. McKean**
James Wilson Department of
Economics
University of Virginia
Charlottesville, Virginia

Norton Nelson
Director
Institute of Environmental Medicine
New York University Medical Center
New York, New York

Oscar M. Ruebhausen
Debevoise, Plimpton, Lyons
and Gates
New York, New York

Laurence H. Tribe
Professor of Law
Harvard Law School
Cambridge, Massachusetts

James L. Whittenberger
Chairman
Department of Physiology
Harvard School of Public Health
Boston, Massachusetts

Bryan Williams
Associate Dean
University of Texas Medical
School (Southwestern)
Dallas, Texas

Carl O. Muehlhause, *Staff Assistant*
Office of the Director
National Bureau of Standards
Department of Commerce
Washington, D.C.

**Until February 1972

ADVISERS

Dr. Herbert E. Carter
Coordinator of Interdisciplinary Programs
University of Arizona
Tucson, Arizona

Dr. J. Clarence Davies
Council on Environmental Quality
Washington, D.C.

Dr. Charles C. Edwards
Commissioner
Food and Drug Administration
Rockville, Maryland

Dr. Stanley Greenfield
Assistant Administrator for
Research and Monitoring
Environmental Protection Agency
Washington, D.C.

Dr. Philip Handler
President
National Academy of Sciences
Washington, D.C.

Dr. Jesse Steinfeld
Surgeon General
Public Health Service
Department of Health, Education, and Welfare
Washington, D.C.

Mr. James H. Wakelin, Jr.***
Assistant Secretary for Science and Technology
Department of Commerce
Washington, D.C.

***Until August 1972

THE PRESIDENT'S SCIENCE ADVISORY COMMITTEE
EXECUTIVE OFFICE BUILDING
WASHINGTON, D.C. 20506

May 1970

Terms of Reference for a PSAC Panel on Chemicals and Health

A very large number of chemical substances are purposefully introduced into society which impinge directly on man. Therapeutic drugs are perhaps the most obvious. In addition, however, there are more than 60,000 registered pesticide formulations on the Federal rolls and there is an uncertain but very long list of food additives which are used to improve certain qualities of food substances.

Large segments of the population are subjected to these chemicals for very long periods of time. In spite of this level of exposure, the understanding in any depth of the physiological hazards and toxicity of many of these chemicals is generally not available. The technology of development of these chemicals has not been matched by corresponding biological understanding of them. Of particular concern are potentially deleterious effects on health resulting from long-term exposures to low levels of these chemicals, alone or in combination.

Occasional incidents call this matter to public attention. Recent examples have included cyclamates, pesticide residues, and oral contraceptives. Thus far, each case has been treated individually—usually in a manner reactive to a variety of pressures of the moment and rarely if ever reflective of a sufficient background of objective information. At the same time, the number of chemical substances in use continues to increase as do the corresponding chances of human exposure. It appears desirable that the whole situation be addressed at once with a view towards ascertaining whether the public health and well-being are adequately safeguarded, and if not, what actions should be set in motion.

A PSAC panel is being established to explore this situation. It should consider such questions as:

1. How much assurance of safety should we require?

2. What kinds and levels of research must be performed to reach a desired level of understanding?

3. What resources will be required? What will be required in terms of organizational and financial arrangements, including research facilities?

4. How are the results of research best put to use in the decision-making process? How should the research and research results be related to the regulatory process? What organizational and institutional arrangements are needed for social decision-making and education at the various levels of decision-making within the Federal Government and in the community-at-large?

Note: There are many other substances that result from man's activities that may affect man directly, such as asbestos fibers, air pollutants, etc. To the extent reasonable, the study may consider these, too, although it is recognized that the actions to control these substances may be quite different from those required to control the previously described substances.

CONTENTS

SECTION I—Summary and Recommendations

CHAPTER 1

INTRODUCTION

The charge to this Panel—Chemicals and Health—could have been unmanageably broad—since both we and our environment are complexes of chemical systems. Choices had to be made. Guided by various public concerns, by scientific and technological developments, and by recent regulatory history, our detailed attention has focused on those established or implied threats to health attendant upon medicines, agricultural chemicals, food additives, household and industrial chemicals and, to a lesser degree, other pollutants of air and water.

We have chosen to exclude from any detailed consideration the admittedly critical areas of drug abuse, dietary choice, and undernutrition, although foods and illicit drugs, as we will later emphasize, are important parts of our chemical environment.

We have attempted to consider the size and nature of the risks inevitably involved in the use of chemicals, and the magnitude and character of the benefits they provide, including the role they play in improving public health. This is a subject as complex as life itself, and just as full of uncertainties and conflicts.

Public attention is now focused on what might once have seemed quite minor threats to health, in large part because our younger citizens are the first generations ever to grow up nearly free of major threats from once common infectious diseases—whooping cough, scarlet fever, typhoid, pneumonia, streptococcal infections. They are also nearly free of the serious nutritional diseases such as rickets, pellagra, and goiter.

Along with a host of other factors, a wide variety of chemicals—drugs, fertilizers, vitamins and pesticides—have helped to achieve these gains. Yet the very absence of these former scourges has left clear the field for the chronic degenerative diseases, some of which are likely to have external chemical causes. We need now to develop ways to deal with these slower acting and less direct causes of death and chronic sickness.

In the area of chemicals and health our country requires, above all, a sense of perspective. Without that we will work on the wrong things, waste irreplaceable effort, and neglect the truly vital. Next, we need balanced judgments and actions. Without them we will do the right things wrongly, or poorly, or not at all.

In seeking an adequate perspective, we have looked broadly at the threats to health linked to chemicals. Several of the largest involve voluntary exposure—cigarette smoking, alcohol abuse, dietary composition—have been extensively discussed elsewhere. (The involuntary aspects of death from alcohol-related automobile accidents and homicides cannot be neglected.) Our recommendations recognize their importance despite the fact that they have not played a central role in our investigation, and we urge increased effort and new measures of education and control.

The bulk of our report and recommendations, however, deal with lesser threats in our environment, and focus on possibilities for their more effective control and more rapid discovery.

Public expectations and government philosophy have called for increasing protection of the public health and welfare and increasing prevention of exposure to dangerous substances, with emphasis on protection from involuntary exposures but with attention to voluntary exposures as well.

The health-related regulatory agencies of the government dealing with chemicals, now the Food and Drug Administration and the Environmental Protection Agency, have evolved stage by stage. Their present organizational positions reflect an increasing public desire to separate health-protection functions from the encouragement of the production and use of products.

With time, the spectrum of items to be regulated and the character of regulation have changed. While the threats to health and the pattern of disease of a century ago have been altered, there has been an enormous increase in the number of substances to be regulated, and the scope and complexity of regulation have correspondingly increased. The tools of analysis and detection and the advances in scientific understanding have combined not only to heighten our awareness of environmental chemical agents and of varied possibilities of disease causation, but also to raise our expectations that these might be better controlled.

During the last few decades many exposures, involuntary and voluntary, have become more recognized, some as they increased in significance like air pollution and cigarette smoking, others as they remained constant or declined. The next few decades, as our knowledge and understanding increases further, will see the recognition of many new exposures, involuntary and voluntary, of some health significance. We will have to learn much more about how we should meet threats from voluntary exposures. (The history of our national experience with prohibition suggests that governmental regulation will not always be a successful tactic for meeting such threats to human health.) Our attention in this report is mainly to regula-

tion, but both our concern and our nation's need extend far beyond it.

For regulation to function properly, we must know more about the biological mechanisms by which chemicals can or do threaten us, we must have more effective and more efficient ways of testing both individual substances and all the materials that will touch or feed us, we must recognize more diverse and more subtle threats more rapidly. To this end we are badly in need of new knowledge today; tomorrow our needs for it will grow greater and greater.

Both to regulate wisely and gain needed new knowledge, we will need more highly skilled people, trained in appropriate specialties. We have not studied the needs in detail, and do not make detailed recommendations. Among many others, the need for a great increase in appropriately trained clinical pharmacologists and toxicologists and the need for persons of diverse specializations in environmental epidemiology are too great, however, not to be at least noted.

It is time to take stock. Is regulation of chemical agents in our environment performing the health-protection function to a degree that coincides with our expectations? More important, can regulation do so? Are regulatory decisions based on a suitable foundation of scientific knowledge—one that is growing fast enough? Do the decisions reflect an appropriately broad set of considerations in each case? Are all the parties of interest able to contribute appropriately to the body of facts and arguments on which decision is based?

The answers to all these questions are encouraging, yet in each case there is more that we can do, as our recommendations show.

The most important thing we can do now is to make our regulatory decisions better balanced, to ensure that positive effects on health are balanced against negative ones and that non-health effects are duly considered.

The next most important thing is to increase public understanding and acceptance of these better balanced regulatory decisions. This involves not only bringing to public attention much more of the pros and cons of administrative actions—and much more about what we do or do not know—but also offering the public more effective channels through which to express its interests, concerns and doubts.

We stress the following themes:

Perfect Safety Is Not Attainable. We must always live with some risks both because nature forever confronts us with hazards, and also because the contributions of chemicals to human welfare are so vital. Our knowledge is never complete; as it increases, it will make us reconsider, and often revise, past decisions.

Improved Safety Is Possible. But to make the greatest possible health advance, we ought to react most to the gravest threats, as judged by their total consequences for all our people, particularly when these threats are either well-established, or both plausibly true and long-delayed in impact. We need also to react appropriately to less-certain threats that can be avoided without appreciable disadvantages. Threats of lower priority should not be neglected but need not be reacted to as strongly.

Our Present Mechanisms Have Generally Worked Well. both in providing useful new chemicals and in safeguarding the public health from involuntary exposures to threatening chemicals, new and old. The Federal Government's basic responsibility, more stringent for involuntary exposures than for voluntary ones, has been effectively implemented through general legislation and detailed administrative actions. The steady growth of knowledge has demanded detailed up-to-date decisions that apply general legislation on a case-by-case basis.

Improvements in These Mechanisms Are Still Needed. We should expand the coverage of regulation in certain areas and should accelerate the functioning of our regulatory institutions. But above all we must increase our knowledge and learn how to make more balanced judgments.

To Improve Our Human Health Substantially by changing our exposure to chemicals, we must turn to:

a. Reducing our consumption—or otherwise reducing the adverse effects—of such voluntary chemicals as alcohol in beverages and substances from cigarette smoke.

b. Learning more about the biological basis of disease, in particular:

- Learning more about the impact of dietary composition on health and altering our choices of what we eat.
- Identifying and learning to deal with, threats from still unidentified chemicals.
- Continuing to develop new medicines, especially for diseases and conditions not now adequately treatable.

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While there are many actions that we recommend, the major points can be summarized under three heads:

a. **Improve the Gathering and Availability of New Knowledge** by increasing support and by strengthening procedures and mechanisms so as to:

(1) Gain further understanding of the biochemical mechanisms by which chemicals—in foods, medicines, and our environment—affect man.

(2) Improve and expand studies, both in the laboratory and in the world at large, of the impact of chemicals to which humans are currently exposed.

(3) Improve our gathering of safety and efficacy information about new chemicals.

(4) Make publicly available, in a routine and appropriately timely way, the data of safety studies for all chemicals submitted for approval, and the data of efficacy studies for all those approved.

b. **Improve Public Information and Understanding:**

(1) Inform the public about the inevitable incompleteness of the knowledge we have gained up to any given date.

(2) Make public the bases of regulatory actions, including both the extent and character of the scientific knowledge involved.

(3) Make clear to the public the content and importance of the themes stressed above.

c. **Improve the Balance of the Decision-making Process:**

(1) Use advisory Committees including both expert and public members, in connection with important decisions.

(2) Make public the pros and cons supporting regulatory decisions of public interest, including both affirmative actions and decisions to delay or refuse to act. These "white papers" should recognize the diversity of interests that each one of us has in such decisions, and should make clear what is not known, as well as what is.

(3) In preparation for each of these "white papers," emphasize the gathering of diverse views and considerations, so as to broaden the range of the pros and cons presented.

(4) Introduce institutional modifications to eliminate undue regulatory delay.

(5) Revise legislation and administrative procedures to make regulation more responsive to increasing knowledge and increasing measurement capability.

CHAPTER 2

PRINCIPLES AND GENERAL RECOMMENDATIONS

Our recommendations need to be based on as clear a view as possible of the overall problem improving human health by reducing threats—and increasing benefits—from chemicals.

To assist in this, we begin with statements of principle. Once these are understood, recommendations concerning individual objectives and detailed actions often follow either automatically or with relative ease.

The order of appearance of recommendations thus does not always reflect the Panel's view of their importance. (A listing of those we stress is given in 2E, page 12.)

2A. KEY PRINCIPLES

The single most important principle of this report is simple to state, but not easy to implement. Indeed, though it may sound obvious, we have found it frequently and conspicuously lacking in many administrative actions. It has led us to a number of our most important recommendations.

Principle A

Regulatory procedures should ensure balanced consideration and balanced decision in regulatory actions. This implies consideration of both direct and indirect consequences that will flow from each of the possible actions. (Leading to General Recommendations 1 to 4, 19 and 22, and to Recommendations A1 to A3.)

The protection of human health, with suitable limited attention to the non-health consequences of possible regulatory actions, is the responsibility of the regulatory agencies discussed in this report.

Many recent regulatory policy decisions have considered only a narrow spectrum of issues. However, experience continues to show the great complexity and diversity of the questions that are involved. Even the balancing of health against health, of life against life, becomes difficult once the indirect consequences to health of a ban or restriction have to be included. As other aspects of public welfare are introduced, difficulties increase rapidly. The public interest can only be properly served when the full range of implications of a possible action are considered carefully and systematically. Moreover it requires that the interests of a variety of parties have been heard, included in the final consideration, and reflected in the ultimate decision.

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Giving proper attention to uncertain threats is a very difficult matter. In general, our history shows contrasting extremes; either a tendency to overreact to uncertain threats or one to do nothing, particularly when the threat, if actual, would be small.

Principle B

Where knowledge is so inadequate as to make the reality of a possible threat quite tenuous, the proper response is to seek more knowledge, not either to take drastic action or to do nothing. (Leading to General Recommendations 7 and 13 to 17.)

Many threats to health from chemicals are quite uncertain, either as to which chemicals are involved or as to the existence or size of the threat. The correct response to uncertain threats is the gaining of new knowledge.

2B. FEDERAL RESPONSIBILITIES

We need to be clear about the responsibilities of the Federal Government.

Principle C

The Federal Government has a particularly strong responsibility to protect all our people from involuntary exposure to threats to their health, including those from chemicals. Both strong and effective regulatory programs and strong programs directed toward recognizing new threats are essential elements in meeting this responsibility. (Leading to nearly every General Recommendation.)

It is not enough to be diligent and effective in protecting health from known and controllable threats. Nor is it enough to speed up the learning about unrecognized or unidentified threats. A satisfactory Federal program must put great emphasis on both.

Principle D

The Federal Government has a responsibility to take vigorous actions to deal with those threats to health which arise from the threatened individual's own choice, and to do this without restricting the essential freedom of choice of the individual. Where alternative choices are not available, it should work toward making them available. Where such dangerous choice is determined by social pressures, these pressures should be weakened. (Leading to General Recommendations 10, 12, and 13, among others.)

We recognize the right of individuals to be free of the consequences of dishonesty or careless-

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ness among producers or sellers, and the responsibility of the Government to protect individuals from such actions by others. Actions that make cigarette smoking a desirable aspect of social life, are actions from which the innocent participant deserves protection as he would from actions that unduly limit his choice of dietary constituents by restricting or failing to broaden patterns of food availability. In dealing with voluntary exposures to threats to health, we also need to notice that it is appropriate to seek to replace large risks to smaller ones, however regrettable the smaller one may be.

Principle E

The Federal Government has a strong responsibility to ensure the rapid growth of new knowledge, so that we may recognize and evaluate new threats, develop new techniques and methods, and guide regulatory actions wisely. (Leading to General Recommendations 7, 10, and 13 to 18.)

This includes responsibility for the support of diverse areas of research and monitoring.

Principle F

The Federal Government has a major responsibility to promote the health of our people by actively encouraging both innovation and speediness in the availability of important new medicines and other health-promoting chemicals. It also has a responsibility to encourage diversity among the chemicals in use so that response to new knowledge can be easier and more effective. (Leading to General Recommendations 5, 8 and 9.)

As noted above, one of the major ways in which the Federal Government can contribute positively is by the support of gaining new knowledge, including the development of knowledge fundamental to new medicines. It is also clear that the regulatory system for medicines must operate neither too hastily nor too slowly.

There is a related responsibility to foster the existence of alternative chemicals for many uses, so that if new knowledge makes regulation or banning of one desirable, an adequate substitute is immediately available.

2C. PRINCIPLES OF IMPLEMENTATION

All of us, but especially the Federal Government, must try to relate the strength of our response to the seriousness of the threat.

Principle G

National policy needs to give the most attention to the largest threats to health, even if these threats have been frequently recognized. (Leading to General Recommendations 10 to 14.)

If one threat is one hundred thousand greater than another, as illustrated for specific parts of threats from chemicals in Chapter 5, it should receive vastly more attention. (Giving each threat attention proportional to its size would, however, give too little attention to the small threats.)

In dealing with both established and uncertain threats to health from chemicals, it is not enough to deal only with the largest threats. We have already made this point in discussion, but it deserves statement as a principle.

Principle H

Medium-sized threats and many small ones deserve serious attention, especially when the risk is well established or can be reduced with little penalty.

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The knowledge that must guide regulatory decisions changes from year to year or even from month to month. Indeed, if we are to continue to move toward better health, it must become steadily larger in scope, greater in detail, and more precise and accurate in content. Our mechanisms of regulation and warning need to be prepared for such changes, and the flow of information to all concerned needs to become more adequate.

Principle I

The growing and changing nature of scientific knowledge demands flexibility in regulatory procedures—not rigidity. Laws, regulatory structures, and styles of administrative action all need to be adapted to a continuing growth and change in knowledge. (Leading to General Recommendation 19 and also General Recommendation 1.)

The implications of this principle are rather more diverse than might at first be expected. Overrigid laws and regulations often cannot accommodate changes in scientific insight and understanding.

Principle J

Wise administrative and legislative judgments about chemicals and health require stimulus and support from a public that is increasingly informed. Information provided to the public must encompass both possible new threats to health and those considerations on which current actions and proposals are based. (Leading to General Recommendations 20 to 22 and also General Recommendations 1 to 4.)

It is vitally important that all interested segments of the public be fully informed and understand the knowledge and judgments which underlie regulatory actions.

2D. GENERAL RECOMMENDATIONS

Some of the more important recommendations that flow from these principles are:

General Recommendation 1

The Chief Administrator of each health-related regulatory agency should have an Advisory Board of Review, consisting of members from outside the Government, that sits in connection with each important regulatory decision. (Implementation: FDA, EPA and probably Agriculture.) (Responsive to Principle A and also to I and J.)

The members of the Advisory Boards could be divided into two classes, each appointed for overlapping terms of seven years:

- one class appointed by the Administrator from a list provided by the National Academy of Sciences—Institute of Medicine.
- one class appointed by the President with regard to the broad interests of the public.

The Chairman of each Board should hold office for a minimum term of three years.

Each Board should be promptly responsive to the requests of the Administrator as its workload permits, and should have the right also to undertake studies and reports on its own motion. Where a report is prepared at the Administrator's request, the Board should expect that the report would normally be made public when the Administrator's action (positive, negative, or suspense) is announced. On those rare occasions where the Board feels it necessary, it should be privileged to address communications directly to the President.

Internal reviews can be very helpful; indeed internal review papers are the natural way to bring problems to the attention of an Advisory Board. In the real world, however, they can never gain the credibility of a report from an Advisory Board of members drawn from outside the Government and serving terms long enough both to develop skills and understanding and to avoid even the shadow of political influence. Moreover, such Boards could elicit public response through, for example, public hearings.

Such Advisory Boards would not only do much to aid balanced decisions but would also increase general understanding and public acceptance of these decisions.

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Improved balance in the making of decisions also require better public understanding of whether or not a decision is balanced.

General Recommendation 2

Government regulatory agencies should make publicly available a "white paper" at the time of each decision. In that paper, the several kinds of considerations, the scientific data, and the rationale should all be clearly laid out and described in a way understandable to the public. (Implementation: EPA, FDA.) (Responsive to Principles A and J.)

For individual routine decisions, such white papers may be quite short. But white papers for policy decisions with broad implications—such as banning a pesticide or class of pesticides, withdrawing a food additive, or telling the public to avoid eating a long-familiar natural food—should both give considerable detail and include an easy-to-understand summary. Such a major white paper should always indicate, as clearly as knowledge and judgment permits, certain elements, including: (i) the size of the direct improvement to health expected from the action, (ii) the size and nature of the indirect effects on health likely to result from such an action, (iii) the implications of the action, in aspects of life other than health, for individuals and for our society.

These are all things that all of us deserve to know about—that we must know about if we are to be able to recognize and support balanced decisions.

General Recommendation 3

Such white papers should be issued, not only when a major action is taken, but when it is clear (as from the holding of hearings not followed by action) that an Administrator has decided not to act. (Implementation: EPA, FDA.) (Responsive to Principles A and J.)

A decision not to act needs to be as well balanced as one to act. In addition, once the techniques and mechanisms of preparing major white papers have been learned, the interests of public knowledge can be well served by the issuance of occasional major white papers of an interim character, setting out a state of knowledge that is not adequate to reach a decision in either direction.

General Recommendation 4

It should become the practice to issue occasional interim white papers outlining what is and is not known about issues of current public concern that are not yet decidable. (Implementation: EPA, FDA.) (Responsive to Principles A and J.)

The preparation and issuance of "white papers" need not—and in the Panel's view, should not—be confined exclusively to the level of the regulatory agency and its administrator. There will be circumstances where such documents, and the reviews needed to support them, would be very much in the public interest if prepared from a broader view.

For example, in view of persistent concern about the balance of the documents underlying the establishment of air pollution regulations (such as "criteria documents," themselves somewhat of the nature of white papers), it would be desirable, to clarify the issues by having such a "higher level white paper" prepared in this field by a group on which EPA is represented but not dominant.

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General Recommendation 5

Each regulatory agency concerned with agents that can affect health as well as threaten it should recognize its twin responsibilities:

to make available without undue delay agents that improve health, and to protect health by restricting the availability of agents that may threaten health. (Implementation: EPA, FDA.) (Responsive to Principle F, and leading to Recommendations B1 to B7.)

This recommendation applies most strongly to the regulation of medicines. Some applications are also likely to pesticides used for disease control and food additives used to prevent spoilage.

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We need to continue and extend our regulatory programs and our programs directed toward recognizing new threats, many of which will be outside the regulatory agencies.

General Conclusion 6

The Federal Government should continue a strong and effective program of regulation emphasizing both (a) policing of existing regulations and (b) assessing and responding to newly-established threats.

It is important to keep clearly separate two main functions of regulation. Striking down violations—whether caused by carelessness, corner-cutting, or fraud—calls for careful surveillance and immediate, even drastic action. Responding to newly established threats—ranging from the serious to the trivial—calls for careful judgment, full and informative public information, and balanced actions. Both kinds of action are essential to public health, but they should not be treated alike.

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General Conclusion 7

The Federal Government should improve and expand it programs directed toward detecting and gaining knowledge about potential threats. (Leading to and implemented through Recommendations C4 to C7.)

The next few decades can, and should, bring us much new knowledge about chemical threats to health. Some as yet unidentified threats are almost sure to be moderately important. Better understanding of both new threats and some of the threats we now recognize will almost certainly allow us to choose better alternatives to combat these threats. We need this knowledge as soon as we can reasonably obtain it.

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To meet its responsibility for encouraging the availability of chemicals to promote health, the Federal Government needs to be active in two distinct ways. First, it must prepare to implement knowledge of new threats with the least disturbance of desired effects.

General Recommendation 8

Federal policy should support diversity of chemicals for every important use. (Implementation: FDA, EPA.) (Responsive to Principle F and leading to Recommendations D1 to D3 and D9.)

The availability of several alternative chemicals that can perform the same, or closely similar, tasks makes it possible not only to tailor our choice of chemicals more closely to fit particular needs but also to abandon the use of one chemical that has been found too hazardous, without abandoning the objectives it served.

Second, it must watch over the mechanisms from which major new contributions to health not only have come but must continue to come.

General Recommendation 9

The effectiveness of the relevant industries in providing important new medicines and other health-supporting chemicals must be a continuing concern of the Federal Government. (Responsive to Principle F. Leading to, and implemented in, Recommendations F4, E4, and F9.)

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The largest threats to health through chemicals are ones in which an individual's own actions play a major role. They ought to be familiar to all, but they still deserve restatement here.

General Recommendation 10

More effective measures should be taken to reduce the smoking of cigarettes. This may require seeking out new approaches. (Implementation: HEW.) Responsive to Principles D and G.)

The increasing adoption of the cigarette smoking habit since 1900, first by men and later by women, has produced a heavy burden of illness and premature death. The seriousness of the health effects has been increasingly evident since 1950, yet there has been little reduction in the *per capita* consumption of cigarettes in the U.S. (The conjectured reduction in smoking by young people, if real, may offer significant hope for twenty or thirty years hence.) The magnitude of the health effects associated with cigarette smoking—corresponding, roughly to four million people who might be alive, but are not—compels a responsible government to take vigorous steps to reduce the habit.

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General Recommendation 11

Stronger measures should be taken to reduce death and injuries linked to alcohol abuse, particularly those associated with accidents (motor vehicles and other). (Implementation: Department of Transportation, HEW.) (Responsive to Principle G.)

Of all threats to health of whose existence and rough size we are certain and which fall involuntarily on people, by far the largest—roughly several hundred thousand who might be alive but are not—are those in-

volving accidents and homicides associated with alcohol abuse. Many of these come from motor vehicle accidents, where—as the example of Sweden shows—really rigorous enforcement can be most effective in reducing deaths from drunken driving.

The health impact of alcohol abuse is not confined to accidental and homicidal death. Many forms of ill-health are involved.

General Recommendation 12

More effective means for the medical and social treatment of alcohol abuse should be sought. (Implementation: HEW.) (Responsive to Principles D and G.)

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We are less sure about the next two threats to health through chemical means. They may well be as large as the two we have just discussed, but we cannot yet be certain.

General Recommendation 13

Continuing investigations of the role of dietary composition in coronary heart disease (and other forms of cardiovascular disease) should be actively supported. (Implementation: HEW.) (Responsive to Principles B, D, E, and G.)

We are still uncertain of the size, almost the very existence, of a major threat to health involving the role of dietary composition in coronary heart disease, particularly the amounts of cholesterol and of fats and the balance of fats among saturated, monounsaturated and polyunsaturated forms. Investigations recently started will take about ten years to produce definitive results. They deserve to be adequately supported; they may well need to be expanded.

Interim actions have been proposed[1] [2] in particular modifications of regulatory definitions of foods, which would allow individuals wider dietary choices with regard to types of fat and content of cholesterol. The public deserves a Federal response to these recommendations, at least in the form of a white paper.

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Cancer is properly a matter of great public concern. Aside from cases linked to recognized chemicals, including cigarette smoking, and occupational exposures, many other deaths from cancer occur.

General Recommendation 14

Diversified and creative research into how other environmental (including dietary) exposures relate to the initiation or acceleration of cancers should be continued and intensified. (Implementation: NCI.) (Responsive to Principles B, E, and G.)

Cancer incitements by so far unrecognized chemicals combine to form a threat to health, that may well be of at least the same general size as the three major threats just discussed (i.e., cigarette smoking, alcohol abuse, and choice of dietary composition). These chemicals may be natural or synthetic. Chemicals that have been part of our diet for centuries may be important here. Since these agents are not as yet identified, we cannot take steps to avoid their consequences without first gaining new knowledge.

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We not only need more knowledge about newly recognizable threats (General Conclusion 7) and about as yet unrecognized sources of cancer (General Recommendation 12), we need more new general knowledge, both to support regulatory activity and to accelerate progress toward these more immediate goals.

General Recommendation 15

Programs in the major regulatory agencies (FDA and EPA) for gathering new knowledge, particularly that which will be almost immediately useful for regulatory guidance, should be strengthened and expanded. (Implementation: FDA, EPA.) (Responsive to Principles B and E.)

The work included in this general recommendation includes all that responsive to General Conclusion 7. The knowledge it will produce is important to wise and careful regulation. The conduct of parts of it within the major regulatory agencies will do much to maintain scientific strength within these agencies, which is important both for the general improvement of regulatory practices and decisions and as a key resource when sudden special problems demand attention.

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The knowledge such programs will produce is important to wise and careful regulation. We can only be sure that these programs will be focused on the needs of the regulatory agencies if they are conducted by or for the regulatory agencies themselves and are supported by their funds.

Scientific strength within the major regulatory agencies is important both for the general improvement of regulatory practices and decisions and as a key resource when sudden special problems demand attention. The conduct of parts of these programs within these agencies will do much to develop and maintain this strength.

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There is an increasing need for new knowledge that will be important for regulation in only a few years time. The pressures on the regulatory agencies are such, however, that it would be unrealistic to suppose that they would in fact do this work adequately, no matter how well they

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[1] Report of the December 1969 White House Conference on Food, Nutrition, and Health, Panel III-4 on Food Quality: Guidelines and Suggested Administrative Structure,

[2] Report of Inter-Society Commission for Heart Disease Resources, Circulation 42:A-55 to A-95m 1970.

might be funded. Effective and wise regulation in the future thus demands that responsibility for intermediate-term research be assigned to an appropriate non-regulatory agency as do needs for guiding non-regulatory approaches to those threats that will require them. This means a major role for the National Institute of Envoironmental Health Sciences, in the area of environmental chemicals. Such a major role for NIEHS presumes a continuation of the environmental health programs of other agencies, such as, for example, the National Cancer Institute. Responsibilities in the fields of medicines and general human nutrition belong elsewhere.

General Recommendation 16

The National Institute of Environmental Health Sciences should be recognized as having lead-agency responsibility for (1) developing understanding of how chemical substances in foods and the environment reach and cause ill-health in human beings, (2) developing the knowledge and techniques required to make regulation effective beyond the near future, (3) supporting the programs that bring new threats to our attention, and (4) maintaining a general view of the broad field of chemical influences on health. The personnel and funds of NIEHS should be expanded to enable it to discharge these broad purposes. (Implementation: OST, HEW.) (Responsive to Principles B and E.)

Threats to health from environmental chemicals of all kinds—whether naturally in or added to the foods we eat, or reaching us through other components of our human environment—are too important, and involve too similar mechanisms within our bodies, not to have a focus for Federal responsibilities for gaining new knowledge and understanding, including the detection of new threats.

The National Institute of Environmental Health Sciences was set up in 1969 in response to continuing criticism over the quality of research performed in behalf of regulatory decisions. The NIEHS was to fill the gap between the long-range investigations characteristic of many NIH components and of university laboratories and the very current inquiries characteristic regulation. To the extent that funds have supported it, NIEHS has performed these tasks extremely well. However, to fulfill adequately either its original role or the expanded one here recommended, it will require substantially more support.

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General Recommendation 17

A similar central responsibility in the field of medicines should be assigned to an appropriate element of NIH. (Implementation: HEW.) (Responsive to Principles B and E.)

We continue, as we should, to look to industry for the development of new medicines, and to the medical profession for their safe and effective use. Without increases in new knowledge and understanding, both about how chemicals work and how our citizens are responding to the use of medicines, neither industry nor the medical profession can do the job we rely on them to do. Gaining this knowledge and understanding is not a regulatory function, nor is it purely a matter of basic research. The opportunities for better health are too important for there to be no focal point in the Federal Government to which we can look—both for helping to seek improvements in general understanding and for a broad view of what is being done and what ought to be done. □ □

Clearly the implementation of the last three general recommendations will require increased funding. In the face of expanding needs for new knowledge in the area as a whole, these increases will have to be part, probably the major part, of an expansion of funding for environmental health science generally.

General Recommendations 15 to 17 urge significant strengthening in the research activities of the regulatory agencies, as focused on immediate problems, and the saddling of other agencies with dual responsibilities for somewhat more forward-looking research and a general overwatch of what we need to know and whether we know it. Some view this combination with concern, asking how we can be sure that the learn-and-watch agencies will provide just the knowledge that the regulatory agencies now think they will require. The Panel would, by contrast, be concerned if just this knowledge were provided.

For this there are at least two main reasons:

- The regulatory agencies are keenly aware of immediate needs, and we have recommended that they have increased ability to meet these needs. For the same reasons, their view of even next-to-immediate needs is somewhat distorted. Just as it would be unwise for them—and unrealistic to expect them—to conduct research directed toward less-than-immediate problems, so would it be unwise and unrealistic for them to have too strong a hand in its direction.

- The threats about which we will most need new knowledge will by no means all be matters of involuntary exposures. Both familiar and as yet unrecognized threats from voluntary exposures will continue to be of high importance. Meeting these threats will often not be a matter of regulation, so that they will not be of as great concern to regulatory agencies as their importance demands.

We look forward to cooperation between regulatory and learn-and-watch agencies. The Panel urges the strengthening of this cooperation by all reasonable means. But the best results will come if the points of view of regulatory and of learn-and-watch agencies are sufficiently distinct, though all directed toward a common goal.

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General Recommendation 18

Programs for new knowledge, like those covered by General Recommendations 13 to 17, should be mixed programs, combining use of government laboratories with use of university—and in some instances, industrial—projects, selected with the guidance of scientific advisory committees. (Responsive to Principle E.)

Experience shows that a suitable combination of government-conducted and government-supported activity lead both to efficiency and high quality of work.

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Laws which mandate action because of any detectable amount of a chemical causing a threat of a certain kind can become dangerous once we are concerned with small enough threats. For, as noted above, the indirect benefits of an agent can perfectly well outweigh its direct evils. When this happens, an overrigid legislative requirement can actually threaten the health of our people. The kind of legislation most likely to give rise to such dangers seems to be that illustrated by the "Delaney Clause" forbidding the addition of any detectable amount of any substance that has been shown—when fed in no matter how large amount—to cause cancer in men or animals. With the ever-increasing skill of scientists in detecting very, very small amounts of a substance, this requirement may well lead to such dangers before many years are past.

General Recommendation 19

A careful study should be promptly begun to investigate the extent to which interpretation—by courts and/or administrators—of such legal requirements as the Delaney Clause can be effective in preventing adverse public health effects which might result from over-literal interpretations of their terms.

Meanwhile, the extension of such inflexible regulatory principles to areas other than cancer should be carefully avoided. (Implementation: OST, HEW, Agriculture.) (Responsive to Principles I and A.)

A "no-detectable amount" clause is a refuge in the face of ignorance. Were mature scientific knowledge presently available regarding dose-response relationships and extrapolation to man, the problem of carcinogenicity could be dealt with a scientifically rational manner. We have good reason to believe—though it is not yet proved—that some, perhaps most, chemical carcinogens will have definable thresholds. Meanwhile, the rigid stipulations of the Delaney Clause, springing from presently inadequate biological knowledge, place the administrator in a very difficult interpretative position. He is not allowed, for example, to weigh any known benefits to human health, no matter how large, against the possible risks of cancer production, no matter how small. (And once he acts, almost all motivation to study either benefits or risks further is gone, thus keeping us from ever learning more about what should have been done.)

The problem is three-fold: scientific, legal, and social. Strong encouragement should be given, particularly at the National Center for Toxicological Research (NCTR), to the solution of the key scientific issues about trace exposures, such as whether or not there exist demonstrable thresholds for carcinogens. In the interim, a restudy should be undertaken of the opportunities for interpretation within the present wording of the law. But even the most optimistic view of possible progress on the scientific and legal issues though, perhaps developing a clear consensus among scientists, will leave untouched a third basic problem: an unexplainable emphasis on certain kinds of risks. So long as our society seeks an unachievable, and therefore illusory, goal of "absolute" safety from added substances, while ignoring the accompanying benefits (and also ignoring other larger risks, some of the same kind), the problems raised by the Delaney Clause will remain unresolved, and we will be unable to decide to what extent it should be modified.

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Public information about chemical threats to health needs to be improved in various ways.

General Recommendation 20

Estimates of the impacts on human health of exposures to various chemicals should be sharpened and strengthened. The results, expressed in broadly understandable terms, should be made part of a regular report to our citizens. (Responsive to Principle J. Leading to and implemented in Recommendation C9.)

What is needed here is indicated, for the special case of death, by the estimates presented in Chapter 4 below, which combine observed facts, epidemiological studies, and professional judgment. Such estimates need to be expanded, both as to the chemicals covered and as to other important aspects of ill-health.

General Recommendation 21

Both the scientific community and the press should take effective means to provide the public with more understandable and better balanced information about suggested new threats to health. (Responsive to Principle J. Leading to and implemented through Recommendations G1 to G4)

If the public is exposed to too many vivid accounts of nonexistent or very minor threats to health, its attention will be misdirected, its priorities will be confused, its responsiveness to

important messages will be decreased. If the public is exposed to too few—or too weak—accounts of threats of intermediate or large size, especially those where individuals can choose to reduce their own risk, we will lose important opportunities for better health. Balanced public information is crucial in improving health.

General Conclusion 22

Greater public appreciation of well-balanced regulatory decisions, both recognition that they have properly considered the public good, and that they have done this in a balanced way, is important, and should be sought in all reasonable ways. (Responsive to Principles J and A.)

Balanced decisions are important, whether or not their balance is visible. To gain credence, decisions need not only to be balanced but to have this balance displayed. This means access both to the rationale for the decision and the data that support it.

General Recommendation 23

A careful study should be made of the needs for additional manpower that are implied by our increasing concern about chemicals and health. The scale and nature of the actions concerning research grants, training grants and fellowships required to meet these needs should be clearly stated and then appropriately implemented. (Implementation: OST, HEW.)

While we have not made the detailed study recommended, the Panel could not avoid recognition of serious specific shortages. There is no doubt of the importance of the need. Its character and dimensions should be made clear to all.

2E. RECOMMENDATIONS DESERVING SPECIAL ATTENTION

We need to give special attention to certain recommendations because of a combination of importance, timeliness, and marked change from past patterns. Among these, we stress most particularly the following five:

- General Recommendation 1, concerning advisory boards of review for the administrators of FDA and EPA (page 7).
- General Recommendations 2-4, concerning white papers in connection with regulatory decisions and nondecisions (page 7).
- General Recommendation 5, concerning the twin responsibilities of regulatory agencies (for benefit by availability and safety by restriction) (pages 7-8), and, in particular Recommendation B3, concerning joint planning of safety and efficacy testing for new medicines (page 14).
- General Recommendations 10 through 14 on well-recognized major threats to health (pages 8-9).
- General Conclusion 7, leading to General Recommendations 16 and 17 (page 10), and their implementation through recommendations C7 (page 17), C10 (page 17), D2 (page 18), and D3 (page 18), concerning the need for focal responsibility concerning environmental chemicals on the one hand and medicines on the other.

We also feel that major stress should be given to the following six:

- General Recommendation 19, concerning the dangers of legal provisions which do not adequately allow for the growth of new knowledge and new techniques.
- General Recommendation 20 (page 11) and its implementation in recommendation C9 (page 17), concerning a continuing perspective for our citizens of the impacts of various chemical threats to health.
- Recommendation A3, concerning temporary establishment of adverse reaction surveillance systems (page13).
- Recommendations E7 and E8, concerning expanded effort on environmental epidemiology (pages 20-21).
- Recommendation H1, concerning the public availability of safety data (and most efficacy data) (page 24).

CHAPTER 3

DETAILED RECOMMENDATIONS

A. BETTER BALANCE IN REGULATORY ACTIONS

The first of the General Recommendations above was for an Advisory Board of Review to assist the Chief Administrator of each of the health-related regulatory agencies. Other steps to help achieve balance are also needed.

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The usefulness and trustworthiness of scientific results arises from a variety of sources. Without the intervention of organized procedures or review or discussion, neither observed "facts" nor interpretations can have their full value. Since many regulatory decisions will inevitably reflect data from recently performed experiments, and since public pressures inevitably influence regulatory decisions, the public interest demands that such data be brought to the public and to the decision makers with their full value. Consequently, the press, the government, and the individual scientists involved ought to combine to give full value to new data—and to its interpretation—by ensuring its review or discussion before it is taken to the public or made the basis of regulatory action.

Recommendations concerning governmental actions to help meet this situation follow at once; those concerning actions by scientists and their organizations and by the press follow in G (page 23).

Recommendation A1

Regulatory agencies should take steps to ensure that new scientific data raising the possibility of new or extended hazards from chemicals in use are subject to a careful process of scientific review for merit and interpretation before using them as the basis of regulation. (Implementation: FDA and EPA.)

Care is needed when new data suggest changes in regulatory position. A hasty decision based on unreviewed new data acquired from any source, external or internal only received a few days earlier is not evidence of good judgment and is not in the public interest. This applies regardless of the pressures the agency may feel because of the source of the data or any premature public exposure it may have received. New "evidence" is not always sound, and evaluating it correctly may take a variety of specialized skills. This does not imply any slowing down of action with respect to the sudden appearance of information about bad lots of food or other specific threats.

Recommendation A2

More restrictive regulation of chemicals already in use on the basis of new data almost always involves a need for a broad evaluation of the situation. Orderly procedures of review should precede administrative action, and public release of the results of the review should accompany it. (Implementation: FDA and EPA.)

Before such a regulatory action is taken, there should be a careful review of the pros and cons of the possible action, both from the narrower scientific aspects and the broader societal ones. The results of this review should be committed to writing, both for the information of the decision maker and for the public release to accompany his decision.

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Finally, the ability of an Administrator to make a balanced decision in difficult cases may depend on his ability to take an intermediate, though drastic, action when that sort of action is appropriate.

Recommendation A3

Regulatory laws dealing with chemicals should be amended to explicitly accommodate temporary limitations on manufacture, sale or use, pending the collection of more definitive information, when there is information which seriously implicates the chemical as a health hazard. (Implementation: FDA, EPA, and the Congress.)

It has to be noticed that this recommendation calls for stronger powers than those now typically held by regulatory administrators. For a power of temporary limitation, by its nature, should not be subject to interruption by the mere existence of an appeal. Instead, lacking a successful completed appeal, it should remain in force. Thus, temporary limitation is a powerful and drastic measure, one that should involve built-in safeguards and only occasional use. We are convinced, however, that it is necessary for the public safety that such a weapon should be available.

B. REGULATION'S SECOND MAJOR RESPONSIBILITY

Regulation has, in addition to its responsibility for safety, a second major responsibility: to see to it that useful new chemicals reach the public as fast as is consistent with safety.

Delay in approval of new medicines may lead to otherwise avoidable suffering or death. While this is not a reason for throwing wide the door, it is a reason for speeding up approval procedures—wherever this can be done with safety or properly controlled risk. We again must balance one risk to health against another, always doing this better than we have in the past. To do this, we must recognize the real problems and find ways to avoid them or reduce their intensity. Similar considerations apply to a variety of regulated chemicals.

Having said that the introduction of useful new medicines should be delayed no longer than is justified by a balanced concern for safety, and that action can be somewhat speeded up, we add that the Panel has found no convincing evidence to support the claim occasionally heard that the FDA has in fact withheld from final approval important medicines that ought to have reached the public.

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Recommendation B1

Criteria and methods for the *evaluation of safety of medicines and other regulated chemicals should not be "frozen" into standard patterns (standard protocols). They require constant re-evaluation and updating. Their application in each instance requires professional judgment both to avoid insufficient investigation and to avoid misapplication of effort and delays.* (Implementation: FDA and EPA.)

Many of the reasons for this broad recommendation, applicable to all chemicals, will be discussed below, in the specific context of potential new medicines.

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A variety of specific ways can be spelled out to meet the basic responsibilities of safety and still bring new medicines more rapidly to patients who badly need them.

Recommendation B2

The decision on how much animal testing should precede human clinical trials of new medicines demands expert judgment rather than a standard pattern of requirements (standard categorical protocol). The decision must always reflect an understanding of the probable biological effects, both adverse and favorable, of the specific medicine. (Implementation: FDA.)

The idea that standard tests should be laid down for medicines of a certain general character (indeed, for any class of regulated chemical) has its superficial attractiveness, both to manufacturers and to regulators. The manufacturers, faced by steadily more intensive testing requirements, look hopefully to advance knowledge of just what tests they must perform. The regulators look forward to a less arduous task of decision, one in which the hard questions, "Have all the right tests been carried out?" may perhaps be bypassed. Regrettably, this Panel sees no reality in either dream. The inevitable consequences of standard testing procedures are three: unnecessary kinds of testing, more frequent omission of unusual but key tests appropriate only in very particular instances, failure to modify test programs to take account of newly gained information (either in the testing programs or elsewhere). No one of these consequences is acceptable.

Recommendation B3

Joint planning of the testing and data-gathering needed to support applications for medicines involving distinctively new chemical entities should be an option available to applicants and regulators alike. To do so would facilitate planning of safety and efficacy tests, ensure continuity of understanding, and avoid unnecessary delays. Such joint planning should include representatives from medicine or biology outside both the government and the sponsoring or petitioning organization. (Implementation: FDA.)

The three-party arrangements proposed would be advisory only, not decision making. This recommendation does not propose to relieve the relevant government employees of their statutory responsibility to make decisions. However, effective functioning of such a three-party arrangement will really be shown when, after a New Drug Application (NDA) is filed, the responsible government examiner finds no need for further safety or efficacy information.

This recommendation proposes a three-party option only for "distinctively new chemical entities" at this time. It is hoped that favorable experience with the option will lead to its being extended to a large fraction of all NDAs. (Some NDAs, for example many of those involving a familiar agent in a new form, will not require much, if anything, beyond routine testing.)

The development and use of such a scheme would be of great value to all parties. The Government would gain, since its representative would be able to follow and consider the development of the potential new medicine over a period of years, under circumstances where he has automatically available the judgments and questions of a specially skilled, neutral expert, and where he can more effectively influence the course of the testing program. To the manufacturer, such an arrangement offers the best the Panel has been able to propose for a decrease in unnecessary delays. To the public, such an arrangement offers a better balanced testing program, tailored to a considerable degree to the known and suspected characteristics of the potential new medicine. (We must remember the public's two-fold interest. Both safety and rapid availability of efficacious medicines are important to all of us.)

Recommendation B4

Full but critical use should be made of safety and efficacy data from other countries, both when such data tend to support as well as when they tend to negate a conclusion of either safety-in-use or efficacy. (Implementation: FDA, and probably EPA.)

There may have been a time when it was hard to judge the quality of safety and efficacy studies made outside the United States. But today studies can be evaluated with adequate care and rigor in an increasing number of countries. Especially with the increase in required testing, and the limited number of skilled investigators available, either here or overseas, the time has come to make as good use as possible of all good work, wherever done. (Full use should not—and does not here—mean use without adequate evaluation.)

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Openness about the extent of delay can help to reduce delay.

Recommendation B5

Both the FDA and the EPA should publish quarterly a concise tabulation of the numbers of each kind of application or petition current, with suitable indications as to number of revisions and duration in process (both from earliest submission and since last revision or resubmission).

There are two important motivations for this recommendation. There would seem to be no better spur for the removal of unnecesary regulatory delays, and there would seem to be no better way for an up-to-date regulatory agency to demonstrate that it is up-to-date than to publish such figures.

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The FDA has had a policy calling for balancing risks of over-hurried introduction against those of over-delayed introduction. We urge a more vigorous implementation and expansion in scope of the policy of balancing the risks to health.

Recommendation B6

The FDA should continue and expand its policy of allowing life-saving medicines, as well as others of prime importance, to come into appropriately restricted use (as reflected by restricted labeling) before all safety testing is completed. As a specific example, medicines for life-threatening and crippling conditions can well be made available to elderly patients after safety studies in animals are completed covering all but long-term risks.

We can also accelerate the bringing into use of certain important new medicines by special policies.

Recommendation B7

Active steps should be taken to encourage orderly staged introduction into use of specific important new medicines, as by their use only in selected hospitals, or only by board-qualified specialists, or only in appropriate health maintenance organizations. This is particularly appropriate where both benefits and risks appear high, and not yet fully determined. (Implementation: FDA.)

The doctrine that all new medicines should either be on an investigative basis, or be freely available to all physicians, is no longer in the public interest. The use of any of a variety of schemes for limited introduction can bring certain badly-needed medicines to patients earlier without taking undue risks. (This would require the approval of specially restricted New Drug Applications.) Bringing vital medicines earlier to some patients is worth the complaints which will arise from other patients, pharmacists, and physicians not yet able to use them.

C. THE NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

We have stressed the varied needs for new knowledge: to recognize threats, to gain an understanding of threats essential to planning appropriate studies and experiments, to develop more effective and more rapid tests as guides for regulatory decisions. Basic new knowledge often comes from programs of basic research in the life sciences. Acquisition of immediately urgent new knowledge is frequently but not always supported by the appropriate regulatory agency. What of the vital Federal programs between these extremes?

We have called for stronger Federal support of environmental epidemiology (Recommendation E7). Who is to take this responsibility? We need a rapidly expanding program to secure basic understanding for many chemical threats, for without this we cannot do the work needed. Whose responsibility is this? We need to begin and expand studies where our limited knowledge leaves us unclear as to the source, extent, and reality of potential threats. Who is to do this? We need better and quicker tests, both to improve regulation and enforcement, and to encourage manufacturers in innovation and diversity. Where are these to be developed? We need an overview of the problems of environmental health, combining strong leadership and broad advisory structure. Where is this to be?

We are convinced that the leading role in all these essential actions should be taken by NIEHS (the National Institute of Environmental Health Sciences). To say this does not decrease the responsibility of the regulatory agencies to do their share. It does not call for NIEHS to take over what other Institutes of the National Institutes of Health, basic or mission-oriented, are doing. It does say, however, that the responsibilities for broad oversight, and for

much of the work, should be in a single agency, adequately staffed and funded.

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We turn first to a growing gap, both in our knowledge and in how new knowledge is sought.

Recommendation C1

There is an urgent need for more new knowledge in the areas intermediate between basic biology on the one hand and research closely related to immediate regulatory problems on the other. Unifying leadership for expanded research in this area should continue to come from the National Institute of Environmental Health Sciences, both through intramural research and extramural support by grants or contracts.

As the pressures of day-to-day and week-to-week regulation increase, support by the FDA and the EPA for the gaining of new knowledge has inevitably focused more and more closely on new knowledge that will be directly applicable to regulation in this year or next. This concentration has reduced the support of that part of the search for new knowledge that will be essential to solving the regulatory problems of later years, at a time when such support should instead have been increased.

It is quite impractical to reverse this trend, and equally impractical to look to the support mechanisms of basic biology for the dollars and leadership this intermediate research requires. This leads us to the NIEHS as the natural, and unique, Government agent for this rapidly increasing responsibility.

Recommendation C2

In particular, the NIEHS should *(1) devote a sizable fraction of its effort to research aimed at understanding the mechanisms by which environmental agents cause biological effects (this is necessary if the actual safety tests are to be properly interpreted), and (2) devote a suitable fraction of its effort to the development of simple but valid in-vitro tests of important biological effects shown by a variety of environmental agents.*

The specific tasks set out in this recommendation are important to effective regulatory inquiries and decisions. They are not so immediately related to the regulatory questions of today and tomorrow that the regulatory agencies themselves will in view of their own pressures, support them adequately. NIEHS is the only other agency whose mission properly embraces their accomplishment.

Recommendation C3

Many studies of chemical effects on human health carried out with Federal funds must continue over considerable time. Continuity of such Federal support is absolutely essential. (Implementation: EPA, (NIEHS, and NSF.)

Many research activities can be expanded or contracted with only moderate inefficiencies. This is not true of many studies of chemical effects on human health, where we can learn what we seek only through long-term follow-up of exposed individuals. Special attention must be given to adequate continuity of support for such studies.

Recommendation C4

An environmental epidemiology program should be established in NIEHS. EPA should develop a mechanism for ongoing review, by experts from outside the Government, of the individual steps taken in its environmental epidemiology programs. The adequacy and balance of the combined Federal programs in environmental epidemiology should be reviewed as a whole, with the assistance of the committee proposed in Recommendation E8, every two years.

Effective conduct by a regulatory agency of a program of measuring human reponses to the factors it regulates is difficult even in principle. Both the need for forward-looking elements and the dangers of overinfluence by regulatory stances already taken are serious. We see no presently viable alternatives, either to establishing the forward-looking elements outside of regulatory agencies, or to providing regulatory agencies with needed balance through repeated external contacts. (We note again the importance of strong scientific activity in a regulatory agency in strengthening its ability to meet its main mission.) Clearly NIEHS is the logical place for establishment of the forward-looking elements in environmental epidemiology. As the Federal responsibility for environmental epidemiology is further dispersed, a mechanism for reviewing both adequacy and balance becomes more important.

Recommendation C5

The increasing responsibility of the Federal Government for the development of new techniques for safety testing should be recognized. This will require, for example, increased funding in NIEHS for better techniques of measurement and interpretation of metabolism and excretion of chemicals.

To gain the needed insights, and the new information needed for the regulatory activities of the future, we need new techniques. We need them sooner—and in broader variety—than any mechanism other than Federal support will provide them. This recommendation focuses on two areas of special importance. It is not intended to diminish concern—or funding—for other areas of related importance. It urges work by FDA in a field within its historical scope, and by NIEHS in an area clearly within its domain of responsibility.

Recommendation C6

Federal support should continue to emphasize toxicology and

pharmacology as fields related to all of biological science, particularly as exemplified by NIEHS and by the NIGMS Pharmacology-Toxicology Program.

Once toxicology and pharmacology were mainly (perhaps only) concerned with immediate overt effects of poisons and medicines. Today, we make much deeper and broader inquiries, for example into slowly developing and remote side effects and into the effects of environmental chemicals and medicines on the "natural history" of chronic diseases. To get what we must, it is vital to strengthen and broaden the base of on-going research and training in these areas in more and more effective ways.

Recommendation C7

The NIEHS should be regarded as the focal point and lead agency for research relating to environmental health.

It would be unrealistic to suppose that NIEHS could or should be made to conduct all the work related to Environmental Health Sciences. It would be wasteful, however, to lose the opportunities for coordination that can still be seized.

Recommendation C8

The NIEHS should be instructed to prepare, drawing on other Federal agencies and outside advice, an annual report to the President and Congress on our current state of knowledge about environmental agents and health, on our on-going programs of research and investigations in this area, and on current needs for increased emphasis.

The public, the Congress, and the Executive Branch all need the sort of information that such a report would provide. The thought and effort that would be required to bring it into existence would ensure a broader perspective and more incisive judgment in the conduct of NIEHS activities and programs. (This report should, we believe, exclude medicines from the catagory of environmental agents.)

Recommendation C9

The NIEHS should be responsible, with the aid of outside consultants, for preparing the regular reports recommended above estimating the impacts on human health of exposures to various chemicals.

The preparation of such reports demands much more than the careful collection and statistical evaluation of data. It demands the use of their best judgments by professionals concerned with medicine, epidemiology, and toxicology-pharmacology. Thus, it would not be an appropriate responsibility, for example, of the National Center for Health Statistics. The NIEHS has a large share of the needed skills, and should be effective in attracting the others, on a consultative basis.

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In sum, we would urge that, if our national needs are to be met, that the role of the NIEHS be expanded and more fully recognized in many ways. More specifically:

Recommendation C10

The NIEHS should develop a sense of immediate mission and pattern of operation closer to those now being developed by the National Cancer Institute than to most of the original components of NIH. Its budget should be systematically and vigorously expanded to meet its increasingly recognized responsibilities.

The NIEHS has a sufficiently strong core program to make budgetary increases of 40 percent to 60 percent within a single year both feasible and cost-effective.

D. OTHER NEEDS FOR NEW KNOWLEDGE

Studies at the "kilomouse" level, where many thousands of mice must be carefully observed in order to detect and assess quite infrequently occurring effects, are now of great importance in a number of areas related to chemical threats to health. Problems related to the importance of low doses have accumulated for some time, in the absence of a facility appropriate for studies in animals of very infrequent biological effects, studies which require large numbers of animals in each experiment. Notable among these questions that should be answered is the rate, and even the existence, of cancer production by very low doses of known carcinogens. The facilities of the new National Center for Toxicological Research are especially suited for such kilomouse experiments. Moreover, the existence of such experiments will offer unusual stimulation for the most basic consideration of toxicology. What we should do about substances that, in larger doses, produce cancers depends more on how fast the probability of cancer production decreases as the dose is increased than on any other single uncertainty.

Recommendation D1

The FDA has taken direct management responsibility for the new National Center for Toxicological Research. The functioning of the NCTR should be re-examined every two years by an ad hoc group of experts, mainly from outside the Government but including some of the most able Government scientists and administrators concerned with environmental health, to assess how well FDA is meeting the challenges offered by NCTR's facilities, particularly in view of the importance of the problems that can only be effectively attacked with its facilities, and the opportunity which such a center offers to stimulate new and deeper insights. (Implementation: OST.)

The former chemical warfare facilities at Pine Bluff, Arkansas, offer exceptional possibilities for the

study of animal response to lower doses of various chemicals, for which many animals are required, and for a variety of related work. It would be unfortunate if the work at NCTR did not contribute to some of tomorow's pressing regulatory decisions. It would be even more unfortunate if it did only this, and did not contribute to our knowledge in deeper and more generally useful ways. The best ways to ensure both kinds of contributions seems to the Panel to be (1) to provide funding in approximately the scale and timing already proposed, (2) to emphasize, at NCTR, studies of comparative metabolic behavior, which almost inevitably will be of the greatest importance for low dose problems, and (3) to develop management arrangements, including university sponsorship, that will attract leadership capable of balancing these goals and of evoking deeply creative insights into the problems studied.

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Just as the problems of a few years ahead in the action of environmental chemicals place a heavy responsibility on NIEHS, so too must the problems of the same intermediate scale of time in the action of medicines place a heavy responsibility on other appropriate parts of NIH. The existence in NIGMS of a substantial Pharmacology-Toxicology Program argues strongly for the placement of this responsibility there.

Recommendation D2

The central responsibility for (1) understanding how medicinal chemicals travel through and affect human beings, (2) developing the advanced knowledge and techniques required to make regulation of medicines more effective, and (3) supporting the programs that bring new threats from medication to our attention should be assigned to the National Institute of General Medical Sciences. The National Institutes of Health should organize itself and its facilities to support this central responsibility. It should also expand research and advanced training in clinical pharmacology, both at NIH and in medical schools. (Implementation: HEW.)

The responsibilities considered here include, but go far beyond, the Pharmacology-Toxicology Program of the NIGMS, which supports 12 extremely important centers of training and research in medical schools. One action essential in such a broadening is the development of a research facility concerned with these problems.

Recommendation D3

The National Institutes of Health should study carefully the importance of establishing a research facility, either on its grounds or at a nearby medical institution, both in meeting the responsibilities set out in Recommendation D2 and in strengthening and making more effective the 12 Pharmacology-Toxicology centers now operating with its support. If the study indicates a strong need for such a facility, it should then be established.

There is at this time no single national facility with a clear charter to provide a focal point for the conversion of recent advances in medical science into principles applicable to new medicines, nor to search in an innovative way for more effective means to bring new medicines rapidly and safely into use.

Such a center would have one focus on clinical pharmacology, a field in which a highly crucial shortage of trained people extends across our country. To be effective, it would have to draw in investigators trained in other specialities and set an example for the effective use of mixed teams. A second focus would involve monitoring the use of medicines, both is to be hoped through other epidemiological tools yet to be developed. As we have noted elsewhere, this very important activity, which deserves immediate expansion, ought not to remain wholly a regulatory function. A third focus, responsive to the Federal responsibility for seeing to it that new useful medicines reach the public in a timely way, would be a concern with safety testing in the broadest sense: Seeking ways to streamline present tests, seeking understanding of which newly discovered types of reaction to medicines reveal important threats to health and which do not, seeking new kinds of tests to detect potential dangers to health for which as yet no satisfactory tests exist.

All these activities would make the development—mainly by industry, just as today—of new medicines easier; the center itself would, of course, not be expected either to develop medicines or to test them.

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We already have called, in General Recommendation 15, for strengthening and expanding efforts by the major regulatory agencies to gather immediately applicable new knowledge. Some examples in which we look toward expanded or initiated work would include these. For EPA: (1) Improvement of analytical techniques for measuring pollutants entering or remaining in air, water, and soils, (2) Improved strategies for patterning samples in time and space. For FDA: (1) Systematic inquiry, using the latest and strongest toxicological procedures, into the safety of selected chemicals in common use, including substances naturally occurring in foods, (2) Improved analytical techniques for trace food constituents (contaminants, additives, natural constituents) of potential health risk, (3) Dietary surveys of the U.S. population whose results are more usefully applicable (a) because they apply to subgroups defined by region, ethnicity, religion, age, or sex, and (b) because they show how many consume untypically large amounts of certain foods. (As full advantage as possible should of course be taken of ongoing surveys conducted by other agencies.)

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There are also needs for new knowledge which is most naturally and effectively conducted in other departments of government such as the Departments of Agriculture and Interior.

Recommendation D4

Research and development devoted to pest control methods which reduce the need for pesticides with notable adverse health effects should be markedly expanded. Special emphasis should be given to methods such as the genetic development of host resistance to pests and to large-scale field trials of integrated chemical, biological and cultural pest control methods. (Implementation: Agriculture.)

As we come to recognize more sharply the side effects and other disadvantages of chemical pest control, we must do more to enhance the development of a suitable diversity of biological replacements. Integrated pest control programs will require coordination of producers over a reasonably large geographic area.

Recommendation D5

Special attention should continue to be given to gaining further knowledge of the wanderings of chemicals through the environment, brought about in part because of man's activities. (Implementation: NSF, with cooperation from Interior, Agriculture and HEW.)

Whenever we ask about human exposure—particulary when we ask about the effects on human exposure of technological change or regulatory action—we are again reminded of how little we really know about how chemicals move about.

Recommendation D6

The Department of Agriculture should make careful studies of the observed economic contributions of specific pesticides.

The Panel was rather astonished to find that, while there has been so much discussion of the economic importance of pesticides, there seems to have been quite insufficient study—allowing for replacement by other agents and changes in agricultural practice—of the actual economic consequences of either reduction or elimination of use of specific pesticides.

As various pesticides have been withdrawn from specific uses, there have been many opportunities to investigate, on a sample basis, the actual economic effect of their withdrawal and to compare this with advance estimates. As one step in responding to the recommendation, such comparisons between actual and estimated effects could both improve our procedures of estimation and give appropriate guidance about the reliability of so-far uncheckable estimates.

Recommendation D7

Government-supported research in the areas discussed in Sections C and D should combine expanded programs of university grants and contracts with in-house programs. (Oversight: OST, OMB.)

We know of no more effective route to quality research than the mixed program of government laboratories and peer judgment guide extramural grants and contracts. It will be important to tap the resources of universities and university centers.

Recommendation D8

A coordinating body, associated with the Office of Science and Technology should bear the responsibility of assuring the appropriate utilization of the several Federal scientific resources in behalf of both environmental health in general and crucial regulatory decisions in particular. To this end, it should manage an appropriate contingency fund.

Federal sponsorship of research aimed at identifying and understanding biological hazards of environmental agents is undertaken in several Government agencies. While a distributed effort is desirable, it requires extra attention to assure an optimum distribution of funds and scientific effort. Further, contingencies not uncommonly arise which require additional research (often short-term) in order to fill in important gaps in knowledge before regulatory decisions are made. This coordinating body should exercise control over the expenditure of a modest budget in order to direct this contingency-related research.

E. PRECAUTIONARY STEPS

We need to take a variety of steps intended both to bring possible threats to health from chemicals to our earlier attention and to provide us with more useful information to help us deal with such problems as they arise.

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There is a need for a selective program of study of the consequences of human exposures.

Recommendation E1

The Federal responsibility for a continuing program of study of human reactions to on-going exposures to chemicals, unregulated or regulated, should be recognized. (Implementation: EPA, NIEHS.)

The Federal Government needs to support work on human reactions to those chemicals to which we are routinely exposed, whether unregulated or regulated, where there is evidence of potential health significance.

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We must learn to recognize and focus our attention on those chemicals today most appropriately objects of concern.

Recommendation E2

As an effective means of making feasible monitoring—and where necessary controlling—human exposure to chemicals beyond the uses now regulated, there should be developed "criteria of environmental appearance" that include both the amount produced and the assessed degree of biological activity of a chemical. (Implementation: EPA, NIEHS, NIOSH.)

Such criteria would class together under "high environmental appearance" very poisonous or biologically very active chemicals, even if produced in small quantities, and all chemicals produced in large quantities which are not transformed into other chemicals before reaching our human environment. Chemicals of intermediate biological activity that are produced in intermediate amounts would also fall in this class. It would probably be desirable to establish lists at two or three levels, including in total only a small fraction of all chemicals produced. Attempts should be made to include identifiable chemical constituents of natural products that are of high environmental appearance. The development of such criteria will not be easy.

Recommendation E3

The concept of "criteria of high environmental appearance," whose development has just now been recommended, should be used to guide a selective program of acquiring information on human exposures, which can then be used to identify chemicals that deserve special environmental health attention. This information can, in particular, alert investigators to important possibilities for both environmental epidemiology and laboratory studies. (Implementation: EPA, NIEHS, NIOSH.)

With adequate focusing, a program of collecting data on human exposures, including numbers and ages, could do much to guide further inquiry.

Recommendation E4

The Federal Government should arrange for, supporting if necessary, both safety and efficacy testing for a selected, very restricted set of chemicals of high environmental health attention. (Overlaps with Recommendation F3.) (Implementation: EPA, NIEHS, NIOSH.)

Where the combination of the general character of the chemical and the extent of human exposure is such as to lead to informed unease, there is an obligation to inquire further through special safety and efficacy testing. These tests may either lead us to relax knowledgeably or to recognize a health problem—either state is valuable.

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Both problems in, and opportunities for, observing unexpected and unfavorable reactions to medicines differ from those for other chemicals.

Recommendation E5

Effective systems for reporting adverse reactions to prescription medicines should be implemented on a relatively large scale, beginning with those hospital environments where we know how to do this most effectively, and extending to other hospital environments as fast as practical. At the same time we should try out the use of these systems for the collection of data on the hazards of other chemical substances. (Implementation: FDA and NIGMS (see D2) with cooperation from EPA and NIEHS.)

As Chapter 5 notices, deaths from unfavorable reactions to medication are frequent enough to constitute an important threat to health. Especially since the proper responses to new knowledge from adverse reaction reporting may often not be regulatory in nature, the responsibility for supporting such systems should be assigned according to Recommendation D3.

Pilot work underway under NIEHS sponsorship has already shown that the addition of a not overlong list of questions to a patient's routine medical history can produce valuable information. Clearly such questions should form a part of adverse reaction systems wherever feasible.

Recommendation E6

Adverse reactions to medicines and to environmental chemicals should also be studied in non-hospitalized populations, beginning with well-planned field trials in out-patient clinics and prepaid health care schemes. (Implementation: FDA and NIEHS, with cooperation from EPA and (NIEHS.)

We do not as yet have experience with the contributions that outpatient clinics and various kinds of health maintenance organizations can make to epidemiological surveillance concerning both chemical exposures and adverse reactions to medicines, but we expect their potential contributions to be large. It is time to learn. As soon as we learn this to be true, ti will be time to establish operational systems.

As modes of delivery of medical care shift, reliable studies may need to combine measurement of adverse reactions in hospital and nonhospital environments, in order to have a well-defined body of patients whose adverse reactions are monitored.

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Epidemiological studies of the consequences of exposure are indispensable.

Recommendation E7

Epidemiology oriented to the study of the major chronic diseases and environmental exposures should be strengthened, both by broadening its scientific base and by supplying such crucial tools as a

national death index. (Implementation: EPA, NIEHS, NCHS.)

Epidemiology is another area where we have asked—and must continue to ask—more and more. Both to bring in diverse skills and to increase available manpower, there is an urgent need to bring in people trained and expert in other fields, such as biology, chemistry, and statistics. There is also a need to increase communication between epidemiology and the related disciplines.

In parallel to the strengthening of skill there is a need for a strengthening of available tools. Many studies, for example, depend on the follow-up of groups of people who have experienced different known exposures, over long periods of time. The beginning of such a follow-up is to find whether the people are still alive. As yet there is no national index showing what state holds the record for a specific individual who may have died in a given year. The effort of following up by inquiry in each of 50 separate states, on the chance that each may be the right one, draws unnecessarily on scarce resources, both among epidemiologists and among state offices handling vital records. As one of a variety of improved tools for epidemiology, a national death index is badly needed.

Recommendation E8

A committee on environmental epidemiology should be set up, charged to recognize and bring to the attention of the appropriate Federal agency or agencies, both special opportunities and special needs. (Implementation: EPA, NIEHS, NCI, and NIOSH with oversight by OST.)

Such a committee could be housed in the National Academy of Sciences-Institute of Medicine. Alternatively it could be an interagency committee in which nongovernment epidemiologists and other scientists were both approximately half the membership.

F. ENCOURAGEMENT OF DIVERSITY

Unforeseen new knowledge inevitably leads to the recognition of new threats and calls for immediate action. To have alternative chemicals available for a use makes easier (1) selecting a chemical for a specific use or situation, (2) learning about side effects without keeping the entire population exposed, and (3) taking firm steps of exclusion when substantial threats are recognized. Moreover, exposure to half as much of each of two chemicals is often safer, though sometimes more dangerous, than full exposure to either alone. There are major reasons for encouraging diversity of available chemicals for each use.

The feeling that it is "safer to stick with the old and avoid the new" is natural and has some support. Long-term experience with human exposure is invaluable. It is also true, however, that with better techniques and stronger requirements, both safety and efficacy testing of new chemicals are (and will be) more complete than was that of older ones. (Of course, carefully studied human exposure gives the best information.)

Thus, when we do our best to balance these and other considerations, the overall interests of health and safety still lead us to favor diversity of chemicals for each use.

Recommendation F1

Where a significant element of risk cannot yet be avoided, as is likely to be the case with many, perhaps most, medicines—that is where exposures much larger than those actually used would be dangerous, a carefully limited requirement of "relative efficacy" is justified and should be adopted. A requirement of "clearly better than the best" would often be dangerous and should be considered quite unacceptable. (Implementation: FDA.)

A limited requirement of "relative efficacy" should be understood to mean that, at least for some well-defined subgroups of people or situations, the safety factor offered by the new chemical is at least as high as the second best choice now available—or is at least nearly as high as the only choice now available. The intent of this requirement is to encourage the development, approval, and use of two or more medicines or other chemicals wherever and whenever this does not seriously raise the undertone of risk.

Notice that, in medical practice, two or more medicines are often valuable because of individual differences in response. Some patients may respond better to one medicine, some better to another.

Recommendation F2

Where the known or probable risk is negligible or absent, there is no excuse for any form of requirement of "higher efficacy" or "relative efficacy." (Implementation: FDA, and probably, EPA.)

In the absence of appreciable known threats to safety, the health advantages of diversity are of controlling importance.

Conclusion F3

Where a chemical deserves special environmental health attention (in the sense of Recommendation E3), even though no known or probable risk has been established, there is a legitimate Federal health concern in its efficacy. (Overlaps with Recommendation E4, implementation there.)

This concern does not extend to regulation, so far as health goes, but may properly include (see Recommendation E4) arrangements for—or a support of—an appropriate testing program. (Concern for the protection of the consumer's pocketbook or for truthfulness of claims is a separate matter, outside the scope of this report.)

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Recommendation F4

The FDA and the Department of Commerce should jointly review, every second year the scale and character of research and development on new medicines, and their probable effect on the rate of introduction of valuable new medicines. (Implementation: FDA.)

While the prescription drug industry has continued to be an effective source of valuable new medicines, it will be in the public interest to keep a keen eye on its current planning and on any new trends that may develop. Concern has been expressed for the consequences of the impact of increasingly severe regulation on the effectiveness of the prescription drug industry as a source of valuable new medicines. So far as numbers of research dollars or employment goes, we have seen no evidence of a slowdown in the past decade. Nor have nations subject to different regulatory systems and production incentives introduced a group of important new medicines not available in the United States.

The public importance of the prescription drug industry as a source of effective new medicines is great; the flow of effective new medicines continues to deserve careful watching.

Requirements, both imposed and voluntary, for more careful testing of safety and efficacy have inevitably contributed to an increase in the capital investment needed to bring one new medicine to approval. Moreover, some concern has been expressed about a tendency for smaller firms to disappear. Such trends toward greater concentration are common in other industries; many factors are usually involved. But there seems to be no evidence that such influences have disproportionately affected the amount of significant research.

The most appropriate way for the Federal Government to assist the expansion of research in this area is to speed up the process of testing and approval along the lines recommended above. (Section C)

Recommendation F5

The EPA and the Departments of Commerce and Agriculture should jointly review, every second year, the scale and character of research and development on new pesticides and their probable effect on the rate of introduction of valuable new pesticides. (Implementation: EPA.)

While the pesticide industry has continued to be an effective source of valuable new pesticides, it will be in the public interest to keep a keen eye on the current planning and on any new trends that may develop. The same remarks apply as to Recommendation D4, with perhaps a slightly increased emphasis on the need for following near future changes.

Recommendation F6

The Federal Government should place under continuing review the development of medicines for the rarer life-threatening or crippling diseases, and should be prepared to consider a program of financial support when and if a serious lag in development is manifest. (Implementation: NIH and FDA.)

Much has been said about how the increased cost of research and development has forced medicine developers to cease work on medicines for rare diseases. The Panel was unable to satisfy itself whether this has occurred to any substantial degree nor to what extent it may occur in the near future. Continuing concern and careful observation are surely warranted.

Recommendation F7

Compensation of particular components of industry, and not others, for the economic consequences of appropriate Federal regulatory action is not generally desirable. The Government may wish to consider establishing an over-all policy with respect to the financial impact on individuals and businesses of Government regulatory and incentive programs. (Implementation: Commerce, OMB.)

Federal regulatory and legislative action may create financial benefits or losses for individual businesses. This is so, for example, in legislation for cleaner rivers, and that requiring automobiles with different exhaust components. Regulations affecting drugs, pesticide and other health-related products also do this. Moreover, regulatory action or inaction will create financial impacts on the incomes or assets of individual families as well.

We find no obvious principles of compensation that apply peculiarly in the health area, much less in only part of that area, that do not warrant action equally in many other fields as well. We therefore see no basis for recommending compensation policies for the health area in the absence of a general policy on compensation.

Conclusion F8

Federal Government cooperation with, or subsidization of, industrial development of selected new medicines deserves careful continuing consideration.

Federal participation may well be appropriate in exceptional situations that combine all three of high social value, high initial investment, and inadequate industrial activity. Tomorrow, the scope for Federal participation may widen, perhaps even drastically—or it may stay the same. Similar questions may arise for other classes of chemicals.

Recommendation F9

For the foreseeable future, the development of information concerning the safety of specific new food additives should remain the responsibility of industry, but should be shared effectively between producers and users of additives.

Government has the responsibility for assisting indirectly in this process by assuring that industry collaborations maintained solely for the purpose of testing safety and usefulness of new or existing food additives are not precluded by the threat of antitrust action. (Implementation: Industries concerned, Justice.)

The supply of new and useful food additives is threatened, since the costs of safety testing are now large, especially for substances whose potential annual use is measured in dozens or hundreds of pounds. Both the food industries and the government need to consider the problem creatively, with the intention of finding a solution.

G. COMMUNICATING THE RESULTS AND MEANING OF RECENT SCIENTIFIC FINDINGS

Recommendation G1

More scientists should take an active role in interpreting the results of scientific investigations in ways that are meaningful to the public and to those responsible for regulatory and legislative decisions. (Implementation: Individual scientists competent by training and experience.)

This recommendation is directed to all scientists with appropriate skills, not just to those who were concerned with specific investigations. The scientific community owes this type of interpretation and guidance to the public, provided through enough different voices to ensure considerations that are still a matter of scientific discussion and uncertainty become clearly separated from considerations that are matters of scientific consensus. The public should not ask the sceintists to make the decision. They must, however, insist that the scientists, as a body, indicate clearly both the range of permissible interpretations and the narrower range of reasonable interpretations.

Recommendation G2

Bold, aggressive and continuing steps should be taken collectively by the scientific community, both during and between scientific meetings and through special background sessions, to brief members of the press on factual material relating to new discoveries and issues of public concern involving chemicals and health and where possible to provide balanced interpretations of this material. (Implementation: Scientific societies and associations whose professional fields include or overlap the areas involved.)

The single most effective way for scientists to meet the obligation laid down in Recommendation G1 is through the press. Both national and local groups can, and should, develop explicit mechanisms to meet their responsibility.

Recommendation G3

The usefulness and trustworthiness of scientific results arises from a variety of sources. Without the intervention of organized procedures of reveiw or discussion, neither observed "facts" or interpretations can have their full value. Since many regulatory decisions will inevitably reflect data from recently performed experiments and since public pressures inevitably influence regulatory decisions, the public interest demands that such data of full value be brought to the public and to the decision makers. Consequently, the press, the government and the individual scientists involved should combine to give full value to new data—and to its interpretation—by ensuring its review or discussion before it is taken to the public or made the basis of regulatory action.

Any discoverer is tempted to believe his discovery is without defects and has earth-shaking consequences. Scientists are not insulated from such temptation. Even though they may be sure about the absence of defects and the size of the consequences, however, they owe to the public a dedication to encouraging deliberate review.

Recommendation G4

In addition to simply providing information, the press should undertake special efforts at public education on the scientific basis for regulation and on certain special issues surrounding it. (Implementation: Individual members of the press, including editors.)

The task set for the press in this recommendation is not an easy one. Nor is it one to be accomplished at once.

The Panel believes, however, that a responsible press can be effective, in various media, with both immediate and continuing action. As it does this, the press will serve the nation well.

Recommendation G5

The press, as it meets its responsibility for balanced coverage, should do all it can to combine any publication of tentative, unreviewed scientific findings with a significant representation of the views of other scientists competent to comment. (Implementation: Individual members of the press, including editors.)

This again asks something not easy of accomplishment, but especially if the scientists respond to Recommendations G1 and G2, the press can do much to meet one of its major responsibilities. Much can be done, all the way from originating reporter to final editor. The news values of reports of differing expert views may

not seem as great as those of "scare stories", but experience shows that responsible elements of the press have used the former effectively.

H. FURTHER RECOMMENDATIONS

Recommendation H1

Federal regulatory agencies should be responsible for ensuring that all safety and efficacy data included in approved applications or petitions are made available to the public. Safety data in unapproved applications or petitions should also be made available within a suitable period of time. (Implementation: FDA, EPA, Agriculture.)

Safety and efficacy data which served as the basis for approval of an applications or petitions could be of fully available for public review, and the public interest will be served by making these data routinely accessible. However, there are legitimate proprietary reasons for not publicly disclosing the performance of new medicines while they are in the investigative stage. So long as we continue to depend on private industry as the primary source of new medicines, protecting these interests in developing new medicines aids the public welfare.

The safety data in unapproved applications or petitions could be of considerable toxicological interest and appropriate mechanisms should be developed to make them available to the scientific community.

One argument raised against the release of safety and/or efficacy information is that the original performer's investment is greatly degraded in value if others can use the same information in their own applications for approval. The potential degrading of investment—and its ultimate negative effect on the production of new effective chemicals—are clear, but various schemes have been proposed which would adequately remove the threat to the original investment without restricting access to the information. Similar considerations apply to other classes of chemicals.

Recommendation H2

Labeling of ingredients in cosmetics, household products and other unregulated materials coming in contact with the public should identify significant chemical components of known health consequences. (Implementation: EPA, in consultation with FDA and NIH, the Congress.)

This necessarily goes beyond the labeling of "active ingredients" and "hazardous substances," which, though useful, is too limited for reasons explored in the text of this report. A sweeping requirement, not proposed here, to list in all products no matter how complex, every ingredient no matter how trivial, would encounter serious practical difficulties. The labeling of all ingredients of "known health consequences" as determined by the appropriate regulatory agencies for products not now regulated would be both practical and protective.

Procedures should be developed for making still more detailed information about product composition available to allergists and other physicians, perhaps through the network of poison control centers. Means of making this information accessible to the consumer should be sought.

The Panel considers that the provision of information is complementary to regulation. This should be done whenever practicable and useful. Beneficial components as well as potentially hazardous ones should be noted, and the Panel favors, wherever possible, ingredient statements which indicate the function of the components. The responsible Government agencies should proceed to exercise as much imagination as possible in developing new methods of labeling and product information.

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Staged introduction for purposes of safety is naturally attractive, but the practical details of identification and surveillance of those exposed limit its usefulness for this purpose.

Recommendation H3

Schemes for staged introduction of chemicals other than prescription medicines, should not be required or requested by the Government for purposes of monitoring safety, unless and until significant new ideas and techniques are found that make staged introduction feasible and effective for this purpose. (Implementation: FDA.)

This Panel has given careful consideration to a variety of ways in which staged introduction of new chemicals other than prescription medicines might contribute to the health of the public, either directly or through more effective epidemiological surveillance. While the Panel had hoped to be able to find and recommend satisfactory schemes or mechanisms, it found none. The introduction of pesticides to one use after another, often a very wise practice, is not a staged introduction in the sense of this recommendation.

I. INDEX TO IMPLEMENTATION ASSIGNMENTS

The Congress is urged to implement Recommendations A3 and H2.

The Department of Agriculture is urged to implement General Recommendations 1 and Recommendations D4 to D6, F5 and H1.

The Department of Commerce is urged to implement Recommendations F4, F5, and F7.

The Environmental Protection Agency (EPA) is urged to implement General Recommendations 1, 2, 3, 4, 5, 8, 15, 18, Recommendations A1 to A3, B1 (B4?), B5, C4, D4, D5, E1 to E8, F2, and H1 to H3.

The Food and Drug Administration (FDA) is urged to implement General

Recommendations 1, 2, 3, 4, 5, 8, 15, 18, Recommendations A1 to A3, B1 to B7, C3, E5, E6, F1, F2, F4, F6, and H1 to H3.

The Department of Health, Education, and Welfare (HEW) is urged to implement General Recommendations 8, 10, 11, 12, 13, 16, 17, 18, 19, and 23 and Recommendations D2 and D5, and encourage implementation of Recommendations assigned to FDA, NCHS, NIEHS, NIGMS, NIH and NIOSH.

The Department of the Interior is urged to implement General Recommendation 19 and Recommendation D5.

The National Bureau of Standards is urged to implement Recommendation E4.

The National Center for Health Statistics (NCHS) is urged to implement Recommendation E7.

The National Cancer Institute (NCI) is urged to implement General Recommendation 14 and Recommendations C3, E7, and E8.

The National Institute of Environmental Health Sciences (NIEHS) is urged to implement General Recommendation 18, Recommendations C1 to C10, and E1 to E8.

The National Institute of General Medical Sciences (NIGMS) is urged to implement General Recommendation 18, Recommendations C6, E5 and E6.

The National Institutes of Health (NIH) is urged to implement Recommendations D2, D3, F6 and F8 and to encourage implementation of the recommendations assigned to NIEHS and NIGMS.

The National Institute for Occupational Safety and Health (NIOSH) is urged to implement Recommendations C3, E2 to E4 and E8.

The National Science Foundation (NSF) is urged to implement Recommendation D5.

The Office of Management and Budget (OMB) is urged generally to support the implementation, by the relevant agencies, of all recommendations, and specifically to implement Recommendations C3, D7, F7, F8.

The Office of Science and Technology (OST), in some cases through the chairmanship of the Federal Council of Science and Technology, is urged to implement General Recommendations 16, 19, and 23, Recommendations D1, D3, D7, E8, and F8.

The Department of Transportation is urged to implement General Recommendation 11.

Individual scientists, competent by training and experience, are urged to implement Recommendation G1.

Scientific societies and associations in appropriate fields are urged to implement Recommendation G2.

Individual members of the press, including editors, are urged to implement Recommendations G3 and G4.

CHAPTER 4

GENERAL SUMMARY

A. CHEMICAL EXPOSURES

What is the role of chemicals in our attempts to protect and advance human health? Are we concerned only with the new chemicals to which attention had been called in recent years? Hardly.

Man has been exposed to chemicals in the environment since time immemorial. Plant, animal and human life have always depended on natural transformations continuously recycling huge quantities of chemical substances through the biosphere. Photochemical smog based on the organic chemicals added to the atmosphere from pine forests, a myriad of mycotoxins, the botulinus toxin, and the "red tide" occasionally seen off our coasts—all these have been with man since prehistoric time.

Man has long been aware that the continuing risk of illness and death cannot be completely avoided by any known substance or mode of existence. He, nevertheless, has persistently utilized chemicals in his attempts to extend life, to minimize ill health, and to reduce both the risks and the labor associated with getting his daily bread. Man has so persisted even while knowing that no single chemical substance, natural or artificial, can be guaranteed harmless to him.

Some of his chemical interventions have brought overwhelmingly beneficial effects. Were 1901 death rates still prevailing, nearly 50 million of this nation's 200 million citizens would now be dead. A significant portion of these lives were saved by suitable uses of chemicals. At the other extreme some uses of chemical interventions, often incidental and unanticipated, were almost wholly undesirable in their effect on man and his environment.

With increasing industrialization, new chemicals have been contributed to the environment. Both new and old chemicals have increased in amount to meet the needs of growing populations and to assist in improving living standards. Opportunities for utilizing a myriad of naturally occurring and synthetically manufactured chemical substances have increased with almost similar speed. The rate of production of petrochemicals from oil and natural gas has been quadrupling every ten years. Large quantities of such inorganic chemicals as chlorine, sulfuric acid and Portland cement are now made. (See Chapter 9, "Industrial Chemicals," for further detail.) The total for manufactured consumer organic chemicals now corresponds to 500 pounds per capita in a population of 200 million!

What adverse impacts do uses of chemicals exercise on man's health today? The firmest basis for answering this question is to begin from estimates of death linked to chemical causes. The available data, which are detailed in chapters 5 and 14 below, reveal that most deaths linked to chemical impact occur primarily because of individuals' own actions, as in smoking cigarettes and in the abuse of alcohol and illicit drugs. A substantial segment of deaths may indeed be linked to dietary choices. A second substantial group of causes depend on unknown chemical factors in the environment, which initiate or promote cancer—possibly in combination with viruses, genetic factors, etc. The third, and smallest, substantial group includes deaths that arise from adverse reactions to medication and from recognized environmental exposures—such as common air pollution and exposures of workers on their jobs.

Action to reduce the first, and largest, group of chemically linked deaths would require society to make difficult choices. Changing the behavior of millions of individuals in their choice of diets, in their decisions to smoke cigarettes or consume alcohol could not be simple. Reducing the deaths associated with unknown risks faces no such difficulties: it requires chiefly a vigorous and persistent attempt to increase our scientific knowledge. Only in this way can we hope to locate and then to strike at the causes of such deaths. (Recommendations to improve such knowledge appear above.)

Adverse reactions to medication are not yet well enough studied, and we have recommended appropriate action. Community air pollution and occupational exposures are being actively attacked. There remain a large variety of chemical exposures which produce few deaths, an uncertain amount of ill-health, but much public concern.

Today's concern about chemicals and health is stimulated by more than the revelations that modern toxicology is making about both the chemicals in natural foods and the chemicals made by man. A large part of this concern comes from the rapid expansion of the latter, which can reach man and the environment through a remarkably complex labyrinth.

Fortunately, many industrial chemicals do not reach the general public. Acrylonitrile, for example, is shipped in sealed tank cars to plants for conversion to synthetic fibers. Textile mills may then weave carpets from the fibers. The carpet buyer will not be exposed to acrylonitrile, only to the synthetic fiber, although some occupational exposures must still be guarded against.

Most of us, by contrast, are at least

somewhat exposed to the gaseous propellants used in spray cans and to the chemicals used to make detergents effective. Further, every paint solvent evaporates into the atmosphere and every detergent drains through sewage systems to lakes, rivers, or oceans. Man is exposed directly to such materials both as they are used and as he uses air and water. Still other groups of chemicals, the drugs and food additives, are intended for primary use by man. Agricultural chemicals reach man to the extent that residues persist in his food.

Thus man's manufacture, distribution, use and disposition of both artificial and naturally-occurring substances can lead to new and possibly significant hazards.

B. THE APPROACH TO PUBLIC POLICY

Amid this vast array of exposures both to naturally occurring toxicants and to chemicals that man produces in increasing volume, what is a proper perspective for public policy on health? Each day's policy must, we believe, turn upon as careful and close a judgment as we can draw from the continuing expansion of knowledge—knowledge of what benefits and risks are associated with chemicals today. That judgment cannot rest simply on the basis of an arbitrary preference for the natural or for the synthetic; for the new or for the old; for the creations of man's technological genius or for the accidents of what chemicals become preferred in certain cultures. We must instead judge by the current values and needs of the American people, a judgment to be closely considered, reviewed and reconsidered as knowledge accumulates and conditions change.

New chemicals, not already in use or mass production, are specially easy to review and regulate. Our procedures have taken advantage of this, and it is with new products that our existing regulatory mechanisms operate most effectively. Chemicals, natural and synthetic, already widely used may also deserve our careful attention, but almost certainly on a selective basis. Here we have not yet adequately developed the procedures we need to guard ourselves from possible threats—and, of course, we have often not acquired the knowledge needed to recognize these threats.

To enforce effective regulation, and to develop principles that can guide regulatory bodies, two kinds of comparisons must constantly be made. One concerns risks and benefits. The more certain a chemical is to save lives the more willing we should be to accept dangers in its use. And the more readily it could be replaced by something harmless—either by nothing at all, or by a very safe product—the more willing we are to deny a new chemical entry into use. The enormous gray area between these extremes is one that regulatory bodies confront constantly. There are no simple principles to guide that choice. But we recognize that the better our scientific knowledge becomes, and the more clearly the public understands this dilemma of choice, the more satisfactory regulatory decisions will be.

Precautionary destruction of foods or beverages because of suspected contamination, or a restriction against the use of some drugs or food additives, does not merely ensure against harm. It also shifts usage to other foods, beverages, drugs, or food additives in ways not always predictable or advantageous. Thus, removal of an implied hazard may entail a hazard of its own, and always restricts freedom of choice.

A second comparison must constantly be made—by scientists, by regulators, and by members of the public—as they assess the soundness of regulation. This is a comparison of two knowledges. One is the knowledge afforded by human experience with chemicals in widespread and prolonged human use. (Such usage typically is so unsystematic and unfocused that untoward effects may be hidden or masked by the complexity, or ignored.) The other knowledge is that following from careful scientific inquiry, in laboratories and/or controlled experimentation. (Such knowledge is also often partial, sometimes rests on observations on organisms whose reactions may not parallel those in man; and rarely measures long-term consequences, particularly in those occurring only in man.) We expect both citizens and regulators to recognize the worth, and the limitations, of each kind of knowledge. And, as the recommendations above indicate, we would urge substantial commitments to needed research as a way to moderate this dilemma by increasing our knowledge of both kinds.

With the aid of scientific understanding, sound medical practice, and public health and preventive measures, the threat of acute infectious bacterial disease has been virtually eliminated as a cause of death in this country. Several chronic degenerative diseases, including cancer, are now the most prominent causes of death. Some, notably lung cancer, are rising to epidemic proportions.

United States mortality rates in the past two decades reveal a recent attenuation—even a reversal—of the previous declining trends. Among the causes of this excess mortality or early death one finds cigarette smoking, dietary patterns, and other voluntary social habits implicated as major or even overwhelming contributing influences.

The American public, in part through the legislative process, has paid a great deal of attention to uncertain or implied risks while ignoring certain large and unequivocal risks to health.

C. KNOWLEDGE FOR DECISION

Knowledge is preeminently important for good decisions. While some

environmental chemical agents seem clear causes of ill-health, we must readily admit that detailed and systematic knowledge in this area lags far behind the levels of quantification and reliability accessible to contemporary science. The acquisition of knowledge may be expensive, but the absence of knowledge may be much more expensive. When considering a decision and faced with incomplete and insufficient information, the administrative and legislative processes tend strongly to the side of a conservative prudence in the name of health. There are several notable examples, in which Congress has replaced scientific discretion by statutory mandates to "protect" human health inflexibly. The Delaney Amendment to the Food, Drug, and Cosmetic Act is probably the best known. It is not clear that such absolute restrictions always achieve the desired protection of human health. At times they may even work against it. (The rigidly prescribed standards for automobile exhaust emissions, mandated by the Clean Air Act Amendments of 1970 raise a clear issue to what extent have resources been diverted from other and perhaps clearer contributions to health.)

There is a further cost of ignorance, one associated with wrongful or injudicious decisions. Regulatory decisions in the name of protection of health and environmental integrity often have expensive consequences. They typically obligate large expenditures of money, they are meant to remain in effect over long periods of time, and they typically rearrange large areas of our lives. Given the large impact of these consequences, the decisions producing them deserve the best foundation possible. Errors in regulatory judgments can be extraordinarily expensive, in human and monetary terms.

Finally, there is another cost implication. Public and private expenditures in the name of human health in the United States are large, yet they must always be limited. Expenditures made for, or as a consequence of, regulatory activity are not available to be made toward health in any other ways. We should always be sure that what we purchase in the way of extra health through regulation does in fact have that benefit, since we thereby remove the option of making the same expenditure toward health in some other way.

Knowledge about environmental concentrations of chemicals and firm information on the probabilities of human exposures to them are not generally available. Except for therapeutic drugs, there is a major accounting problem to be solved if one is even to begin to appreciate the routes and quantities distributed. Knowledge about inherent biological effects is much less available than is generally appreciated. The technology to produce and distribute chemicals has outstripped the ability to understand their pathways in the environment and their biological effects.

What kinds of knowledge are needed? A wide spectrum of different kinds of information is necessary. At one extreme is an aggregate of fundamental information about disease processes in general as well as about those that may derive from exposure to environmental agents. We generally are better informed about the details of acute toxicity and acute disease processes than we are for chronic ones. There are many chronic degenerative diseases for which we know little about causes or mechanisms.

There is, in addition, a clear need for more research on an intermediate level, applying sound scientific insight and the current tools of scientific investigation toward the understanding of how chemical agents act on biological systems and toward the utilization of this knowledge. In the past, our evaluation of such actions has often been confined to "testing" using relatively unsophisticated techniques of classical toxicology. Clearly the improvement of testing depends on utilization of the newest concepts and methods developed in pharmacologic and biochemical research. Much of our knowledge of the health effects of chemical exposures in man must come from population group studies made by epidemiologists oriented toward the major chronic diseases and the major environmental exposures. If we look to epidemiology for the amount of new knowledge and guidance we require, we must encourage this orientation and the inclusion of a wider variety of scientists in this field. We must, moreover, face the need for assured support over several years for those studies that cannot be done any faster. We must give epidemiologists better access to relevant data, for example through the institution of a National Death Index. Such questions as "has a specific person exposed long ago to some possible cause of ill health in fact died? What state holds his death certificate?" might be more quickly answered with the aid of the index.

D. ACQUIRING KNOWLEDGE AND ACTING ON IT

Having declared the importance of knowledge what do we as a society do to acquire it?

For new regulated chemical products, such as food additives, pesticides and therapeutic drugs, the government generally relies on the manufacturer and developer of the product to underwrite or perform all necessary research. The results of this work are used by the government in its regulatory decision-making.

There remain, even here, some areas where there is no clear responsibility for research and information. Prominent among these is the problem of old decisions versus new scientific insight or information. For products once approved or certified, there exists little or no incentive for either the manufacturer or the government regulator to consider

and seek out new (and sometimes discomforting) scientific information.

Knowledge about utility or benefit is typically as deficient as information about risk or hazard. Judgments about risks versus benefits or about penalties to be paid for restrictions on use appear particularly difficult to exercise in the face of this ignorance.

Although it is clear that in selected cases such new or additional information on safety or utility would be of great value, it has to be gathered selectively. Otherwise we would drown in a sea of unmanageable, and largely, valueless data. The mechanisms to select what is needed, especially in advance of data acquisition efforts, are not obvious.

E. HOW REGULATION IS—AND SHOULD BE—DONE

The regulatory outcome cannot be treated symptomatically. Any serious consideration of the patterns and products of regulation in behalf of health must include a serious examination of how regulation is done.

Risk-benefit and cost-benefit analyses have become commonplace concepts. In the litany of many administrators and public officials such concepts are included as desirable elements in regulatory decision-making. In fact they are desirable; yet the practicality of rigorous risk-benefit and cost-benefit analyses in any detailed sense may be quite circumscribed. What is both desirable and attainable is the concept of balanced decisions. Balancing should be done in a way to account for all of the important considerations and implications of each decision. Balancing should include the several important points of view espoused by both those with general as well as special interests. Regulatory decisions are always difficult decisions. It is clear that, no matter what the outcome, they can never satisfy all parties. Explicit examination and candid explanation are essential if the decisions are to be understood and be credible.

We have relied too long on isolated or apparently isolated administrative decision-makers. Balanced decision implies a broad audience of constituents, and a broadly based group of participants. The rewards and penalties for reulatory decision-making have traditionally resided strongly in the direction of narrowly-based considerations of protection alone. True balancing has generally not been encouraged and, at times, has been actively discouraged. It is not to the benefit of the American people to sustain this pattern.

The administrative agency responsible for regulatory decisions should be fully and appropriately equipped with the resources for arriving at balanced judgments. It must be careful, and able, to separate the scientific issues requiring only skilled professional judgments from those broader value determinations in which a more diverse assemblage of backgrounds and perspectives should be involved. The pattern of bolstering the administrator's own judgment by a competent, high-level advisory panel appears to have great merit. This pattern, traditional in many Western European countries, deserves consideration.

Health related regulatory judgments will necessarily reflect a changing scientific base. This fact dictates flexibility and discretion in the decision process rather than rigidity and legislatively-mandated actions.

Habitual reliance on appeal mechanisms for ultimate regulatory decisions is unwise. Avenues of appeal should clearly be available. Yet, the continuous expectation that an administrator's decision will be supplanted by later administrative and judicial appeals renders the primary process perfunctory, and undermines its credibility. Most or all of the elements of appeal processes are clearly desirable and generally are in the direction of broadening the base of the decision. Thus, it would be logical to incorporate such institutions as the external advisory board, the public hearing, broad information gathering, and public information into the original decision process and to lead to relatively less reliance on the appeal processes by making the decision less vulnerable to subsequent reversal upon appeal.

Balanced, well supported decisions deserve and need clear and explicit presentation to the public in order to improve their understanding, acceptance, and the prospects for balanced decisions in the future. A number of mechanisms, public, private, and professional, need to be improved, expanded, or added to achieve this goal.

F. WHERE DO WE STAND?

The panel is confident that we can cope capably with out natural and man-altered chemical environment if we reorder our priorities soundly with the help of more and better data, improve regulatory mechanisms, strive for more balanced decisions, and achieve a higher level of public understanding and support.

Looking ahead, we give primary emphasis to gaining new knowledge, all the way from principles of chemical action to details of impacts of particular chemicals. As reliable knowledge of chemical impacts is expanded, regulatory agencies become able to monitor for safety more promptly and exactly. They thereby achieve a better balance between losses because improved chemicals are unavailable and losses that arise because specific chemicals are unwisely used. Finally, as basic knowledge expands and as new insights are uncovered by Federal and other non-profit research enterprises and by individual firms through their research activities, ways to produce safer and more efficacious chemicals will be dis-

covered. Given the vast market that has in the past snapped up new life-saving medicines, and other chemicals of high social value, private firms have major incentives to continue developing ever more socially useful products.

Our recommendations for advancing scientific knowledge of chemical impacts are central because they would lead those who use, regulate or produce chemicals to act more prudently. Our recommendations for stimulating creation of new and more desirable chemicals rely primarily on the private market given the incentives that are already and effectively operative. But we would add Federal research for intermediate biological and chemical investigation, plus Federal support for certain rare health needs of high social value. We rely on the combination of direct Federal regulation (to rule unsafe products off the market) and of private incentives (to create new products) that together will replace existing products by ones of greater, or more certain, safety.

CHAPTER 5

PERSPECTIVES ON HEALTH

A. INTRODUCTION

To deal effectively with chemicals and health we must do as good a job of looking at health as we can—asking what state it is in and what threats of what sizes can be identified. We are far from being able to do this as well as we would like. The crucial difficulty is that we have not learned how to measure health in any direct or satisfactory way.

"Good health" is usually regarded as absence of disease, while a "disease" is anything which disturbs or destroys "good health." Some forms if ill health are comparatively easy to specify, but instances of even these are not carefully collected and counted, in part perhaps because of cost, in part certainly because we have not wanted to know.

Deaths are, however, counted with considerable care and completeness. In spite of inaccuracies and other shortcomings of death certificates, today they provide the major data for measuring health and sickness, either for all our people or part of them, and for measuring changes over time.

When we look at deaths as a measure of ill health, we learn the main facts about such diseases as cancer. We will, however, miss the truth about such diseases as arthritis, which are often serious or crippling for many years, yet are almost never recorded by physicians as the cause of death. We must recognize this bias and take it seriously. Indeed, it is hard, once we have faced its existence, not to say that there is an urgent need for much better information about non-fatal kinds of ill-health. For the present, though, we can learn much by looking at deaths, either simply or with considerable care. It is fair to say that, if we give due attention to such matters as the nature of a disease, the accuracy of its diagnosis, and the patterns of its distribution, that counts of deaths can be used to give very sensitive and accurate gages of health for identifiable groups of people.

Our problem is to assess risks and benefits to health from various chemicals. Both the way the threat affects health and the way we assess its importance are far from direct. No one dies labeled: "I died from cigarette smoking." In relatively few cases can we say, "This person died from this threat." Indirect yet sometimes very strong evidence may, however, make it relatively clear how many deaths should be linked to that threat.

A particular threat may cause death in quite different ways. Abuse of alcohol, for example, causes both death from cirrhosis of the liver and death from drunken driving causing a fatal auto accident. Cigarette smoking appears to increase deaths from many causes; we consider about a dozen and a half below in Appendix C. Most threats are the apparent cause of more than one disease. Most diseases would exist, and kill, if any one chemical threat were removed. All deaths involve a combination of causes, and might be postponed by avoiding any one of them—as when a roadside pedestrian is killed by a drunken driver, something that might have been avoided by any one of (1) providing sidewalks, (2) preventing drunken persons from driving cars, (3) keeping that person from becoming drunk.

Our information about the relation of threats, through diseases, to deaths is often indirect. Take cigarette smoking as an example. It is a typically long-term chemical exposure from which no immediate health effect is evident to the individual. Animal studies have been disappointing and difficult to interpret. Epidemiologic studies, however, involving long-term observations of smokers and non-smokers have been quite definitive.

Repeated studies made at various times and in various countries show that deaths from many causes are more frequent for cigarette smokers. Moreover, those who once smoked but later stopped show declining death rates as the period of ex-smoking grows longer. The evidence is diverse in kind, broad in place and time, extensive in amount, and certainly by the mid-1960s, had convinced scientists that cigarette smoking was having serious adverse effects on health. Today there is proportionately more evidence, and no basis for weakening the conclusion. For all of this, we can never be sure that any individual death is linked to cigarette smoking—though there are groups of deaths of which we can be reasonably confident that 90-odd percent are so linked. Similar studies have been made of other chemical threats, but thus far on a much smaller scale.

B. HISTORY, BOTH OF DEATHS AND OF OUR KNOWLEDGE

If we look at deaths at the beginning of this century and then at deaths today, we see quite different pictures—more different than most of us have realized. In the early years of this century, the leading causes of death were communicable diseases, led by pneumonia and tuberculosis, each about 10 percent of all deaths. Diseases of the heart caused 8 percent of the deaths in the U.S. and

cancer caused less than 4 percent. By 1960 influenza and pneumonia were the only infectious diseases ranking in the top 10 causes of death (together less than 4 percent in 1969), while diseases of the heart were responsible for over 38 percent of all deaths, and cancer for over 15 percent. These increases were substantially greater than could be accounted for by the decreases in deaths from infectious diseases.

What has this meant to length of life? For U.S. females at any specified age between 2 and 80, about 30 percent more years of further life are expected for 1968 death rates as compared with 1901 death rates. For U.S. males the improvement is much smaller (4 percent to 23 percent over this range of ages).

The extent of early death has changed as follows:

Dying in the first year of life

	Females (Percent)	Males (Percent)
1901	12.7	15.2
1968	2.3	2.2

Dying in the two first years

	Females (Percent)	Males (Percent)
1901	15.9	19.6
1968	2.5	2.3

The ratios of expected years of further life (that under 1968 death rates divided by that for 1901 death rates) are as follows:

Age from which to continue	Ratio of expected continuing life	
	Females	Males
(1)	(1.37)	(1.34)
2	1.33	1.23
about 20	1.31	1.17
about 40	1.30	1.12
about 60	1.32	1.04
80	1.29	1.23
(85)	(1.17)	(1.23)

Clearly the improvement for females is both large and (when described in this way) quite constant, while the improvement for males is relatively disappointing. Clearly there has been a very great improvement due largely to control of the infections which affected young children.

How much of this improvement in health, as measured by the postponement of death, has been due to chemicals—medicines, water purifiers, food preservatives, insecticides, etc.—would be extremely difficult to assess. The value of antibiotics in treating infectious diseases has been enormous. Yet antibiotics and other medicines cannot be given full credit, for some combination of improved sanitation, better nutrition and other known and unknown factors were causing marked reductions in infectious diseases before antibiotics were discovered. These visible improvements have been made less by increase in certain diseases that affect older adults.

The increases in deaths from diseases of the heart and cancer, already noticed, accompanied the introduction and steady growth of cigarette smoking. This started early in this century and was taken up by many more men than women. The use of other forms of tobacco decreased as cigarette smoking increased steadily from 1900 to 1960. The simultaneous increases in cigarette smoking and in deaths from cancer and heart disease might have been coincidence, since large changes in patterns of living and working were also occurring.

Starting in the 1950s, a number of large-scale epidemiologic studies were undertaken in Britain, Canada and the United States. Some were prospective studies in which groups with different smoking habits were identified at the start of the study and followed over a long enough period of years to make clear the relationships between different levels (and kinds) of smoking and specific causes of death.

Another piece of evidence, of a rather different character, is at least as striking. We have noted the great improvement in length of life since 1900, even for men. This has, until recently, been reflected in a steady decrease in the total death rate for men of each age. In the last decade, this decrease has first halted and then reversed. When a search was made for causes of death that were increasing, many were found to be causes that are significantly linked to cigarette smoking, alcohol abuse, or air pollution. (See Appendix B for details). These facts are a clear warning of the increasing importance of such threats.

C. CURRENT PERCENTAGES OF DEATHS

Exhibit 5-1 displays a variety of known and surmised threats to health from chemicals in terms of these categories and the percentage of all deaths (in 1967) that can be reasonably linked to each.

The type of attribution involved in this linkage is illustrated in Exhibit 5-2 (for the complete forms of this and related tables, see the exhibits of Appendix C).

The main disadvantage of looking at—and thinking about—raw percentages of deaths is that this summary takes no account of whether deaths occur early or late, yet we are all more concerned about early deaths than late ones. We shall soon see that, while making reasonable adjustments for age at death changes the picture somewhat, it does not change either the overall impression made by such a display or the conclusions to be drawn. After all, large percentages in Exhibit 5-1 are so many times larger than the small ones, that doubling some and halving others has little effect.

This also means that the rather approximate character of the numbers of linked deaths is not a matter of serious concern. When doublings and halvings do not affect our views and conclusions, the numbers involved do not need to be known with high precision.

EXHIBIT 5-1

NUMBERS AND PERCENTAGES OF DEATHS IN 1967 LINKED TO VARIOUS CHEMICAL FACTORS

(100% = total deaths from all causes = 1,850,000)

Numbers of deaths linked to factor in 1967	Percentage of all deaths in 1967 linked to factor	Factor	Adjusted percentages of death allowing for age at which death occurs[1]	
			Adjustment A	Adjustment B
300,000	17	Cigarette smoking	13	8
56,000	3	Alcohol abuse[2]	6	9
0 to 400,000	0 to 20	Dietary composition	0 to 13	0 to 8
60,000 to 150,000	3 to 8	Unknown factors which act as initiators & promoters of cancer	3 to 7	2 to 5
75,000	4	Adverse reactions to medication	1.4	1.2
10,000	0.6	Narcotic and addictive drugs	1.2	1.2
9,000	0.5	Community air pollution	0.3	0.1
9,000	0.5	Airborne particles (occupational)	0.3	0.1
4,600	0.25	Suicides involving chemicals	0.5	0.7
2,800	0.15	Coffee drinking (bladder cancer)	0.1	0.03
2,200	0.01	Accidents with chemicals	0.25	0.35
150	0.01	Oral contraceptives	0.02	0.04

[1] See Appendix D (page 167) for definitions and discussion.

[2] Includes accidental deaths in which alcohol was a contributor as well as diseases primarily linked to alcohol.

D. ADJUSTMENTS FOR AGES AT DEATH

If we choose to make allowance for age at death, counting early deaths as more important, we can do this in many ways. Adjustment A (Exhibit 5-1) takes the importance of a death at a specified age as proportional to the average number of years of remaining life at that age. Adjustment B does something quite similar, but counts only that part of continuing life before age 65. As we might expect, the latter adjustment produces a bigger effect than the former essentially in every case.

Deaths linked to cigarette smoking fall from 17 percent to an adjusted value of 9 percent in the extreme case. Deaths linked to alcohol abuse rise from 3 percent to an adjusted value of 8 percent. What was a 5-to-1 ratio (deaths linked to cigarette smoking compared with those linked to alcohol abuse) changes to a 1-to-1 ratio. This is a substantial change.

The major relationships in the display, however, and hence the conclusions we draw from them as to

EXHIBIT 5-2

HOW THE NUMBER OF LINKED DEATHS IS APPROACHED. PARTIAL EXAMPLE FOR 1967 DEATHS OF MALES LINKED TO CIGARETTE SMOKING

(for detail see Appendix C)

Cause of cancer	Proportion associated with smoking[1]	Male deaths U.S. 1967	Linked Male deaths
Cancer of lung	.86	45,383	39,000
Cancer of larynx	.68	2,468	1,700
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-------	---	-----	-----
Cancer, other	.18	54,132	9,700
Subtotal			(62,000)
Arteriosclerotic heart disease	.27	345,154	93,000
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-------	---	-----	-----
Other circulatory	.44	17,752	8,000
Subtotal			129,000
Bronchitis and emphysema	.72	21,507	15,500
Stomach and duodenal ulcers	.47	6,793	3,200
Cirrhosis of liver	.40	17,903	7,200
Influenza and pneumonia	.16	31,904	5,100
TOTAL			222,000

[1] Calculated from the results of the summary paper in the W.H.O. Chronicle Vol. 24, No. 8, 1970, assuming that 50 percent of males smoke. Note: The tendency for heavy smokers to also be heavy drinkers (and heavy coffee drinkers) has usually not been allowed for in the studies on which these figures are based.

what threats are most important are not seriously affected by these changes. In this instance, the important message is simple—the story told by raw percentages of deaths is essentially correct. We needed to look at the effects of adjustment; in this case we learned that adjustment did NOT change the story.

E. THREATS DIVIDED BY TYPE

The number of deaths involved is an important aspect of a threat, but not the only one. Other aspects of the threat, particularly whether it comes from the victim's actions or those of others are also important.

The most helpful classification of threats from chemicals rests on answers to a number of important questions:

- does the threat to health accompany a larger benefit to health?
- is one's exposure primarily the result of one's own actions, or those of others?
- if of others, are they primarily (for exposed persons) those of an individual or organization, or are they those of many people or organizations?
- are the consequences known, at least in broad terms, or unknown? (Was this true at the time of exposure?)

From the answers to these questions, threats can be divided into five classes in order of necessary public concern, namely:

- as yet unremovable byproducts of health-preserving or health-restoring actions.
- primarily own actions with known consequences (e.g., by cigarette smoking).
- unknown risks (e.g., coffee drinking).
- primarily collective actions of others with generally known consequences.
- primarily individual actions of others with at least broadly known consequences.

In general, we feel greater public concern (1) as we move down this list, and (2) as there are judged to be more people who might be alive had the threat been removed. The percentages of linked deaths are presented in Exhibit 5-3 in relation to the voluntary or involuntary nature of exposure, the known or unknown nature of the risk is offset by potential health benefit. (For simplicity, these are unadjusted percentages.)

Let us consider this exhibit in terms of the relative concern with which we should view the results. At

EXHIBIT 5-3

RECOGNIZED THREATS ARRAYED BOTH BY THEIR SIZE (% OF DEATHS IN 1967) AND BY THE CHARACTER OF THE ACTIONS INVOLVED

Deaths linked to by-products of health favoring actions	Deaths linked to one's own actions or choices	Deaths linked to unknown sources	Deaths linked to collective actions of others	Deaths linked to individual[1] actions of others
	Cigarette smoking (17%)			
Adverse reactions to medication (4%)	Dietary composition (0 to 20%)	Unknown promoters & initiators of cancer (3 to 8%)		
	Alcohol abuse (1/5%)			Alcohol abuse (1.5%)
			Air pollution (0.5%)	Airborne particles (0.5%)
	Narcotic & addicting drugs (0.3%)			Narcotic & addicting drugs (0.3%)
	Suicides (0.25%)			
	Coffee (0.15%)			
	Accidents involving chemicals (0.05%)			Accidents involving chemicals (0.05%)
Oral Contraceptives (0.01%), .				
	Swordfish (0 to 0.0001%)			
	DTT[2] (0 to 0.00001%)			

[1] Individual organizations and firms as well as individual persons.

[2] The effects of accumulated body burden of DDT are unknown; the range given is recognized acute poisoning which accounts for at most a small fraction of a death per year. No deaths traceable to the intended uses of DDT have been recorded.

the head of our list, we find drunken driving, unknown initiators and promoters of cancer, and cigarette smoking, followed rather closely by the effects (still quite uncertain in size) of choice of dietary composition (as it affects the frequency of coronary heart disease and other cardiovascular heart disease). On balance, drunken driving seems the least tolerable of these, while cigarette smoking accounts for the largest number of deaths.

In most cases it is easy to place a threat in a single category (in a single column) and be generally correct. The outstanding exception is alcohol abuse, where drunken drivers kill both themselves and others. (The same is true of other accidents.) The exact division, fortunately, is not important, since both percentages must be relatively large.

After these, in some order, we will have to pay attention to threats from air pollution, illicit drug abuse, diseases due to air-borne particles, and adverse reactions to medication.

Far down the list, we find such threats as oral contraceptives, swordfish, and DDT, which have recently received much public attention. Notice first, that the known threat from oral contraceptives is more than balanced by the lives saved (avoidance of complications from pregnancy); second, that the threat from cigarette smoking is about one hundred thousand times as large as that from swordfish, and third, that the threat from choice of dietary composition is perhaps two million times as that from DDT.

F. FURTHER INFORMATION

The reader who would like more detail about recent changes in mortality should read Appendix A. The reader who would like to see from another angle what has been discussed above in terms of linked deaths should read Appendix B, as should those concerned with the mechanisms of Adjustments A and B in Exhibit 5-1. The reader who wishes to see more detail about the numbers and assumptions used in finding the number of linked deaths should read Appendix C.

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SECTION II — Types of Chemical Exposures

CHAPTER 6

CHEMICALS TO IMPROVE HUMAN HEALTH

INTRODUCTION

Much has been written in the past few years as commentary on invention, innovation and development of pharmaceutical products useful as aids in the treatment of human disease. Much of what has been written has been prompted by a continuing argument over the character, the blessings and the hazards of the pharmaceutical manufacturing industry as well as of the products of this part of the private sector. A HEW Task Force on Prescription Drugs published a series of reports in 1968 on a number of aspects of prescription products.[1] This was reviewed by an additional task force in 1969.[2]

Most reviews of purposeful drugs and the drug industry take note of the fact that chemical agents as adjuncts to therapy of disease are very old in origin. There is thus a very long legacy of the use of plant materials and extracts, other natural products, preparations of various metals and their salts, etc., for relief of disease or at least of its overt manifestations. Most of these early drug "discoveries" were empirical in the true sense and there was little foundation in biological understanding of disease processes and in their mechanisms.

By contrast, the search for the pharmaceutical opportunities in therapy on a systematic basis and the development of a drug industry are very recent endeavors. The pace of drug development has mushroomed within the last generation owing, to a variety of different contributing factors. One was the advance of a number of disciplines to the point where purposeful drug development could become a scientific reality Pathology, biochemistry, microbiology, and physiology each contributed a rapidly accumulating fund of knowledge of the basic processes of diseases. Although these were not complete, they did afford enough insight to permit speculation and experimentation into possible routes of therapeutic intervention. Chemistry and especially organic chemistry developed to the point where synthesis, modification and analysis of drug substances could be done deliberately and in a controlled fashion. As new drug research has evolved, organic medicinal chemistry and pharmacology have loomed large as perhaps the major contributors to this field.

The development of a drug industry in the United States appears to have been spurred on by the threat of curtailment of imported substances from abroad by each of the two World Wars. As has been suggested, ". . . the modern drug industry was born almost overnight."[3] Drugs, their development, the methods used in their testing and evaluation, and the industry which underwrites them are all under serious and critical examination and the subject of intensive review by both the public and professionals.[1 3 4 5]

TYPES

The subject of this chapter is therapeutic drugs—drugs used intentionally in therapy of human disease. It excludes narcotic and addicting substances used without presumed therapeutic benefit in medical practice. Therapeutic drugs include biological preparations (such as vaccines), naturally derived chemical substances (such as morphine and digitalis), and synthetic chemical substances. The majority are the latter type. Drugs are categorized in various ways. Proprietary drugs are those products which are commonly promoted and sold directly to the consumer. Ethical drugs are those preparations which are generally marketed through the medical profession as an intermediary. Ethical drugs, in turn, are divided between prescription drugs (sold to the public only with a prescription) and over-the-counter drugs (sold without a prescription but often on the advice of a physician).

The distinction among these classes is sometimes blurred. Most of the present discussion concerns prescription drugs.

BENEFITS

There is no questioning the fact that pharmaceutical products have been enormous assets in the therapy and prevention of human disease. The evolution of antibiotic materials following upon the understanding of the bacterial causation of much of infective disease was clearly due in large part to the introduction of new drugs and biologicals. Life expectancy at birth has increased from 62.9 to 70.8 years between 1940 (the time just prior to the introduction of antibiotics) and 1970.

It is perhaps worth reviewing a few of these specific drug benefits according to a convenient classification (a) curative, (b) corrective (pharmacodynamic), (c) palliative, (d) substitutive, and (e) preventive (prophylactic).

Curative Drugs—Practically every drug that exerts a curative action is a chemotherapeutic agent directed toward the treatment of infectious disease. In the 1930's, there were only a few examples of drugs that were at

all effective in the treatment of infectious disease. The outstanding agents in this class were quinine in the treatment of malaria, and the heavy metals in the treatment of syphilis. In the case of the latter drugs, treatment was long and protracted and the patient was almost as susceptible to the noxious effects of the drug as was the parasite. The attitude of medical scientists was one of pessimism that safe and effective drugs for the treatment of infectious diseases could be developed. It was felt at that time that metabolic processes in the host and invading organisms were so similar that any agent that was toxic to a pathogenic organism would exert a similar deleterious effect on the host. Thus, it was not surprising that the claims that Prontosil, the first of the sulfonamides, was highly toxic to a fairly wide range of pathogenic microorganisms, without having a significant deleterious effect on the host, were greeted with skepticism. Indeed, close to five years elapsed between the discovery of this chemotherapeutic agent and its wide use in the United States.

After sulfanilamide was recognized to be the active portion of the Prontosil rubrum molecule (an azo dye), a vast number of congeners were synthesized. This study of structure-activity relationship resulted in the availability of a wide variety of sulfonamide derivatives that were much less toxic and equally or more effective than the parent compound, sulfanilamide. In fact, the superiority of the current sulfonamide derivatives over the first examples employed in chemotherapy (sulfanilamide, sulfapyridine, sulfathiazole) is so great that the three drugs named are no longer available in the United States for use as chemotherapeutic agents (except for a single claim for sulfapyridine), not because of inefficacy, but because of the greatly higher incidence of toxic side effects. It is interesting that the drugs responsible for one of the greatest advances in chemotherapy have been discarded because of the superiority of related substances developed later. At the time of their introduction, they were hailed as wonder drugs. Despite their untoward side effects, some of which were serious enough to cause an occasional death, the initial three were universally employed and changed the concept of the treatment of infectious disease.

In the late 1930s, it would not have been predicted that the sulfonamides would be superseded by another group of chemotherapeutic agents, the antibiotics. However, with the discovery of streptomycin and penicillin, followed by the tetracyclines, chloramphenicol and a wide variety of other antibiotics, including the semi-synthetic penicillins and the cephalosporins, the sulfonamides became second choice drugs in all but a few infectious diseases. The family of antibiotics greatly increased the number of infectious diseases that were susceptible to drug therapy. Their toxicity varies greatly from one antibiotic to another. Therefore, despite this striking advance, a consideration of relative risks and benefits in the use of antibiotic drugs is still with us. For example, chloramphenicol, a highly effective antibiotic with a broad spectrum of activity, is now reserved for the treatment of those potentially fatal diseases for which it is highly specific, e.g. typhoid fever. Streptomycin, another antibiotic with a broad spectrum of activity, must be used with caution because of the dangers of disturbances in vestibular and auditory functions. Yet it would be clearly unwise to discard these antibiotics because under certain circumstances, despite their toxic potential, they are still the drugs of choice.

With the advent of our family of modern chemotherapeutic agents, infectious disease is no longer the terrifying threat that it was in the past. Bacterial septicemias and meningitides that were once considered to be 100 percent fatal can now be cured with regularity. Although the great majority of the drugs used are relatively safe, one would not hesitate to employ a fairly toxic agent where the benefit is life versus death.

The chemotherapy of tuberculosis is one of the brightest chapters in the treatment of infectious disease. Until the discovery of streptomycin, there was no drug to which the tubercle bacillus was susceptible. The incidence of the disease was falling, but still high and there was little more than rest that could be prescribed for the tuberculosis patient in the hope that resistance to the organism would eventually be developed by the host. Streptomycin proved to be a highly effective tuberculocidal agent. However, the organism rapidly developed resistance to the antibiotic and it soon became evident that treatment with streptomycin had to be reserved for critical situations. However, continued effort in this field has led to the introduction of a substantial number of tuberculocidal or tuberculostatic drugs which, when given in combination, can halt progress of the disease, prevent the development of resistance, and eventually effect a cure.

Although other factors, as yet not understood, have led to major decreases in tuberculosis incidence rates, chemotherapy has nevertheless saved many lives.

Venereal disease (which includes syphilis and gonorrhea as the major diseases) underwent a rapid and dramatic reduction in incidence, in residual complications and in mortality during the 1940s and 1950s. Their results reflect the combination of effective drugs for treatment and vigorous control and educational programs. In 1919 there were 113 cases of syphilis per 100,000 population reported to the Public Health Service. This incidence rose to 213 in 1963 and to 447 per 100,000 in 1943 and fell to 68 per 100,000 in 1960, and has since risen again. Yet, syphilis as a cause of death has been reduced dramatically. In 1900, 12 persons in each 100,000 died from the cause. In 1960, the rate was 1.7.[6] The infant mortal-

ity due to this disease was 140.3 deaths per 100,000 live births in 1916, compared to 0.7 in 1959.[6]

Corrective (Pharmacodynamic) Drugs—This group of drugs acts directly on the host to correct physiological or biochemical abnormalities. None is capable of curing a disease, but they can reverse pathological processes to the extent that the patient can enjoy a long and productive life. The list of pharmacodynamic agents that have been introduced within the last few decades is long. It includes new general anesthetics, hypnotics, anticonvulsants, local anesthetics, neuromuscular-blocking agents, drugs for Parkinson's disease, antipsychotics, antidepressants, antihistamines, antiarrhythmic drugs, antihypertensive agents, hypoglycemic agents, diuretics, antiinflammatory agents, drugs for the treatment of gout, etc. Some of the diseases for which these drugs are employed can be fatal, others crippling, and still others only discomforting. All of the classes of drugs mentioned above have toxic potentials. One of the oldest and most familiar agents, used since the eighteenth century, is digitalis, still the mainstay in the treatment of heart failure. Originally employed as a crude Galenical preparation, the chemically pure glycosides of the plant (Foxglove) are now available.

Digitalis has the lowest range of safety of any of our commonly used agents. If the therapeutic dose is exceeded by 50 percent, death can result. However, since it has been with us for close to two centuries, the physician has gained respect for both its efficacy and toxicity. No effective substitute has been discovered during this long period of time.

One of the major contributions in pharmacotherapy has been the introduction of drugs for the treatment of certain types of mental illness, including psychoses. Mental illness has probably always been present.

In the United States its importance, at least as measured in terms of reported incidence and of numbers of patients occupying beds in prolonged-care hospitals, increased steadily until 1955. The introduction of tranquilizing and antidepressant drugs combined with other changes in therapy and changes in attitudes toward mental illness coincided with a decline in state mental hospital populations from 558,000 in 1955 to 338,592 in 1970 as shown in Exhibit 6-1. Prior to 1954, the average inpatient hospital stay was eight years, but by 1968, the average stay had been reduced to 1.4 years.[7]

A number of factors were operating in this picture. The apparent rise in the incidence of mental illness and of hospitalization because of it (which exceeded the rate of growth in the population) were probably reflections of changing patterns of life, increasing urbanization, recognition of patterns of illness which previously had been ignored, and changing concepts of treatment. The dramatic shift in the patterns of therapy which began in 1955, ambulatory treatment instead of prolonged in-patient care, earlier release from hospitals, etc., seem to have been due at least in part to the introduction of new chemicals—new psychotropic agents. The first of these drugs to be of proven value was reserpine. This was largely replaced by the phenothiazines of which chlorpromazine is the prototype drug. Finally, it must be noticed that statistics do not reveal the entire story of this success. As a result of new avenues for treatment of mental patients, the atmosphere in mental hospitals has changed markedly. Patients who were restricted to maximum security wards are now permitted freedom. Formerly incommunicative patients have become cooperative and are candidates for group psychotherapy. The duration of hospitalization has been greatly reduced and inmates who would have represented a financial responsibility for the state for their lifetime have been returned to their homes and after to their jobs.

One of the outstanding advances of the past decade has occurred in the treatment of gout. Gout, which can be a life-threatening disease, is due to a biochemical defect in the production of uric acid or a physiologic defect in its excretion. The disease may cause death from renal failure as a result of the deposition of urate stones in the kidney. Other individuals may be crippled from gouty arthritis. Two classes of drugs have been developed for the control of gout: uricosuric agents that lower blood levels by enhancing urinary excretion (such as probenecid), and another type of compound that blocks the formation of uric acid (such as allopurinol). Gout is still not a curable disease. However, control over its manifestations and its ultimate prognosis have been improved through the use of these drugs and patients who have sustained a limited amount of renal damage can benefit to the extent of complete remission.

Antihypertensive drugs have established themselves as effective agents in changing the course of progressive hypertensive disease although they are by no means curative. A large number of these agents are available and they are used singly or in combination. When used early in the course of hypertension, they can prevent the pathological changes that occur in blood vessels and eventually result in malignant hypertension. In the case of malignant hypertension and hypertensive crises, blood pressure can be reduced and the life expectancy of the patient prolonged.

Major advances have been made in the area of diuretic drug therapy. These drugs are widely employed for the treatment of the edema of heart failure and the ascites of hepatic cirrhosis, where mobilization of edema fluid is of extreme importance, and where, the use of diuretics greatly reduces the necessity for rigid salt restriction in these patients and thus allows life to be much more comfortable. Only a few decades ago organic mercurials were the only available effective agents and had to be given by injection. This class of diuretic agents had to be used with

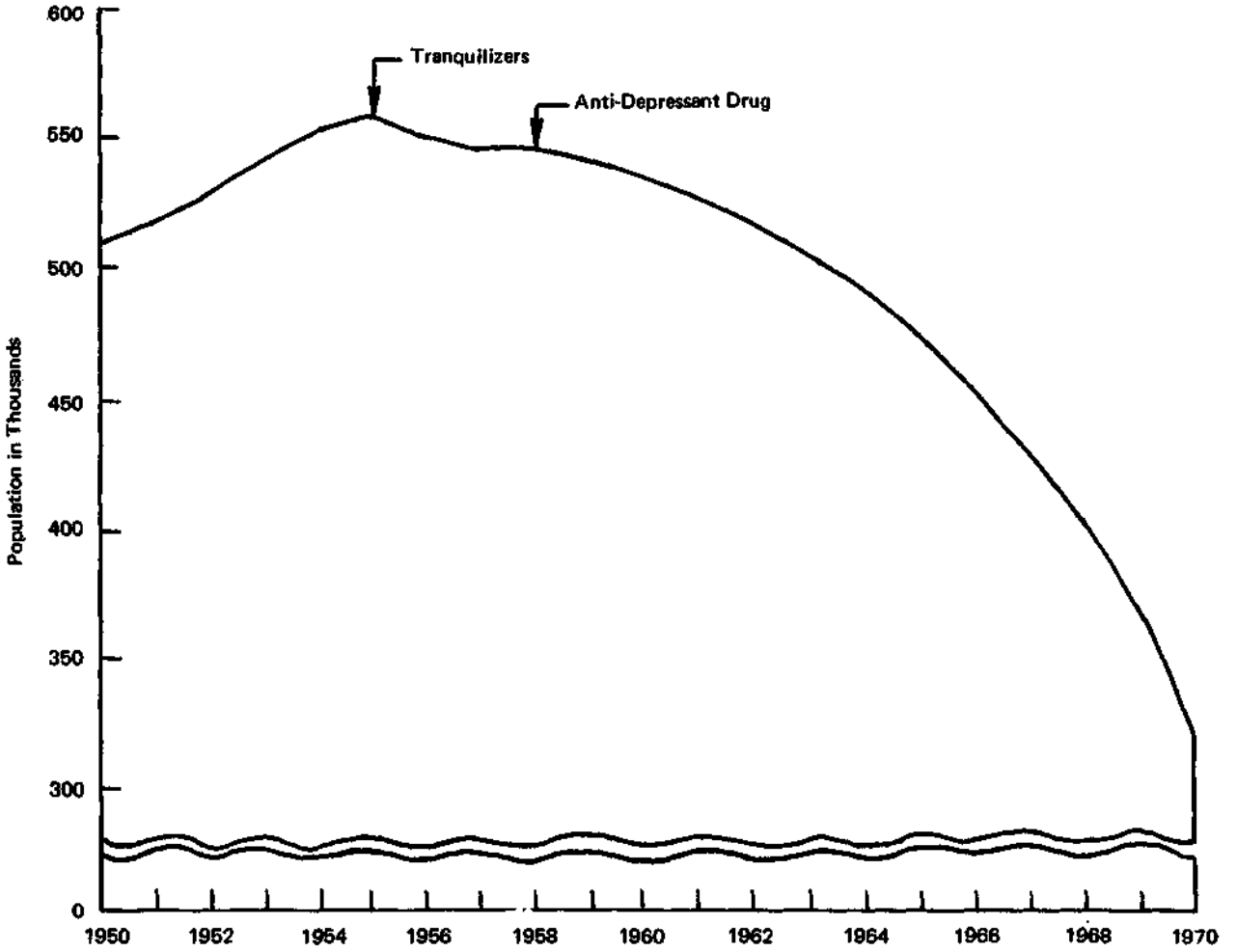
caution since, if not rapidly excreted, they can exert toxic effects on the kidney. Nevertheless, they were the definitive therapy of the time. Tremendous strides in the development of highly effective and safe oral diuretics have been made in the past ten years. Representative examples are chlorothiazide, furosemide and ethacrynic acid.

Palliative Drugs—Palliative drugs contribute to the comfort of a patient without curing any biochemical or physiological abnormality. Physicians may have a feeling of inadequacy when they can offer only palliative therapy, but even in this instance drugs can make a major contribution, since palliation is a very important function of the physician. Following pallinative (the relief of pain), functional, social, and economic rehabilitation may be achieved. Some palliative drugs are used for the relief of pain in minimal disorders such as simple headache, myositis, menstrual discomfort, etc. while others block the pain of major disease such as cancer.

Drug cure of malignancy has been achieved only for rare types of that disease. In certain instances (for example, acute leukemia) life expectancy has been increased from a few months to three or more years. In other situations, patients may enjoy remission of symptoms and live a productive life even though life expectancy and the natural history of the disease are essentially unchanged.

Although not always regarded as such, methadone can be a palliative drug in the treatment of narcotics addiction. When methadone therapy is properly supervised, the rehabiliatation of the addict can be

EXHIBIT 6-1
DECLINE IN STATE MENTAL HOSPITAL POPULATION
(1950-1970)



extensive despite the fact that his addicted state is in no way influenced.

Substitutive Drugs—Substitutive drugs comprise natural or synthetic substances for the treatment of diseases associated with their deficiency in the organism. Many of these are endocrine or hormonal substances. Many deficiency states can be treated effectively to correct the manifestations of the deficiency. For example, a hypothyroid patient can be returned to a normal state with the use of thyroid extract or more recently of synthetic, chemically-pure thyroid hormones. The patient with adrenal insufficiency was at one time given little chance for survival. Now, however, with the availability of synthetic corticosteroids he can lead a long and productive life.

Preventive (Prophylactic) Drugs—Prophylactic drugs are those used to prevent the occurrence of a disease process. The best known perhaps are those biological preparations prepared specifically to counter infectious disease. Anti-poliomyelitis vaccine and smallpox vaccine are two well-known examples. Poliomyelitis has been the subject of a recent study aimed at estimating the monetary benefits which have accrued from the development and use of polio vaccines. These estimates were based on an expected incidence of polio of 36,000 cases per year and a mean dollar loss of $1,350 per case (reflecting both direct treatment costs and losses in earning power from death and disability.)[8]

The prophylactic use of penicillin to prevent recurrences of rheumatic fever is commonplace. Many patients with recurrent pyelonephritis are placed on drug therapy for an indefinite period of time in order to protect them from life-threatening recurrent renal infection.

HAZARDS

Any discussion concerning hazards of drugs has to take into consideration the balance of risk vs. benefit expected in their use. Toxic effects which may be acceptable for a drug to treat cancer or a life-threatening infection are hardly acceptable in a drug to relieve relatively mild conditions.

The toxicity associated with administration of a drug can be predictable or unpredictable. Among the predictable toxicities are those which represent an extension of the pharmacological action of a drug which was observed in animal studies. For instance, a drug that lowers blood pressure may lower the blood pressure too far in some individuals. A drug which decreases ability of the blood to clot may in some individuals have too great an effect and thus cause bleeding. However there are other varieties of toxicity which cannot be predicted, either from the known pharmacology of the drug or from animal studies. Allergic reactions such as bone marrow depression or severe skin eruptions are examples. Other toxicities may be caused by some unique factor in a particular patient so that he would respond differently to a drug than the average patient. The predictable toxic effects can usually be observed when the drug is given to a relatively small human population whereas unpredictable toxic effects can often only be detected after the drug has been given to a large number of people with different genetic backgrounds.

In recent years a number of hazards of drug therapy have attracted special attention.

1. Drug Interactions

Patients who receive more than one drug at the same time may experience an unexpected adverse reaction. This is now a particularly important problem because of the large number of drugs which are likely to be prescribed simultaneously. Fortunately pharmacological studies have pointed out the mechanism for some of the more harmful drug interactions, whose possible occurrence is now predictable. Not only is it possible for a drug to influence the action of another drug but is has recently been found that exposure of humans to certain environmental chemicals, i.e., insecticides, atmospheric pollutants and cigarette smoking, may influence drug action. This new type of interaction must be explored to determine its full significance in drug therapy.

2. Long Term Safety and Efficacy

Concern has been expressed about the safety and efficacy of new drugs which have to be given for prolonged periods. This is especially the case for a drug which has a novel mode of action. An example of such a drug is L-dopa which must be given for years to treat patients with Parkinson's disease. Pharmaceutical firms were required by the FDA to conduct special clinical studies after the drug's NDA approval in order to evaluate long-term safety and efficacy. Questions have also been raised about the long-term safety and efficacy of drugs which have been used for a number of years. Recently such concern has been expressed about the widely used oral anti-diabetic agent, tolbutamide. Although the results of the long-term study with tolbutamide (five to eight years) are disputed, an increased number of deaths were observed in diabetic patients receiving the drug over those receiving insulin or on diet alone.

3. Safety of Drugs in Infants and Children

Information exists that the young, especially newborn infants, are more sensitive than adults to adverse effects of drugs. An example is brain damage which may result when certain sulfa drugs are given to the newborn (kernicterus). However, much of these data about potential toxicity of drugs in the young come from studies carried out in young animals. A number of anticonvulsants and antibiotics have a warning in the information to physicians (labeling) against their use in children below a certain age. The difficulty in establishing criteria for safety and effi-

cacy of pediatric drugs has led to the use of the term "therapeutic orphan" to describe children who can't receive certain medication for lack of adequate testing.

4. Teratology (Birth Defects)

The thalidomide tragedy in the early 1960's caused great concern about the possibility of drugs inducing congenital malformations. Except for certain potent drugs used to treat cancer, there is no clear evidence that drugs in general use cause birth defects. One of the most difficult problems is determining the significance of malformations produced in experimental animals when high doses of a drug are given in terms of possible risk in humans. Such a commonly used drug as aspirin causes malformations when given under experimental conditions to rats. In view of the serious nature of birth defects, labeling of almost all new drugs, and for that matter many old ones, carries a warning about the use in pregnancy, especially during the first three months.

5. Carcinogenic Threat

Perhaps the greatest concern about toxicity in recent years has been the implied threat based upon animal experiments which suggests that a new drug, or for that matter even old drugs, may have carcinogenic effects. Our scientific knowledge for the interpretation of results of such animal tests in terms of potential harm is still most primitive. The long latency period in humans (ten or more years) from the time of exposure to an observed effect makes it difficult to establish a cause-and-effect relationship in man. Some of the problems faced in establishing safety of drugs in terms of possible carcinogenic risk are illustrated by the following examples.

a) *Oral contraceptives.* The finding of breast tumors in beagle dogs after prolonged exposure to certain steroid oral contraceptives has led to the removal of these drugs from medical use until the nature of these tumors is determined and the possible carcinogenic risk to human females is established. It will require many years of monitoring a large fraction of the women exposed to these particular contraceptives to determine whether an increased incidence of breast tumors will occur. The legitimate concern that new oral contraceptives may cause cancer may be having a dampening effect on research on chemical methods for population control.

b) *Estrogens.* These compounds have long been known to cause cancer in mice, but in the thirty years of their wide use in human beings no such effect had been reported until recently. Evidence is strongly suggestive that young women whose mothers had taken a synthetic estrogen, diethylstilbestrol, in large doses during pregnancy were at increased risk of developing vaginal cancer. This observation is under intensive study to determine the extent of the problem and the mechanisms involved.

c) *The anti-tuberculosis drug, isoniazid,* has been shown to be carcinogenic in experimental animals when given in high doses. Despite the wide use of isoniazid for protracted periods of treatment, there is no evidence thus far that the drug has produced malignant lesions in man.

6. Mutagenic Risk

There is increased concern that chemicals in our environment can be mutagenic. Tests in animals and bacteria are now being carried out with many substances, but the relevance of such tests in terms of human risk is not known. Recently, certain phenothiazines have been shown to be mutagenic in some of these tests. It would indeed be unfortunate to lose the use of these valuable drugs for the treatment of mental disease before the meaning of this observation is understood. There is some question that routine testing of all new drugs for mutagenicity will be required. This would present an entirely new set of problems in evaluating the safety of new as well as old drugs.

TRENDS

1. Drug Industry

The total value of domestic and worldwide shipments of U.S. drug manufactuers is currently around $7 billion/year. Exhibit 6-2 shows the value of manufacturers' shipments of all drugs from 1939 onward. It also includes estimated projections through 1980.

In the 30-year period from 1939 to 1969, drug industry shipments increased over 1,600 percent. Note in particular the very large expansion during and after World War II. The data in Exhibit 2 show that the pharmaceutical preparations segment of the industry accounts for 90 percent of the value of the manufactuers' shipments for any one year while medicinals and botanicals account for about 7 percent and biological 3 percent. The 1980 projection of $16.1 billion is based on a continuing average annual growth rate of 9 percent.

The U.S. pharmaceutical industry has repeatedly been singled out as one of the most research intensive of American industries.[10] There have been several reviews of the research and development investments in the drug industry. Figures completed by both the National Science Foundation and the Pharmaceutical Manufacturers Association have demonstrated that investments in research and development by members of the pharmaceutical industry have risen with time.[11] According to PMA figures R&D expenditures have risen during the 20-year period of 1950 to 1970 from $39 million to $616 million, an increase of over 1,500 percent or an annual rate of increase of 14.8 percent. In a similar period, the value of manufacturer's shipments of pharmaceuticals rose from $1.45 billion in 1951 to an estimated $6.8 billion in 1970, an increase of 480 percent or 7.4 percent annually. (These research and development investments will be considered later in Chapters 12 and 13 and Appendix C which contain

EXHIBIT 6-2

MANUFACTURERS SHIPMENTS OF COMPONENT PARTS OF DRUG INDUSTRY
(Millions)

Year	(S.I.C. 283) Drug Industry	(S.I.C. 2834) Pharmaceutical Preparations Industry[3]	(S.I.C. 2833) Medicinals and Botanicals Industry[3]	(S.I.C. 2831) Biologicals Preparations Industry[3]
1939	$ 386	$ 338	$ 29	$ 19
1947	1,197	941	218	38
1954	2,048	1,700	281	67
1958	2,977	2,592	322	64
1959	3,129	2,692	369	68
1960	3,214	2,772	351	91
1961	3,312	2,927	284	101
1962	3,541	3,142	296	103
1963	3,716	3,314	306	96
1964	3,922	3,571	253	98
1965	4,403	4,050	256	97
1966	4,825	4,432	285	108
1967	5,301	4,696	445	160
1968	5,645	5,008	N.A.	N.A.
1969	6,228	5,529	N.A.	N.A.
1970	6,790(4)	6,020[1]	N.A.	N.A.
1971	7,400[1]	6,556[1]	N.A.	N.A.
1972	8,065[1]	7,140[1]	N.A.	N.A.
1975	10,444[2]	.....	.....	.....
1980	16,070[2]	.....	.....	.....

Source: U.S. Department of Commerce, Census of Manufacturers
[1] Estimate by U.S. Department of Commerce, B.D.S.A. Outlook 1972
[2] Estimate based on 9 percent average annual growth rate.
Note: These data include the value of both primary and small amounts of secondary products for each industry.
[3] As categorized by the Federal Government.(9) Pharmaceutical Preparations Industry primarily engaged in manufacturing or processing drugs into pharmaceutical preparation for human or veterinary use. Medicinals and Botanicals Industry primarily engaged in manufacture of bulk medicinal organic and inorganic chemicals and in processing bulk botanical drugs and herbs. Biologicals Preparations Industry primarily engaged in the production of bacterial and virus vaccines, toxoids and analogous products, serums, plasmas and blood derivatives.

discussions of economic aspects of research and development and regulation.)

The intermediate output of this system can be thought of as the number of applications submitted to the Food and Drug Administration to market a new drug entity. (The regulatory laws of the FDA since 1938 have required the filing and the approval of a New Drug Application—an NDA—before permission is granted to introduce a new drug into interstate commerce. Since 1962, a prospective manufacturer has been required to submit to the FDA an application for approval of a new drug under investigation—an IND—before clinical experimentation prior to an NDA.) Exhibit 6-3 lists the number of NDA's submitted to the FDA for approval between 1950 and 1970 together with the number of NDA's approval each year.

It is instructive to examine the ultimate output by examining the totality of new products introduced into the market place. Exhibit 6-3 lists these totals for the years 1950 to 1970. There is an obvious peaking of new products during the middle 1950's followed by a decline. In Exhibit 6-4 the totals are further divided into types of new drug entity according to four classes—new single chemicals, duplicate products, combination products, and new dosage forms.

2. Aspects of Drug Development

Although society has benefited from drugs and from pharmaceutical development, it is also probably true that there has been some degree of over-expectation and over-promotion. For one thing, the public concerned with drug development, nor has it been privy to much of the technical detail. Pharmaceutical manufacturers traditionally have promoted their products directly to physicians. The notion of risk along with benefit for therapeutic drugs has generally not been a common public image until, perhaps, recent years. From time to time cracks have appeared in what was otherwise

EXHIBIT 6-3

Calendar Year	Original NDA Receipts[1]	NDA's Approved
1950	359	245
1951	319	236
1952	325	244
1953	303	243
1954	400	278
1955	501	357
1956	415	295
1057	420	246
1958	353	219
1959	378	257
1960	322	188
1961	245	137
1962	222	86
1963	192	70
1964	160	70
1965	221	50
1966	216	50
1967	128	74
1968	108	56
1969	60	39
1970	87	53

SOURCE: NDA & IND Data Supplied by FDA
New Chemical Entities - Paul de Haen, Inc., N.Y., N.Y.

[1] Initial submission of original NDA's only

thought of as a watertight and totally beneficial system of drug development.*

One thoughtful observer has noted that the "...pharmaceutical revolution has produced both public benefit and public concern. Active chemicals inevitably carry with them the capacity for both good and harm."[3]

There has been a sizable effort in recent years to ascertain whether or not the large number of new drug products placed on the market represent a true net benefit. The argu-

*It is interesting that it has been under the climate of crises concerning new drugs that major revisions in the Food, Drug and Cosmetic Act have been passed by Congress. In 1938, this basic drug regulatory structure was born folowing on a series of deaths due to an inappropriate and untested solvent used in the drug, sulfanilimide. The 1962 drug amendments came in the wake of the thalidomide disaster. Insert Exhibits 5 and 6

EXHIBIT 6-4

NUMBER OF NEW DRUGS MARKETED IN U.S. FROM 1950 – 1971

	1950	'51	'52	'53	'54	'55	'56	'57	'58	'59	'60	'61	'62	'63	'64	'65	'66	'67	'68	'69	'70	'71	TOTAL
Total New Products	326	321	314	353	380	403	401	400	370	315	311	265	255	213	162	119	82	83	101	71	110	83	5,438
New Single Products	28	35	35	48	38	31	42	51	44	63	45	41	28	18	17	23	13	25	14	11	16	14	680
Duplicate Single Products	100	74	77	79	87	90	79	88	73	49	64	33	47	43	34	23	16	26	36	26	52	48	1,236
Combination Products	198	212	202	226	255	282	280	261	253	203	202	191	180	152	111	73	53	32	51	34	42	29	3,522
New Dosage Forms[1]	118	120	170	97	108	96	66	96	109	104	98	106	84	52	41	22	26	14	21	12	23	30	1,613

Source: Basic Data, Paul deHaen, Inc., N.Y., N.Y.

[1] Not included in Total New Products

New Single Chemicals: Products that are newly synthesized single chemical agents not previously known, including salts.
Duplicate Single Products: Products such as ampicillin which are put out by various manufacturers.
Combination Products: Any product having more than one active ingredient.
New Dosage Forms: A product which has originally been marketed in tablets is now offered in ampuls, suppositories, etc.

ments are usually based on the observations that the total number of new drugs (new chemical entities, duplicate single products, compounded products and new dosage forms) swelled considerably during the 1950's and then tapered off. The question usually posed is how many of the drugs marketed have represented significant therapeutic advances and what has been the rate of their entry into the market. A recent review by the FDA of this subject has suggested that, while the total number of new drug applications has declined since the 1950s, the rate of submission and approval of drugs representing important therapeutic advances has remained generally constant over twenty years.[12] Exhibits 6-5 and 6-6 are taken from this study. The problem with this type of analysis is that it becomes a "battle of lists" and rests clearly on the judgment of which drugs represent significant advances or benefits. Bloom, in a review of the introduction of new single entity drug products between 1941 and 1970, noted that while the total number of "basic new agents" introduced each year declined in the 1960's, some classes regularly achieved approval while others did not. Thus the rate of introduction of new antibiotics did not decline along with central nervous system drugs and anticancer drugs. Drugs for cardiovascular and pulmonary diseases are not notably common among these lists.[13]

There continues to be much discussion over the character of research and development carried out or underwritten by the drug industry. Here the question posed concerns what type of research really contributes to the output of significant new drug opportunities.

The following points do seem clear. With an accelerating investment in R&D by the drug industry, there has been an increasing turn by it toward a quest for more fundamental knowledge. The establishment by some drug firms of research institutes is a reflection of this trend. In a study of sources of innovation in the pharma-

EXHIBIT 6-5

NUMBER OF NEW DRUGS MARKETED IN U.S. FROM 1950 – 1971

	1950	'51	'52	'53	'54	'55	'56	'57	'58	'59	'60	'61	'62	'63	'64	'65	'66	'67	'68	'69	'70	'71	TOTAL
Total New Products	326	321	314	353	380	403	401	400	370	315	311	275	255	213	162	119	82	83	101	71	110	83	5,438
New Single Products	28	35	35	48	38	31	42	51	44	63	45	41	28	18	17	23	13	25	14	11	16	14	680
Important Therapeutic Advances[1]	6	6	14	10	8	14	10	13	12	21	15	15	16	10	10	12	8	12	9	4	8		233
Duplicate Single Products	100	74	77	79	87	90	79	88	73	49	64	33	47	43	34	23	16	26	36	26	52	40	1,236
Compounded Products	198	212	202	226	255	282	280	261	253	203	202	191	180	152	111	73	53	32	51	34	42	29	3,522
New Dosage Forms[2]	118	120	170	97	108	96	77	96	109	104	98	106	84	52	41	22	26	14	21	12	23	30	1,613

Source: Basic Data, Paul deHaen Inc., New York, N.Y.

[1] New single chemicals that have been classified as therapeutic advances by Dr. Marvin Seife, Office of Scientific Evaluation, Bureau of Drugs, FDA.

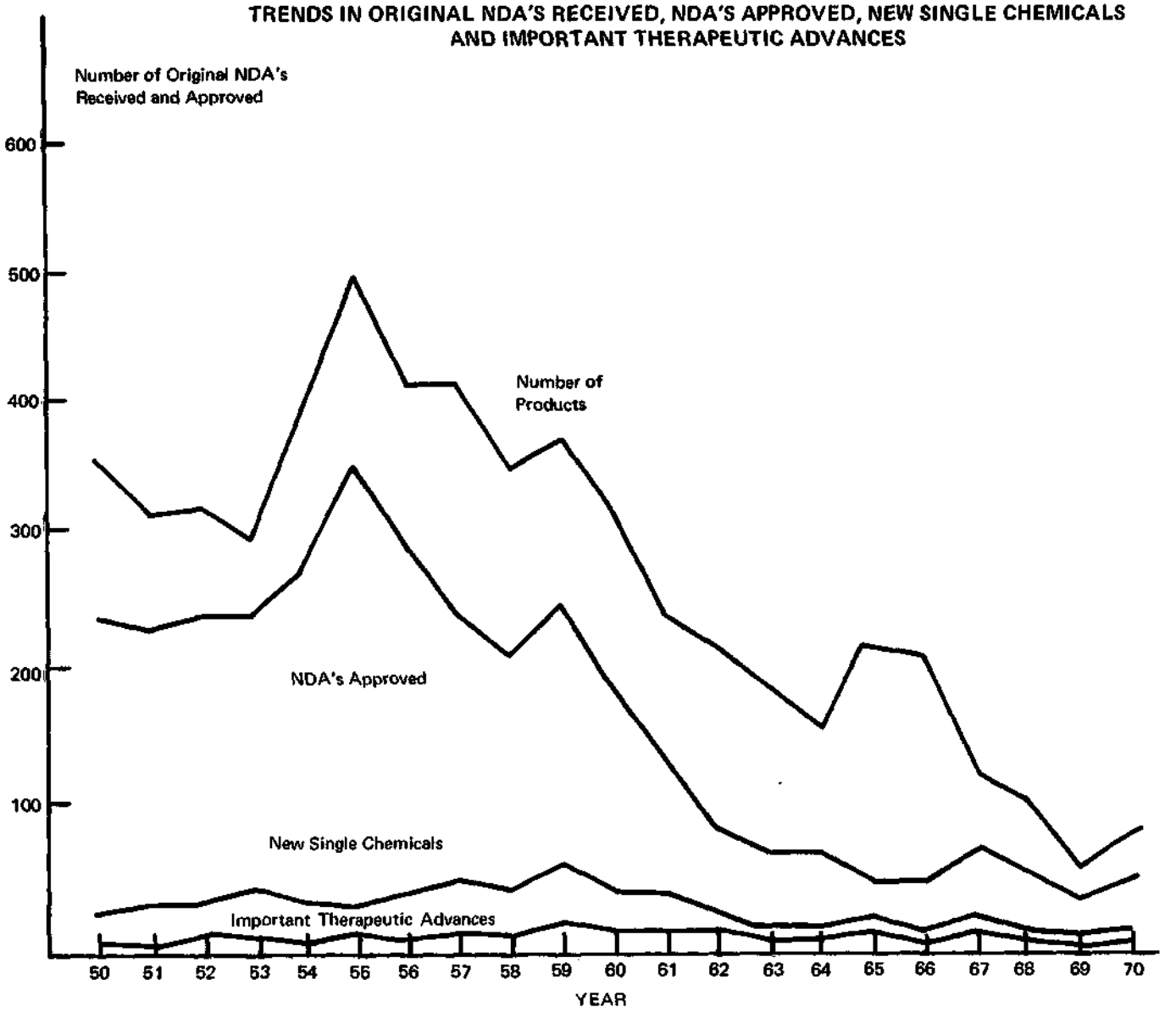
[2] Not included in Total New Products.

ceutical field, Mansfield *et al* have noted that external sources (such as universities, hospitals and research institutes) have played a major role in the technological program of the ethical pharmaceutical industry in the United States.[10] Interestingly, the importance of external sources has declined in recent years - presumably a reflection of an intensification and an increased sophistication of the research effort within the industry.[15]

A mainstay of traditional pharmaceutical research seems to have been medicinal chemistry. The astute combination of organic molecular synthesis and clinical pharmacology has led to a very large number of new drug entities or drugs with improved characteristics which have ultimately replaced older ones. Lessened frequency or severity of side effects, increased potency, etc., are among these improvements. That this has not always been the outcome, that molecular modifications have produced more rather than less toxic drugs, also seems to be an admitted fact.[4] Most thoughtful observers have concluded that some benefits do accrue from this search for new chemical entities but that they are not inevitable. The most rational approach appears to be one based on an understanding of the fundamental mechanisms of the diseases in question. This pursuit of hypothetical leads is clearly in the

EXHIBIT 6-6

TRENDS IN ORIGINAL NDA'S RECEIVED, NDA'S APPROVED, NEW SINGLE CHEMICALS AND IMPORTANT THERAPEUTIC ADVANCES



best tradition of science. However, it appears clearly that there is now a science limitation prevailing. Burns has observed that new drug development which proceeded so rapidly during the past 20 years has now slowed mainly because advances in biological science have failed to keep pace with those in medicinal chemistry.[13] [14]

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CHAPTER 7

ANIMAL MEDICINES, FEED ADDITIVES, AND PESTICIDES

FEED ADDITIVES AND ANIMAL MEDICINES

Chemical materials are used widely in the production of farm animals both as growth promoting agents and as medicines. There are three main classes of materials used:

(1) Growth promoting agents—usually either antibiotics or hormones.

(2) Prophylactic agents to prevent disease.

(3) Therapeutic agents to treat disease.

Growth Promoting Agents

About twenty-five years ago Moore *et al.*, discovered that the addition of a small amount of the antibiotic, streptomycin, to the diet of chicks led to their more rapid growth.[1] Since then a wide variety of other antibiotics have been shown to produce similar effects and they are now in widespred use. It was also found that certain hormonally active compounds, for example, diethylstilbestrol (DES), improved both growth and efficiency of feed utilization in cattle and this class is also extensively used. The use of antibiotics in cattle feed also proved beneficial and became established. By one current estimate, 80 percent of all the animal proteins produced in this country for foodstuff comes from animals that have received medicated feeds for at least part of their lives. Figure 1 gives examples of growth promoting chemicals currently in use.

The economic benefit in more rapid growth and more efficient feed utilization from the use of such agents seems well established. (See Benefits, page 7.)

The mechanism of action of these substances as growth-promoting agents is not clear and has been the subject of a great deal of debate. The suggestions include a suppression of normal bacterial flora in the intestine, or an alteration of the metabolic rate, a relief from low-grade infections, a protein conserving effect, and in the case of hormones, the induction of a prolonged rapid growth akin to adolescence. It has also been suggested that one mode of action of the antibiotics is to compensate for poor management of the degree of environmental contamination under which the animals are raised, but this aspect deserves further study.[3]

The doses used are generally low. In the case of antibiotics, the doses appear to lie below those useful in countering disease organisms. There does seem to be a positive dose-response relationship. The larger the dose in the feed, the greater the growth-promotion which results. Accordingly, the originally recommended dose of diethylstilbesterol for cattle was 10/mg/head/day. This was later increased to 20 mg/head/day.

Prophylactic Agents to Prevent Disease

The practice of adding pharmaceutical drugs (mostly antibiotics) to animal feedstuffs at moderate dosages (50 to 400 mg/kg of feed ration) has developed partially in the belief that disease is thereby minimized or prevented. Examples of drugs being used are shown in Exhibit 7-1. This practice of mass medication has become exceedingly popular as a labor saving device with the advent of large-scale, concentration feeding arrangements for cattle, poultry, etc. There is a widespread belief that, as larger and larger numbers of animals are aggregated together, the likelihood of a devastating infectious process has increased proportionately. However, this practice permits less control over the dosages administered and over other safety features than when drugs are used to treat a specific disease, animal by animal.[7]

It has been estimated that 1,268 tons of antibiotics are incorporated annually into animal feeds.[8]

The suggested[9] modes of action of antibiotics introduced into feed at prophylactic levels presumably include those discussed earlier under growth promotion, with additional reliance on their disease-controlling capabilities.[8]

Therapeutic Agents to Treat Disease

A large number of pharmaceutical agents are employed in therapeutic doses in veterinary medicine just as they are in human medicine for the treatment of specific diseases. Examples are listed in Exhibit 7-1. Sales of U.S. manufactured pharmaceutical products for veterinary use in 1970 amounted to $256MM domestic and $171MM foreign. In general, these drugs are employed well in advance of the use of the animal for food.

Quantities Used

A 1969 Department of Agriculture survey of the livestock feed industry is one recent indicator of the extent of

usage of feed additives. This indicated a total production of 96 million tons of livestock feed. It is estimated that 50 percent of all feeds produced contained animal drugs and that nearly all feeds contained some non-drug additives (food additives, chemical preservatives, etc.). The FDA has estimated that of all the animal protein produced, 80 percent comes from animals which have been fed medicated feeds all or part of their lives. An approximate dollar value (1970) of drugs at feed mills or other feed outlets is as follows:

	($'s million)
Antibiotics	72
Arsenicals	3
Coccidiostats	27
Antihelmithics	5.3
Histomonostats	3
Nitrofurans	12
Diethylstilbestrol	2.8

Hazards

With roughly twenty years' experience in the use of growth promoters as animal feed additives there continues to be a great area of uncertainty and controversy over the degree to which these substances represent a hazard. The suggested or implied risks are of several types:

1. Residues of drugs used in animal feed emerging in the meat for human consumption.

2. Development of antimicrobial resistant pathogenic bacteria harmful to other animals.

3. Development of resistant bacteria potentially pathogenic to man.

4. Transfer of pathogenic organisms from animals to man:

a. Drug residues—Residues of diethylstilbestrol have been the subject of a great deal of attention.[4] Deithylstilbestrol has a number of recognized uses in human drug therapy. Since the early 1940's, it has been recognized that DES can produce both benign anl malignant tumors in experimental animals in high doses.

Of more concern was the recent finding of vaginal cancer in a number of young women whose mothers had taken DES during pregnancy (at therapeutic levels enormously higher than those used in feeds). Recent findings of the U.S. Department of Agriculture by tracer techniques, of residues, presumed to be DES, in meats are the basis for action by the Food and Drug Administration to cancel the use of this chemical as a feed additive.

b. Development of resistant strains of pathogenic organisms—One of the consequences of the treatment of a disease caused by a microbial organism with antibiotics may be the development of a strain of resistant organism which can survive for further reproduction. It may involve a genetic alteration in the microorganism. Alternatively, it has been suggested that a trait of resistance (R-factor) may be cultivated and, itself, passed on genetically. Whatever the mechanism, the phenomenon is recognized as a real one.

There is evidence of an increase in the number of strains of enteric bacteria of animal origin which show resistance to one or more antibiotics.

EXHIBIT 7-1

EXAMPLES OF DRUGS AND OTHER PROMOTING CHEMICALS ADDED TO ANIMAL FEEDS IN THE UNITED STATES

GROWTH PROMOTANTS

Hormonal	Arsenicals	Antibiotics
Diethylstilbesterol	Roxarsone	Chlortetracycline
Zeralanol		Bacitracin
Dinestrol diacetate		Oleandromycin
		Tylosin
		Sulfamethazine

USED FOR DISEASE PROPHYLAXIS

Antibacterials	Antiprotozoals	Pesticides
Chlortetracycline	Aklomide	Ronnel
Furazolidone	Buquinolate	Coumaphos
Racephenicol	Amprolium	Famphur
Bacitracin	Zoalene	
	Ipronidazole	**Anthelmintics**
Antimycotics	Monensin	
		Coumaphos
Copper sulfate		Hygromycin
Griseofulvin		

Physiological Disease Prevention

Antibloat—poloxalene
Ketosis—propylene glycol
Aortic rupture—reserpine

USED FOR DISEASE TREATMENT

Bacterial	Antimycotics	Antiprotozoals	Anthelmintics
Novobiocin	Griseofulvin	Sulfadimethoxine	Dichlorvos
Sulfaethoxypyridazine	Nystatin	Amprolium	Levamisole
Oxytetracycline			Thiabendazole
Furazolidone			
Streptomycin			

Benefits

The benefits of pharmaceutical agents in the treatment of specific diseases do not appear to be in question. These are of the same order as those enjoyed in human medicine.

The utility of hormonal and various antibiotic substances as growth-promoting agents when added to feed has been the subject of several reviews.[3 6 9 10] The growth-promotion properties (measure in terms of increased rate of growth and efficiency of feed conversion) has been analyzed for the case of diethylstilbestrol and cattle.[10] In steers, the addition of diethylstilbestrol to feed will increase their rate of weight gain by 15 percent, feed conversion by 11 percent and will lead to the addition of 18 percent more protein to the carcass.[4] The corresponding figures for lambs are 25 percent increase in rate of weight gain and 25 percent increase in feed conversion.[2] Melengestrol acetate has found some utility as an additive to feed for heifers. Here, the increase in weight gain has been estimated as 10 percent with an 8 percent decrease in feed consumption.[4] One estimate suggests that (until recently) 90 percent of heifers fed received diethylstilbestrol or melengestrol acetate.[6]

There have been several recent attempts to document the utility of antibiotic substances in feed as growth promoting agents.[3 6 10] In 1969, in a review of the use of antibiotics in animal feed and for veterinary use in Great Britain (Swann Report), the benefit as growth-promotants of antibiotics was examined.[6] This report summarized a number of American findings and described the utility of the British agricultural industry.

The degree of growth-promotion appears to vary among species and among antibiotics. The degree of benefit also varies with the age of the animals and with the environmental conditions and in which they are raised. A recent FDA task force report noted that "the observation that degree of environmental contamination is associated with degree of antibiotic response implies that antibiotics may be a partial substitute for good management.[3] This task force concluded that the efficacy of antibiotics as feed additives was properly the subject of further study. The economic benefit to meat producers of the feed use of antibiotics was estimated as $414 million in 1970 roughly half of which comes from swine (Exhibit 7-2).[3]

The benefits associated with moderate dosages of antibiotics in feedstuffs as a way of disease prevention seems to be less well understood. Whitehair and Pomeroy noted some of the difficulties in making this assessment and pointed out the degree of uncertainty and contention.[7] The recent FDA task force observed that while the control of clinical illness in animals was an effective short-term use of antibiotics, the efficacy of long-term feeding at subtherapeutic levels had not been demonstrated.

EXHIBIT 7-2

ESTIMATED ECONOMIC VALUE OF ANTIBIOTICS TO FARM ANIMAL PRODUCERS AND TO THE PHARMACEUTICAL INDUSTRY[1]

Animal Class	Annual Economic Value ($ thousands) to: Producers (1970)	Pharmaceutical Industry (1968-69)
Broilers	33,120	2,173
Turkeys	13,920	584
Swine	202,489	46,400
Cattle	164,606	14,874
Total	414,135	64,030

Source: FDA Task Force report on "The Use of Antibiotics in Animal Feeds" 1972.

PESTICIDES

Introduction

Man has struggled through the centuries to protect himself, his food, and belongings from the ravages of pests. Among the tools he has long used and more recently developed in numbers are pesticides—chemicals that kill or suppress pests. Some naturally occurring chemicals such as pyrethrum and sulfur have been used for centuries to kill pests. For example, "pest-averting" sulfur was recommended by Homer, and arsenicals were known to the Greeks, Romans, and Chinese some 3,000 years ago. Ground tobacco (nicotine), kerosene, and turpentine have been used as insecticides since the 18th century. Inorganic compounds such as Paris green, lead arsenate and lime-sulfur combinations came into use in the 19th century and were in common use by the 1920's.

The discovery of the insecticidal properties of DDT in 1939 and of the herbicidal value of 2,4-D in 1941 revolutionized man's use of pesticides. The synthesis and testing of literally thousands of chemicals followed. Extensive screening and testing eliminated most of them, but more than 900 active pesticidal compounds survived and are in use in the United States today in a great variety of preparations. The total dollar value of pesticides produced in the U.S. has risen rapidly, being $307 million in 1960 and $1.1 billion in 1969[17]. This dramatic increase is due largely to the economic value of these chemicals in increasing the efficiency of production and marketing of agri-

cultural products. It should be pointed out, however, that most of the crop acres in the U.S. are not treated with insecticides, suggesting that farmers depend primarily upon the natural course of events or non-chemical means of controlling or limiting pest insects.

Pesticides vary greatly in their spectrum of toxicity of organisms. Some kill a wide variety of organisms, not only the target pests. Research is underway to replace these "broad spectrum" non-selective chemicals with more selective chemicals which harm a narrower spectrum of organisms.

Most pesticides are contact chemicals, i.e. they are effective only if they are sprayed directly on the target pests or if the pests come in contact with chemicals which have been sprayed on the surface of leaves and other plant parts. Since many pesticides lose their effectiveness rather quickly after application due to photochemical breakdown or removal by rain, frequent sprayings are required, especially in humid climates. A few chemicals are "systemics" which are absorbed by the roots or aerial plant parts and are translocated throughout the plant, thereby providing a built-in protection against the target pest, sometimes throughout most of the growing season. Systemics have many advantages, although their residues must be lowered to safe levels before harvest.

The quantities of organic pesticides needed to control pests commonly vary from a few tenths of a pound to about 10 pounds per acre. Residues remaining from such applications of even the more persistent pesticides are commonly found to be a few parts per billion or even a few parts per trillion. Such small but effective dosages are reminders of the high potency of these chemicals.

Pesticide usage is normally associated in the mind of the public with commercial agriculture. In the United States about 50 percent of these chemicals is used to protect crops and animals from pests. The remainder is used mostly by industry, governmental agencies and home owners. The most important and world-wide use of pesticides is for the control of mosquitoes, lice and other pests which can transmit human diseases such as malaria, yellow fever and sleeping sickness. Other important uses include control of insects and disease organisms which attack food and fiber during processing and marketing; preservation of wood products from termites and fungus attack; control of household and garden pests; and direct medicinal use in the treatment of pediculosis lice and scabies.

Types

Pesticides are commonly classified according to the target organisms to be controlled. Thus they are termed insecticides, fungicides, herbicides, nematocides, rodenticides, etc. A few of these chemicals are inorganic or metal-organic combinations, but most are synthesized organic compounds. They have been screened from thousands of candidate chemicals and their efficacy and safety determined. Examples of different classes of pesticides are shown in Exhibit 7-3.

Insecticides

Until recently, most public attention and concern have been directed to insecticides. This is probably due to the fact that a larger quantity of these chemicals is used than of any other class of pesticides. It also results from the publicity given DDT and other chlorinated hydrocarbons, prompted by their persistence in the environment and toxicity to non-target organisms. The slow biodegradability of chlorinated hydrocarbons is a desirable characteristic from the point of view of efficacy in pest control; but, unfortunately, these chemicals persist in the environment, ultimately accumulate in the natural food chain and thereby can cause serious ill effects to non-target organisms such as fish, birds, and other wildlife.[14]

Most insecticides are termed "broad spectrum." They are toxic to many species of insects other than the target organism, including in some cases predators of the very organisms to be controlled. This fact, coupled with the breakdown or wash off of the toxicant may make it necessary to make frequent applications during a crop season, thereby increasing the possibilities of residues in soils, water and plants.

The mode of action of most chlorinated hydrocarbons is uncertain. DDT, which has been in use throughout the world since World War II, is thought to affect the central nervous system of the target organisms, although its effect on fish is apparently through blocking of oxygen uptake at the gills.

In addition to the chlorinated hydrocarbons, two other general types of insecticides are currently in use in the United States—the organophosphates and the carbamates. These groups are generally more readily biodegradable than most of the chlorinated hydrocarbons and hence are less apt to persist in nature. They can adversely affect non-target organisms, however, and in the case of the organophospates, are much more toxic to humans than are most chlorinated hydrocarbons.

The organosphosphates are generally somewhat more versatile than the chlorinated hydrocarbons mostly because they are more readily biodegradable. A few are very excellent systemics since they are translocated from the point of absorption throughout the plant, thereby protecting the plant against piercing, sucking insects. Together with their fairly rapid biodegradability, these characteristics give them some advantages over the chlorinated hydrocarbons.

The carbamates have come into prominence as insecticides only in the past few years. They are readily degraded *in vivo* and generally have a lower mammalian toxicity than the organophosphates, though some are

highly toxic. Carbamates can be used effectively in integrated control programs. Together, the carbamates and organophosphates offer promising replacements for the more persistent of the chlorinated hydrocarbons.

The primary mode of action of both the organophosphates and the carbamates is the inhibition of the neural enzyme acetylcholinesterase. The organophosphates are particularly potent inactivators of this enzyme.

Fungicides

In crop production farmers use fungicides less than insecticides or herbicides. This is due largely to the development and use of disease resistant crop varieties. Even so, about 180 million pounds of fungicides were used in 1969 to control a myriad of rusts, molds, and mildews caused by fungi and related organisms[7]. Inorganic chemicals such as copper sulfate and bordeaux mixture are still used. Several metal-organic compounds containing copper, sulfur or mercury are effective fungicides. Dithiocarbamates are also used extensively.

Fungicides are used to treat seed, to control leaf diseases, and to prevent decay or deterioration after the plants are harvested. Wood and clothing preservatives are examples of "after-harvest" uses as are treatments to protect from decay during marketing crops such as bananas, citrus and apples.

EXHIBIT 7-3
MAJOR CLASSES OF PESTICIDES AND EXAMPLES OF EACH CLASS

Classes	Examples
Insecticides	
Inorganics	Lead arsenate, Calcium arsenate, Sulfur
Botanicals and Derivatives	Pyrethrum, Rotenone, Nicotine sulfate
Chlorinated Hydrocarbons	DDT, Aldrin, Endrin, Dieldrin, Heptachlor
Organophosphates	Parathion, Malathion, Diazinon
Carbamates	Carbaryl (Sevin), Furadan
Dinitrophenols	DNOC, Binapacryl
Oils	
Fungicides and Bactericides	
Inorganics	Bordeaux Mixture, Copper Sulfate, Lime Sulfur
Metal Organics	Phenylmercuric Acetate, Ceresan, Semasan
Dithiocarbamates	Vapam, Zerlate, Maneb, Nabam
Chlorinated Compounds	Captan, PCNB, Pentachlorophenol
Herbicides	
Inorganics	Sodium arsenate, Sodium borate, Ammonium sulfamate
Aromatic Acid Derivatives	
a) Phenoxy	2,4-D, 2,4,5-T, MCPA, 2,4DB
b) Phenylacetic	Fenac
c) Benzoic	2,3,6-Trichlorobenzoic Acid, Chloramben, Dicamba
d) Phtalic	Dacthal, Endothall
e) Phthalamic	Alanap
Aliphatic Acid Derivatives	Dalapan, TCA
Aliphatic Organic Nitrogen Compounds	
a) Substituted Ureas	Diuron, Monuron, Fenuron
b) Substituted Amides	CDAA, Diphenamid, Propanil, NPA
c) Carbamates	Cloro IPC, Eptam, Vegedex
Nitroanalines	Trifluralin, Benefin
Nitrogen Heterocylics	Atrazine, Propazine, Aminotriazole, Picloram
Rodenticides	
Inorganics	Arsenic Trioxide, Arsenic Sulfide
Botanicals	Strychnine
Hydroxycoumarins	Warfarin, Fumarin, Tomorin
Indadiones	Pival, Valone, Diphacin

Herbicides

Herbicides vary greatly in their chemical makeup[13]. A widely used herbicide — 2,4 - dichlorophenoxyacetic acid (2,4-D)—is an example of a number of organic acids or their derivatives which have herbicidal properties. Many of these compounds are systemics, being readily absorbed from soil and translocated throughout the plant. Others are contact chemicals and must be sprayed directly on the growing plant tissue to be effective. The effectiveness of these acid compounds is determined in part by the nature of the associated cation, ester, or halogen atoms in the structure. In general, these herbicides have low acute mammalian toxicity.

The mode of action of most of these acid derivative herbicides is uncertain. Even though 2,4-D has been in use since the early forties, the mechanism by which it kills plants is still obscure. It is known to affect respiration, cellular proliferation, and nucleic acid metabolism, but which if any of these processes are related to the lethal action is uncertain.

A number of organic nitrogen herbicides are in use today. Most are "preemergence" chemicals which are added to the soil previous to or just after planting. The chemicals are absorbed by the roots but are not readily translocated to the aerial plant parts. Their effectiveness is on either the young seedlings or the germinated seed. These compounds

kill a wide range of grasses and broadleaf weeds and are relatively low in mammalian toxicity.

The nitroaniline herbicides are applied before the plants emerge from the soil and are effective against annual grasses and a few broadleaf weeds. They are degraded by ultraviolet light and so must be incorporated into the soil. These compounds have low acute mammalian toxicity, although one of them (trifluralin) is quite toxic to fish.

Heterocyclic nitrogen derivatives (triazines) such as atrazine and propazine constitute an important group of herbicides. Substitutions in the triazine nucleus provide a wide range of compounds effective on a variety of weeds. The chemicals markedly reduce the process of photosynthesis in many weeds and plants. In contrast, tolerant plants are able to detoxify these chemicals rendering them harmless. For example, the ability of the corn plant to detoxify triazines by hydroxylating one of the ring positions accounts for the tolerance of this plant for these compounds. Most common weed plants do not show this ability. Such differential tolerance has made possible the chemical weeding of vast acreages of corn. The triazines have helped revolutionize corn culture by substituting chemical control for methods dependent upon cultivation and land preparation.

The nitrogen heterocyclics are commonly applied as preemergence chemicals. They degrade fairly rapidly in the soil but can persist long enough after treatment of a tolerant crop to prevent the subsequent growth of a more sensitive crop. Thus beans and other sensitive crops grown after corn in soil heavily treated with triazines are sometimes adversely affected.

Benefits

Pesticides have contributed to human welfare in many ways, perhaps the most important of which relates to human health. Pesticides are used to control mosquitoes and other vectors for organisms that cause human diseases. Through mosquito control alone, DDT is credited with having saved 10 million lives and prevented 200 million illnesses from diseases such as malaria, yellow fever, encephalitis, filariasis, and dengue fever. Other vector-borne diseases controllable through pesticide use include scrub typhus and sleeping sickness caused by a protozoan carried by the dreaded tsetse fly.

There are no accurate estimates of the losses in agriculture due to pests. However, estimates have been made that worldwide, 20-30 percent of the total food produced is devoured or destroyed by pests,[5] much of this in the less developed nations which can least afford it. These losses may be due to competition from weeds, attack of growing crops by insects, fungi, or bacteria, or by rodents attacking either the growing crop or the harvested produce. At any rate, the economic loss to pests is enormous, probably equaling $10 billion annually in the United States alone in spite of sophisticated chemical and other efforts to control them.

The agricultural revolution of the past quarter century is due to a considerable extent to pesticides and other chemicals. Pesticides provide control of insects, diseases, and weeds which heretofore went uncontrolled or were controlled only with considerable labor and monetary inputs. The absence of blemishes, rots, and molds on fresh fruits and vegtables, so common in our grocery stores a quarter of a century ago, is due largely to the use of pesticides. These chemicals have helped increase agricultural production efficiency which has improved in the United States at an average annual rate of six percent during the past decade or so compared to three percent for non-agricultural industires.

Pesticides have generally provided a very favorable margin of return for farmers and ranchers. On modern, well-managed farms one dollar invested in pesticides is associated with an increase in the value of farm sales of about four dollars[2]. Almost no other farm inputs rival pesticides.

Although those in the agricultural complex who first adopt the use of pesticides are the initial beneficiaries, the ultimate beneficiary is the consuming public. This accounts at least in part for the fact that in the United States the percentage of the family income used to purchase food was 15.6 percent in 1971—lower than at any time in our history and lower than in any other country.

Pesticides are used to control pests in a number of "non-agricultural" situations. For example, homeowners protect shrubs, lawns, and flower gardens, as well as their homes from insects, diseases, and weeds. Pesticides are used to protect wood and wood products from insect, fungus, and bacterial attack. They are added to paints and to clothing to reduce mildew and to pond and swimming pools to prevent the growth of aquatic species. The control of unwanted vegetation along highways and under power line rights-of-way is an example of non-agricultural benefits from pesticides.

Pesticides are an important component of the "Green Revolution" which resulted from the introduction of new varieties of wheat, rice, and corn. The control of weeds, insects and diseases is essential for optimum performance of these new crops, especially if they receive adequate fertilizers. Pesticides have proven especially effective for weed control, and are being used extensively, especially where labor is in short supply. National average yields of major crops are reasonably well correlated with pesticide usage per acre.

Toxicity and Hazards

Toxicity is the inherent capacity of a chemical to cause harm; hazard is the risk that, under any particular set of conditions, harm will occur. A highly toxic pesticide may be safely manufactured, handled and applied with little hazard; conversely, a

pesticide of relatively low toxicity may be handled or used in a hazardous manner. Pesticide residues on foodstuffs, if present in sufficient quantities, can be toxic to man or animals, and non-target organisms may be affected by pesticides, either by direct consumption of applied chemicals or by accumulation of the pesticide as it moves through the food chain.

There is great variability in toxicity of pesticides. Most figures are based on tests with rats (oral) or rabbits (dermal) and cannot with certainty be extrapolated to man, since there is a wide difference in toxicity of the same chemical to various organisms, even to different species of the same genus of insects. However, toxicity figures are valuable as a general guide in comparing the relative toxicity of one pesticide with another. DDT, the most widely used insecticide has low mammalian toxicity. (Oral LD_{50}=113 mg/kg; dermal LD_{50}=2510 mg/kg.) Even among workers in factories where the chemical is manufactured and in whose body tissues DDT appears at many time the "normal" level, there appear to be no serious health effects. In contrast, most of the rodenticides and many of the organophosphate insecticides are extremely toxic. Parathion, for example, has acute oral and dermal LD_{50} ranges of 3.6-130 and 6.8-21 mg/kg respectively. Most of the chlorinated hydrocarbons are intermediate in their toxicity while the carbamates vary from slightly to highly toxic to humans. Even though chlorinated hydrocarbons have been widely used for years human poisonings from their use are not nearly as common as from the use of organophosphates.

The problem of acute toxicity of some organophosphates is quite serious, and accidental deaths associated with the use of these chemicals are not at all uncommon. Deaths of children having access to chemicals such as parathion have been reported along with those of workers occupationally exposed. Organophosphates can be absorbed through the lungs or by penetrating the skin of the worker, making the use of gloves and other protective equipment necessary. Also, the entry of field workers into areas recently sprayed can be hazardous. The testing for the acetylcholinesterase level of workers in plants and in fields where organophosphates are used has helped diagnose organophosphate poisoning and has prevented fatalities.

There is relatively little information on the direct effect of pesticides on man. In most cases inferences must be drawn from animal experiments. Only with DDT and the aldrin-dieldrin group of chlorinated hydrocarbons are there long-term observations on human subjects. These studies suggest no adverse effect to man from present levels of exposure to these chemicals.

There is no evidence from human experience that pesticides currently in use have been the cause of cancer or birth defects in man. However, a few animal studies at very high dosage levels have shown such effects as well as a few cases of suspected mutagenesis. For example, tumor induction in the mouse has been found with aldrin, DDT, and dieldrin, although the dosages used were far in excess of those to which man is exposed. Likewise, at very high levels, teratogenic effects have been demonstrated for several chlorinated hydrocarbons, carbamates and organophosphates, as well as a few pesticides among other groups. The teratogenic effect of dioxin impurities in 2,4,5-T and possible 2,4,5-T itself has been well publicized. In general, however, the level of pesticide required to demonstrate the carcinogenic and teratogenic effects is hundreds or thousands of times that to which human subjects are commonly exposed. Monitoring of pesticide residues in foods shows the levels of pesticides present to be generally well below those permitted by law. In view of the conservative margins of safety employed in setting tolerances for residues, normal (oral) intake from foods is quite unlikely to present any hazard. The chronic effects of long-term exposure of man to pesticides have not been fully determined, however, suggesting the desirability of caution and continued surveillance and of using pesticides only where acceptable nonchemical means of pest control are not available.

Several characteristics of the chlorinated hydrocarbons DDT and deildrin have made them hazardous, not through direct effects on man, but through indirect effects on nontarget organisms. Their persistence and ubiquitous nature, coupled with a tendency for them to concentrate in organisms as they move up the food chain, increase their chances of toxicity to fish, birds and other wildlife and in turn to man. Other chlorinated hydrocarbons may act in a similar manner, although there are few data to substantiate such action.

DDT has been found to inhibit the reproduction of lake trout and other fish. The effect of this chemical and its metabolites on birds through the reduction of egg shell thickness and consequent failure of reproduction has been demonstrated in controlled experiments. There is strong circumstantial evidence that DDT and its metabolites have significantly reduced reproduction in some bird populations under field conditions.

The adverse effects of pesticides on non-target organisms have aroused public opinion perhaps more so than possible ill effects on human health. In fact, some changes in pesticide usage dictated by concern for organisms other than man have inadvertently increased the direct hazards to man. For example, DDT which has relatively low mammalian toxicity is being replaced in some instances by some organophosphates which are highly toxic to man. Efforts to protect fish and wildlife have resulted in increased danger to man. This illustrates the very complexity of pest control and of the use of chemicals to attain it.

Trends in Usage

Pesticide production and use have increased dramatically since the introduction of the synthetic organics in World War II. In 1939, the year the insecticidal properties of DDT were discovered, the pesticide sales volume in the United States was about $40 million and was dominated by naturally occurring chemicals and inorganics. Following the advent of DDT and 2,4-D, the use of synthetic organics soon dominated the pesticide market. Today these compounds account for about 90 percent of the pesticide sales in this country. Their value in 1969 exceeded $1 billion. (Exhibit 7-4.)

EXHIBIT 7-4
THE PRODUCTION AND SALES OF ORGANIC PESTICIDES PRODUCED IN THE UNITED STATES 1960-70

	Quantity Million Pounds	Value Million Dollars
1960	648	307
1962	730	427
1964	783	482
1966	1,013	728
1968	1,192	1,067
1969	1,104	1,052
1970	1,034	1,072

Source: U.S. Department of Agriculture (6,7)

The rate of growth of pesticide production in the United States was phenomenal during the mid-1960's. For 1963-67 the annual growth rate in the value of synthetic organic pesticides was between 20 and 30 percent.

As late as 1969, continued growth at about a 15 percent annual rate was predicted, at least through 1975[8]. Subsequent events, however, proved this prediction to be much too high.

Public concern over the possible effects of pesticides on the quality of the environment, especially as they relate to the well-being of non-target organisms such as fish, birds, and other wildlife, seems to have brought about at least a temporary halt in the rapid upward trend of organic pesticide production. The controversy over the use of herbicides in Viet Nam was also a factor in discouraging pesticide usage. In 1969 for the first time since World War II, the production of pesticides was lower than for the previous year.[16] The 7 percent reduction in 1969 was quite in contrast to the marked increases that had occurred during the previous two decades. Pesticide usage figures for 1970 suggest that the slight reduction in 1969 may not be temporary and that the rapid rate of increase in the use of these chemicals so characteristic of the 1960's appears to have ceased.

Insecticides and related compounds are used in larger quantities than are either herbicides or fungicides (Exhibit 7-5). However, in recent years, use of herbicides has increased more rapidly than has that of either of the other two classes. From 1964 to 1969 herbicide production increased at an annual rate of 22 percent compared to 9.5 percent for all pesticides. The dollar value of herbicides exceeds that of even the insecticides—accounting for more than 57 percent of the synthetic organic pesticide sales in 1970.

The overall decrease in pesticide production in 1969 was probably due to several factors. DDT and other chlorinated hydrocarbons have been under concerted attack by ecologists and conservationists because of their persistence in the environment and because of known or suspected adverse effects of these chemicals on fish, birds, and other wildlife. These chemicals are fat soluble and tend to accumulate in fat tissue in the bodies of animals, including man. They have been found to build up in the natural food chain to levels that are toxic for some fish and certain birds.

Several states have passed laws prohibiting or seriously restricting the use of DDT and related compounds. Likewise, the Environmental Protection Agency has canceled the use of DDT on all crops with only a few minor exceptions.

The production figures for some of the chlorinated hydrocarbons reflect this public concern. The production of DDT in the United States dropped from about 141 million pounds in 1966 to 123 million pounds in 1969 and to 59 million pounds in 1970. Comparable figures for the aldrin-toxaphene group of chlorinated hydrocarbons was 130 million pounds in 1966 and 107 million pounds in 1969. The number of firms in the United States producing DDT was reduced from 8 to 5 during the period 1964 to 1968 and to 1 by 1971. Had it not been for the outbreaks of insect-borne diseases requiring pesticide treatments, both in the United States and overseas, the reduction in DDT usage might well have been greater than did in fact occur.

Public concern over the possible adverse effects of mercury-containing pesticides and of the brush killer 2,4,5-T are likewise reflected in the 1969 production figures. About 19.1 percent of the United States mercury consumption was used in the manufacture of pesticides in 1968. This figure was reduced to 16.4 percent in 1969. Of this nearly 12 percent was used to mildew-proof paints and only 3 1/3 percent for pesticides used in agriculture. Seed treatment of mercury-containing fungicides was almost eliminated in 1970.

The use of 2,4,5-T (mixed with 2,4-D) as a defoliant in Viet Nam, coupled with the discovery of teratogenetic effects of an impurity (dioxins) in some commercial lots of 2,4,5-T (and perhaps even of 2,4,5-T itself), probably accounted for the dramatic decrease in the production of these compounds. The quantity of 2,4,5-T produced declined from 42.5 million pounds in 1968 to 11.6 million pounds in 1969. Comparable figures for 2, 4-D were 94.1 million pounds in

EXHIBIT 7-5

THE APPROXIMATE VOLUME AND VALUE OF THE THREE MAJOR CLASSES OF SYNTHETIC ORGANIC PESTICIDES, 1967-70

Class	Volume (Million Pounds)				Sales ($Million)			
	1967	1968	1969	1970	1967	1968	1969	1970
Fungicides	120	130	124	129	56	62	61	65
Herbicides and Plant Hormones	288	318	311	308	430	483	496	498
Insecticides, Fumigants, Rodenticides, and Soil Conditioners	489	511	493	444	301	304	294	307
Total	897	960	929	881	787	849	851	870

Source: U.S. Department of Agriculture (6,7)

1968 and 57 million pounds in 1969[17] The recent suspension of the registration of 2,4,5-T for use around the home and on food crops may further reduce the use of this chemical as an herbicide.

Factors Affecting the Future

The future of pesticides depends upon a number of factors including: a) their need in the control of pests affecting man, his crops, animals, and his environment; b) restrictions in their use as determined by benefit-risk considerations relating to the welfare of man and other creatures, and c) economic factors affecting the industry which discovers, tests, and produces them.

Future Need for Pesticides

There seems to be little disagreement with the essentiality of pest control. Man's historical battles with insects, diseases, weeds, and other pests are reminders that we continually compete with these other creatures for our food and fiber, in fact, for our very existence. For Americans, pest control is essential if we are to maintain our current level of living. For Pakistanis and Indians, it is essential if they are to live.

The future need is for pest control, but not necessarily for pesticides as we now know them. At the present time, however, pesticides are one of the most effective and inexpensive means, and sometimes the only means, of controlling most pests. In the absence of effective alternatives, they will likely continue to be our first line of defense unless they are removed from the market by restrictive legislation or regulatory control.

Much has been said and written in recent years about alternatives to the use of pesticides. Some interesting developments give rise to cautious optimism as to the feasibility of these alternatives. Among the most important are so-called biological controls. Some biological controls have been used commercially for many years, including scale insect control in citrus by lady-bird beetles and the control of Japanese beetle larvae by a bacterial disease. Others have been only recently developed. The partial control by parasites of the alfalfa weevil in the northeast and of the cereal leaf beetle in the midwest are cases in point as is the control by an imported flea beetle of alligator weed in some sections of the southeast.

Perhaps the most promising long-term biological control technique is through the development of plant varieties with pest resistance. The ineffectiveness of pesticides in the control of some plant diseases has made it necessary to use this genetic route for disease control. Unfortunately, however, it has not been pursued to any appreciable extent in developing varieties resistant to insects. As economic and political considerations restrict insecticide usage, the pressure for insect resistant crop varieties will become more universal.

Other biologically related alternatives to pesticides include the sexual sterilization of insects by radiation or chemical means. The radiation technique proved successful in the control of the screwworm fly in the southern states and of tropical fruit flies in pilot studies on Pacific islands.

Other techniques for controlling insects without pesticides include the use of chemical attractants and repellents, of hormones which interfere with normal life cycles, and of light traps which take advantage of the attraction of insects to selected bands of light. Each of these techniques shows promise under controlled pilot conditions but none has been widely used on a practical field scale. They must be considered along with well-established practices such as crop rotation which for centuries helped limit the attack of crop pests.

The integration of two or more techniques of pest control appears to have more promise than reliance on a single technique only. The expec-

tation is that by combining the biological and chemical control methods with cultural techniques already proven, the quantities of pesticides needed would be reduced, thereby alleviating possible problems of residues on the crops and plants and of adverse effects on non-target organisms.

It should not be assumed that methods of controlling pests through means other than the use of pesticides are necessarily free from human or environmental hazards. For example, materials used as repellants, sterilants and attractants are chemicals whose health and environmental hazards must be ascertained before their general use can be approved. Likewise, side effects adverse to man and other target organisms from the use of biological entities such as insect pathogens and predators must be looked for prior to permitting general use of these techniques. In spite of such cautions, however, these tools for controlling pests must be thoroughly evaluated as alternatives or as complementary to chemical pesticides.

The future of pest control by techniques which eliminate or minimize the use of pesticides will probably be determined primarily by public inputs into research and development and even into practical control operations. A high proportion of the R & D expenditures associated with pesticides is borne by the private sector which can recoup these expenditures through profits from patent-protected manufactured products. Alternatives to narrow-spectrum pesticides, and pesticides generally do not offer as much attraction. There is no easy mechanism, for example, for direct reimbursement for R&D expenditures relating to parasite or predator discovery, testing, and release, or to sterilization by radiation of insect pests. Likewise, repellants and sex attractant chemicals which require very large R&D inputs may be needed in only very small quantities, perhaps a few tons or hundreds of tons in total. Profits for industry from these chemicals may not justify large R&D inputs although the public good coming from the chemicals might well justify large Government expenditures.

The breeding of plant varieties resistant to insects and diseases should attract considerable commercial R & D input since the product (improved seeds) can be marketed with some proprietary protection for the developer. Experience has shown, however, that a paired R & D input from public sources is essential for the most effective plant improvement programs. The recent near catastrophe in corn production resulting from the southern corn leaf blight epidemic was in part due to the use of breeding techniques which were least expensive but which permitted the development of a too-narrow genetic base for the vast majority of our corn hybrids in this country. There is need for public agency involvement along with private industry to help keep as broad a genetic base as feasible. Improved plant varieties of the future will likely be developed through team efforts of public and private organizations.

The public sector may also be called upon to adequately test and perhaps even operate large-scale, integrated pest-management projects. The need for public agency inputs stems from the fact that the integrated control techniques depend to a considerable extent on group action rather than individual grower action. They also depend on careful monitoring or surveying of the pests to be controlled, feats which call for collective or public agency action. These projects will require field teams to monitor the numbers of the pest in question. Release of parasites or predators or the placement of light or chemical traps will likely be at least guided by public agency representatives. While large-scale integrated control operations may reduce the flexibility for any given operator, they have the potential of greatly decreasing chemical pesticide usage.

The Future of the Pesticide Industry

Alternatives to pesticides may provide long-term future controls. Even so, pesticides will likely continue to be an important means of controlling pests, at least for the next decade and probably for a much longer period of time. A number of factors suggest a continued critical need for new and improved chemicals. The development of resistance to pesticides currently in use calls for replacements. The trend to replace persistent chemicals with others more easily biodegraded should be continued. More research is needed to determine the potential of chemicals currently in use. Concern for non-target organisms forces greater stress on narrow-spectrum chemicals that are quite selective in their action. All of these factors suggest an increased need for inputs from the private sector, particularly in R & D areas.

Another distressing factor which tends to increase the difficulty of industry's obtaining clearance of pesticides is the general slowdown in decision-making by regulatory agencies. Sensitivity of personnel concerned with registration and clearance of chemicals to public opinions and pressures and inadequacy of staff have tended to delay decisions on registration applications, on the testing to be required and on general policy relating to pesticide regulations.

Industry's ability to supply new chemical pesticides is hampered by a number of factors. Higher R & D costs are made necessary by the increasingly stringent regulatory agency requirements relating to human health and safety and more particularly to the well-being of fish and wildlife and other non-target organisms. For example, increased sophistication and sensitivity of analytical tools have greatly increased research costs and at the

same time have made possible the detection of infinitesimal amounts of residues of pesticides and of their metabolites which have previously gone unnoticed. This is particularly troublesome in cases where the zero tolerance concept must be applied even though the trace quantities identified have little if any biological significance.

Uncertain markets for pesticides already under production together with expanded industry efforts needed to maintain the registration of these products give management a less favorable view of pesticides than in the past. Also, industry is greatly narrowing its market potential for each new chemical in responding to pressures to replace broad-spectrumed pesticides with those more specific for given target organisms. Furthermore, the generally unfavorable publicity given pesticides in the past few years tends to discourage corporate investments in pesticides for fear that sales of other company products will be adversely affected by emotional and other reactions against pesticides.

The discovery, testing, development, production, and initial marketing of new pesticides is a time-consuming process requiring on an average about five years. Full market development commonly takes an additional three years. Because of this time lag, it is difficult to assess the true effects of negative factors on the development of new pesticides. However, a study of the pesticide industry made in 1971 by the Ernst and Ernst Trade Association Department suggests some significant trends.[13] There was no suggestion from this study that industry planned to reduce significantly its immediate input into pesticide R&D. Planned R&D estimated for 1971 ($71.6 million) exceeded slightly that expended in 1970 ($69.9 million). A modest 5 percent inflationary factor would suggest a slight reduction in R&D effort which was substantiated by a planned similar reduction in R&D personnel numbers. The total R&D dollar inputs increased 33 percent from 1967 to 1970. The percent of R&D costs devoted to regulatory maintenance of existing products increased from 13 percent to 23 percent during the same period. Significantly, the total R&D costs as percent of sales increased from 8.2 percent in 1967 to 9.7 percent in 1970. This suggests continued commitment of the industry to research and development, although this commitment seemingly plateaued in 1971.

The average research and development costs for each pesticide registered is about $5.0 million. These costs include the screening and synthesis of thousands of compounds to select the very few that are finally registered. Some 60,000 compounds are screened annually to produce about a dozen new pesticide chemicals (Exhibit 7-6).

EXHIBIT 7-6

NUMBERS OF COMPOUNDS SYNTHESIZED, SCREENED FOR PESTICIDAL ACTIVITIES AND REGISTERED BY 33 UNITED STATES PESTICIDE MANUFACTURERS

Number of Compounds	1967	1970
1. Screened for Pesticidal Activity	60,200	62,800
2. Synthesized by the Company	23,500	28,000
3. Registered by Marketing	8	11

Source: Ernst & Ernst Trade Association Department (1)

Public concern for human health and well-being, along with general concern for environmental quality, present increasing challenges to all concerned with the control of pests. The ability to meet these challenges will be strengthened by:

1) Actions of public agencies to accelerate research and development activities directed toward practical alternatives to the use of potentially hazardous pesticides.

2) A concerted effort on the part of industry, in cooperation with public agencies, to develop pesticides that present less hazard both to man and to other creatures than do pesticides currently available.

3) Wise public policies relating to pesticides and their use.

4) A political environment that will permit decision-making in regulatory agencies to reflect a balance of factors rather than emotional pressure.

5) A scientific environment that insists on adequate review of new data, gives due consideration to the public need for an adequate and reasonably priced supply of food, and encourages effective public information programs by the appropriate scientific groups and regulatory agencies.

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CHAPTER 8

NATURALLY OCCURRING TOXICANTS, FOOD ADDITIVES, AND COSMETICS

1. INTRODUCTION

That part of our environment which is our food presents some aspects which are unique and some which are shared with other major environmental components.

Food, like air and water, is a continuing necessity. It thus differs from medicines and pesticides which are theoretically dispensable if we were prepared to accept the costs and risks involved. As with air and water, the composition and usefulness of food can be greatly affected by the actions of others beyond our control or knowledge, and hence many of the exposures it involves are involuntary. Yet, we have much more scope for individual choices over the timing and content of our intake of food than we do our needs for air and water. That scope or choice, however, is in part illusory. Our food supply is chemically exceedingly complex—far more complex than air or water. Our effective control over it is severely restricted by that complexity, and by ignorance, misconceptions, and economic and cultural limits.

No other part of our environment presents quite so forcefully the problems of meeting divergent and conflicting requirements, of balancing costs and benefits, of choosing on the basis of incomplete information, and of increasing general comprehension of complex choices, thereby improving the quality of both individual and regulatory decisions.

This chapter begins with a brief and necessarily incomplete review of the hazards from certain components of food which are present naturally. It then discusses food additives, i.e., those ingredients present as a result of human action, even if, as is often the case, they also occur naturally. Finally, the chapter concludes with a section on cosmetics. While cosmetics clearly differ from foods in many respects, they share certain ingredients. Some considerations of safety apply to both, and they have traditionally been grouped together for regulatory purposes.

2. FOODS IN GENERAL

All components of food—natural or synthetic, intentional or accidental, biological or mineral—are chemically definable. Such definition is not easy; it has been a substantial preoccupation of nutritionists and food scientists for years. Yet our knowledge of detailed chemical composition and structure is still far from complete, even with respect to some components of major nutritional significance. Foods almost invariably are complex mixtures, and their effects on those who consume them are correspondingly complex, and often interrelated.

The minor components are relatively poorly known, and their physiological effects, if any, even less well studied. Certain trace metals, for example, such as cobalt and copper, are known to be essential for human growth and survival, yet both reach toxic levels of intake at only few hundred milligrams per day. It is typical of our still limited knowledge that for a number of these trace constituents, known or thought to be essential in the diet, neither the minimum daily requirements nor the levels which would present a chronic hazard are yet defined.

The composition of our food supply varies widely with culture, geography, economy, and individual preference. In the United States, most of it consists of major components, such as proteins, fats, and carbohydrates (principally cellulose, starches, and sugars). About 0.5 percent consists of intentional additives ranging from lysine used as a nutritional supplement (at a few percent), through leavening mixtures or preservatives (used at a fraction of a percent), down to some flavors, used at less than one part in a hundred million, 0.000001 percent.

About 3 percent of the food supply consists of naturally occurring minor ingredients. These include (among the more common categories) the nucleic acids, minerals, vitamins, alkaloids, essential oils, oleoresins, and an almost limitless number of other chemically varied trace constituents.

None of this complex, varied, and varying mix acts or can be understood by itself. As Golberg[1] has pointed out, ". . .We accept the presence in our food of additives and trace residues of various sorts whose biological implications can ultimately be understood only be considering them in the context of their presence in foods, and what is known of the toxicology of the foods themselves, rather than by regarding them as isolated 'foreign' chemical entities."

3. SOME SPECIFIC HAZARDS FROM NATURAL CONSTITUENTS

All categories of food constituents present potential safety problems, which become actual hazards under

conditions of stress (such as starvation), abuse (such as overconsumption or improper choice or processing) of from inborn errors of metabolism (such as phenylketonuria or diabetes).

The nature and consequences of malnutrition and overnutrition have been well covered elsewhere, and are not of direct concern here, except to acknowledge the serious and frequent impact of these hazards.

What is less well known are the numerous hazards from naturally occuring constituents of food that are encountered out of ignorance or necessity or through only minor departures from normal processing or consumption patterns.

A large number of common food plants, particularly those of the cabbage and mustard (*Brassica*) and onion (*Allium*) families, contain goitrogens; i.e., substances which promote thyroid enlargement, or goiter, these act directly, through human consumption of such vegetables. They may also act indirectly as through the use of milk from cows which have fed on the vegetables. There is little doubt that marginally insufficient iodine intakes, and the consumption of foods containing various goitrogens, which act in concert on different phases of iodine metabolism[1] play a significant role in the present common occurrence of endemic goiter. Additionally, goitrogens when consumed at levels far higher than those found in foods, can produce thyroid tumors.

Potatoes and other members of the genus *Solanum*, contain an alkaloid, solanine, which is a potent cholinesterase inhibitor. Such substances interfere with the transmission of nerve impulses, and in this respect solanine is pharmcologically, though not chemically, similar to the "nerve gases" and organophosphorus pesticides. All potatoes contain some solanine; it is concentrated particularly in the green portions of the plant. In the potato tubers themselves, the solanine, along with Vitamin C, is found mostly near the skin. New potatoes, because of their high skin-to-volume ratio, and those green from exposure to the sun contain relatively high levels. Patil *et al.*[2] have reported a four-fold increase in solanine levels in potatoes exposed to normal illumination levels in supermarkets. Solanine poisoning [3,4] has occurred intermittently but fairly frequently over the years, sometimes in outbreaks involving hundreds of people. Occasional deaths have been reported. The safety factor between the normal level in some potatoes and the amounts which cause human injury is less than ten.

Oxalic acid salts and some free oxalic acid are found in spinach and in rhubarb. A normal serving of rhubarb contains about a gram of oxalate, about 1/5 the toxic dose for humans. Moreover, there are theoretically possible anti-nutritional effects, resulting from the ability of oxalic acid to combine with dietary calcium so as to render it nutritionally unavailable. Although such effects have been demonstrated in animals, particularly under conditions of calcium, phosphorus, or Vitamin D deficiency,[5] human feeding trials indicate little likelihood of any effects from normal diets.

A number of different foods contain substances which produce cyanide during digestion and some traces of free cyanide ion. Among these are tapioca, almonds, and lima beans. High-cyanide varieties of lima beans (not sold in the United States) have been responsible for many cases of human poisoning.

Pressor amines, which increase the blood pressure, are found naturally in pharmacologically significant quantities in cheeses, wine, and some fruits. A few fatalities have resulted from consuming these foods while under medication with tranquilizers such as Parnate, which inhibit the body's enzyme, monoamine oxidase. The pressor amines are normally oxidized by these enzymes, and thus held to levels the body can safely tolerate. But individuals with reduced monoamine oxidase capacity incur some hazard.

Vitamin A is teratogenic, i.e., causes fetal deformations in several species of test animals both in deficiency and in excess. Vitamin D in moderate excess causes calcium deposition in soft tissues and altered physical and mental development in children. Here again, by toxicological standards, the safety factor for infants and very young children is very small—in the order of five or ten.

Although dropped from use as an intentional flavoring ingredient, safrol, a weak hepatic carcinogen, is so widespread in nature its comsumption is unavoidable.

Evidence is now conclusive [6,7] for the presence in vegetables of the potent carcinogens 3,4-benzpyrene, 1,2-benzanthracene, and other polynuclear aromatic hydrocarbons, as normal products of plant biosynthesis, rather than from contamination.

Beyond the known or possible direct effects of naturally occurring toxicants, there are apparently endless complications from indirect effects of a second or higher order. Goldstein has suggested[8] that excessively bland diets, i.e., those low in roughage, decrease intestinal motility and lead to longer retention of fecal matter, thus increasing the opportunity for contact with or absorption of toxic substances. If this hypothesis is correct, a moderate intake of roughage would reduce this opportunity by some degree. At the same time, it raises the question of what are the optimum and upper safe levels of roughage intake.

The fiber, or roughage content has a major effect on the intestinal flora (bacteria in the intestine, particularly the large intestine) which are known to play a decisive role in chemical transformation of dietary components, as in the conversion of cyclamate to cyclohexylamine[9]. The numbers, kind, and activity of these bacteria are dependent on the individual's diet, state of health and activity. The total pattern is exceedingly complex, and very incompletely known.

These are only a few examples. While it is important for human health that our knowledge of such effects be deepened and greatly broadened, we cannot expect to be able to avoid natural materials which sometimes contrib-bute to hazards. (The members of this Panel, for instance, do not expect to avoid the specific foods mentioned, nor the many others that could have been included, because of what they have learned about them.)

The variety of naturally occurring "chemicals" in food is enormous. Over 350 substances have been isolated and identified in coffee—including the stimulant caffeine and the antithiamin, chlorogenic acid. While 42 substances have been found in orange oil[10] many more remain to be identified. All of these necesarily possess some sort of pharmacological potential—occasionally at levels of use near those at which they occur. Most of these have not been studied toxicologically, and in contrast with the intentional additives, their effects have not been systematically evaluated.

It is clear that nothing is wholly safe or dangerous per se; it is the quantity involved, the manner and conditions of use, and the susceptibility of the organism which determines degree of hazard or safety.

There is no scientific basis for making safety judgments which distinguish addded from naturally occurring ingredients. The judgment regarding safety in each case must involve some knowledge of its inherent capacity to cause harm (toxicity) and of the conditions of use which determine to what extent this capacity will be realized.

We must recognize that safety is a pathway between hazards, some of which are visible and measured, others indistinct, others unknown. Sometimes the path is wide, and the margins of safety are large. At times, as with Vitamin D or solanine, the path is narrow. There is no escape from all risk, no matter how remote. There are only choices among risks. Safety lies in staying on the path—through balance and moderation—rather than indulgence in dietary extremes.

FOOD ADDITIVES

Definitions

The term "food additive" is used in a general sense to mean any minor ingredient intentionally added to a food to achieve some specific technical effect. It may also include those which get into food incidentally through their use in packaging materials or as residues from application pesticides used on seeds, crops or from drugs on animals raised for food. These latter groups are often called indirect additives. In the United States, the legal definition is both peculiar and more narrow. The Food Additives Amendment of 1958[11] provides that a food additive is any substance which is or may become a part of food "...if such substance is not generally recognized, among experts qualified by scientific training and experiment to evaluate its safety, as having been adequately shown...to be safe under the conditions of its intended use (italics added);. . ." The amendment further provides that for substances in use before 1958, the basis of such expert judgment could be either "scientific procedures" or "experience based on common use in food," whereas for substances used only after 1958, the basis could only be "scientific procedures." This is the statutory foundation of "GRAS"—"generally recognized as safe." In this section, we shall use the term "additive" in its broad general sense.

History

Prior to the Food Additives Amendment and for some time thereafter, both the Food and Drug Administration and the Department of Agriculture expressed approval for the use of additives by a group of measures collectively known as "prior sanctions." Frequently such approval was expressed in private correspondence, sometimes published in so-called trade correspondence, and sometimes in the "Federal Register" or regulatory manuals. Such prior sanctions covered only a small fraction of the additives then in use.

At the time of passage of the Food Additive Amendments, there was only a very incomplete appreciation of the complexity and extent of food additive (FA) use. Congressional testimony referred variously to "437" and to other poorly supported numbers as the number of additives actually in use. A 1956 publication of the Food Protection Committee of the NAS-NRC[12] listed 517. Actually, we now know the total number to be about 4,000.[13] It seems safe to assume that no one really knew the extent of food additive usage.

There was considerable disagreement over how to deal with this backlog of unknown size and composition. The extremes of a sweeping "Grandfather Clause" on the one hand, or governmental testing, review and approval of each substance on the other, seemed unwise and impractical. The GRAS concept was a compromise which attempted to apply scientific judgment, and by implication, common sense, to a modified "Grandfather Clause," so that the limited scientific and regulatory resources available might be directed toward those situations most needing them.

Shortly after passage of the Food Additive Amendments, the FDA began to assemble an intentionally incomplete list of substances, each presumably generally recognized as safe under the conditions of its intended use. This was the beginning of the misnamed and widely misunderstood "GRAS List." By design, and by inherent nature, this listing was incomplete; there was never a single, unified GRAS list. And that portion of the statutory provision italicized above was largely ignored.

Partly because of uncertainty about how best to apply the provisions of the new Amendment, and because of a lack of both information

and procedures for collecting information, the FDA effort to establish a partial GRAS list met with difficulties. Two lists were published in the Federal Register on November 20, 1959 and August 12, 1960.

Thereafter, the FDA ceased formal publication of GRAS status. From then until 1970, it gave its opinion in so-called "GRAS letters," on whether or not a particular ingredient was GRAS.

After the initial Federal Register publication, most developments concerning GRAS took place outside of FDA. The 1958 Amendment does not specify the FDA as the arbiter of GRAS status; it merely requires such general recognition of safety to be among "experts qualified by training and experience to judge its safety." Thus, it is possible for there to be extra-governmental determinations of GRAS status, although such a status ordinarily would not persist if the FDA knew of it *and* disagreed. In practice, there are two kinds of such judgments, private and published. Although a *private* determination that a substance is *generally* recognized as safe is an anomaly, the law permits it, and it has probably happened in a few instances. There is some reason to believe that most of these have had a degree of expert judgment in support.

The major activity in establishing GRAS status outside of FDA has taken place with flavoring substances, which make up far more than half of the intentional additives in foods.[14] As FDA interest in GRAS determinations waned, the flavor industry's trade association, the Flavor and Extract Manufacturers' Association (FEMA) chose the route of independent review. It surveyed the industry to collect data on identity, specifications, safety, and levels and manner of use, and engaged a panel of six qualified experts to review the available information. Only those substances on which the panel agreed unanimously were held to be GRAS. In a program extending over several years, the panel reviewed approximately 1,400 substances. Of these, 1,124 were determined to be GRAS, and 267 were dropped from use. These actions were widely published in the Federal Register on administrative reasons, received both tacit and explicit FDA consent.

By 1964, however, the FDA had concluded that it should take some official position on the individual substances. It therefore adopted essentially the entire FEMA list, not into the FDA GRAS list, but into regulation.[15]

Simultaneously, there has been a steady, though declining flow of petitions for food additive regulations to the FDA followed eventually in a number of cases by the issuance of regulations.

Types of Additives

These may be classified in several ways. Among these are:

1. *Current legal status.* Although this gives some indication of the size and complexity of the situation, a more meaningful classification is shown in Exhibit 8-3.

2. *Intended technical effect.* Two classifications of the direct or intentional food additives are shown in Exhibit 8-4, together with the number in each category and an indication of the dollar sales of some of the major categories.

3. *Chemical classification.* It is useful for some purposes to subdivide certain groups of additives by chemical classification, as for example, synthetic food colors into azo, triphenylmethane, and isoprenoid dyes. The total number of additives and chemical classifications involved is very large, and a single substance will often belong in several chemical classifications (ascorbic acid, for example, is a lactone, and enediol, a secondary alcohol, and a primary alcohol). Moreover, both additives and their chemical classifications cut across several technical effects (ascorbic acid is both the nutrient, Vitamin C, and also an antioxidant). As a consequence, chemical classification tends to be both complex and of somewhat limited value.

EXHIBIT 8-1

NUMBER OF NEW CHEMICAL ENTITIES INTRODUCED EACH YEAR AS INTENTIONAL FOOD ADDITIVES

Year	GRAS added to §101.1163 (C.F.R.)	GRAS added to §101.1164 (C.F.R.)	GRAS added to other regulations	NON-GRAS
1960	---	---	1	10
1961	---	---	8	67
1962	---	---	1	16
1963	---	---	---	9
1964	---	574	---	22
1965	51	2	---	87
1966	---	---	2	5
1967	7	40	---	47
1968	---	1	---	9
1969	---	---	---	4
1970	---	---	---	4
1971	---	---	---	4

Note: For 1965 and prior years, particularly, the figures represent the inclusion in regulation of items already in use at the time of passage of the Food Additives Amendment of 1958, rather than new introductions.

EXHIBIT 8-2
NUMBER OF NEW CHEMICAL ENTITIES INTRODUCED EACH YEAR AS INTENTIONAL FOOD ADDITIVES

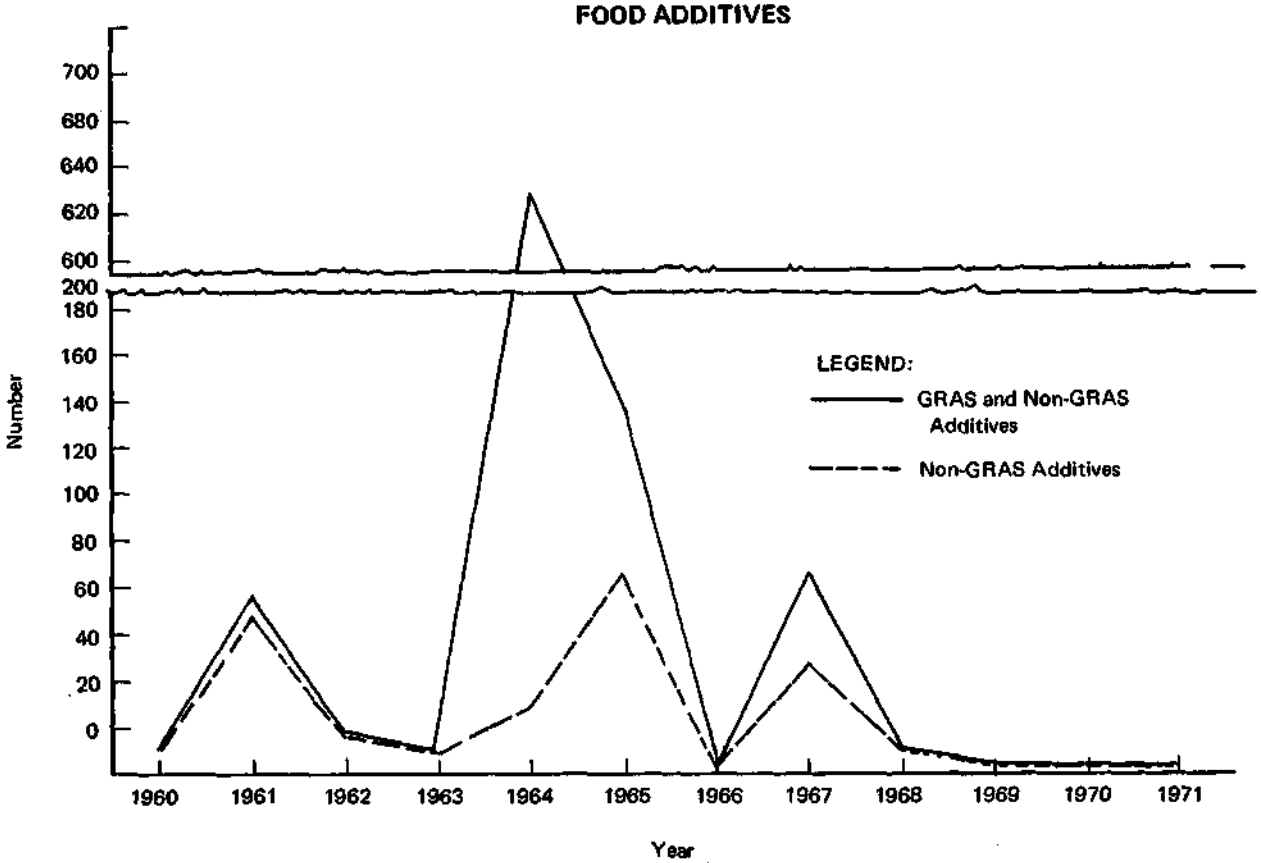

EXHIBIT 8-3
SUBSTANCES ADDED TO FOODS FOR SPECIFIC TECHNICAL EFFECTS

	GRAS	(GRAS + REG.)	Regulated Additives
Direct			
Flavors	1300	(860)	860
Other	290		120
	110(?)		
Color			30
Indirect			
Packaging	110		1710
Pesticides	.....		220
	1810	(860)	2940
			1810
			4750
			-860
			3890

4. *Natural and synthetic.* People often assume that the classification of food constituents into those "normally present" and those "added," or into "natural" and "synthetic," is of some interest or value. However, the majority of intentional additives are identical in chemical structure—and therefore in human effect—to components which are found naturally in food (though *not in all foods*). The intentional addition serves to restore, enhance, or introduce a characteristic into that particular food.

The nutrients, almost by definition, occur naturally in either identical or chemically closely related forms. The same is true of almost all flavoring materials, and many thickeners, humectants, solvents, and agents to control acidity and

alkalinity. By contrast, the non-nutritive sweeteners, colors, fumigants, and flour-treating agents include many substances of an exclusively synthetic origin.

A classification into "natural" and "synthetic" is rendered still less meaningful by the steady and rapid progress of analytical chemistry in isolating, and identifying as naturally occurring components, substances previously known only from synthetic sources.

Natural occurrence is very far from a guarantee of safety, as the earlier sections on naturally occurring toxicants illustrate. It may, however, be relevant to safety evaluation to the extent it permits conclusions based on some knowledge of human exposure. The key question is not one of "natural" or "synthetic," but of safety under conditions of use. As discussed elsewhere in this report, for almost any area of our environment, including foods, the state of our knowledge and the size of the margins of safety are usually considerably better for the synthetic.

The indirect additives, residues of which are permitted in food from packaging ingredients or the application of pesticides or drugs. As Exhibit 3 shows, by far the largest group of indirect additives are those used in packaging. Exhibit 8-5 presents a rough tabulation of these according to uses covered by regulations published in the "Federal Register."

EXHIBIT 8-4
CLASSIFICATION OF INTENTIONAL FOOD ADDITIVES BY TECHNICAL EFFECT

General Classification	Detailed Classification	Estimated $ Sales 1970 (in Millions) MCW[1]	CW[2]	Number in Category
Nutritional	Nutrient supplements			86
Aesthetic	Flavor enhancers	185	83	1580
	Flavoring agents, adjuvants			
	pH control agents	34 (acidulants only)	33	
	Colors, coloring adjuncts			
	Non-nutritive sweeteners			
	Enzymes			
	Surface-finishing agents			
Preservative	Preservatives	14	36	110
	Antioxidants			
	Sequestrants			
	Fumigants			
Texturizing and Stabilizing	Emulsifiers	62	52	340
	Surface-active agents			
	Stabilizers, thickeners	71	104	
	Humectants, etc.			
	Firming agents			
	Texturizers			
Processing Aids	Processing aids			430
	Propellants, aerating agents, etc.			
	Solvents, vehicles			
	Anticaking agents			
	Curing, pickling agents			
	Dough conditioners			
	Drying agents			
	Flour-treating agents			
	Formulation aids			
	Leavening agents			
	Lubricants, release agents	Total of all others		
	Synergists	118	58	

Sources: [1]Mallinckrodt Chemical Company
[2]Chemical Week

Trends

Due to increasing application of technology to food production and processing, the total use of food additives has increased somewhat more rapidly than population, nearly doubling in the decade 1960-70. This increase is more marked in some segments of the food industry than in others. In general, the fastest growing segments of the food industry correspond to those areas with the highest rate of usage of food additives (Exhibits 8-6 and 8-7). For example, the use of nitrogen as a protective gas to prevent deterioration of packaged foods has increased about 7-fold from 1960 to 1970 even after allowing for population growth. Hydrolyzed vegetable protein and MSG, used in formulated foods, have increased about 5-fold in the same decade.

The figures in Exhibit 8-7 present use in food, but not necessisarily human consumption. Aside from considerable wastage, sugar is destroyed by fermentation in making bread, salt is partially washed away in cooking, flavors evaporate, fats (and fat-soluble substances) may be drained off. Actual consumption is thus exceedingly difficult to determine, but is lower than "usage".

Of all food additives, that consumed in by far the largest quantity is ordinary sugar (sucrose) of which we use annually in the United States about 20,000,000,000 pounds, or about 102 pounds per person.[18] Al-

though this has not changed much in the last decade, such a high level of consumption is characteristc of most developed, affluent societies. Over the last few generations, the level of carbohydrate intake has remained fairly constant, but sucrose has gradually displaced the more complex carbohydrates, mainly starch.

The next most used additives are salt, corn syrup, and dextrose.

Combinations of estimates from a variety of sources lead to a figure of approximately 1,900,000,000 pounds of various other additives (other than salt, sugar, corn syrup, and dextrose) currently used annually in the United States. This amounts to slightly over nine pounds per person per year.

Eighty percent (7.4 pounds) of this is accounted for by about 30 of the most commonly used materials, of which about half are agents for leavening (e.g., yeasts, monocalciumphosphate) and agents for control of acidity and alkalinity (citric and acetic acids, sodium bicarbonate). The rest of these most commonly used materials serve a variety of purposes such as flavor (mustard, pepper, MSG); propellants, carbonating, and protective gases (carbon dioxide and nitrogen); and nutrient supplements (calcium salts and sodium caseinate).

Thus, the nearly 1,900 other direct additives account for only 20 percent of the total usage (1.8 pounds per person per year). The average annual use of additives is slightly less than 1,000,000 pounds of each additive or 0.005 pounds per person per year. This average figure is highly misleading with such a skewed distribution since a very small numbuer are used in much larger amounts, and a very large number are used in much smaller quantity. The median usage per additive of all direct additives appears to be between 100 and 200 pounds per year nationally or about 0.000001 pounds per person per year.

The reasons for the increase in the use of additives can be specified. They include:

1. Increasing use of processed, rather than raw foods.

2. Increasing trend toward meals eaten away from home.

3. Increasing trned toward new patterns of food intake and away from the traditional three meals per day. This involves more convenience and more snack foods, more ready-to-eat foods, all of which are larger users of additives.

4. The impact of economic factors, most specifically competition to reduce costs.

5. The impact of population factors, principally the rural to urban shift, and secondarily, a greater sophistication in the use of "ethnic" foods.

6. Social pressures, including more working women with less time to spend in the kitchen and therefore greater demand for convenience foods.

7. Greater interest in a wider variety of foods, available without seasonal or geographic limitations.

EXHIBIT 8-5

ADDITIVES PERMITTED FOR USE IN FOOD PACKAGING MATERIALS

Prior sanctions (various uses)	108
Polymers and resins	
Acrylic and modified acrylic	72
Polyurethane	40
Cross-linked polyester	69
Polysulfide-polyepoxide	22
Polycarbonate	8
Olefin	11
Nylon	8
Epichlorhydrin/epoxy	8
Other	47
Modifiers, plasticizers, antioxidants and stabilizers for polymers	71
Resinous and polymer coatings	370
Resinous and polymer coatings for various films	56
Polymeric films	19
Paper and paperboard components	
—for aqueous and fatty foods	188
—for dry foods	89
Rubber article components	247
Cellophane	146
Fibers	
—cotton and cotton fabrics	41
—textiles	50
Adhesives	632
Pressure sensitive adhesives	22
Animal glue	19
Sealing gaskets for closures	75
Pesticides, santizing solutions, wood preservatives, slimicides	53
Defoaming agents	137
In coatings	84
Lubricants	
—for metallic products	46
—with incidental food contact	17
Emulsifiers and surface-active agents	35
Filters, resin bonded	26
Other (release agents, chelating agents, antifogging agents, corrosion inhibitors, etc.)	80

(The figures are approximate only, and cannot be totaled since many substances are listed for more than one application. Additionally, many components are themselves complex mixtures.)

Simultaneously, with this trend toward greater use of additives is the current concern over safety. A third concurrent factor is the progress of toxicology with the development of scientific understanding and insight into the possible relationships between exposure to chemicals and human disease. It appears inevitable that there will be pressure for additional scientific examination of these questions in conjunction with the economic and technological pressures for greater use of food additives. Decisions and judgments will involve greater public understanding of and confidence in the regulatory process. They clearly will involve improved procedures for safety evaluation and for relating animal testing results to human safety.

Economics of Development

The economics of the use of food additives present some curious problems. Distribution in dollar value among various sections of the food industry is shown in Exhibit 8. In general, the introduction and production of food additives differ from the development and manufacture of pesticides, drugs, and other categories of useful chemicals. The food additive is usually produced by a general manufacturer of chemicals which, at least in the past, has been responsible for some initial demonstration of a useful technical effect in food and for proof of safety. A detailed definition of the technical effect, however, and exploitation of it, together with such related requirements as product specifications, has been in the hands of the food producer. Frequently, a substance is found to be a useful food additive after it has had a history of industrial application in other higher volume and therefore more profitable uses.

Since the passage of the Food Additives Amendment, more than 350 additives, once in use or proposed for use, have been abandoned. In only a few—and relatively well publicized-cases* has this happened because of adverse evidence concerning safety.

EXHIBIT 8-6
FASTEST GROWING INDUSTRY SEGMENTS: 1963-1967

Industry Segment	Percent Increase
Natural and Processed Cheese	10.0
Packaged Fish	9.8
Canned and Bottled Soft Drinks	9.1
Shortening and Cooking Oils	8.4
Frozen Fruits and Vegetables	8.4
Dehydrated Foods	7.8
Rice Milling	7.7
Soybean Oil	7.6
Chewing Gum	7.1
Flavor Extracts	7.0
Total Food Industry	5.3

Source: Bureau of Commerce Industry Census—1963 and 1967.[7]

* Principal cases have included cyclamates, the anti-oxidant nordihydroguiaretic acid, the color Red #1, and the flavors safrol and coumarin.

EXHIBIT 8-7
U.S. TOTAL AND PER CAPITA USE OF FOOD ADDITIVES (ALL FIGURES ROUNDED)

Additive(s) (grouped)	Number in the Group	Total Annual Use (pounds)	Per Capita Annual Use (pounds)		
			Total Use of the Group	Average Use for each Substance in the Group	Median Use per Substance in the Group
Sugar (sucrose)	1	20,000,000,000	102	102	102
Salt	1	3,000,000,000	15	15	15
Corn Syrup and Dextrose	2	2,600,000,000	13	(Corn Syrup 8.4 Dextrose 4.2)	—
All Other Direct Additives	1,926	1,900,000,000	9.3	0.005	<0.000001

In most instances the available information relating to safety was insufficient and the manufacturer of the additive could not economically justify the cost of gathering the additional data needed for the relatively small market. In other cases the manufacturer was uninterested in producing to the necessary specifications.

For approval of a food additive, substantial information is required concerning its process of manufacture, which is normally regarded as valuable proprietary information by the manufacturer. The food processor has seldom had the skills or resources to engage in chemical manufacture or safety evaluation, yet it is in the processors' hands that half a billion dollars worth of additives affect over 100 billion dollars' worth of food. Potential users have generally been reluctant to add the costs of testing to their normal costs and risks of developing food products, since when the additive is approved, all users will benefit. Collaboration between additive producer and users, and among users has been restrained by concern over possible anti-trust implications. Meanwhile the kinds of data needed to establish safety-in-use, and the cost of obtaining them have steadily increased. All of this has acted to reduce considerably the ease of introducing new food additives, even when no problems of safety have arisen. In view of these factors and trends, it is quite clear that to maintain a flow of properly studied new additives, mechanisms must be developed to share equitably between producer and potential users the cost of testing and safety evaluation.

Benefits

The use of additives is inextricably tied up with the processing and packaging food in an interdependent relationship. The nature of the additives, processing, and packaging, together with the characteristics of the principal raw materials, determine the characteristics of the final food.

It has been commonplace to point out that our modern food supply is no longer restricted by geography or season. The combination of organized production and distribution of food along with methods of processing and preservation have gone far toward assuring a wide variety of attractive, safe, and nutritious foodstuffs in most all marketplaces. At the same time urbanization, the fact that people now tend to live predominantly clustered in cities, has proved to be a strong factor in dictating the preserving and processing methods for food. The channel of distribution from a grower through the processor to the consumer (in a city) may be a lengthy one. The length of time in transit and the problems of quality control at the retail end of the distribution chain make desirable the use of processing methods or added materials which will permit the food to retain its desired characteristics.

The principal benefits from the use of food additives fall in the areas of cost reduction, user convenience, nutrition, safety, acceptability, and increase in the variety of foods available (with a consequent impact on nutrition and acceptability). These benefits may be measured in specific terms. Cost reduction may, for example, result from greater stability with a consequent lack of waste. Thus, calcium propionate is used to retard the growth of mold in bread. An additive may avoid the need for more expensive processing. For example, beverages preserved with sodium benzoate do not need to be heat processed or concentrated and frozen, both of which are substantially more expensive processes.

Additives extend the range of applicability of processing methods. The number of basic processes is relatively few. These are (1) heat processing, including both retorting and aseptic canning, (2) freezing, (3) dehydration, and (4) irradiation (not yet available in the United States to any significant extent). There are

EXHIBIT 8-8

FOOD ADDITIVE SALES BY PRIMARY TECHNICAL EFFECT AND MARKETS

(million of dollars)

Industry	Nutrition	Aesthetics	Preservation	Stability	Processing Aid	Unclassified	TOTAL
Meat and Poultry	....	8.7	0.3	4.7	6.9	....	20.6
Dairy	0.3	23.0	2.4	17.6	21.6	0.7	65.6
Canning and Freezing	....	25.1	0.8	13.4	3.9	....	43.2
Grain Killing	4.5	4.5	0.1	4.9	5.5	....	19.5
Bakery	3.0	26.2	5.0	10.5	15.3	....	60.0
Confectionery	....	38.6	0.4	5.7	1.9	5.0	51.6
Beverage	....	96.5	1.8	8.4	62.2	11.1	124.0
Fats and Oils	2.4	1.6	2.6	35.6	....	0.3	42.5
Misc.	0.5	18.7	0.6	31.9	5.0	....	56.7
Total	10.7	242.9	14.0	132.7	66.3	17.3	483.7

variations and combinations of these four basic procedures, all of which are intended to render food more palatable or to preserve it during its journey from processor to consumer. Not only are these methods few in number, but they are not universally applicable. It is, for example, impossible to preserve lettuce by freezing, dehydration, or heat processing. Pork does not freeze well or keep long in the frozen state. All the processes, except irradiation, tend to alter texture, sometimes drastically. Freezing usually has little effect on flavor, but other processes alter it in rough proportion to the severity of the process conditions. Thus, the options available to the manufacturer are relatively limited. Additives perform an invaluable function in extending these options. It is worth pointing out, however, that the relatively low cost of chemical additives has relieved the food industry of any sizable incentive toward more rapid and varied development of food processing. It seems unlikely that the number of basic processes (dehydration, freezing, heat processing, etc.) would be very large in any case. Additives are undoubtedly an economical and functionally preferable alternative to the costly and tedious exploration of process variations.

Another respect in which additives lower cost is in the possibilities they offer for large-scale processing. Potatoes, for example, can be peeled by an abrasive peeler or a lye peeler far more economically than by hand in the restaurant. Once they have been peeled, however, they must either be canned which changes and limits texture or flavor, or they must be frozen or dehydrated in order to preserve them. Dehydration, which is the least expensive of these processes, and for some purposes the most satisfactory, involves the use of sulfite to prevent browning, an antioxidant, such as butylated hydroxyanisole, to avoid rancidity, a phosphate to assist in water reabsorption by the potato cells, and frequently the addition of Vitamin C to assure the presence of a principal nutritional value of potatoes.

Additives may also reduce cost by permitting the upgrading of products such as through the use of clarifiers, hydrolytic enzymes, and other processing aids.

In objective technological terms, it is possible to measure the increase in nutritive value from the addition of vitamins or amino acids, or increase in shelf life due to an antioxidant or a preservative. Sensory evaluation panels can measure fairly accurately the increase in acceptability due to improvement of aesthetic factors. A further point related to shelf life is the additional margin of safety which additives confer in rendering the product in which they are used more resistant to abuse by food handlers during transportation and sale, and by the housewife in storage at home or in preparation. Thus, Vitamin C and citric acid added to fruits prevent browning if the frozen fruit is exposed to the air for an undue length of time. Emulsifiers and stabilizers provide a degree of assurance of success with such convenience foods as angel food cakes, an assurance that was simply unobtainable by the older method of preparation. The manufacturer must assume that his product will be abused, and that his directions will not be followed adequately. Additives aid in several ways to protect against these risks.

It is a temptation to set up a scale of benefits from the use of food additives, placing at the top the preservation of food from life-threatening contamination, and moving down through the slightly less important nutritional benefits, to cost savings or reductions, and finally to what have sometimes been called cosmetic or aesthetic benefits. One can select examples of each. Yet to set up such a scale and say "forget all but the highest" is naive and simplistic.

A foods policy predicated on the slogan, "let them eat unattractive, tasteless food, so long as it is free of threatening contamination and serious losses of nutrients" would meet universal resistance, since it would ignore the social, religious, and personal aspects which actually dominate our food habits. Factors affecting acceptability are far from dispensable; there is a very large body of evidence[19] which points to the vital role of appearance and taste in staying well nourished. Such factors affect both proper food choice and adequate physiological response to food intake. To keep our fellow man healthy, we cannot neglect the taste and appearance of his food.

If we are to keep human welfare in mind, we dare not confine "food additives" to their "higher" uses. We would also find it difficult or impossible to be sure to which single benefit a given additive in a given food is supposed to contribute. And we would have to face the difficulty that for almost every additive, in almost every application, there exists a substitute—either another additive or a change in processing—slightly less effective, convenient, or attractive, or more expensive. And for most cases, the benefits are exchangeable, and interrelated, and largely overlap. Examples of consumer choices in which attractiveness and palatability outweigh economy and nutrition are countless. Yet personally weighed cost factors always enter into food choices and may be absolute determinants, considerations of preference, nutrition, and even safety notwithstanding. Safety aspects are so poorly understood by the public, and so frequently violated, that public choices often frustrate both governmental regulation and manufacturers' designs.

The application of food additives and processing are shaped to meet public demands as measured in the marketplace. The partial solution to these problems lies in making these demands as well informed as possible, rather than in making deceptively simple administrative choices magically insulated from public preference, among values that in reality are nearly always complex, shifting, and subjective.

Hazards

An answer to the question, do food additives represent a hazard to human health, will always be impossible to answer conclusively. It is difficult to answer it as adequately as we should, because our information is not, and never will be sufficient. Hazard implies the probability of human exposure as well as the inherent biological effects which take place with sufficient exposure. By virtue of the previous discussion, it can be predicted with some certainty that exposure to some food additives is very widespread.

We have discussed the size of our sucrose intake. There is currently controversy about the role of sucrose in the development of coronary artery disease[20 21]. It appears that its effect is probably smaller than that of other risk factors such as calorie intake[22], lipid composition, and hypertension. The role of sucrose in dental decay, however, is clearly established[23].

Intakes of salt only slightly higher than normal are widely suspected of contributing to hypertension.[24] By definition, to the extent that we are dependent upon processed food, ingestion of food additives, direct and indirect, will occur. In fact, such exposure is reasonably judged as involuntary, inexcapably of lifetime duration, and involves a very large segment of the population. However, the levels of all but a few added materials in individual food items are relatively low. Given this near ubiquity of low-level additions to the diet, it might be hoped that there existed a reasonable fund of scientific information to define biological effects and some information on human biological effects.

In fact, the biological information is probably less available in the case of food additives than for other regulated chemicals (drugs and pesticides, for example). One reason for this situation is the way in which legal authorities have dealt with this class of materials over the years. As discussed earlier in this section, when the 1958 Food Additives Amendment was adopted, there was relatively little known in a general and systematic way about the food additives in use at that time. Through these amendments, Congress demanded judgments on the safety of food additives where appropriate scientific information did not exist and within a time limit prohibiting the systematic collection of these data. The result was the GRAS list which was, indeed, based on the best judgments of scientists in this field. As a result of the GRAS review process, some food additives were removed from a list of candidates for GRAS approval. One of the criteria for judgment of general recognition of safety was a record of apparent safety associated with use of the chemical by the general population. In most cases, however, there had been little attempt to search systematically for biological effects either in human populations or among laboratory animals. The majority of food additives are permitted for use through judgments based on data which were considered adequate at one time but must now be ranked as "preliminary." There is no present evidence from epidemiological or other sources that points particularly to food additives as possible sources of hazards meriting special investigation. Rather, our knowledge should be pushed forward in this area consistently with our knowledge in other areas of environmental exposure.

A second reason for the insufficiency of information is the relative uncertainty over the composition of many food additives. Food additives represent a wide variety of materials—some better characterized than others. Synthetic materials, in general, are better defined than are naturally occurring additives or the naturally occurring food components themselves. Impurities in the latter case are more likely than in the former. In other cases, a generic name, such as caramel, may cover a variety of methods of manufacture that can lead to distinctly different products some of whose components have yet to be identified. On top of this, there are possibilities and instances of interaction of food constituents and added components.

A third reason for a lack of information is the relatively unsophisticated biological science which has been applied to that research and testing done in behalf of food additives. We have already mentioned that up to now there has been little incentive on the part of food additives manufacturers to make large investments in behalf of an understanding of biological effects. Where food additives originate with large chemical producers, they typically represent a small fraction of their total business and their profitability does not encourage large extra expenditures. Where they are the product of small concerns, these manufacturers often cannot afford to underwrite sophisticated background research. Food processors, who are the users of food additives, have typically not shared in the responsibility of supporting or performing the evaluation research. (In Great Britain, it is the food processing industry which undertakes the responsibility of evaluating food additives for safety and of demonstrating their benefits.)

For these and other reasons, much of the research on safety evaluation of food additives has been carried on in independent commercial laboratories on a contract basis. The quality of this work has varied over a wide range. In part this resulting quality is a reflection of the types of scientific questions posed. As with other categories of chemicals in our environment, there has been a strong tendency to seek answers through "standard" tests of toxicology. There has been a corresponding tendency on the part of the supplier of information to substitute a mass of data for quality and for sophistication of research. As a result, there has been relatively little in the way of good scientific insight applied to the design of experiments which would re-

veal data on mechanisms of biological action, on metabolism and on dose-response relationships. Further, there is little in the way of information collected systematically from studies in humans.

Others have suggested a series of scientific questions which deserve examination.[25] Some of these are genetically - determined intolerance due to inborn metabolic deficiencies, induction and inhibition of microsomal enzymes, biochemical, physiologic and pharmacologic actions, immuniological effects, and pathological effects.

All these questions should be asked. The sense of urgency with which we seek answers, and the degree of confidence the answers need to possess, should be proportionate to the implied hazard. It should, however, be emphasized that there is little evidence to suggest that current food additive usage involves significant health hazards. There are many examples showing that the advancing science of toxicology, industry response, and government regulation have progressively and promptly eliminated known hazards, including some that were doubtless extremely remote—far more remote than some of the hazards from naturally occurring toxicants mentioned earlier. What science and regulation are now being asked to do is to eliminate or reduce *unknown* hazards, or those known hazards that spring from causes still unknown. This becomes constantly a more difficult, expensive, and time-consuming activity.

COSMETICS

Other than food and religious practices, there are few areas of human activity in which large, private expenditures of time, money, and effort are more culturally controlled, and supported or modified by subjective preference than in the use of cosmetics. Examples drawn from ancient civilizations and from contemporary, primitive, and "advanced" societies support this statement. Next to food for the body, and food for the soul, comes food for the ego.

The ancient history of cosmetics, like that of foods and drugs, offers many instances of the use of hazardous materials, usually through ignorance, sometimes through indifference. As our knowledge of toxicity of the materials we use has increased, those that present known hazards have been dropped (as happened with thallium compounds in depilatories) or restricted in use so that the remaining hazards are minimal (as with lead salts or aniline dyes used in hair coloring).

Cosmetics usage covers a wide range of types and frequencies of exposure. Some may be ingested, as lipstick. Others involve exposure solely on or through the skin. Still others, such as hair spray, may be partially or unintentionally inhaled, and a number are applied to sensitive areas like the eyes or genital regions. Some cosmetics are used daily by a large fraction of the population. Others, such as moustache wax, are used rarely, or by only a few. Some are on the hazy borderline between cosmetics and drugs, such as mouth washes; others are clearly drugs; e.g., dandruff treatments and antiperspirants.

The total market for cosmetics is about $6 billion annually. One published source[26] reports estimates that cosmetics and toiletries can be divided into 30 major product categories which in 1971 consumed 2 billion pounds of chemical raw materials valued at $520 million. Clearly, this industry spends a high proportion of its sales on packaging and promotion. A breakdown of the categories is in Exhibit 8-9 and of the raw materials in Exhibit 8-10.

From what may be judged from human experience, the incidence of injury is small. There have been no reported recent deaths. In 1971, FDA had 314 complaints reporting injuries from cosmetics. Obviously, these are a small fraction of the total.

The total injuries from the use or misuse of cosmetics are unknown; one rough and doubtful estimate from the report of the National Commission on Product Safety, is about 60,000 cases per year[27]. Important as these are to the individuals involved, even this estimate is only 0.4 percent of the reported accidents or injuries from a partial list of consumer products, not including foods, drugs, automobiles, firearms, or cigarettes. These figures receive a degree of confirmation elsewhere in the Commission's report. Beauty aids were responsible for 48 injury cases, or 0.5 percent out of 9,376 cases reported in a physicians' survey. In the total pattern of environmental risks, those from cosmetics are both infrequent and slight.

The majority of injuries, whether judged by complaints which FDA has recieved and investigated[28] or by the insurance claim data used by the Commission on Product Safety[29,30], involve allergic responses—skin eruptions, itching, asthma, etc. Unfortunately, allergenicity is one of the adverse effects for which animal tests have quite limited predictive value. Animal tests may be helpful in ruling out potent sensitizers or irritants in preparation for decision as to the safety of proceeding with human studies. The latter are essential—even though cumbersome, expensive, and uncertain—for prediction of very weak or infrequent effects. It is customary to carry out not only experimental human prophetic patch testing, but also some form of practical usage tests. A combination of such testing, chance anecdotal observations recorded in the literature, and the reported results of accidental or occupational exposures, have provided some basis for judgments.

As a result of such information and judgments, a number of sensitizers and other potentially hazardous ingredients have either been dropped from use or accompanied by suitable instructions and precautionary labeling. It seems likely, though solid information is lacking, that the actual injury rate from cosmetics has

declined, while the complaint rate has increased as a result of greater consumer awareness of the Food and Drug Administration as a regulatory agency, and of the existence of legal and insurance remedies.

While there are no formal pretesting or preclearance requirements for cosmetics, the total effect of individual and informal review (usually private rather than governmental), together with the innocuousness of most materials used, has made the injury rate fairly low by comparison with other widely prevalent sources of hazard. As March and Fisher comment.[31] "Dermatitis due to the use of cosmetics is uncommon. The low incidence is especially noteworthy when one considers the innumerable cosmetics that are used daily by both men and women." Trade associations, such as the Cosmetic, Toiletry and Fragrance Association (CTFA), provide an advisory service on materials and standards. The CTFA has recently petitioned[32] the FDA to issue a regulation for the voluntary reporting of cosmetic product experience. This arrangement, if it works well, will provide a far more adequate basis for assessing product safety and the possible need for further measures. The manufacturers have also agreed to make available information on the identity of the ingredients to assist users with specific allergies in avoiding those to which they are sensitive. Additionally, the fragrance industry has currently under way a comprehensive review of fragrance ingredients which seems likely to eliminate from use any remaining agents, not now recognized, which may be significantly sensitizing.

EXHIBIT 8-9
ESTIMATED U.S. PRODUCTION OF MAJOR COSMETICS AND TOILETRIES (1968 AND 1971)

	Million lb		Avg. increase
	1968	1971	Percent per year
Toilet soaps	550	600	2.8
Women's hair sprays	350	420	6.3
Mouthwashes	200	250	4.8
Dentifrices	150	175	5.2
Shampoos	125	160	8.6
Face creams	100	130	9.2
Deodorants	60	95	16.4
Shaving creams	43	50	5.0
Hand lotions and creams	40	45	4.0
Shaving lotions and colognes	36	58	10.0
Baby powder	40	45	4.0
Hair colorings	35	40	4.5
Men's hair dressings	29	30	1.5
Men's hair sprays	--	30	--
Denture products	20	25	7.8
Talcum powder	15	17	4.2
Cream rinses	13	17	9.5
Face powder	13	14	2.5
Women's fragrances	8	11	11.2
Women's hair dressings	7	10	12.7
Suntan preparations	7	10	12.7
Bath oils and salts	6	9	14.6
Nail and cuticle removers	8	9	4.0
Makeup bases	6	7	5.2
Feminine hygiene sprays	--	7	--
Permanent wave kits	6	5	(9.4)
Lipstick	4	5	7.5
Nail polish	4	5	7.5
Eye products	1	2	26.0
Depilatories and other	3	4	10.0
Total	1,879	2,285	6.7

EXHIBIT 8-10
ROUGHLY ESTIMATED U.S. SALES OF PRINCIPAL COSMETIC RAW MATERIALS IN 1971

Millions of Dollars	
Perfume oils	$170
Fluorocarbon propellants	90
Tallow	40
Coconut oil	30
Alcohol, denatured	25
Surfactants	25
Flavors	15
Glycerine	15
Mineral oil	10
Fatty acids	10
Fatty esters	8
Sorbitol	8
Antiperspirants	7
Bacteriostats	7
Calcium phosphates	7
Dyes	7
Hair polymers—proteins	7
Lanolin and derivatives	5
Caustic soda	4
Pigments	4
Thickeners and gums	4
Sunscreen agents	2
Talc	2
Thioglycolic acid and salts	2
Miscellaneous inorganic chemicals	4
Miscellaneous organic chemicals	7
All other materials	5
Total	$520

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CHAPTER 9

HOUSEHOLD PRODUCTS AND INDUSTRIAL CHEMICALS

HOUSEHOLD PRODUCTS

Some or most of the exposure to the major classes of chemicals discussed elsewhere in this report takes place in the home. Among these are prescription and over the counter (OTC) drugs, pesticides for household, pet, or garden use, food additives, and cosmetics. These product categories also are covered by specific statutory and regulatory provisions.

Additionally, there are indirect exposures from pesticide residues and environmental contamination.

Beyond these categories, we purchase for home use a myriad of materials needed or convenient in the operation of a household. These include:

Adhesives
Solvents
Soaps, detergents, polishes, and cleaning supplies
Toiletries
Space deodorants
Hobby supplies
Plastic articles and toys
Synthetic fabrics, and many others.

In many of these cases, the quantities involved are large. For example, over a billion pounds of soaps and detergents were purchased for household use.[1]

The public is warned against possible dangers arising from the purchase and use of these chemicals by the Federal Hazardous Substances Act (1969) which was originally titled the Federal Hazardous Substances Labeling Act (1961). These acts define a hazardous substance very broadly as: "Any substance or mixture of substances which (i) is toxic, (ii) is corrosive, (iii) is an irritant, (iv) is a strong sensitizer, (v) is flammable, or (vi) generates pressure through decomposition, heat, or other means, if such substance or mixture of substances may cause substantial personal injury or substantial illness during or as a proximate result of any customary or reasonably foreseeable handling or use, including reasonably foreseeable ingestion by children." The acts also define the word "toxic" to mean any substance "which has the capacity to produce personal injury or illness to man through ingestion, inhalation or absorption through any body surface." The acts then go on to specify how materials classed as hazardous must be labeled when they are made available to the public. Special attention is given to identification of hazards to children.

To provide background information, the Department of Health, Education and Welfare issues an annual list of toxic substances. The 1972 list reports on the toxic characteristics of over 13,300 compounds.[2]

These safeguards provide useful information on acute toxic effects and on proper usage to avoid such effects. There are no controls over the composition of household substances and, providing the labeling properly spells out the hazard, actual contents may be substantially altered and new materials added without an opportunity for the consumer to realize it. The use of the expression, "inert ingredients", is generally intended to mean inert for the main purpose of the composition. Such ingredients may not be inert from other points of view. Thus, a hydrocarbon propellant in an insecticide spray would be inert with respect to killing insects, but highly active from the point of view of catching fire although, again, this hazard would have to be identified on the label.

As with all other classes of chemicals with which we deal, the less obvious and slower consequences of exposure to household agents are not well enough studied or understood, either through epidemiological studies or animal testing. Long-term chronic toxicity testing is not required for most common household substances, and the potential hazard from such exposure is undefined as it is for most of the materials, natural and man-made, which man encounters in the environment.

Industrial Chemicals and Occupational Exposures

Industrial economies have expanded to meet the needs of growing populations and to assist in improving living standards. The opportunities for using a myriad of manufactured chemicals of naturally occurring chemical substances have increased with proportionate rapidity. Exhibit 9-1 illustrates the consumption of raw materials for the manufacture of synthetic organic chemicals and the rate of production of various classes of consumer products from these between 1949 and 1969.

It is worth noting the large percentage increases in these substances over the twenty-year period. A study in 1963 which contemplated resource needs in the future took note of the fact that the rate of production

of hydrocarbons from oil and natural gas had been growing at a rate of 15 percent per year compounded.[3] This was equivalent to a quadrupling every ten years.

However, the manufacture of these materials accounts only for a small fraction of the total quantity of oil and gas consumed. Similar or even larger quantities are involved in the manufacture of inorganic chemicals such as chlorine, sulfuric acid and Portland cement. To aid in grasping the significance of the quantities involved, the total for manufactured consumer organic chemicals of 100 billion pounds corresponds to 500 pounds per capita in a population of 200 million.

Certain chemical exposures occur only in occupational environments; e.g., chemical intermediates which neither exist in consumer products nor are released intentionally or inadvertently to the environment.

Most occupational exposures involve substances with which the public has some contact. The occupational exposure will generally involve higher concentrations, more frequent and extended contact periods, and, very often, different routes of exposure (e.g., through skin contact or inhalation rather than the diet) than the consumer experiences. In many cases, partly because of these differences, the industrial exposure may be better monitored and controlled, and the industrial worker more trained to exercise appropriate precautions. Unfortunately, the appropriate safeguards are often not available or are disregarded.

Until recently, it was widely accepted that a certain amount of risk to health or life was a normal condition of gainful employment. Extreme risks to health were encountered during the Industrial Revolution in England and are being encountered today in countries undergoing rapid industrialization. As acute hazards were recognized in the form of deaths due to occupational diseases and injuries, control measures were introduced to reduce greatly the human toll in most industries. This trend occurred earliest and most completely where the effect was obvious, and easily associated with a specific cause. It has happened more slowly or less completely where the effect was subtle, slow in becoming evident, and less easily ascribed to a causative agent.

In spite of progress, occupational diseases and injuries have continued to be serious problems and the "environmental awakening" has led workers to question why the environment they work in should be any more hazardous than the community expects for the general environment. Today, approximately 125,000 coal miners have lung disease t attributable to inhalation of coal dust and thousands more have respiratory disease from other kinds of exposure in mines. Byssinosis, a lung disease of cotton textile workers, is highly prevalent, though exact numbers are not available. There are several current epidemics of disease related to asbestos exposure, which can produce a crippling scarring of the lung and two different highly malignant tumors of the lung and the lining of the chest and abdomen. Various other cancers are known to occur from chemical exposures in the working environment.

Over 2,000 new cases of silicosis occur each year in the United States. Other "old" occupational diseases, such as lead and mercury poisoning, still occur with regularity. The above diseases are well known, well-recognized forms of occupational disease. Reliable estimates are available for toxic doses; that is, we know what level of exposure is safe. However, working environments are not being controlled as they should or could be, particularly in smaller or less modern firms, and in "depressed" industries.

In addition to these existing diseases related to occupational exposure, the introduction each year of new chemicals and industrial processes, inevitably involving disease-producing potential, poses serious problems in prevention. Small wonder that there has been a tremendous increase in interest in occupational health in the United States on many fronts. Companies, union officials, and workers have become much more interested in

EXHIBIT 9-1

PRODUCTION OF SYNTHETIC ORGANIC CHEMICALS IN THE U.S. BETWEEN 1949 AND 1969

	1949 (lbs.)	1969 (lbs.)	% Increase
Raw Materials and Intermediates*	8×10^9	1×10^{11}	1150
Consumer Products Grand Total:	1.6×10^{10}	1.1×10^{11}	581
Pesticides & Related Products	1.4×10^8	1.1×10^9	686
Medicinal Chemicals	4.2×10^7	2×10^8	376
Flavors & Perfumes	2.4×10^7	1.2×10^8	400
Plastics & Resins	1.5×10^9	1.9×10^{10}	1167
Elastomers	9.5×10^8	4.5×10^9	374
Surfactants	4.3×10^8	3.9×10^9	807
Plasticizers	1.7×10^8	1.4×10^9	724
Rubber Chemicals	8×10^7	3×10^8	275
Dyes	1.4×10^8	2.4×10^8	71
Organic Pigments	3.7×10^7	6.1×10^7	65
Miscellaneous	1.2×10^{10}	7.6×10^{10}	533

* Includes crude products from petroleum and natural gas, and intermediates derived therefrom.
Source: Data from the U.S. Tariff Commission.

hazardous exposures and their control.

Partly from this interest, an important piece of health legislation was produced. The *Occupational Safety and Health Act* of 1970 has far-ranging implications. In essence, its goal is to assure that workers sustain no harm or loss of functional capactiy as a result of their work environment. This goal will require much *manpower* and money to fulfill.

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CHAPTER 10

EFFLUENTS AND BY-PRODUCTS

Under this heading we will consider those pollutants which, after discharge into one of the media on which man and the biosphere depend (air, water, soils), expose people or their environment. Exposures of workers in the course of their occupation are thus not covered here. Exposures incidental to the use of specific products, e.g., household chemicals, are similarly dealt with elsewhere. Hazards and benefits relating to drugs and food additives are likewise considered in other sections.

These unintentional general pollutants have been the central focus of the increasing and widespread concern for environmental contamination that has emerged in the last decade. Both air and water pollution have received widespread public and legislative concern. The former, particularly, has been extensively studied and technological controls and legislative restraints have matured very rapidly in the last fifteen years.

TYPES

The problem can be examined in many different ways: by the medium that is polluted (air, water, soil); by the polluting chemical (organic, inorganic, etc.); by the target organisms (people, plants, wildlife); by the nature of the effects (odors, respiratory irritants, carcinogens, teratogens, mutagens, egg shell thinning of birds as with DDT, DDE, and other chlorinated hydrocarbons); or they can be examined with respect to the sources of the pollutants (natural or man-made, direct discharge or secondary products, single or major sources in contrast to widely disseminated multiple sources). Each point of view brings with it certain insights and understanding which provide useful instruction.

EXTENT AND RECENT TRENDS

Massive collections of data exist on certain pollutants in some geographic regions. Consistent country-wide data are much more scarce. There are at this time increasing efforts to develop uniform and consistent regional data which would make it possible to evaluate comparative regional patterns and time trends. EPA has collected air and water data nationally for some years, and the Geological Survey has now started a "Reconnaissance of Selected Minor Elements in Surface Waters of the United States."

Exhibit 10-1 illustrates estimates of selected total emissions to the air in the United States by source. Transportation (primarily the automobile) is clearly the major source of carbon monoxide (CO) and hydrocarbons (HC). Fuel combustion in stationary sources (space heating and power production) accounts for most of the sulfur dioxide, while industry is credited with most of the particulates.

Time trends in these emissions are illustrated in Exhibit 10-2. Although total emissions of sulfur dioxide or carbon monoxide show no significant change, an analysis of ambient air levels (Exhibit 10-3) does show recent decrease in concentration. In New York City, the decline in ambient SO_2 concentrations over recent years (Exhibit 10-4) is clearly traceable to restrictions on the sulfur content of fuels used in New York City.

With a few exceptions reliable figures to describe the extent of water pollution in specific bodies of water are difficult to find. Five year (1965-1970) water pollution trends are shown in Exhibit 10-5; these data show a major deterioration in the number of stations showing significant increase in nutrients, the cause of stream eutrophication.

EXHIBIT 10-1
ESTIMATED EMISSIONS OF AIR POLLUTANTS BY WEIGHT, NATIONWIDE, 1970 (PRELIMINARY DATA)

Source	(in millions of tons per year)				
	CO	Particulates	SO_x	HC	NO_x
Transportation	111.0	0.7	1.0	19.5	11.7
Fuel combustion in stationary sources	0.8	6.8	26.5	0.6	10.0
Industrial processes	11.4	13.1	6.0	5.5	0.2
Solid waste disposal	7.2	1.4	0.1	2.0	0.4
Miscellaneous	16.8	3.4	0.3	7.1	0.4
Total	147.2	25.4	33.9	34.7	22.7
% change 1969-1970	-4.5	7.4	0.0	0.0	+4.5

Source: Environmental Protection Agency

EFFECTS

How extensive is the problem? The answer is that we have some and limited information in a few areas and substantial ignorance in others. Thus, it is very clear that major air pollution episodes have resulted in significant and identifiable deaths and illnesses, notably the classic Donora episode in 1948 with some 20 deaths and many illnesses, and the still more disasterous week in London in December of 1952 for which some 4,000 excess deaths were recorded. Although the consequence of those levels of air pollution routinely found in our large urban and industrial centers are poorly assessed both quantitatively and qualitatively, we can nevertheless put these effects into a rough scale. Thus, it has been estimated that air pollutants in our large urban centers may be responsible for some 15 percent of the 40,000 deaths per year from respiratory diseases other than cancer. The uncertainty in these estimates derives from the fact that these effects are in fact relatively small in terms of the "normal" levels of these diseases. Were the effects overwhelming, they would be more susceptible to easy quantification. A similar uncertainty surrounds the contribution of air pollutants to cancer and in particular to lung cancer. Cigarette smoking is clearly the major contributor to lung cancer in this and in most developed countries. If urban air pollution contributes, it is clearly a much smaller contribution than that of cigarette smoking. When cigarette smoking is accounted for, there does remain in essentially all studies to date, a slight excess of urban lung cancer over the rates in the rural areas. It has not been possible to correlate this small difference in any quantitative way with levels of air pollutants found in cities studied. Other factors than air pollution could account for these differences, e.g., ethnic, occupational or dietary differences; but air pollution could also be responsible. Again, here as with respiratory disease, although precise quantification cannot be established, upper limits can be estimated. One estimate suggests that perhaps 5 percent of the 55,000 annual lung cancer deaths arise from air pollution.

Although these effects may be relatively small in comparison to other factors, they are clearly and obviously of consequence, especially in that they represent controllable influences on human health; similarly the effects are obviously of intense moment to those affected.

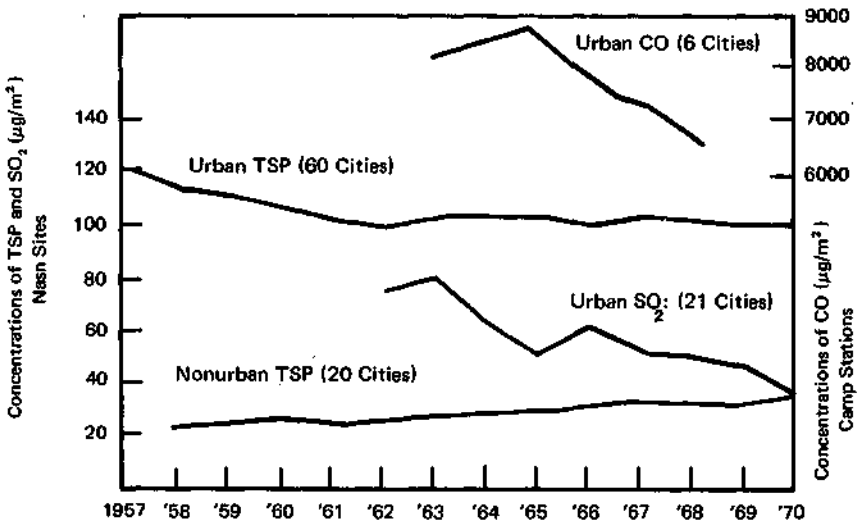
Our understanding of water pollution is less well matured than that of air pollution, particularly as it relates to human health. Thus, there are relatively few examples where water pollutants have been clearly indentified with human health effects. Methylmercury poisoning, as exemplified by Minamata Disease, arising from the comsumption of fish with heavy burdens of methylmercury derived from mercury contaminated waterways, is one of the most vivid examples. Another disease, Itai-Itai, also described in

EXHIBIT 10-2
WEIGHT OF EMISSIONS, 1940-1970
POLLUTANTS (TONS X 10^6)

Year	SO_x	CO	Particulates	HC	NO_x
1940	22	85	27	19	7
1950	24	103	26	26	10
1960	23	128	25	32	14
1968	31	150	26	35	21
1969	34	154	27	35	22
1970	34	147	25	35	23

Source: EPA, "Nationwide Air Pollutant Emission Trends, 1940-1970."

EXHIBIT 10-3
TRENDS IN AMBIENT LEVELS OF SELECTED AIR POLLUTANTS



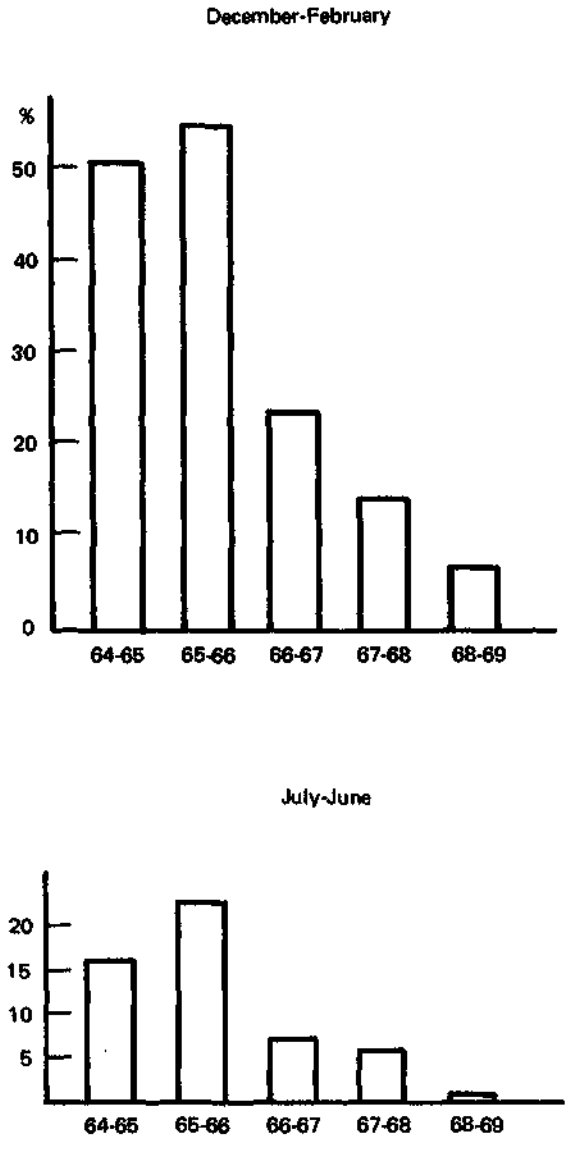
Source: The Mitre Corp. MTR-6013. Based on Environmental Protection Agency data.

Japan, has been associated with the metal, cadmium. DDT poisoning in fish-eating birds has been well established and bears close analogy to the hazards of eating contaminated fish as in the case of mercury.

Eutrophication, which has aroused so much concern, is often traceable to "pollution" by an excess of a normal nutrient, namely phosphate. In this case, the normal balance of biota in the waterway is shifted in favor of algae and against other forms of aquatic life such as fish.

We have even less direct information on soil contaminants and their relation to health or environmental effects. We have nevertheless many hints that selenium in certain regions is incorporated into grazed plants in sufficiently high levels to produce killing of livestock. Nitrate, which moves through soils, waters and the atmosphere in enormous quantities in the natural nitrogen cycle, can also under certain circumstances be accumulated in plants in quantities toxic to livestock. Despite the immense quantities involved in this natural cycle, man's intervention, through the use of nitrogen in fertilizers and the nitrogen in the excreta of livestock in feedlots, can produce significantly excessive local concentrations /of nitrate. Similarly nitrogen fixation in space heating, power production and the operation of internal combustion engines contributes significantly to the nitrogen cycle. This normal material when found in excessive quantities, for example in some rural wells, has produced toxic methemoglobinemia in infants whose formula was prepared from well water with high concentrations of nitrate.

EXHIBIT 10-4



PERCENT OF HOURLY SO_2 AVERAGE ABOVE 0.25 PPM

BENEFITS

A discussion of the benefits associated with pollutants such as those we have been considering leads one into strained banalities. It is obvious to all that the heavily polluting automobile is a useful and sometimes a pleasant thing to have with us, that we need to warm our homes in the cold season, that the mercury that fills our teeth or goes into our radio batteries brings benefit, and that the electricity that lights our homes and cooks our food is virtually indispensable. In retrospect, it seems clear that the DDT that constitutes a heavy burden in our agricultural soils and many waterways was, for most agricultural purposes, a poor choice among the pesticides which became available in increasing variety. At the time, it commended itself for its effectiveness, low cost, and low mammalian toxicity. Furthermore, in malaria control, DDT has been a major success story and has saved millions of lives. Thus, in most instances, the benefits are

readily apparent and probably in most cases have more than justified the adverse side effects. It may be a defendable proposition that the availability of electricity has saved as many lives of the elderly through its use for air conditioning during episodes of high ambient temperature as it has taken through the pollutants produced in its production.

SOURCES

It is equally apparent that we have been casual, careless and thoughtless in our indiscriminant pollution of the environment. In most instances we have learned, and invariably belatedly, that the benefits could be retained while instituting controls of acceptable cost. Thus, restriction in the sulfur content of fuels used in power production has lead to a progressive decline in sulfur dioxide content of the air of New York City over the last six years without sacrifice in the extent of power production or any major impact on price. The next stage of reduction will, however, be much more costly. In the area of power production, uninformed apprehension could well delay the attainment of the next stage of benefit by unduly inhibiting conversion to nuclear power.

Alertness and pressures for controls are essential. It was only under regulatory pressure that we learned that chlorine and alkali could be produced by the electrolytic process with virtually zero loss of mercury to the environment rather than the half pound and more mercury per ton of chlorine that was discharged earlier to waste waters.

The problem is sometimes a relatively simple one in which sources and distribution are straightforward and identifiable, for example, the discharge of carbon monoxide from the tailpipe of automobiles. In others and perhaps in most instances, the problem can be very much more complicated. Mercury is perhaps a good example of these complexities. It is very clear that the fish taken from inland and estuarine waters adjacent to industrial discharges of mercury gained their mercury burden from these industrial sources, albeit indirectly. That is to say, the fish drawn from industrially contaminated waters do not directly ingest the discharged mercury; their mercury burden is traceable to a previously unknown microbial process whereby the inorganic mercury in the bottom sediments is converted into the very toxic compound, methylmercury, which is then progressively concentrated in the aquatic predator chain leading to the highest concentration in those at the top of the food chain. A similar biological process of accumulation of the highly toxic methylmercury is presumably responsible for the methylmercury in swordfish. On the other hand, the swordfish is a deep-sea feeder and it seems certain that much of the mercury contributing to this burden is of a natural and not man-made origin.

It has been proposed (in rough analogy to the nitrate cycle alluded to above) that there is a vast system of global transport, distribution and conversion of mercury. Thus, one estimate places the amount of mer-

EXHIBIT 10-5
POLLUTANT SOURCE TYPE AND TRENDS FOR DRAINAGE BASINS WITH LOW AGRICULTURE AND HIGH POPULATION OR HIGH INDUSTRY, OR BOTH HIGH – % OF STATIONS IN EACH CLASS

Pollutant Type*	Dominant Flow Effect			Time Trend, 1965-1970		
	Dilution	Mixed	Runoff	Better	No Trend	Worse
Dissolved Oxygen (± 10%)	4	76	20	11	75	14
(Number of Stations)	(1)	(19)	(5)	(4)	(27)	(5)
Oxygen-Demanding Load (± 25% BOD, ± 20% COD, TOC)	11	58	31	48	29	23
(Number of Stations)	(2)	(11)	(6)	(15)	(9)	(7)
Nutrients—Total Phosphorus, Organic Nitrogen & Ammonia (± 30%)	0	80	20	18	18	64
(Number of Stations)	(0)	(12)	(3)	(4)	(4)	(14)
Nutrients—Soluble Phosphates (± 30%)	17	83	0	0	64	36
(Number of Stations)	(1)	(5)	(0)	(0)	(7)	(4)
Nutrients—Nitrite & Nitrate (± 30%)	7	86	7	5	30	65
(Number of Stations)	(1)	(12)	(1)	(1)	(6)	(13)
Salinity—Total Dissolved Solids (± 15%)	46	54	0	9	67	24
(Number of Stations)	(7)	(8)	(0)	(2)	(14)	(5)
Suspended Solids & Turbidity (± 40%)	0	65	35	21	76	3
(Number of Stations	(0)	(15)	(8)	(7)	(26)	(1)

*Thresholds used for determining existence of trends are given in parentheses after pollutant type. Actual levels are based on observed variability of concentration versus flow curves.

Source: Enviro Control, Inc.

cury in the earth's atmosphere at about 80,000 metric tons. This appears to be in a continual state of flux with complete turnover 2-3 times per year. Another estimate concludes that the mercury content of the oceans approximates 10^8 tons, presumably with a very slow turnover. These large amounts may be contrasted with the total world production of some 12,000 tons of which obviously only a portion is lost to the environment. Added to this is an estimated maximal inadvertent discharge (e.g., through burning of coal and oil), of a few thousand tons. Thus, much of the mercury in the atmosphere natural cycle may be of natural origin. Despite this very extensive cycle of transport and turnover, it is clear that man can locally alter environmental mercury concentrations dangerously by careless practices.

In other instances man has in a major and dramatic way contaminated the global biosphere with certain materials. Thus, it has been estimated that lead is now 20 times more concentrated in the biosphere than it was in primitive times, several millenia ago. The same trend has been more tentatively suggested with respect to cadmium in the last half century. DDT and PCB, both products of relatively recent technology, are now found widely disseminated throughout the world.

CONTROL

Effective control procedures are most efficiently aimed at source control or substitution. In some instances sources are identifiable, in others, they are not. In some instances subsequent alteration of the pollutant dramatically alters the problem. The example of methylmercury is a recently discovered one. Another is the incidental generation of ozone in the development of photochemical smog discovered some 25 years ago. A first step in control is the identification of sources. This involves a series of approaches which we recommend the appropriate regulatory agencies should be encouraged and authorized to pursue.

A. Identification of Industrial Sources

1. Registration of industrial chemicals with the regulatory agencies.

2. Periodic reporting to regulatory agencies of production amounts and distribution patterns.

3. Required and continuing inventory in industrial processes of losses through stacks and sewers. These records would be open to inspection. This would be precedent to,

4. A deliberate and staged progression towards attaining zero loss of all contaminants and byproducts in industrial processing. In the attainment of this, it may be desirable to,

5. Develop such systems as sequestered water sources in which the same water is reused repeatedly by industry.

These seem realistic approaches for identifiable major sources. Some may be readily attainable now, others may require improved technology before becoming feasible. They can define some elements of a national policy in pollution control.

B. Non-industrial Sources

The situation is more complicated where one is dealing with a large number of sources. Thus,

1. Substantial reduction of individual discharges from the internal combustion engine is clearly attainable.

2. Agricultural chemicals have been obviously misused in the past with a resulting widespread overuse of the persistent pesticides and probably of some fertilizers. A policy based on substitution to more acceptable chemicals or forms of chemicals (e.g., non-persistent pesticides, ammonium ion as a nitrogen source) is one imperative step to take. Another is to establish a firm policy of restricting use of agricultural chemicals to the quantity actually needed.

3. Disseminated incidental sources of environmental contamination present still different problems. Examples of these include lead, cadmium and mercury from discarded batteries. PCB contained in small electrical units and plastics is another example. Such contaminants find their way into municipal wastes and eventually may produce contamination through leaching from dumps and volatilization during inadequate incineration. The identification and interception of such sources will require development of techniques for waste handling, for the most part, not now available.

4. In all of the above instances, substitution represents an alternate and often preferable approach (less dangerous, less persistent, less likely to escape.

C. New Knowledge Needed

The two preceding categories relate primarily to identified pollutants whose sources and transport are known. This is only a portion of the totality of the pollutants of importance. There are still many areas of uncertainty as to: the relative importance of the various sources of contaminants or pollutants, the manner and time scale by which they reach the environment, their conversion and distribution patterns, and finally, their effects on the environment and on people.

These issues collectively define major needs in the way of needed new knowledge.

FUTURE TRENDS

It seems likely that the future will show several major patterns. The period of very rapid growth and great diversity in industrial chemicals may

be coming to a close. With the intense scrutiny now given to chemical hazards and the apprehension and concern directed to new and unknown chemicals, industry may tend to introduce fewer new chemical products and processes in the future.

Automation is already well underway and with it a trend toward continuous rather than batch processing. It seems possible that both automation and continuous processing will favor lesser pollutant discharge and more feasible control procedures.

Although the diversity of new industrial chemicals may decrease, some not so new materials will probably assume larger roles in future technology—e.g., increasing use of titanium, the growth and displacement of other competing plastics by such success materials as the polyethylenes, nylons and vinyls.

It is quite unclear at the moment whether or not concern for pollution and recycling will lead to the production of longer lived and more readily repairable products. This would run counter to recent trends which strongly seek economy and minimization of all labor inputs, both in manufacture and service. It would also reverse the frequent pattern of designing for early obsolescence and rapid turnover.

SECTION III—Major Issues

Chapter 11

Acquisition of Knowledge, Toxicology and Regulatory Information

CHAPTER 11

ACQUISITION OF KNOWLEDGE, TOXICOLOGY AND REGULATORY INFORMATION*

INTRODUCTION

Regulatory decisions of the type taken by the FDA and the EPA are characteristically perceived as resting on a foundation of scientific information. A New Drug Application for a pharmaceutical product is approved because the developer and would-be manufacturer of that drug has offered evidence of efficacy and safety of use.

A national standard for automobile emissions is proposed because of some evidence relating the state of human health to exposure to the emitted pollutants. One can logically pose a number of questions concerning the adequacy of the fund of information available to the regulatory agencies at any point in time. An examination of this sort reveals a highly variable picture depending upon the substance under consideration. Variability occurs in the absolute amount of information, its quality and in the resources available to produce it.

Elsewhere in this report the subject of balanced decisions is discussed. Balancing, in this context, refers to judgments about several issues, only one of which may be the hazard to human health. Economic consequences of alternative courses of action, utility or benefit, etc. are among the other issues. Here again one is entitled to ask some critical questions about the quantity and quality of information available to decision-makers. The following paragraphs examine the state of the knowledge base available to regulatory decisions as well as the sources and resources for this information.

SOME ELEMENTARY STATISTICS

A straightforward method of beginning any analysis of chemicals in relation to health is to review the amount of material or product outstanding and to estimate its distribution physically or among population groups. Such information has utility in defining exposed population groups and in deriving an estimate of the probability of human exposure.

It often turns out that data describing quantities of chemical products manufactured and their distribution are not available. In cases where legal authorities for regulation apply, this information is most easily available. The Federal Government is fairly well apprised of the number of different pesticidal products ("formulations") which are produced, sold domestically, exported and used in each of various applications. From this universe, it can be ascertained how many different chemical entities exist. These data are compiled by the Department of Agriculture,[1 2 3] and by the Environmental Protection Agency.[4]

For industrial chemicals, household products, and other commercially available functional chemical substances, questions of production and distri bution are less easily answered. The Tariff Commission is the major source of information on production of industrial chemicals. Yet there are legal limitations to this source in the cases of small numbers of manufacturers. The pending Toxic Substance Control Act would permit the Administrator to seek this information from manufacturers.

Information on impurities is not systematically collected. For drugs, pesticides, food additives, and cosmetics, assurances of various degrees of purity are demanded of the developers of new products. However, the identification and amounts of specific impurities are not required.

KNOWLEDGE ABOUT RISK AND BIOLOGICAL HAZARD

The production of knowledge from biological testing comes from several sources and is the result of programs of research in both the public and private sectors. The patterns vary widely according to the class of substance under consideration. That is, knowledge about unwanted side effects of a new pesticide generally comes from a different set of laboratories than those supplying information on the biological effects of air pollutants. The mixture of private and public efforts varies widely but according to patterns which can be explained in terms of incentives, legal obligations and the type of research needed in each case.

Several Federal agencies support research aimed at improving understanding of the health effects of

* The Panel, during its deliberations, arrived at a number of findings which are underlined in this chapter. In some cases these led to formal recommendations which are presented in Chapters 2 and 3.

physical and chemical environmental agents. This Panel had the advantage of the product of another committee, one of whose tasks was to take stock of the present Federal investments and programs of environmental health research.[6] This review took the form of a detailed and critical perusal of each of the research projects submitted by the several contributing Government agencies. This survey of the Government's effort (for fiscal year 1972) covered biological agents as well as chemical and physical ones. Research on therapeutic drugs and their side effects was not included. This critical sorting included research which clearly met the strict definition of the area and excluded supporting and peripheral areas which are sometimes reflected in agency budgets under research categories (such as physical measurement, monitoring, control, etc.). Administrative costs and expenditures for training were also excluded. Hence, the total figures appeared to be less than those in ordinary budget documents.

There are four principal contributing agencies (EPA, AEC, HEW and DOD). The major contributors in HEW are the National Cancer Institute, the National Institute of Environmental Health Sciences, National Institute of Occupational Safety and Health and FDA. In addition, there is a residue of research scattered widely among a number of other agencies (USDA, USDI, NSF, NASA and other National Institutes of Health).

The total level of investment in environmental health research (according to a broad, inclusive definition) for FY '72 is $215 million. This includes research on infectious agents as well as chemical and physical ones. It also includes work dedicated to physical measurement and characterization of environmental agents as well as research in behalf of control.

If one excludes biological infectious agents, the total investment in this research area is $124 million. This is summarized in Exhibit 11-2. Note that of the total of $124 million, nearly $46 million or 37 percent is spent supporting research on ionizing and electromagnetic radiation—mostly by AEC.

EXHIBIT 11-1
TOTAL LEVEL OF FEDERAL EFFORT IN ENVIRONMENTAL HEALTH RESEARCH FOR FY '72

Agency	$'s million
AEC	40.1
EPA	16.8
DOD	23.4
HEW	23.4
NCI	(38.6)
NIEHS	(15.6)
FDA	(49.7)
NIOSH	(14.8)
Other	60.9
	215.1

EXHIBIT 11-2
TOTAL FEDERAL RESEARCH EFFORT (BROADLY DEFINED) IN BEHALF OF PHYSICAL AND CHEMICAL AGENTS FOR FY '72 ($'s MILLIONS)

Agency	Physical	Chemical	Total
EPA	3.6	11.6	15.2
AEC	35.7	4.3	39.9
HEW	9.9	32.6	42.5
NCI	(.9)	(12.7)	(13.7)
NIEHS	(1.6)	(11.6)	(13.2)
NIOSH	(5.4)	(5.9)	(11.3)
FDA	(2.0	(2.3)	(4.3)
DOD	6.7	0.8	7.5
Other	5.7	12.9	18.6
	61.6	62.2	123.8

To determine the amount of effort aimed solely at an understanding of the effects of chemical and physical agents on biological organisms in a narrow sense, figures corresponding to certain categories have been extracted from these tables. These reflect the research done to promote understanding of absorption (or entry) of the agents into the organism, metabolism, distribution and mechanisms of biological action, modification, interactions and biological consequences or end-points. *It is these figures which come closest to a representation of the meaningful biological research effort in this field* (Exhibit 11-3).

From these figures one can conclude that the FDA and EPA are generally poorly equipped scientifically (16 percent of the total research effort). The AEC contributes 32 percent and NIH 28 percent. There is a heavy emphasis on radiation research—most of it on effects of ionizing radiation and most of this in the AEC. The DOD contributes less than eight percent and almost all of this is concerned with radiation and other physical agents.

In addition, the committee's report from which these figures were taken observed that the investment in research on mechanisms of biological action may be thought of as an index of the sophistication of this research effort. The total investment in this research amounts to $11.9 million and 80 percent of this research is supported by NIH (64 percent of it within the National Cancer Institute).

The following is an estimate of the distribution of these research funds according to their route of expenditure (in-house, contract, or grant): (See Exhibit 11-4)

It is instructive to consider the magnitude of the industries regulated by such agencies as the Food and Drug Administration in judging the appropriateness of the expenditures aimed at assembling background information used in their regulation. In 1970, the total value

(manufacturers' shipments) of foods, drugs and cosmetics regulated by the FDA was $82.5 billion. These were divided among the several categories as follows:*

	($'s billion)
Foods	73.5
Prescription drugs	3.5
Proprietary drugs	1.5
Cosmetics	4.0
Total	82.5

The FDA has responsibility for the regulation of products amounting to approximately 38 cents out of every consumer dollar spent. Of the total FDA budget of $110 million in 1971, approximately one-fifth was spent on gathering scientific data with which to make regulatory decisions.

It is interesting to contrast these figures with expenditures in behalf of health and regulation in another field, radiation:

Total sales of electric power/year.	$20 billion
Of this, approximately 1 percent of all power is now being generated from nuclear fuel.	$200 million
Total capital expenditures per year for electric generating and transmission equipment.	$4-6 billion

In 1971, the budgets for research and regulation in this area were:

AEC	
Division of Biology and Medicine (Research)	$88 million
Regulation	121
EPA	
Radiation research and regulation	7
Total	$216 million

The private sector's contribution to this field is more difficult to estimate since typically this research is accounted for as part of a total research and development program. Exhibit 11-5 gives figures for R&D for the major drug manufacturers.

* Figures provided by the Food and Drug Administration. The value of manufacturers' shipments were estimated for 1970 from figures describing 1969 experience.

EXHIBIT 11-3
FEDERAL RESEARCH EFFORT AIMED AT UNDERSTANDING THE HUMAN BIOLOGICAL EFFECTS OF PHYSICAL AND CHEMICAL ENVIRONMENTAL AGENTS

TOTAL—PHYSICAL AND CHEMICAL AGENTS HUMAN DIRECTED BIOLOGICAL RESEARCH ONLY*

Agency	Physical $'s million	Chemical $'s million	Total $'s million	Percent of total
EPA	2.8	7.3	10.2	11.8
AEC	25.1	2.7	27.8	32.2
HEW	6.9	26.2	33.1	38.6
NCI	(0.8)	(11.6)	(12.4)	(14.5)
NIEHS	(1.6)	(10.0)	(11.5)	(13.4)
NIOSH	(2.7)	(2.8)	(5.6)	(6.5)
FDA	(1.8)	(1.8)	(3.6)	(4.2)
DOD	6.2	0.6	6.9	7.9
Other	4.9	3.2	8.1	9.5
Total	46.0	40.0	86.0	100.0

* These amounts do not include the appropriation for the Pharmacology/Toxicology Program of the National Institute of General Medical Sciences.

Source: Report of the OST-CEQ Ad Hoc Committee on Environmental Health Research.[6]

EXHIBIT 11-4
DISTRIBUTION OF FEDERAL SUPPORT FOR ENVIRONMENTAL HEALTH RESEARCH

Agency	Percent In-House	Contract	Grant
AEC	0	100	0
EPA	59	37	4
DOD	74	25	1
HEW			
NIOSH	60	30	10
NCI	0	51	49
NIEHS	27	3	70
FDA	53	47	0
Average	39	42	19

Source: Report of the OST-CEQ Ad Hoc Committee on Environmental Health Research.[6]

EXHIBIT 11-5
INDUSTRY-FINANCED R&D ON DRUGS FOR HUMAN USE

[$'s million]

1968 Actual	1969 Actual	1970 Actual	1971 Budgeted
449.5	505.8	565.8	625.3

DATA FROM THE PHARMACEUTICAL MANUFACTURER'S ASSOCIATION

Included in these figures are expenditures for both basic and applied research, expenditures on R&D directed toward new product opportunities as well as those directed toward an understanding of pharmacology and side effects. They include funds expended both within drug company facilities and those spent in medical schools, commercial laboratories, hospitals, etc. These figures may also reflect some non-drug research carried on by

those companies which have some diversification.

These figures in Exhibit 11-6 are those portions of the values from Exhibit 11-2 which are the specific expenditures within drug firms for R&D work on human-use drugs aimed at animal safety and toxicology, other pharmacologic animal testing and human clinical research.

EXHIBIT 11-6
INDUSTRY-FINANCED R&D ON DRUGS FOR HUMAN USE CONCERNED WITH PHARMACOLOGICAL ANIMAL TESTING AND HUMAN CLINICAL DRUG RESEARCH AND WITH INVESTIGATION OF SIDE EFFECTS AND TOXICOLOGY

[$'s million]

1968 Actual	1969 Estimated	1970 Estimated	1971 Estimated
167.6	188	211	233

Data for 1968 were provided by the Pharmaceutical Manufacturers Association. Figures for 1969, 1970 and 1971 were calculated from the figures contained in Exhibit 11-2 assuming that the 1968 percentage remained constant.

The pesticide industry spends proportionately much less in examining the biological side effects of its products. From a survey performed for the National Agricultural Chemicals Association expenditures by industry for toxicology and metabolism were estimated (Exhibit 11-7):

The evaluation and testing underwritten by industry is actually performed partly within the manufacturer's own laboratories, in clinics, medical schools and hospitals, and in independent testing laboratories.

There are estimated to be under 30 independent biological research and testing laboratories in the United States. From a sample of these institutions, the following estimates were made of the total size of this industry (Exhibit 11-8):

EXHIBIT 11-7
EXPENDITURES FOR TOXICOLOGY AND METABOLISM BY MEMBERS OF THE PESTICIDES INDUSTRY 1967-1971

[$'s million]

1967	1970	1971 Estimated
8.5	11.2	12.0

Original data gathered from a study, Pesticide Industry Profile Study, performed by the Ernst and Ernst Trade Association Department, Washington, D.C., 1971. The figures contained in this report were collected from a sample of pesticide manufacturers representing 81 percent of the total pesticide sales. The figures in Exhibit 11-7 were projected to the total industry.

These laboratories vary widely in the pattern of research. Very little (perhaps less than five percent) of their work can be considered basic research. Most of it is related to testing for safety and adverse effects of products and a smaller proportion for efficacy. The majority of the testing is for drugs and food ingredients or additives.

Finally, academic institutions play an important role. These laboratories, which generally perform the most sophisticated and fundamental research in this area, are supported heavily by Federal and State Governments.

It is useful for this discussion to divide the universe of materials into products and non-products (environmental pollutants, for example) and to consider separately those products for which there is a clear and forceful regulatory authority and those which are not tightly regulated. For regulated products (such as therapeutic drugs, pesticides, food additives) the traditional philosophic and legal stance taken by Federal Government has been that the developer or manufacturer of the

EXHIBIT 11-8
TOTAL VALUE OF THE RESEARCH AND TESTING PERFORMED BY INDEPENDENT TESTING LABORATORIES IN THE UNITED STATES, 1966-1971

[$'s millions]

YEAR					
1966	1967	1968	1969	1970	1971
13.5	16.4	16.0	18.4	18.8	21.8

Source: Estimates made from an industry survey.

products was obliged to "prove his material safe" before being permitted a license to "enter them into interstate commerce." In practice, this has meant that the necessity to evaluate (or underwrite the evaluation of) the biological effects and unwanted side effects of new products has rested with the manufacturer. This evaluation is characteristically performed during the course of development and the costs of this research are considered part of development costs.

The particular research and evaluation studies performed on prospective new drugs follow a pattern of steps from an investigational or experimental status through the satisfying of requirements for a New Drug Application. There exists a broad schedule for this research. The particular design of the studies to be performed is the product of negotiation between the Government agency (FDA) and the manufacturer. Generally this takes the form of the manufacturer's responding to advice and requests for specific types of information from the FDA.

Large manufacturers of agricultural chemicals follow a

pattern similar to that in the drug industry by performing animal studies in their own laboratories. The regulatory agency (EPA) prescribes the general types of studies required for registration of pesticides. In the case of pesticides used on food crops, an additional petition for a tolerance (tolerated amount of pesticide residue) is required and an additional amount of biological information is necessary to achieve this.

Food additives are typically manufactured by large chemical firms, where they represent a very small fraction of their total production, or by a number of relatively small specialty manufacturers (whose research budgets and facilities are correspondingly thin). Incentives to engage in extensive evaluation of biological effects and safety testing in either case have not been outstanding. Much of the work performed in this area has been done by private, independent testing laboratories on contract to the manufacturer and the quality and sophistication of this work have varied considerably.

At least as important is the fact that of the total food additives in use, laboratory investigation of biological effects and safety has been applied to only a small fraction. This subject has been examined in the section above on food additives where it was pointed out that technology of development outpaced corresponding efforts to understand and a series of intermediate measures such as the GRAS review were instituted in order to bring to bear some degree of scientific judgment.

The patterns of research described thus far result essentially from the existence of specific regulatory laws under which the Government is able to solicit from manufacturers the information it requires to make its decisions on new products. The Food, Drug and Cosmetic Act applies to food additives and drugs. The Federal Insecticide, Fungicide and Rodenticide Act supplies this information gathering requirement for pesticides (along with a few other chemical substances). Beyond these classes of products the legal authorities are much less clear and permit the Federal Government much less authority to seek this type of information from private sources. A similar regulatory philosophy has prevailed in other areas such as household and consumer products. That is, the manufacturer is expected to assure at least himself that his products are safe before marketing them. However, the authorities which apply (such as the Federal Hazardous Substances Act) are not explicit on the subject of responsibility for performing tests or research in order to arrive at a judgment of safety. The Federal leverage of the Hazardous Substances Act (administered by FDA) is in its ability to insist on the use of a product label denoting a hazard. In practice, however, it is the Federal Government which is obliged to gather the scientific evidence to make a determination of a hazard before exercising its leverage. The Federal Government has up to now been poorly equipped to engage in research and evaluation of a scale which would be required to seek out this knowledge.

For industrial chemical substances, the laws and patterns of research are even less clear. There are no clear obligations on the part of any of the interested parties (producers, users, consumers, government) to gather information on unintended side effects of these chemical products. It should not be surprising, therefore that the storehouse of knowledge on the biological effects of materials such as polychlorinated biphenyls are as recently gathered as they are.

The above discussion has considered new chemical products. It became evident during the Panel's deliberations that special attention should be paid to the case of chemical products already on the market—some of which may have been passed upon at one time by a certification or registration process and all of which had been viewed as safe for their intended uses. This turned out to be an important area and was clearly one where the Government faced recurrent problems. This area might be described as the "old decision—new science" problem. Philosophically, it has generally been assumed that once a drug or a pesticide has achieved an approval which permits marketing, it is acceptable for all time or at least for a period of time which is long compared to the expected period of marketing. The regulatory laws themselves reflect this philosophy, in the admonitions to manufacturers to "...prove safety..." at the time of the original application.[7] What has become clearly apparent is that, because science is by nature dynamic, it will raise new questions from time to time which will displace confidence in any notion of absolute safety. In fact, absolute safety is a misnomer. The point to be made here is that if it is desired that science be exercised in behalf of questions of biological effect and safety of chemicals, such an effort would by definition have to be a continuing one which would reflect the changes in the state of scientific understanding.

It is apparent that the present arrangements for gathering new biological information on already marketed products do not accommodate this need. There are unclear obligations on the part of the private sector to perform additional research on products already approved and, understandably, the incentive to seek answers to questions which conceivably could destroy the market outlook for a product is not strong.

Some of the regulatory laws do allude to the questions raised by new knowledge. For example, the present law governing pesticides obligates the Environmental Protection Agency to review with a 5-year periodicity each of the pesticide registrations. However, it has been unusual for these reviews to provoke additional research on the basis of some new scientific insight or body of scientific knowledge.

In the face of uncertainty of obli-

gation in the private sector to perform additional research, the Federal Government has drifted without explicit policy toward the performance of increasing amounts of evaluation of marketed products. Between 1964 and 1968, the National Cancer Institute performed through contract an animal screening study of over a hundred pesticides to ascertain their potential for producing tumors, birth defects or genetic alteration.[8] The results of this study have provoked an additional series of investigations of the same type presently underway in NIH. Similarly, the National Institute of Child Health and Human Development of NIH currently supports a program of research on the side effects of currently marketed oral contraceptives. It is accurate to say that these Federal programs of research were prompted by a realization that there was a disparity between the amount and quality of scientific information supplied at the time of original introduction and registration of certain products and those questions which were raised by the science of the present day. These disparities have been highlighted in several of the crisis-laden reviews and decisions which the Government has undertaken in the past few years.[9]

It is important to note that Government-sponsored research on marketed pesticides and oral contraceptives does not by any means cover the total range of products. In fact, rather than adopting an orderly, long-term research plan, the Government often finds itself confronted with a deadline for a regulatory decision so close at hand that its own participation in this research area is severely limited. Further, since there is no set policy for this activity, the resources available for this research have been relatively scarce. Limited, pilot-type investigations are the rule and, not infrequently, they displace the on-going research program of an agency. The Panel is impressed that a sizable portion of the information used in regulatory decision-making is derived from investigations completed only a short time before the decisions were made. This implies that the research and its results have not been submitted to the critical processes of evaluation and interpretation characteristic of an established body of scientific knowledge. Research for regulation is surprisingly often performed in an atmosphere of urgency which further compromises its quality. Another serious shortcoming of research in a regulatory agency is the pressure on investigators to obtain results which support a regulatory decision or policy, even if this means discarding research results which are equivocal or contrary to the hoped-for result.

For substances clearly in the public domain (water and air pollutants, for example) the Federal Government has assumed increasing responsibilities for research over the past several years, in spite of these limitations on the nature and the quality of the research. However, the total effort is modest when compared to the investments implicated by the regulatory decisions.

STUDIES ON HUMANS, CLINICAL RESEARCH, EPIDEMIOLOGY

Ideally, research aimed at understanding the human health effects of environmental agents would include the study of man. Such studies are severely limited by ethical, legal, and other constraints. There are, however, some organized research programs designed to collect observations resulting from accidental human exposures, to gather biochemical and physiological and clinical data from experimental subjects, and to study by epidemiologic methods the associations between human exposure and mortality or morbidity.

There are fewer constraints in the study of potentially beneficial new drugs. Intensive clinical trials are the rule in pre-market evaluation. These trials are performed by physicians and clinical pharmacologists typically on the basis of contractual arrangements with drug manufacturers.

Programs designed to detect adverse reactions or side effects from drugs among members of the general population after the drug has been placed on the market remain very modest. A recent symposium on this subject held by the National Academy of Sciences indicated a number of directions for any such program. Two considerations stand out as particularly important. One is the importance of "denominator" information—valid data designating an exposed population. The other is the quality of the observations judged as adverse reactions. Thus far, successful schemes have been demonstrated for collecting data on hospitalized patients in an intensive and rigorous fashion. There is not yet a working system for ambulatory patients. Better advantage could be taken of prepaid health delivery systems where subscribers can be followed medically over long periods of time.

Epidemiological studies of environmentally associated disease are not numerous. This area has been reviewed recently and a number of recommendations made in an HEW report on research needs in environmental health.[10] One of the factors which has curtailed such studies has been a lack of professionals qualified to work in this field. Another has been a lack of a sizable commitment of resources and talent for studies of the very long duration which may be entailed. A third has been a lack of a number of simple but highly useful data sources such as registries of mortality. Within the Federal establishment, the major chronic disease epidemiologic programs concerned with physical and chemical environmental agents as cancer-inducers are supported by the National Cancer Institute of NIH and the Environmental Protection Agency (for air pollutants and pesticides).

Occupational exposures to environmental agents represent

special opportunities for relatively controlled study. Studies in occupational settings have been mounted sometimes on the initiative of a group of university- or Government-based researchers who have perceived a particular exposure situation of interest. These latter studies are almost entirely supported by the National Institute of Occupational Safety and Health of HEW.

KNOWLEDGE ABOUT BENEFIT, UTILITY, EFFICACY, AND ESSENTIALITY

To a great extent, utility or benefit of products is assumed and taken for granted. The test of acceptance in the marketplace is often the one on which this judgment is based. Documentation of utility or benefit, however, is often very difficult to derive. Once a product has achieved acceptance in the market, it is difficult to return to a posture of questioning its benefit in any rigorous sense. Once a drug or a pesticide has gained such a high degree of use that a dependence (or a perceived dependence) develops, the asking of hard questions about value and utility is troublesome, embarassing, and often impossible. Finally, cost enters this picture also. In cases where the unit price of a substance is relatively low, large amounts of the material may be used or applied simply under the assumption that if a small amount is useful, increasing amounts will bring proportionally greater or at least equal benefits. This last point may, perhaps, best be illustrated by chemical insecticides and herbicides. The cost of these materials is low compared to the costs of other investments in the agricultural industry. This fact has made the heavy, and at times, injudicious use of pesticides a not uncommon practice. It is felt that there is a dependence on these adjuncts. Yet, as the Panel learned, the documentation of the marginal productivity of the investments made in these implements is very difficult to arrive at. The few attempts which have been made to describe the productivity of these chemicals have given some conclusions which run counter to traditional views.[11]

From time to time new scientific evidence is uncovered which alters the estimate of hazard or biological risk of a chemical material. A so-called risk-benefit analysis is called for. Typically, there is found very little information on which to determine benefit or to document the penalty occasioned by removing the material from use. A recent analysis of this type was performed in behalf of the chemical materials known as polychlorinated biphenyls (PCB's). This family of compounds possessed a number of unusual chemical-physical properties and had found their way into a large number of uses. It was only after an intensive examination of each of these applications (in this case by the National Bureau of Standards) that the essentiality or particular utility of PCB's in certain applications could be identified for certain. The moral which emerges is that sound information descriptive of benefit is generally not readily available.

Efficacy has been considered at length for therapeutic drugs by the National Academy of Sciences.[12] This study was occasioned by an amendment to the Food, Drug and Cosmetic Act in 1962 which obligated manufacturers of new drugs to present evidence for effectiveness. The Commissioner of the Food and Drug Administration interpreted this amendment as pertaining to drugs already marketed as well as to new ones. The Drug Efficacy Study was undertaken to assist him in reviewing the existing evidence for the current inventory of drugs. These were classified into 30 categories and each category was reviewed by a separate panel devoted to a therapeutic class. Each drug was then evaluated according to a scale of effective, probably effective, possibly effective and ineffective. Among the conclusions reached by this study was the observation that evidence of efficacy of the drugs reviewed was of generally poor quality.

> Many of the presentations submitted by manufacturers in support of the claims made for the use of their drugs consisted of bulky files of reports of uncontrolled observations and testimonial-type endorsements. The lack of substantial evidence based on well-controlled investigations by experienced investigators was conspicuous. Moreover, searches of the medical literature indicated that there existed little convincing scientific evidence to support many of the cited indications for the use of drugs that are currently in good standing in medical practice. There is every reason to believe that industry is aware of the need for, and seeks to obtain, the best scientific endorsement of its products. The failure, therefore, must be attributed to the difficulty that industry has in commanding the needed clinical facilities and the services of experienced investigators. This is not a fault of industry alone, but rather is a reflection of a serious gap in the programming and management of the national effort in therapeutic research.[12]

One of the most important social principles recognized in the health-related regulatory laws is the idea that the safety of an article should be officially established before it is permitted to be marketed.* This is fundamental to the workings of the legal instruments governing therapeutic drugs, food additives, and pesticides. The principle is to be applied in the case of other chemical products and medical devices in legislative initiatives now pending before Congress. Most important for the present discussion, this principle places the burden of providing scientific information on the manufacturer.

The present arrangement of placing upon industry the responsibility to supply information on hazards of its products to the Government before receiving permission to market them should be continued.

This system is most highly developed in the case of therapeutic drugs

* The concept is not a new one. It was established first in the Agriculture Department's Meat Inspection Act in 1907. It was not embodied in the early Pure Food and Drug Act in 1906 but only later in the Food, Drug and Cosmetic Act in 1938.

and is perhaps less clear in the case of food additives. The case of food additives is further complicated by a series of prior sorting or screening arrangements which have been used in the face of a lack of prior experimental evidence.

Ways should be found for bringing the food processing industry into a position of becoming more involved in research on food additives.

One piece of criticism which has been voiced about this scheme is that, in the name of uniformity and expediency, Government regulatory agencies tend to impose standardized scientific questions and test protocols on the industries petitioning for certification or registration. In part this arises from a request from industry to "tell us well in advance what we have to do to satisfy our obligation and we will do it." It is also a reflection of a desire for an orderly legal vehicle in the face of scientific uncertainty. In fact, however, such a system tends to substitute voluminous responses to standard test questions for astute scientific insight and this can be both expensive and non-productive.

The development of understanding and practically useful knowledge of the biological effects of chemical substances comes only very incompletely from the routine application of conventional toxicological testing, no matter how ambitious. Such understanding usually must come by carefully and expertly choosing from a wide variety of nonstandard approaches, those most likely to confirm or deny implied threats, and those which will reveal metabolic mechanisms and capacities in both humans and test animals. There should be both legal and administrative accomodations made to encourage this and to discourage perfunctory reliance upon standardized routines.

New products for which regulatory provisions do not exist or where research is not specifically accommodated in the regulatory laws are generally without a legacy of background scientific information on biological effects and hazard. The pending Toxic Substances Control Act would go far in the direction of correcting that void.

Products already on the market, for which prior approval or sanction may have been obtained but for which new scientific questions may be raised, represent a special class of problems.

There is a public responsibility to explore from time to time new scientific questions about commercial products which may have been passed on previously, the new scientific questions arising from the evolving character of science itself. This should be an explicit Federal policy and should be provided for both administratively and resourcewise.

For substances clearly in the public domain (environmental pollutants, for example) the responsibility for performing biological research leading to an understanding of effects on human health would appear to be in the public sector. Decisions here in the form of environmental standards, strategies for abatement, etc., are typically very expensive and very far-reaching in time. Therefore, they deserve the best possible scientific basis. This places a particular responsibility on both the regulatory agencies, such as the Environmental Protection Agency, and other supporting scientific agencies, such as NIH, to foster a sound and appropriate program of research in this area.

The Panel is concerned with the frequent inadequacy of the scientific evidence available at the time an environmental standard is set or a regulatory decision is proposed. In part this derives from the sparsity of resources available within the Government for performing the necessary research particularly when compared to the importance of these issues to the public. Such far-reaching decisions deserve a better background of information.

All too frequently one hears the statement that public use of a product or public exposure to an agent has not appeared to have been associated with any disease process. In fact, in a remarkably large number of instances, questions of association between human disease and exposure to environmental agents have never been examined systematically and scientifically.

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The Panel devoted much thought to the question to the adequacy of the Federal investment in research in environmental health. The Panel gave careful consideration to the present responsibilities of the Federal regulatory agencies for information and of the variety of sources of this information. Elsewhere in the report are listed a number of the policy issues which, in the Panel's view, lead to responsibilities for research which, up to now, have not been recognized. (Notable among these was the strong recommendation that the Federal Government must assume responsibilities for raising and studying new scientific questions from time to time regarding products previously registered or approved for marketing (page 32). The Panel has taken into consideration, also, the additional legislative initiatives now pending in Congress. New statutes, such as the Toxic Substances Control Act, will provide new regulatory jurisdictions. With new regulatory responsibilities will come correspondingly increased demands for scientific information based on research. Some of this investigation will be performed by industry. Some of it, however, will necessarily emanate from Government sponsorship and Government laboratories.

With this as background, the Panel feels strongly that the present level of Federal support for this present area of research is seriously inadequate. The accounting of Federal monies strictly dedicated to research on the health effects of physical and chemical agents of $86 million

(Exhibit 11-3) is not proportionate to either the magnitude of the obligation or the ability of science to contribute. By fiscal year 1977, the Federal Government should expect to spend roughly three times per year what it is now spending in behalf of this subject. This estimate was based in part from a detailed estimate of the cost of accommodating research needs for environmental health, considering the present level of Federal expenditure for each of these needs and estimating the degree of Federal responsibility in each case. The Panel relied in this exercise on a recent review of environmental health research needs performed for NIH.[10]

The Report to Congress on the Health Effects of Environmental Pollutants transmitted by the President several months ago, contained a number of recommendations dealing with research needs.[15] We concur with those recommendations but are persuaded that this fulfillment will be dependent on increased funding of the magnitude we have suggested.

Government programs of environmental health research, in the aggregate, are widely distributed among several agencies. There is virtue in maintaining a distributed research effort. The variety of interests and objectives of the several agencies that foster this research assures a portfolio of different kinds of complementary research. It seems highly unlikely that a single agency can or would be inclined to support this wide spectrum of effort. Regulatory agencies (FDA and EPA) require sound scientific resources of their own, but theirr missions, which characteristically obligate them to rapid responses, inhibit their dedication to long-term research projects. The regulatory agencies also have no incentive to initiate totally new investigations in areas where problems have not been suggested.

Thus, considering the totality of the Government's research on environmental health, complementary research programs should be supported to span the distance between the very applied investigations and some testing to more basic mechanistic research.

In practice, it is the research area which is intermediate between fundamental investigations and applied studies which appears to be of critical importance and which is for the most part the Government's responsibility. It is this responsibility which has been relatively poorly discharged up to now. Some (but not all) of this research can be directed. Some of it is of short duration, but a portion represents a lengthy dedication and a necessary investment in future earnings.

The pattern of diversity yields a level of specialization, coupled with a level of sensitivity to needs, that could not be duplicated in a consolidated organizational setting. The complementary character of this research is illustrated in Exhibit 11-9.

Of any increase in funds for environmental health research, the majority should be distributed among three agencies, *the National Institute of Environmental Health Sciences, Food and Drug Administration, and the Environmental Protection Agency.*

1. The National Institute of Environmental Health Sciences, established in 1967 as the major governmental scientific resource on the health effects of environmental agents, has remained the smallest of the National Institutes of Health. It is the Panel's strong recommendation that this Institute be permitted to develop its full potential and that it be looked upon as the primary source of goal-oriented yet sophisticated scientific endeavor. NIEHS was conceived as a bridge between the best of fundamental scientists in universities and NIH and the applied regulatory problems characteristic of regulatory agencies. It is this agency which is best equipped to undertake this intermediate level of research discussed above which is so important today. The Panel recognizes that the rate at which a research program can grow in any one year is limited. The NIEHS, however, should continue to grow over the next few years at a rate which is faster than for

EXHIBIT 11-9
BIOMEDICAL RESEARCH

	Extent of Involvement			
Reason for Research	EPA	FDA	NIEHS (NIH)	NCI (NIH) Cancer
To set standards and limits	++++	++++		
To confirm sponsors' results	++++	++++		
To validate test systems	++++	++++	+	
To assess effects of regulatory action	++++	++		
To attract and hold good scientists	+++	+++		
To test old compounds	++	++	++	++
To test orphan compounds	+	+	+	+
To develop new test systems	+	+	+++	+++
To understand mechanism of action	+	+	++++	++++
To understand pharmacological disposition	+	+	++++	++++
To study long-range problems	+	+	++++	++++
To synthesize unifying concepts	+	+	++++	++++

the other components of this Federal research program.

2. The Food and Drug Administration's research budget should be permitted to increase, as it has in the past few years, in proportion to its regulatory obligations.*

3. The budget for research into the health effects of environmental agents in the Environmental Protection Agency should be adequate to accommodate its statutory obligations to set standards and make informed regulatory decisions.

4. National Institute of Occupational Safety and Health should be supported to an extent to provide for both of its functions of supplying advice and criteria for occupational standards and for performing the research necessary to derive these criteria.

5. Division of Biology and Medicine of the AEC reflects a legacy of very high quality—both within universities and within the Government. This pattern should be maintained as this represents the backbone of scientific information for ionizing radiation for the electric power industry. On the other hand, this program, as a component of environmental health research, should not be encouraged to grow in the same proportion as that for research on chemical environmental agents. The support for research on the biological effects of chemical environmental agents should be increased while that for physical agents should remain roughly level. Within the funding for research on the biological effect of radiation, additional effort should be directed toward the effects of non-ionizing radiation.

The Panel is impressed with the need particularly for research of an increased degree of sophistication in this area. The understanding of the biological processes and of the mechanisms of action of environmental agents on biological systems is understood in relatively few instances; such understanding is clearly necessary in order to make reasonable assessments of hazards to health.

The Panel recognizes the high desirability of developing simple *in-vitro* test systems in order to foreshorten the present lengthy and expensive pathways of testing for association with or causation of chronic disease. Although sucesss in this matter is by no means assured, there are theoretical possibilities and the pay-off of success would be enormous.

The National Insititute of Environmental Health Sciences should devote a sizable fraction of its effort to research aimed at understanding of the biological effects of environmental agents so that proper interpretation can be given to the results of testing.

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NIEHS should devote a suitable fraction of its effort toward the development of simple but valid in-vitro tests of biological effects of a variety of environmental agents.

The Panel is aware of the wide variation of patterns of extra- versus intra-mural research supported by the several contributing agencies in this field (Exhibit 11-4). The Panel has many clear indications that the full potential of universtiy laboratories has not been brought to bear on these problems—even though many are willing to contribute to this field.

A greater proportion of funds should be made available for contract and especially for grant research.

While much attention has been devoted to absolute level of budgetary support of research programs, the Panel is additionally impressed with the necessity of maintaining continuity of support. By its very nature, much of the research in this area is characterized by its necessity of long-term dedication and follow-up without which meaningful results cannot be expected.

The Panel strongly urges that steps be taken to the extent possible to assure the continuity of support of research programs and projects dealing with environmental health.

The new National Center for Toxicological Research at Pine Bluff, Arkansas, presents a special opportunity. This new laboratory has the potential of being an extraordinary resource available to develop essential background scientific information relating to safety assessments and regulatory decisions. However, to achieve this potential, sufficient funding, stability, and continuity of support are requisite. The Panel recommends that the level of support for the National Center for Toxicological Research match the need as detailed in the planning documents for that Center. A scientific staff of exceptional quality is necessary. Finally, appropriate management is needed. The Panel believes that special attention should be given to how the scientific program is to be directed. This choice may be expected to influence strongly the quality of professionals attracted to the laboratory, the continuity of the scientific endeavors, and the confidence which is ultimately placed in the laboratory's results. We urge that serious consideration be given to the concept of a contractual laboratory associated with academic sciences, as through a consortium of universities.

The national laboratory at Pine Bluff, Arkansas should be viewed not as an end in itself but as the nucleus of a broader scientific resource available to the regulatory segment of the Government.

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The Panel took note of the Pharmacology/Toxicology Program of the National Institute of General Medical Sciences which was not

* The core support for the National Center for Toxicological Research is presently derived from the health research budgets of FDA and EPA. Therefore these budgets should be adequate to support this laboratory appropriately.

included in the compilation of Research and Federal Agencies on the health effects of environmental chemicals given in Exhibits 11-2 and 11-3. This program deals with clinical pharmacological studies on the safety and efficacy of drugs and with basic investigations on the biological effects of drugs, including their metabolism and distribution. This information is applicable to understanding the action of environmental chemicals in general. The Pharmacology/Toxicology Program is a coordinated national effort which supports centers and major projects in academic medical centers, together with approximately fifty additional research projects in research institutes of various sorts.

The Pharmacology/Toxicology Program is not generally concerned with studies on specific drugs, but stresses the development of basic principles for evaluation and understanding of the pharmacological action of therapeutic agents in general. Information is obtained in this Program which is of importance to the Food and Drug Administration and other groups, both public and private, in the study of the safety and efficacy of drugs in humans and animals. For example, the Program was responsible for setting up the first fully coordinated adverse drug reaction monitoring system which serves as a model for those now being set up in a number of other medical centers.

The fiscal year 1972 budget for the research aspect of the Program was $13.4 million and an additional $5.6 million was devoted to training in pharmacology, clinical pharmacology and toxicology.

The Pharmacology/Toxicology Program of the National Institute of General Medical Sciences is fulfilling an important mission in obtaining information on the general principles required in evaluation of the safety and efficacy of drugs. This program should continue to be supported in increasing amounts consistent with national needs.

The need for data on human experience and experiments presents a special challenge.

Better and more systematic use should be made of occupationally exposed groups for epidemiologic studies relating to specific environmental agents.

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Group practice pre-paid health care schemes, as envisaged in health Maintenance Organizations and as represented by such organizations as the Kaiser Health Care Plan, should be utilized as settings for more systematic observation of associations between environmental agents and clinical disease.

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Epidemiologic studies of environmentally related disease should be encouraged. Two measures which would go far in this direction are (1) some modest instruments for collecting data such as a National Death Index and (2) the training and accommodation of non-physician epidemiologists.

The discussion earlier in this section noted that what was termed "some elementary information" was often not available to decision-makers. This elementary information includes data on the amount of a substance produced and on its distribution and uses.

A systematic accounting of the amounts of chemical substances produced and their routes of distribution in commerce and use should be made available.

ANALYTIC TECHNIQUES AND KNOWLEDGE FROM MONITORING

Physical measurements and monitoring of substances in foodstuffs and in the environment are undertaken by a number of Government agencies. The motivation for these monitoring efforts varies widely yet the results of these dispersed measurement programs have come to be of some importance in understanding human exposures to chemicals. The U.S. Geological Survey and the Environmental Protection Agency perform measurements of elemental substances in waters and sediments. The Interior Department measures a variety of substances in wildlife. The FDA and the Department of Agriculture sample foodstuffs for chemical residues of various types. Some of these measurements are made in order to understand better some of the natural processes in the environment. Some are made as part of a program of enforcement of the law governing pesticide residues.

Generally, the results of this dispersed monitoring effort are not aggregated except as needed. From time to time, special compilations are made of certain aspects. Pesticides residues are measured by various Government departments in wildlife, food, human tissue, air, etc. The results of these several measurements are compiled regularly under a loose system termed the Pesticides Monitoring Program and the selected results are published quarterly in the Pesticides Monitoring Journal.

Government programs responsible for the development of analytic techniques which are used eventually in monitoring have been highly successful. The Food and Drug Administration has supported a program of high quality aimed at developing new methods of analysis of trace substances in foods and animal feeds.

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If one is really to offer a useful analysis of risks and benefits, some assessment of usefulness or betterment must be offered. In general, as in the case of risks, there is much less information available on benefits of a particular product than would be desirable.

A common practice is to view a product's attractiveness in the marketplace as an index of its social

value. Hopefully these two are related but the relationship may not be a proportional one.

A second common practice is to assume that a certain level of use of a class of materials implies an essentiality of use or dependence. In practice it characteristically is difficult to separate facts from opinion. It is very difficult to assess the true utility or efficacy of a pharmaceutical agent after it has been introduced into clinical use. Similarly, the assessment of the quantitative value or marginal productivity of pesticides in agriculture has proven particularly difficult, although their utility is often unquestioned anecdotally. The economic utility of pesticides and the consequences of a shift away from chemical pest control agents remain elusive to analysis.

The Panel was impressed that the utility or benefit of many chemical substances was as difficult to articulate as the risks associated with their use. Good quantitative studies of benefit should be undertaken.

It is suggested from time to time that some products carry with them very high degrees of social value or essentiality. Oral contraceptives, for example, would probably be considered by most observers as items of particular value. If balanced decisions are to be found, there will necessarily have to be available at the time of performing the balance at least a valid qualitative assessment of the benefit or utility function of the material or product in question. Some notion of the degree of dependence, of opportunities for making substitutions and of the penalties which would follow the loss of the product must be supplied in order to arrive at a reasonably studied judgment.

The Food and Drug Administration, in carrying out its charter of endeavoring to assure a supply of healthful foods and safe and useful drugs, should regularly engage in a systematic estimate of the utility of the products it regulates.

The Environmental Protection Agency together with the Department of Agriculture should develop valid assessments in economic terms of the usefulness of agricultural chemicals, feed additives and pesticides.

The National Bureau of Standards should be engaged where appropriate to examine and judge the utility of industrial chemical products which may come under scrutiny as human or environmental hazards.

Efficacy of chemical products has become a matter of increasing concern. This is perhaps no more clearly noted than in the field of therapeutic drugs. The question which commonly arises is how sophisticated must the information on efficacy be before accepting the product into practice. Are empirical observations of relief of symptoms or alterations of one or more of the components of a disease sufficient or should chemotherapeutic intervention depend on documented evidence of an effect on the fundamental mechanisms of the pathological process? There is always the hazard that through symptomatic treatment, the natural course of a disease may not be altered or even that an undesirable complication may ensue. Unfortunately, we lack knowledge of the fundamental causes and mechanisms of many diseases and evidence of pharmacological intervention at this level is often science limited.

INFORMATION FOR BALANCED DECISIONS ASIDE FROM RISKS AND BENEFITS

A review of almost any of the recent examples of decision-making about chemical substances which become thought of as "environmental chemicals" reveals a heavy overlay of a climate of crisis. This remark applies as well to the gathering of information as to the making of judgments on the basis of the information. One characteristic is clear. In general, knowledge about biological processes and effects has typically lagged far behind the technological processes which developed and produced new chemical products. The universe of these is now very large. Some would say, it is overwhelming and would strike a pose of resignation when asked, where should one make a beginning at improving knowledge of biological effects for this universe. An admission, probably accurate, that biological understanding will inevitably lag behind, suggests the need for some systematically set priorities for this research endeavor. The following represents a suggested scheme of setting these priorities. It rests on some explicit assumptions:

1. In general, knowledge of biological properties of chemical products will be less complete than will information on chemical and physical properties.

2. It is possible to infer certain types of environmental behavior (persistence, adsorption on particulate matter, migration, etc.) from a knowledge of certain physical and chemical properties.

The proposed scheme calls for the derivation of an index (or indices) which would give some probability of human exposure to the chemical.* A series of these indices (with suitable qualifications) could then be used to select from a universe of substances those which could conceivably become a hazard to health. This information would be used to derive research priorities to seek out inherent biological properties. A true hazard, simplistically, would be represented by a material which possessed both a high probability of coming into contact with members of the general population and biological properties which render it a risk.

* The same considerations could be applied to other, non-human targets so that probabilities of wildlife or other environmental exposures could be derived.

A principal, first approximation screen would arise from information on the magnitude of production and on the distribution of the chemical. The next step would be to take note of certain chemical and physical properties. The particular list which could be useful in this case is unclear but the following are offered as suggestions:

1. Physical stability
2. Solubility
3. Vapor pressure
4. Chemical reactivity
5. Degree of polarity

As suggested, these would be used to derive some useful hints as to how materials would behave if released into various environments. Here one can admit to a number of cautionary statements or qualifications.

1. Valid prediction of environmental behavior may be correct in only a minority of cases via this scheme. A prediction which is valid 10 to 20 percent of the time could be sufficient to make this effort profitable.

2. A number of second- and higher-order effects may ensue in the real environment and overshadow the relatively simplistic predictions from this scheme. Biological routes of degradation, biological magnification, photolytic events, production of new entities, interactions, etc., may be the most important events. The extent to which this is true strengthens the case for imposing on any standard or routine sorting scheme the judgment and scientific insight of a handful (1 to 3) of professionals.

3. Specific local concentrations of materials may be more important than average distributions.

*Pilot studies should be initiated to explore the responsibility of sorting various classes of chemical products to ascertain their likelihood of becoming a measurable human exposure so that this information could be used to direct priorities for research on biological properties as they might influence human health.**

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FORECASTING—HOW TO LOOK AROUND THE CORNER

There is a widely recognized need for a national center capable of providing guidance on the effects of future technologies on the environment. A recent HEW Task Force on Research Planning for Environmental Health Sciences in its report, "Man's Health and the Environment—Some Research Needs," called attention to the urgent need for a forecasting program ". . .capable of timely and effective warning of technology induced perturbations of environmental factors which may have health implications." Both new technologies and evolving established technologies are of interest. The important purposes of such a center would be to: (1) predict forthcoming technological developments in direction and size which could, in turn, lead to new materials, new distributions of materials, or greatly augmented uses of materials, which themselves, could represent environmental hazards, (2) apply scientific intuition to the pattern of materials in the physical environment searching especially for important second- or higher-order interactions, (3) develop priorities for research aimed at illuminating effects on human health and the environment as far in advance of major decisions and developments as possible, (4) predict needs for and probabilities of the development of appropriate control technologies corresponding to present or future environmental hazards, and (5) predict forthcoming developments in analytic methodologies useful in detection of environmental hazards.

A limited number of environmental forecasts exist in the published literature. For the most part, these are concerned with emission sources and to a lesser extent with the control technology. The spectrum of such forecasts is broad and it is useful to divide them into two groups according to the accuracy with which projections can be made, namely, conventional pollution, and new products and processes with environmental implications. Examples of conventional pollution include sulfur dioxide and photochemical smog and projections are available in the literature for both types of air pollution. There have been a number of recent examples of products which reflected new technological developments where environmental and human health implications were unknown but were thought worthy of investigation. Some of these examples have included phosphate substitutes in detergents, fuel additives for automotive use, new modes and facilities for transportation, etc. Important, also, to the maintenance of environmental quality is the development of instrumentation and monitoring systems capable of detecting very low levels of primary pollutants and their reaction products. The formation of new substances in the environment as a result of physical, chemical and biological interactions poses a major challenge in the environmental forecasting field. Recent examples of this latter include the formation of photochemical smog and the biological methylation of mercury.

The methodology developed in recent years for technology forecasting should be of value in the environmental field, but as yet has received only rudimentary application. Such techniques as the Delphi method (refined expert opinion), trend extrapolation and monitoring should prove useful in evaluating the impact of new technology on the environment. Examination of patterns of technological innovation indicates (contrary to common

* The Panel is greatly encouraged by a project of this sort already underway, termed the Cancer Hazards Ranking and Information System, supported by the National Cancer Institute.

opinion) that the full process from scientific discovery to widespread adoption usually takes upwards of ten years with twenty to twenty-five years more likely. Thus there will, in general, be time to plan for the environmental effects of new technologies. Prediction of the events forthcoming within only the next two years into the future would be exceedingly useful, especially as an aid to directing biological research designed to discover the implications for human health of environmental agents.

Serious attention should be given to the establishment of a small but highly capable, analytically oriented group to engage in forecasting of new technologies which could lead to new materials or new uses of materials, prediction of new technologies of environmental control and trends in analytic capabilities in behalf of priority-setting for environmental health research.

The Panel found much to commend the distributed character of Federal support and programs for environmental health research *(vide supra)*. At the same time, in order to make the most efficient use of these resources, an instrument of coordination appears vital. The importance of this matter is highlighted during the period of decision-making on an important, impending regulatory decision where it is discovered that an additional, short-term piece of investigation would in all probability add the appropriate bit of evidence to strengthen the decision. This type of contingency is extremely common. A coordinating body with authority to direct small expenditures for short-term studies would go far toward increasing the quality of scientific evidence ultimately used in decision-making.

A coordinating body, associated with the Office of Science and Technology should bear the responsibility of assuring the appropriate utilization of the several Federal scientific resources in behalf of environmental health and the associated regulatory decisions. This body should have control of a suitable contingency fund.

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The proprietary nature of certain types of information has proven to be a stumbling block to improving the quality of decision-making. On occasion, information concerning quantities of materials produced and patterns of distribution or use are known but are closely held. At least as important is a failure to share biological information concerning efficacy and unintended side effects. The failure to share this information prevents the scrutiny of it by much of the scientific community—a matter recognized by a previous PSAC Panel. Industry would like not to give away their monetary investment in this research to firms which "ride on the coattails" of the original developers.

*Toxicological and efficacy information submitted by industry in behalf of the registration or premarketing clearance of new products should be made available to the scientific community and to the public if the products are successfully registered.**

For those products for which the petitions for registration are not successful, the submitted information accompanying the petition should similarly be made available. However, a suitable scheme should be arranged for assuring adequate compensation for the original developers and researchers.

Finally, the Panel is impressed, as are others, with the potential benefits to be gained from international cooperation in the performance of environmental health research and in the exchange of information for regulatory decisions. The recently concluded series of agreements for cooperation between the United States and the United Kingdom, Japan, the U.S.S.R. in behalf of environmental health research are to be highly commended. We are pleased to add our encouragement to the proposals made by the President in his message on Science and Technology[14] and to the recommendation contained in his report to Congress on the Health Effects of Environmental Pollution.[15]

The fullest possible use should be made of international cooperative agreements for the performance of research and the exchange of scientific information in behalf of our understanding of the health effects of environmental agents including chemicals.

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* The Panel finds the recent proposal of the Food and Drug Administration entirely consistent with this recommendation.

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Chapter 12

Economic Issues

CHAPTER 12

ECONOMIC ISSUES*

INTRODUCTION

This section of the report is devoted to an examination of various economic issues. The questions raised in this section are not considered in isolation for their own sake. The intent is rather to examine the relationship if any, between the regulatory practices of the two principal Federal agencies engaged in regulation of chemical products, the Food and Drug Administration and the Environmental Protection Agency, and the flow of research, development and new products in the industries which they regulate. The Panel was moved to examine in some detail a number of anecdotal and exhortative statements widely espoused which claimed that there was a relationship between regulatory behavior of the Government for regulated chemical products and productivity of the industries, the character and vigor of their research and development activities, the flow of innovative new products into the market, the competitive position of the U.S. industries compared to their counterparts abroad, etc. In many cases, the exhortations assumed a negative viewpoint—urging that the penalty of what was viewed in some quarters as prudent regulation outweighed the intended benefits.

Therefore, this chapter will attempt to take stock of the recent trends in R&D in the regulated private sector which develops and markets new chemical products.

This chapter is concerned almost entirely with chemical products. Analyses of the economic impact of regulation of air and water pollutants have been attempted by others. These are reflected in this chapter but no corresponding, independent analysis was done by the Panel. A major preoccupation of the Panel was the impact, if any, of regulation on industrial R&D activities. Finally, the Panel considered the need for Federal efforts to "compensate" or balance any of the apparently negative effects of product regulation. Throughout this section, experience of the pharmaceutical and the agricultural chemicals industries is offered. These are the major regulated industries. There exist more data about them than for others. Industries producing food additives represent some peculiarities of their own which set them somewhat apart from the other two. Finally, the Panel ventured some speculations concerning the probable economic impact of new regulatory legislation presently under consideration by the Congress.

GENERAL CHARACTER AND ECONOMIC HEALTH OF REGULATED INDUSTRIES

1. Pharmaceutical products

Of the 6,330 pharmaceutical firms subject to FDA regulatory activities in 1969, 1,129 were primarily engaged in drug manufacturing and 875 of these primarily dedicated to the manufacture of pharmaceutical preparations (as opposed to biologicals and botanicals). Commerce Department data have demonstrated a decline in the total number of manufacturers of pharmaceutical preparations although the total number of large manufacturers has remained almost constant since 1954.

In spite of a decline in the total number of manufacturers, the total value of sales (manufacturers' shipments) of the U.S. drug industry has risen consistently. Pharmaceutical preparations ranked 15th among industries according to value of shipments in 1969. Foreign sales, in recent years, have increased at a rate roughly twice that of domestic sales.

As discussed in more detail later in this chapter, the drug industry is highly research-intensive and appears to be becoming even more so. If only company-funded research and development is considered, no other industry surpasses the R&D investment fraction of pharmaceutical preparations. As a percent of net sales, industrial R&D investment appears to have remained high for all of the years for which data are available.

If R&D investment is considered as an input, the output of successful new drugs does not seem to have been proportionately related. The total number of new drugs marketed in the U.S. each year, which includes new single chemical entities as well as duplicate products, compounded products and new dosage forms declined each year beginning in the 1950's. The number of new single chemical entities reached a peak in 1959 and has generally fallen since then. However, the number of new significant chemical entities developed year by year has remained fairly constant.

There are limitations to even the best of attempts at estimating the costs of development of successful new drug products. However, with an acceptance of these limitations, it is clear that: 1) the dollar costs of development have risen with time over the past several years and, 2) the length of time required for development has increased. Between 1950

* The Panel, during its deliberations, arrived at a number of findings, which are underlined in this chapter. In some cases these led to formal recommendations which are presented in Chapters 2 and 3.

and 1967 (reflecting mainly drugs developed before 1960) the experience of one company was that it required two years' development time and $1.5 million (considering the combined costs of successful and unsuccessful products) to arrive at a new single chemical entity. In 1971, a similar estimate suggested that the cost of a successful drug development varied between $2.7 and $4.7 million and required 4.5 to 8.5 years.

2. Agricultural products

The agricultural chemicals industry ranked 46th in 1969 in terms of value of sales. In 1964, basic pesticide chemicals were produced by 106 firms. In addition, there were 1,542 plants engaged in formulation of pesticide mixtures and in distribution of products. The value of sales of basic pesticide chemicals has increased consistently each year between 1962 and 1970.

According to a survey by the National Agricultural Chemicals Association, sales of basic materials increased at a rate of 13 percent between 1967 and 1970 while research and development expenditures over the same period rose 33 percent. In 1962, the Department of Agriculture estimated that it required an investment of $1 million to $1.5 million to achieve a successful marketed pesticide product. In 1969, according to a different survey, the cost of successful development (taking the cost of unsuccessful candidates into consideration) was said to be $5.6 million. The corresponding experience of one firm between 1960 and 1970 was $11 million of R&D expense per successful product.

There is some evidence (although it is only now begining to emerge) that some firms are discontinuing further investment in behalf of pesticides and that others are merging with larger companies. Smaller firms are finding it difficult to support the size and sophistication of research needed to develop successful new chemical entities. However, there is no evidence that mergers or the discontinuation of chemical manufacturing by individual firms is more pronounced in the case of pesticides than in any other segment of the chemical industry during the past five years.

CANCELLATION AND RECALLS

The 1962 amendments to the basic enabling act of the Food and Drug Administration marked a watershed in American attitudes toward the use of chemicals. By that Act, and by subsequent legislation, the Congress, in effect, divided all existing chemical products into two categories. In one were most chemicals. The other included chemicals that failed to meet contemporary standards of safety and efficacy. The Congressional goal was to force the second class off the market as promptly as feasible.

As was to be expected, the great mass of chemicals remained in use; they met the newer standards well. But numbers did not. And, pursuant to the Congressional mandate, they were withdrawn. For example, 5, 189 New Drug Applications were withdrawn by the FDA from 1967 to 1971. The majority of these withdrawals stemmed from recommendations made in the Drug Efficacy Study of the National Academy of Sciences.* A companion study by the National Academy of Sciences, on allowable pesticide residues on food crops, led the Environmental Protection Agency to de-register a significant number of pesticides. Thus the EPA cancelled some 3,544 registrations in 1969, 5,236 in 1970 and 7,005 in 1971. In many cases public safety was afforded by limiting the pesticide to certain uses where it was both essential and of limited impact on the environment. But other pesticides, herbicides, fungicides were totally removed.**

Such tightened controls followed through not merely the expressed Congressional intent but also the increasing public concern for assuring adequate safety and efficacy in the use of chemicals. It would, therefore, not be surprising if the threat of recalls, the commercial concerns of producers, and the risks associated with investment in the industry had all increased. Indeed, unless Congress were legislating against phantom problems, and unless the executive agencies failed to carry through on these tighter standards, it is hard to see how such commercial consequences would not occur. The consequences of concern to this panel are those with respect to possible impact on research and development of new and significant chemicals. (That question is taken up in Section E below.) It is sufficient here to note that producers can cover the risks associated with governmental recalls and cancellations, by the purchase of insurance available from private companies. The fact that such insurance seems still not to be widely demanded indicates that current regulatory activities, and those in the near future, do not seem to add significantly to the uncertainty in the operations of chemical producers.†

* That study listed a greater number for possible scrutiny. The difference is accounted for by those drugs for which manufacturers submitted additional data giving satisfactory new findings on the drugs in question.

** Further detail appears in Appendix D. Taking the proportion of products removed entirely from the market to total restrictions as reported by the National Agricultural Chemicals Association something like 175 products were apparently removed from the market in 1969 and 1,750 in 1970. However, the total removal rate might have been different among the companies not included in the survey.

†Obviously product cancellations and failures, occur for reasons of commercial inadequacy, public concern as well as because of government regulations. Hence, the cost of insurance would be greater than that specifically arising from Federal executive actions, however sudden and however arbitrary. Hence, insurance rates of one percent on sales—to take what seems a not unreasonable figure—tends to overstate the costs from Federal action, and far overstates the costs of sudden, unanticipated Federal actions.

It is important to note that the normal code of responsibility of chemical producers would lead them to withdraw from the market some of the products included in the list canceled by the FDA. For example, discovery that a certain serum container had been causing deaths in hospitals reached both the producing company and FDA at much the same time. It is difficult to believe that the company would have continued producing that container even if the FDA had not been there to cancel. Hence, we cannot assume that the uncertainties linked to FDA cancellations, even sudden cancellations, are all ones that would fail to exist if the FDA did not. Their commercial result cannot therefore be entirely attributable to the FDA.

The chemical industry is a vastly creative, rapidly advancing industry. It has been so for many years. Both the social contribution it makes, and the profits its investors earn, jointly come from the rapid creation of newer, and usually better products. But virtually every one of these newer products tends to force an existing one off the market, ending its commercial life. The additional impact of those government recalls which industry would not itself voluntarily make appears to add little to that uncertainty. We are left with a recognition that Federal agencies must continue to recall dubious products as promptly as possible once accumulating scientific knowledge warrants that action. It is by speeding the expansion of tested knowledge about chemicals that we will reduce both dangers to man and his environment and losses to enterprise.

The Panel is impressed that the abruptness and the unexpected character of some product bans and recalls may be as perturbing as is the ban itself. Displacement of products by others and of industries by other industries takes place naturally over an extended period of time. FDA and EPA decisions, typically based on the acquisition of new scientific knowledge, are often perceived as very abrupt moves. That these decisions deserve to be founded on the best information possible should be evident. The Federal Government has a primary responsibility of assuring that its decisions are based on the best evidence that science can provide and that a thorough and deliberate exercise of scientific interpretation accompanies every regulatory judgment.

The Panel has not found evidence of startling changes in the fabric of the chemical manufacturing industries (for drugs or pesticides, for example). There does seem to have been some displacement of secondary distributors and formulators of products by primary manufacturers.

This has been accompanied by a more critical scrutiny by management of new lines of product development. There has been some effort at diversification—especially among drug manufacturers. Finally, there has been a review of pricing policies with a thought of increasing the unit return on a smaller volume of material.

There have been changes in the industrial research and development efforts of chemical manufacturers. These are discussed more fully in the next section and reflect a variety of new pressures on manufacturers. There is some evidence that some manufacturers have attempted to anticipate the threat of recall by including during the course of development some investigations as "insurance" against later questioning.

We conclude that the risks of failure that confront a company when it begins to investigate a set of chemical compounds for marketing are already enormous. At that stage, the additional risks of failure, because of the prospect of Government ban or recall, are small—but of course do enhance the total risk. One final piece of evidence for this conclusion is the fact that, although it has been commercially available for some time, recall insurance has been purchased in only a few instances. One reason for not doing so is presumably that self-insurance is less expensive than purchasing insurance. However, another reason may well be that the insurable risk adds so little to the risk of failure that it is not worth separate planning, but is simply another business risk.

COMPENSATION

Federal actions may create substantial losses to some companies, and substantial gains to others. In the U.S. economy those uncertainties that stem from Government actions are but part of the entire range of uncertainties and risks with which private businesses are confronted, and for which they necessarily seek compensation. In a market economy their compensation for bearing such risks is typically a cost that consumers of their products must pay if the product is to continue on the market. Tighter safety regulations for mining coal, producing automobiles, designing ships—what product or industry is not affected by Federal regulation of one sort or another? Such regulations are part of the risks of engaging in business in a mixed economy. Investors will not continue to provide funds for production in an industry if they are not compensated adequately, including an allowance for the varying impact of such uncertainties and risks.

Compensation for these uncertainties and risks is typically provided by the ultimate consumer of the product being produced. It becomes one necessary element in the price he pays. If he is unwilling to pay a price sufficient to cover the total compensation required by investors, then resources will leave the industry. Such a result is not peculiar to chemicals, nor to just a few industries in our economy. It is in fact typical of virtually every industry in the nation. For this reason proposals to compensate for particular government actions are not often made, and still more rarely supported by Congress and the courts.

Does the impact of Federal action produce greater gains (or losses) in the chemical industry than in other industries? If so the government might charge for these extra gains, or compensate for these extra losses. Clearly, merely to charge for gains, or merely to compensate for losses, would make the government a closer financial partner in this single industry than in others—and therefore be relatively over generous (or overly harsh) to investors in this one industry.

Are the gains to investors from Federal regulation of the industry really greater than in other industries? The investor gains in the industry come primarily in the form of the capital values available as the result of the award of an FDA approval. A company marketing a product marked "Approved by the FDA" has a more desirable, and hence more valuable product, than one lacking such certification—even if both could be freely marketed. On the other hand investors sustain losses from withdrawals abruptly imposed on producers when evidence of dangerous side-effects is discovered.

To measure the gains net of losses in the industry per se is not an easy matter. Even to measure the losses imposed by withdrawal orders is a difficult affair. What is at issue is a comparison between a) the total of such losses and b) the total of such losses if there had been no Federal order to withdraw the product. And for such a comparison the issue is not at all clear: it is conceivable that the Federal contribution to impact may be small. It could even be negative for the company as a whole.

On October 12, 1969 a leading producer provided evidence to the FDA that cyclamates had caused cancer in animals. It seems highly likely that even if no Delaney provision in the law existed, and no FDA edict had been issued, that any responsible producer of ethical pharmaceuticals, would have taken action to limit the use of cyclamates or perhaps even to have withdrawn them. And given either action would an outpouring of publicity, and consequent drop in sales not have been all but inevitable? Surely combining a) new information with b) a climate of acute publicity and concern would have created losses for the company without any explicit action by the FDA.

In today's world we must take as given wide public concern about health. Such concern leads to newspaper and TV stories on such topics, even ignoring the further contribution made by special interest groups. Therefore even if the FDA failed to act whenever scientific evidence warranted action, then the mere withdrawal of a product by a responsible producer might, in today's world, set up shock waves of response. Such intensified doubts would bring declines in sales, and inquiries of all kinds about the entire corpus of pharmaceuticals already on the market.

The presence of an FDA or an EPA, therefore, provides substantial assurance that the public can continue to place confidence in the thousands of pharmaceuticals now on the market—because the government agency will remove doubtful ones as soon as scientific evidence appears.

In sum, it is by no means clear that government regulatory agency orders to withdraw chemicals from the market have imposed net costs on the industry for which particular Federal compensation acts are required.

To warrant compensation merely for the chemical industry there would first have to be some demonstration:

a. That Federal negative impacts on other industries were somehow different, and less worthy of public compensation (surely difficult to argue in the light of intensified regulation of coal mining, automobile exhaust systems, effluent discharges, etc.).

b. That only negative impacts should be considered, while the positive Federal contributions to the financial well being of the industry were to be ignored.

c. That the normal private market mechanism by which investors cover their risks from the price freely charged in the market should not apply here as in much of the rest of the economy.

There is an alternative argument for compensation. Some have tended to believe that the implied assurances of safety involved in registration or approval are—or at least should be—immutable. It was because they read the FDA's "generally recognized as safe" as being "forever recognized as safe" that some aggrieved parties have protested and sought compensation for that agency's cyclamate decision. Throughout this report the Panel has tried to stress the dynamic character of the scientific endeavor and the ways in which this character will inevitably be reflected in regulatory actions. Accordingly, we find no merit in this argument for compensation.

There is no compelling argument for a policy of compensating manufacturers for the economic impact of cancellations and withdrawals. Exceptions must be considered on their special merits.

RESEARCH AND DEVELOPMENT TOWARD NEW CHEMICAL PRODUCTS

This Panel finds that research and development in the chemical industry has been vigorous and growing in the decade since the 1962 FDA amendments. Moreover, we conclude that such R&D promises to continue a healthy rate of growth in the immediate future despite increased government regulation, and in part because of regulation. Such a conclusion may seem striking to those who have read a variety of statements and studies that see faltering research effort by the chemical industry, largely as a result of tightened

regulation. It is therefore desirable to indicate just why the strength and structure of the U. S. chemical industry both encourages R&D and is likely to continue to do so.

A plethora of predictions have pointed to Federal regulation as creating disincentives for private R&D. A variety of writers have concluded that the prospects for discovering new products have darkened, that R&D has been declining, has become defensive, that research is increasingly being transferred overseas, etc.[8 17 20 22-27] Many of these propositions have been supported by cogent anecdotes, or assurances of bleak days ahead. There has been some reference to factual measures, even if biased ones.*

The measurement of R&D is not unique. It is relatively easy to measure the effort applied to R&D; much more difficult to measure the usefulness to the community of its output. In an era where the real cost of advances is steadily increasing, particularly because of increased requirements for testing, a growth situation that might be regarded as neutral will almost inevitably involve increasing effort and decreasing output. Thus both effort and output deserve our careful attention. We cannot expect any simple answers to general questions about the health of R&D on chemicals.

The strength of R&D in the chemical industry in recent years is readily understandable once it is clear what R&D is. The research and development process is one that creates information—not just products. R&D in the U.S. chemical industry involves extended and often expensive investigation—which in turn occasionally yields successfully marketed products. Other than the high quality of the research effort, and the energy in developing market applications, this pattern is characteristic of chemical R&D of every other nation as well, in economies based on the market and those relying on central direction. No known approach, in any nation, guarantees shorter, less expensive ways to create safe and efficacious chemical products to conquer disease or protest against crop failure and noxious insects.

Most of the products that the laboratories of pharmaceutical houses initially take up for investigations, or firms making pesticides, prove to be commercial failures. Five to ten thousand chemicals are initially studied as serious possibilities for every single product that makes its successful way clear through the R&D process to the market. Yet the endeavor, and expense, put forth for these unsuccessful tries is put forth as R&D no less than is that put forth to the successes. The same quality personnel, laboratories and materials are used to investigate the duds as the enormous successes. Indeed, at the start of any given investigation there is usually little basis for guaranteeing (perhaps even for knowing) whether it will succeed. Hence a nation, or a company or an industry is increasing its R&D in chemicals whenever it devotes more of its chemists to developing chemicals, more physicians and biologists to testing their safety and efficacy. That is so whether those investigations yield a profit to private firms or not. It is also so whether they yield bonanza medical discoveries to society or not.

To judge the trend of chemicals R&D effort in recent years, therefore, our most suitable measure would be the trend of expenditures for R&D allowing for price changes (i.e. in constant dollars). Precisely such estimates are available only for the pharmaceutical industry: Exhibit 12-1 shows the upward trend they report since 1960.* An upward trend for other sectors of the chemical

* Reference has frequently been made to the count of new single chemical entities. Both industry representatives and some government spokesmen have relied on such measures to reach directly opposite conclusions as to why R&D declines occurred. As we indicate below, such measures do not indicate the trend in R&D, hence they cannot warrant either set of conclusions.

* Data on actual R&D expenditures, of course, rise even more given the inflation of prices in recent years.

EXHIBIT 12-1
RESEARCH AND DEVELOPMENT EXPENDITURES OF UNITED STATES HEADQUARTERS FIRMS ON ETHICAL DRUGS FOR HUMAN CONSUMPTION

($'s Million)

Year	Worldwide	Foreign	Domestic	Domestic[2] Constant 1960 Dollars
1960	206.5	10.4[1]	196.1[1]	196.1
1961	227.3	11.4	215.9	213.7
1962	237.8	13.0	224.8	220.1
1963	267.1	18.9	248.2	240.2
1964	278.3	24.0	254.3	242.8
1965	328.7	24.5	304.2	285.6
1966	374.4	30.2	344.2	314.0
1967	412.4	34.5	377.9	335.3
1968	449.5	39.1	410.4	349.2
1969	505.8	41.7	464.1	374.8
1970	565.8	47.2	518.6	395.5

[1] Estimated

[2] Deflated using Consumer Price Index

Source: Pharmaceutical Manufacturers Association, Annual Survey Reports, various issues.

EXHIBIT 12-2

R&D SCIENTISTS AND ENGINEERS, BY INDUSTRY 1957-1970

(Full-time-equivalent number in January)

	1957	1958	1959	1960	1961	1962	1963	1964	1965	1966	1967	1968	1969	1970
Chemicals and Allied Products. .	29,400	31,000	33,500	36,100	37,000	36,500	38,300	37,800	40,000	40,000	38,700	40,800	42,200	42,000
Industrial Chemicals	18,000	18,800	20,200	21,800	22,900	21,600	22,900	23,600	25,700	24,700	22,700	23,300	23,600	23,000
Drugs and Medicines	4,700	5,100	5,900	6,000	6,200	6,800	6,900	7,300	7,700	8,000	9,300	10,000	10,300	11,000
Other Chemicals	6,700	7,100	7,400	8,300	7,900	8,100	8,500	6,900	6,600	7,400	6,700	7,500	8,300	8,000

Source: National Science Foundation.

industry is also indicated by figures on R&D personnel in those sectors. (Exhibits 12-2 and 12-3) These figures offer a reliable indication of strong R&D effort over the past decade. For increases in personnel would be linked to increases in materials consumption, laboratory facilities and other physical research inputs, together accounting for R&D growth. The overall growth indicated occurred in the face of failures of firms in the industry, closing down of laboratories in some instances, reductions of staffs in others. Actual R&D effort in existing companies rose even more, and effort deployed to products now going into production rose even more. The overall increases in Exhibits 12-1, 12-2 and 12-3 reveal the strength of research effort put forth by the chemical industry.

Over the past decade, therefore, as during earlier years, scientists in the chemical industry continued to discover new research possibilities, while managements discerned new market opportunities—together generating sharp increases in R&D effort. How was such a marked upward trend possible in the face of tightened Federal regulations and the various prophecies of gloom for the industry's future? The answer turns primarily on the vigor of the chemical industry, and on its commitment to research.

It is important to begin by distinguishing the trend of R&D in the industry from the fate of any particular firm, plant or product in the market. Some 50,000 businesses fail every year in the U. S. economy, even in times of high prosperity. It would be unbelievable if none of them were in the chemicals industry. The commercial life of products in the chemical industry may be estimated as about five years.[7] With 3,000 to 4,000 prescription drugs on the market, plus an unknown number of over-the-counter pharmaceuticals plus 35,000 pesticide registrations, it is to be expected that thousands of chemical products and applications will disappear from the market in every year even without the shadow of government intervention. They fail as a consequence of the vigorous process by which the chemicals industry creates and markets ever newer and more serviceable products. Part of this change comes as competitors vigorously attack the market position of existing products. Part comes as producers forcefully pursue so-called "defensive research," in which they seek to add elements of convenience, safety or other advantages to products they are already marketing. (And there is no reason to believe that such product advances yield any lesser contribution to social welfare than R&D that leads to products more obviously new in the market.)

Now the destruction of investments in certain existing products—by regulatory actions, cancellations, etc.—in no way requires a decline in R&D. In fact the firms affected may intensify their R&D, to find replacements for their defunct product lines, to generate income that would compensate for their reduced profits. By ending the market for broad spectrum pesticides, such as 2,4,5-T and DDT, the government did not do away with weeds and insects. It opened a market for narrow spectrum sub-

EXHIBIT 12-3

R&D TRENDS IN PESTICIDE CHEMICALS*

	1967	1968	1969	1970	Estimated 1971
Man Years in R&D	2,368	2,462	2,666	2,768	2,678
Personnel in R&D	2,238	2,349	2,498	2,547	2,495

* Data for companies accounting for 80 percent of sales.
National Agricultural Chemicals Association

stitutes able to meet the new standards. Such substitutes had a market waiting for them among the farmers, householders, and state highway authorities who had bought broad spectrum weed killers, and who showed few signs of rejecting pesticides.

Similarly when the government ended the use of cyclamates it did not thereby persuade children that soft drinks had become undesirable. Nor did it moderate the desire of their parents to keep down their sugar intake. In the short run, children and parents turned to sugar and saccharin. But a market had opened up for a new chemical that had neither the shortcomings of sugar nor saccharin—those shortcomings that had originally made consumers turn to cyclamates. Hence, sharply intensified government regulation of chemicals could sharply intensify R&D—to replace chemicals forced off the market by Federal action.

Now it is possible that such opportunities did develop but have not been seized because investors have withdrawn their capital from the industry. They could well have lacked confidence in what the chemists and biologists could create. They could have concluded that no research opportunities existed, or that the industry could not pass on to the consumer the costs required by prolonged and extensive FDA scrutiny, etc. Had they shifted resources out of the industry they would have precluded the availability of financing required for more R&D. Suffice it to say that there is little evidence of capital flight having taken place. Indeed industry discussion of the consequences of regulation has focused on many aspects, but no particular mention of this one appears.

Does this imply that tightened government regulation was a matter to which investors were indifferent? Hardly. Recognition of strikingly increased government regulations would have tended to bring an immediate fall in the value of chemical stocks. Such a fall would mean a loss, and an irretrievable loss, for investors who owned such stocks at the time of such recognitions. But the live option confronting them was: retain their assets in the industry or no. And that choice depended on future earnings in chemicals versus other investments. If investors had anticipated only a future of ever-intensified government regulation they would have shifted their investment to other areas. But presumably the expanded prospects for new chemicals—narrow spectrum, safer, more reliable—more than compensated for anticipated future increases in regulation. And such prospects shored up investor confidence in the ingenuity of industry personnel who had made such spectacular contributions to American health over the past thirty to forty years.

One measure of output for R&D in chemicals—one that seems naively closer to input but is actually output—is the number of chemical entities going into investigation. (Allowance must be made for the fraction of compounds not carried to a terminus of inefficacy, unsafety, or informed decision about marketability.)

ECONOMICS, R&D AND THE INTERNATIONAL SCENE

1. The State of the Industry

The United States has for many years been a net exporter of the products of its chemicals industry. Not only has it exported the commercial products themselves but it has been an exporter of the technology in many cases.

There have been a number of statements made in recent times suggesting that, as a result of the regulatory behavior of the U.S. Government agencies, the formerly preeminent position of the United States as a leading innovator and producer of drugs and other chemical products would decline. At the same time, others have urged, basing their arguments on the same pattern of regulatory actions, that certain new and socially desirable products (e.g. pharmaceutical preparations) were becoming available earlier in countries outside the United States than in the United States.

There is evidence that the development of new drugs worldwide is limited by present levels of scientific understanding of a number of disease processes. One observer noted a conspicuous absence of novelty in new drug therapy in 1971 and termed that year one of "...stocktaking of scientific knowledge..."[10]

According to a study in 1969 by the OECD, the United States pharmaceutical industry supports a research and development effort in dollar terms which far overshadows that of any other country and exceeds the total invested by the combined industries of the OECD countries (Exhibit 12-4).[11] On a per capita basis, R&D expenditures are exceeded only by those of Switzerland. The rate growth of R&D in the drug industry in the U.S. appears to be comparable to that of other industrialized nations with the possible exception of Japan.[11] In terms of research manpower for the drug industry, the divergence between the United States and other countries appears to be less than it is for research expenditures. Except for Switzerland and Germany, the United States employs almost twenty times as many people in pharmaceutical research as do other industrialized nations.[11] The total employed in the OECD countries exceeds the number employed in the United States. (This has been interpreted in part as a reflection of the higher productivity and more highly mechanized nature of U.S. R&D.)[11]

It is interesting to compare the average periods required for innovation among the pharmaceutical firms of different countries. The character of development of drugs in the U.S. is not much diffeent than abroad. The OECD study surveyed seven countries and found a fair concurrence of responses ranging from four to seven years. (Belgium 4 to 7, France 4 to 5,

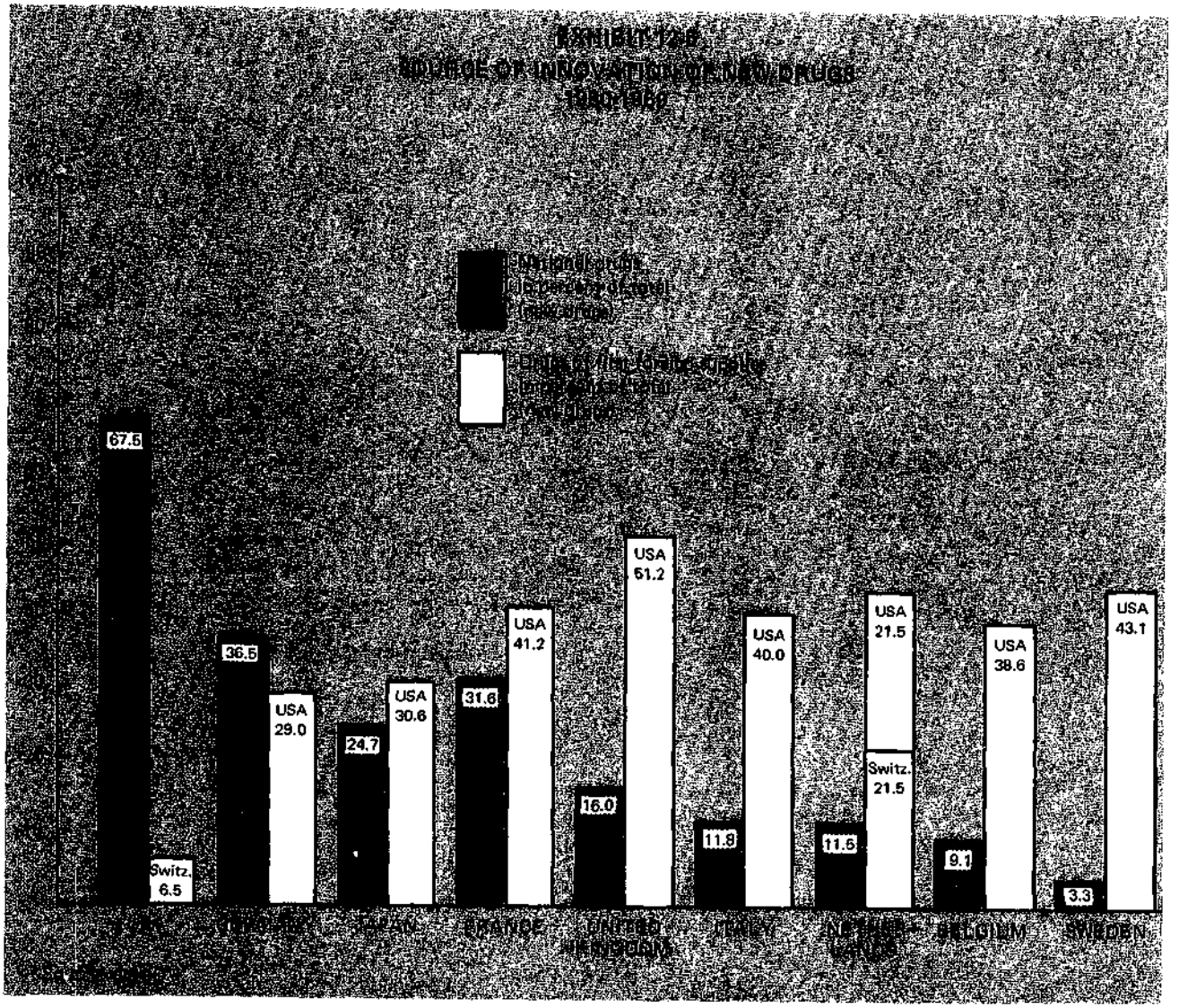
EXHIBIT 12-4
RESEARCH EXPENDITURES IN THE PHARMACEUTICAL SECTOR IN MILLIONS OF UNITED STATES DOLLARS

	1960	1961	1962	1963	1964	1965	1966
Belgium				4.3		5.2	
France				24.36*	27.55	28.42*	
Germany					40.00*		
Italy	10.4	14.4	14.4	14.4	15.0	15.0	20.0
Japan	10.3	19.0	19.8	27.9	36.9		
Netherlands					9.03		
Sweden	3.8	4.8	5.9	7.9	8.7	10.8	12.9
United Kingdom*	21.0	21.8	23.2		29.1	32.5	
United States	212.0	238.0	251.0	270.0	282.0	365.0	399.0

Source: Country replies to OECD[11]
* International Statistical Year on R&D Statistical Tables and Notes OECD DAS/SPR/66.14.

Italy 3, Japan 3 to 5, Holland 5 to 7, United Kingdom 5, United States 7).[11]

If one examines the national sources of innovation of pharmaceutical products, one finds an overwhelming preponderance of drugs of U.S. origin over those of any other foreign origin. At least up to 1969, in eight of nine OECD nations, the number of important marketed drugs discovered by the U.S. exceeded the number of drugs from any other single country (Exhibit 12-5). In Germany, that nation itself is the primary source of innovation with the U.S. second. In the Netherlands, the U.S. and Switzerland have supplied



new drugs in about equal proportions. This pattern appears to have been sustained through 1971.[10]

The U.S. pharmaceutical industry has not only been more agressive and successful in research and innovation, it has also been more productive when measured in output of pharmaceutical products. It has been found to be substantially above that of European countries and Japan. However, the productivity in the United States is increasing more slowly and the gap between the figures for the United States and other countries has been declining. The export trends of drugs and other chemical products of U.S. manufacture over the past several years are seen in Exhibit 12-6.

An important factor in this picture has been the place of the multinational company. In recent years, U.S. drug firms have established and increasingly supported foreign subsidiaries for both research and development and manufacturing. R&D expenditures of U.S. headquartered firms abroad have increased 513 percent from $10.4 million in 1960 to $55.9 million in 1971 (Exhibit 12-7). Note that while this export of R&D capital has been increasing, it has been rising much more slowly as a percentage of total U.S. expenditure in drug R&D and remains less than nine percent.

At first glance one might assume that the increase in U. S. investment in drug R&D abroad is a reflection of the industry's desire to take advantage of lower costs of development in foreign countries. While this may be true to some extent, it appears to be a minor factor. The investments in foreign R&D are made most often to satisfy requirements laid on by host governments. Some countries (e.g., France and Japan) require that pre-clinical research (animal studies) be conducted locally as a condition for drug approval. In addition, some countries prefer to have clinical studies conducted locally as well and consider this factor when passing on an application for approval to market.

2. The Issues

Attention has recently been called to a possible "innovation lag": new products are introduced into the U. S. after they have appeared in European markets.[8,9] Indeed, it has been asserted that U.S. companies often introduce new drugs first in foreign markets because of a "...monstrous concentration of overlapping controls, precautions, and delays in drug research (in the U. S.)."[8] According to the argument, patients in the United States are deprived of many useful therapeutic agents (and, by inference, of better health) because these new drugs are not available to U.S. residents. By considering the nature and cause of this lag we may gain some useful insight into how U.S. regulations may affect the rate of innovation in the chemical industry.

Why are some new products introduced into one country but not into another? Why, to take a specific example, should a useful medicine be made available in England in 1961, but not be introduced into the U.S. until 1967? Introduction rates will vary, given the combined effects of three different factors: (1) the expected lack of commercial markets; (2) failure to offer an advantage over existing products, as judged by physicians and/or consumers; (3) company concern about the costs and difficulties of government regulation.

In any nation hundreds of chemicals are marketed in a given year. Some survive to become priceless therapeutic adjuncts. Most disappear. Therefore chemicals

EXHIBIT 12-6

PATTERNS OF IMPORT AND EXPORT OF VARIOUS CLASSES OF CHEMICAL PRODUCTS—1967-1972

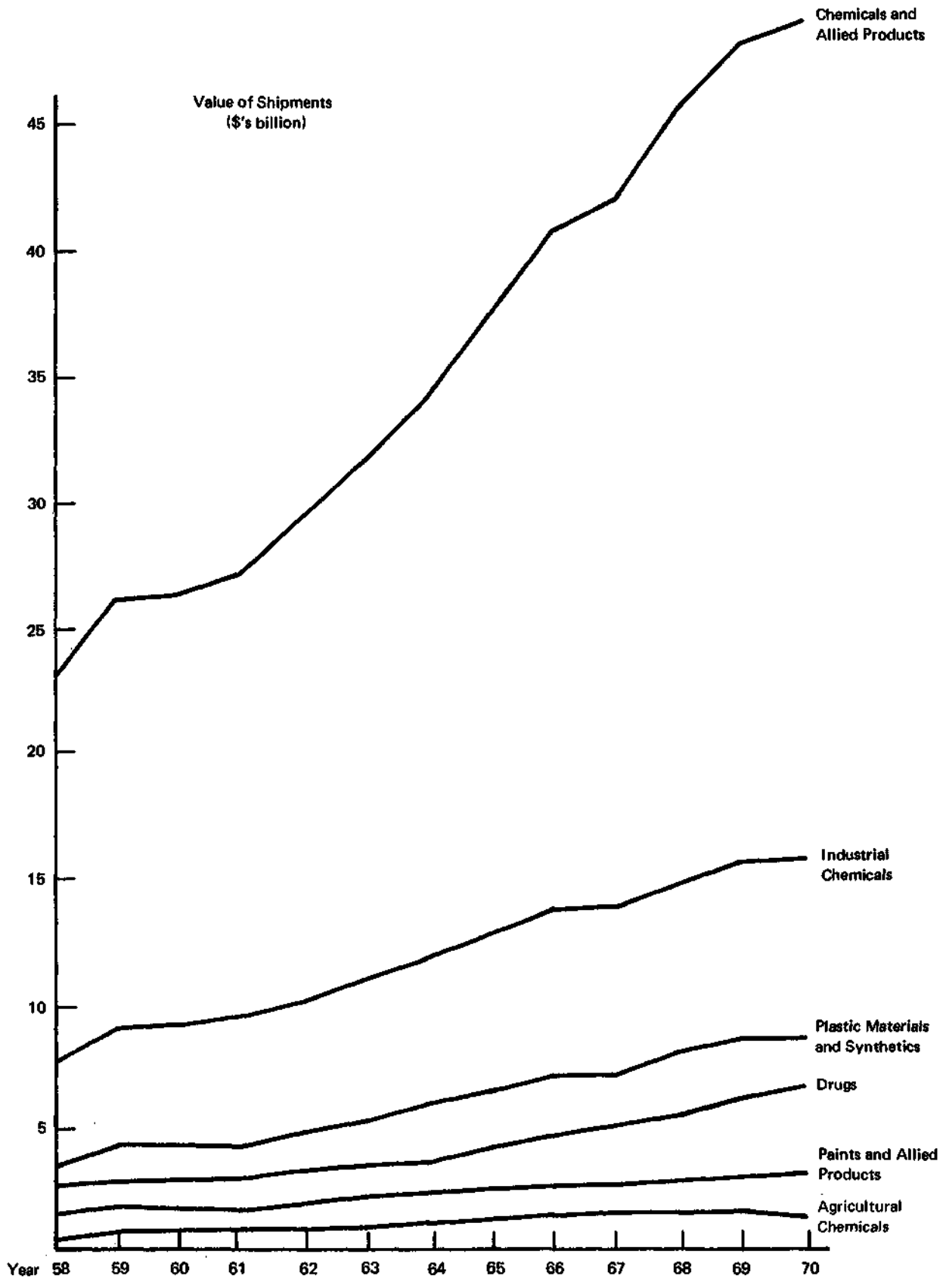
($'s million)

Industry	1967		1968		1969		1970		1971*		1972*	
	Value of Import	Value of Export	Value of Import	Value of Export	Value of Import	Value of Export	Value of Import	Value of Export	Value of Import	Value of Export	Value of Import	Value of Export
Industrial Chem.	301	1,134	510	1,332	590	1,480	710	1,650	795	1,666	872	1,757
Plastic Materials & Resins	61	473	94	590	99	590	123	653	140	655	160	740
Drugs & Pharmaceuticals	72	288	76	314	84	363	87	420	119	396	125	432
Soaps, detergents & cleaning compounds	3	30	2	35	3	33	2	36	2	36	2	38
Cosmetics & Toilet Preparations	12	36	13	41	14	42	16	45	17	48	18	51
Paints & allied products	0.4	52	1.1	62	1.0	61	0.9	65	0.9	66	0.8	70
Fertilizers	40	143	35	156	38	109	49	104	49	115	50	135

Source: U. S. Department of Commerce, U. S. Industrial Outlook, 1972.

(*Estimates)

EXHIBIT 12-9



Based on data from the National Science Foundation.

Reversals (cancellations or suspensions) of previous approvals for products have occurred—sometimes in batches—characteristically reflecting the alterations in scientific understanding mentioned above. The abruptness and unexpected nature of cancellations and product recalls appear to be almost more perturbing to industry than the fact of the recalls.

This, of course, adds one more argument for an explicit and systematic gathering of the best available scientific information as the basis for regulatory decisions. Deliberate and unhurried effort at critical interpretation of scientific data for regulatory decisions will decrease the characteristic of the unexpected and still result in the most prudent of decisions.

The Panel did not find a compelling case for monetary compensation or indemnification for regulatory decisions and product recalls. Exceptions must be considered on their particular merit. Products recognized as safe are not forever recognized as safe. Public attitudes and regulatory patterns will inevitably change since the scientific understanding behind them will change. The costs of recalls that producers would not willingly make on their own must be considered as a risk along with other components of economic risk.

The chemical industries continue to be among the most research intensive of all industries (Exhibit 12-10). Considering only company-funded research, the chemical industries are far out in front with drugs clearly at the top (Exhibit 12-11). Furthermore, the drug industry has become increasingly reliant on its own R&D enterprise bringing forth an increasing proportion of its innovation from within its own house. (There are a few striking exceptions at the moment where Federal funds are directed toward the development of specific end-products such as cancer chemotherapeutic agents and oral contraceptives.)

There is every indication that the degree of research intensity is increasing rather than decreasing. Compared to that of other industrialized nations, the U.S. pharmaceutical industry spends more on R&D than the aggregate of the industry in the OECD countries combined. Further, its R&D enterprise appears to be more productive.

The Panel noted with some interest that in spite of the increased sophistication and degree of scientific insight over the last several decades, the process of new chemical product development (including drugs) is still largely an empirical endeavor based heavily on screening.

The cost of development of successful new chemical products (pesticides and therapeutic drugs) has risen in both time and money several fold over the years. From industry's point of view, the barrier to entry of a new product into the market is increased. The costs of increased delay in time are perceived as much more meaningful than are the direct costs of performing the premarketing evaluations—mainly because of the costs of servicing the large investments made toward the latter parts of the development process. This increased barrier to entry into the market place, to the extent that it reflects a more careful and thorough examination and understanding of the behavior of chemical products (biological effects, unintended side effects, environmental behavior, etc.) can be said to be an appropriate reflection of the public's desire to be critical about the character of its chemical environment. Although the barrier to entry is increased in some cases, there are compensations as the probabilities of displacement by competing products are correspondingly decreased and the periods of commercialization should be expected to be lengthened.

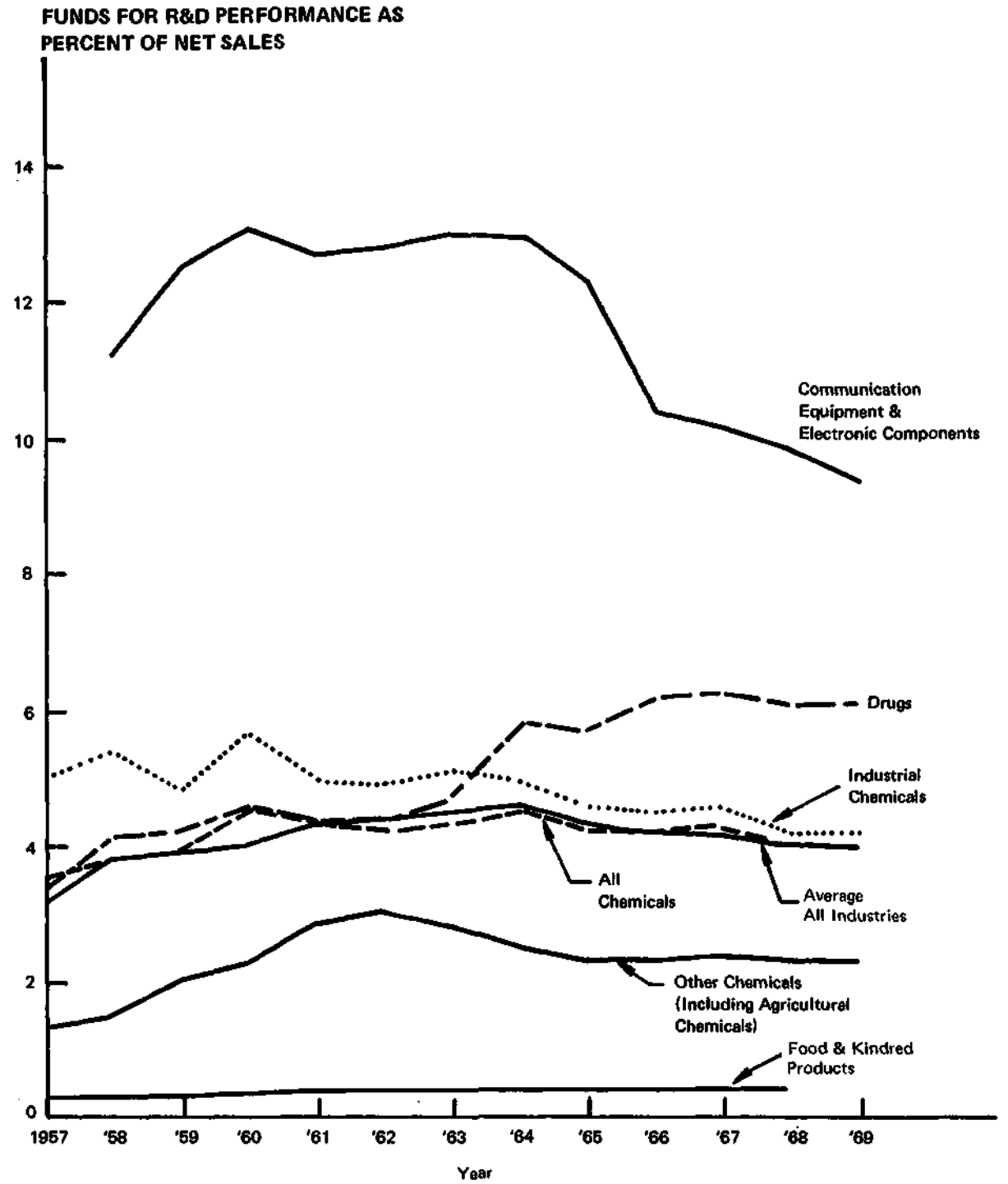
It seems clear that the lengthening of the development process cannot continue indefinitely and be compatible with innovations in new generations of desirable products. There is, for example, some indication (although good data are not available) that pharmaceutical firms may find less attractive the lengthy development of drugs for chronic administration (such as oral contraceptives) and drugs for serious but low-incidence diseases. The Panel feels that it may be appropriate for the Federal Government to encourage the development of certain products from time to time which are recognized to be of particularly high social value and for which the private sector does not perceive sufficient incentives for its own efforts.

Throughout its deliberations, the Panel has been impressed that, rather than acting as a perturbing force, the net result of much of the Government regulatory activity towards new products has been to provide reasonably systematic judgment and arbitration among inevitably competing interests. There is clearly much room for improvement. Yet in the absence of an FDA, for example, there would seem to have been less public confidence in outcomes and decisions. This had led the Panel to the conclusion that a Government regulatory agency, if it performs appropriately, represents in the form of its approval or certification for marketing, a capital asset value to the industries petitioning to it. It is in the industries' best interest to assure that the best scientific information is obtained for decisions.

The United States has consistently been a net exporter of chemical products. It is also an exporter of technology and research and development but with repatriation of profits through multinational firms. The regulatory process does not seem to have been a major force in this trend. Rather it simply reflects business opportunities and the regulations prevailing in other nations.

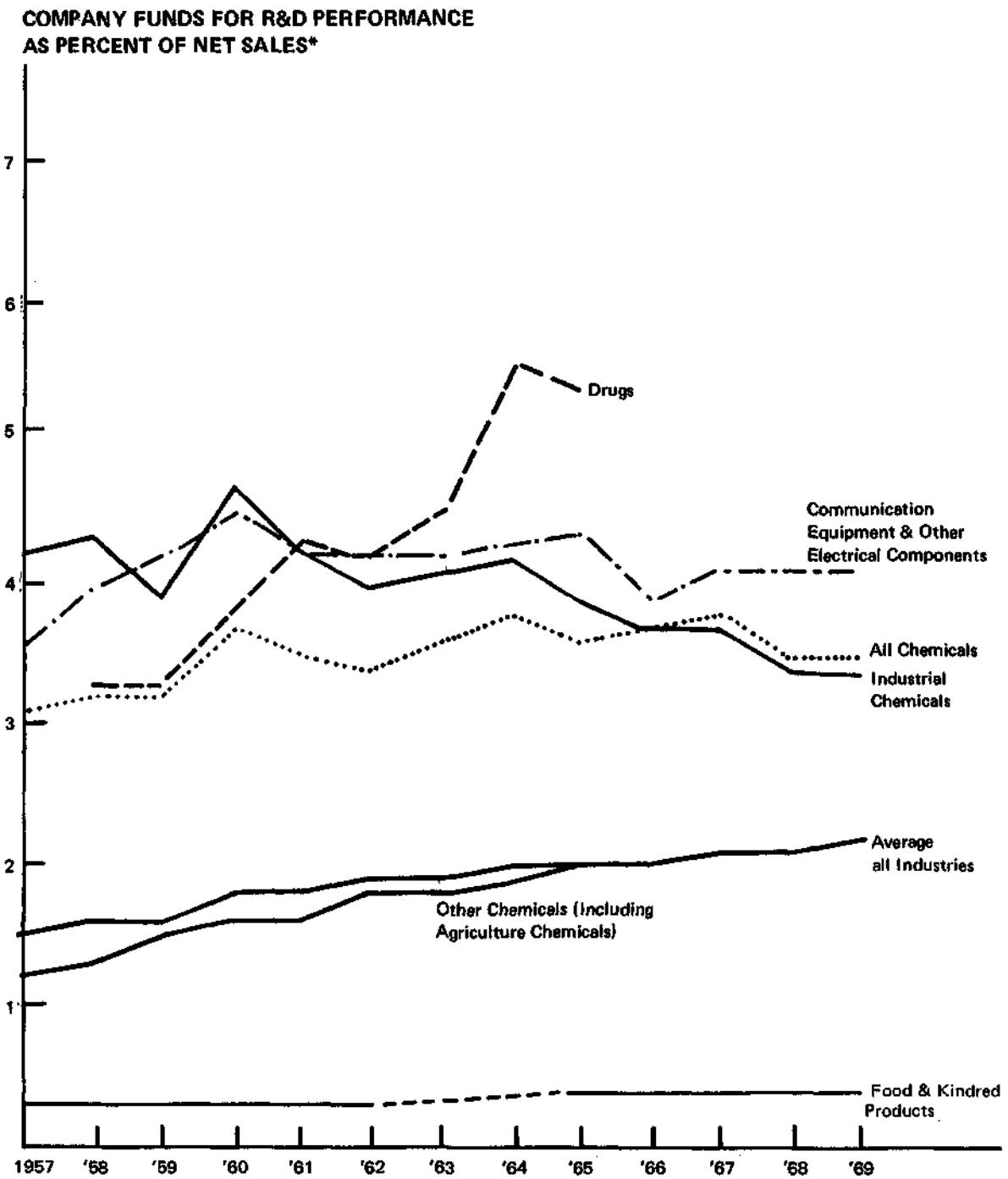
The Panel is persuaded that much or all of the industrialized world is moving towards a pattern of regulation which resembles that of the U.S. The United States leads in the R&D for new drugs products. There is no

EXHIBIT 12-10



Based on data from the National Science Foundation.

EXHIBIT 12-11



*NOTE: If value added to shipments is used as the denominator rather than sales, the rank order of this curve is not altered.

Based on data from the National Science Foundation.

indication that this country lacks important and safe new drug entities which are available abroad. The Panel agrees with the view which sees a worldwide slowing of new drug development mainly as a result of limitations of scientific understanding of biological actions and disease processes.

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Chapter 13

Regulatory Practices and Issues

CHAPTER 13

REGULATORY PRACTICES AND ISSUES*

1. INTRODUCTION

A. Freedom versus restrained safety

Our governments continue to play an ever increasing role in our lives; undoubtedly they will play an even larger role in the future. We dare not either encourage this expansion to be as rapid as possible or demand that it come to a halt. We urgently need to understand the conflicting values that must be balanced in arranging for expansion to be at a well-chosen rate and in well-chosen directions.

In general, the growth of government responsibility responds to (1) our living closer and closer to each other, (2) the division of labor and function into smaller and smaller pieces, and (3) the increasing geographical spread from which each of us draws materials and products. To these three we must add the ever-growing complexity of our society, where no one of us can understand the details—or even the main considerations—of all the diverse actions that interlink and interact. No one individual holds enough knowldge to make all the decisions that affect his actions. Some must be made by others who have gained the relevant understanding.

Today, in the area of chemicals and health, other factors are effective in increasing the role of our governments. The expansion of scientific and technical knowledge—more particularly our skill and sophistication in the use of various ways of gathering knowledge—has made us able to detect the presence or absence of very tiny traces of many substances. Traces that would have been wholly undetectable not long ago, are now not only detectable but measurable. The same is coming to be the case with the detection of subtle effects in humans, other mammals, and plants. This new knowledge does not, of course, change the risks to which each individual American is subject. It makes it possible, however, to be aware of and concerned about dangers that could not have been imagined just a few years ago.

We need to separate four classes of situations quite clearly:

- Situations where alternative suppliers offer the consumer very different quality or very different safety.
- Situations where all sources of supply provide an equivalent product whose dangers have been more or less widely understood for a long time.
- Situations where all sources of supply provide an equivalent product whose dangers have only recently been confirmed.
- Situations where all sources of supply provide an equivalent product whose safety is open to some question, but where there is no established danger.

Examples of these four, according to recent newspapers and recent acts of Congress, would include (1) detergents, (2) automobiles, (3) cigarettes, (4) various subjects of current newspaper headlines.

The case for using inspection and seizure to attack isolated cases of either clear or probable threats to safety is strong; such actions are, as they deserve to be, broadly supported. The second class of situations is treated rather differently. Seat belts have now been mandated in new cars for some time. This could be regarded as forcing suppliers up to an equal level of quality. In several Australian states, the use of seat belts is now mandatory. So far, this still seems unlikely in the United States, perhaps because, for many people, such a requirement would destroy the carefree enjoyment of "taking a ride." Cigarette packages must bear warnings, but a serious attempt to forbid cigarette smoking does not seem to be in sight.

The recent decision about swordfish follows a quite different line. The position taken was not that some swordfish contain more mercury than others (though this is doubtless true), but only that all swordfish contain—as has presumably been the case all along—more mercury than is deemed safe. The contrast with cigarettes (and alcohol), where evidence supports a presumption of contribution to many deaths, is striking. Cigarettes, which the Surgeon General and the Congress are convinced have health-impairing effects on many people are left on sale. Swordfish, where there is no clear evidence of individual ill effects, are taken off the market.

In addition, the area of chemicals and health faces a horror of the "unnatural" that has been growing for decades. If cigarettes were synthesized in a chemical factory, it is not clear that they would still be on the market. Because tobacco grows—as do poisonous plants—it is somehow thought to be the nicer for this, the fact that botulinus toxin is far more poisonous than cyanide or any humanly synthesized chemical notwithstanding.

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* The Panel, during its deliberations, arrived at a number of findings which are underlined in this chapter. In some cases these led to the formal recommendations which are presented in Chapters 2 and 3.

B. Where do we draw the lines?

When do the interests of protecting the public from some danger outweigh the public's interests in its members' freedom to use, eat, or drink some product? How are we to make the more difficult judgments, balancing an uncertain risk against the freedom to use and enjoy? We cannot find in today's practices a set of consistent answers.

The balancing of safety with freedom would be easier if the freedoms were all minor. The consequences of over-restricting freedom might then be small enough to be taken in stride. But the freedoms in question are not all minor, either cumulatively or individually, as this country's experience with prohibition testifies clearly and vigorously. Today much of what we do depends upon chemicals that are relatively new. Growing our food without pesticides would surely be very much more expensive in the 1970's. Operating modern automobiles without modern gasolines, many of whose constituents, not found in crude oil, are the results of pyrolysis and synthesis, would be impossible. We would, on the average, be more diseased, and die somewhat sooner, were it not for a broad variety of prescription drugs. Our foods would be much less satisfactory in taste without some additives, in appearance without others, and in keeping quality without a third set. Our electric devices depend critically on other chemicals, as do our paints and building materials.

What principles ought to govern our balancing of safety and freedom? No simple set of principles will guide all the many detailed decisions, but those principles on which we can agree can do much to make our decisions more consistent with one another and more satisfactory.

The following principles seem useful:

1. When a risk is an inevitable consequence of exercising a freedom, we must balance human freedom against human risk.

2. The more the risk is confined to those that exercise the freedom, the more willing we are to bear the risk. Risks to the same individuals who make use of the freedoms are less a governmental concern than risks to other individuals.

3. We must prepare for the consequences of steady improvement in scientific knowledge and measurement technique—we will inevitably learn of more and more risks, many of them quite minor, as this improvement continues. We must become used to living with the knowledge of many small risks, just as we live with the risks of being struck by lightning, meteorites, or golf-ball sized hailstones.

4. We must understand, and act upon, the distinctions between the possibility of a risk, an established risk that is so small as to be judged negligible, and a small meaningful risk.

5. Larger risks are more likely to be the concern of government, especially when the freedoms involved are not especially dear to the individuals.

6. The more dearly held the freedom, the less wise for the government to try to eliminate it by regulation rather than by persuasion.

C. Balanced judgments

We have just discussed balancing risks and freedoms, giving some general principles that may help us to be more consistent but not prescribing exactly what choices ought to be made. At first thought, this balancing may seem unduly difficult, especially to those who wish to weigh everything in monetary terms.

Monetary systems and market mechanisms have been great social inventions, whose advantages—so easy to forget or neglect—far outweigh their disadvantages—all too often so obtrusive and unfortunate. But it would be very wrong to forget that they possess advantages only because they do rather well in approximating what we all, on other grounds, find desirable or acceptable. The basic issues of chemicals and health are human issues; incidentally, though often significantly, they are economic.

Rather than trying hard to convert the human issues into economic ones, we should seek balanced judgments about chemicals and health by going the other way. To say that cutting out some food additives would raise the costs of food through increased spoilage and requirements for more expensive handling and packaging is true, but it is more meaningful to say that such an action would take away from many people some of their freedom to consume such foods.

Even after we have gone as far as our understanding will take us in converting benefits to freedoms, these freedoms will be but some of the benefits associated with whatever risks we face from natural or synthetic chemicals.

D. Information is often vital

We cannot ask an individual to balance a risk he does not understand against a clear and visible freedom. From this point of view, the warning on the cigarette package is an essential if each of us is to retain the freedom to smoke.

How little—or much—information is needed to clear our consciences as citizens and voters? How little—or much—is needed to clear the consciences of our elected representatives and those government officials responsible for protecting our health? How little—or much—to clear the consciences of physiologists and medical workers directly concerned with a particular hazard?

Clearly the answer depends more on how much we know—and how much we can reasonably infer—than on what some find it possible to fear. Clearly we cannot expect everyone who thinks of smoking a cigarette to

acquire all available information about the effects of smoking. The present warning is part of a spectrum of social choice, ranging from prohibition, through varying degrees of regulation, then through intensities of information, to a wholly laissez faire position. In the case of cigarettes we have clearly entered upon the middle way of spreading information, a way between the extremes of forbidding on the one hand and no discouragement on the other.

This is not a course with which we have decades or centuries of broad experience. Indeed it is only relatively recently that the general public has been well enough educated for information to seem to be a realistic means of responding to hazards. Yet it is an alternative that we shall have to understand and use effectively, since it offers real advantages by allowing each individual to balance risk and benefit, thus preserving his freedom of choice, which inevitably includes his freedom to make the risky choice. Individuals are different, and can often make good use of freedom to make different choices.

2. RIGIDITY OF REGULATORY TOOLS VERSUS THE SHADES OF GRAY DEMANDED BY SCIENCE

Regulatory laws for such items as drugs and pesticides are legislative and political responses to limit and control these products in ways to serve the best public interest. Where they deal with scientific issues they necessarily reflect the state of knowledge at the time of their writing. As the applicable sciences evolve, not uncommonly new insight and knowledge bring into question the original concepts which formed the basis of the statutory regulation. The statute then appears more rigid than would be desirable in the light of this new information.

The concept of zero tolerance (zero amount of pesticide residue tolerated on food crops) which had been central to a previous regulatory scheme, was shown to be untenable as analytic techniques improved. What had been thought of as zero or non-detectable levels of a chemical became finite recognizable levels.

Another view of this subject would suggest that it is because of a lack of scientific information that the legislative process develops rigid regulatory authorities. The most familiar example, perhaps, is the amendment of the Food, Drug and Cosmetic Act which directs the banning of a food additive if it has been shown ". . . to cause cancer in man or experimental animals."

It can be argued that as additional understanding accumulates as to the biological mechanisms underlying neoplastic disease, and as one obtains more detailed information on how chemicals interact with biological tissue, the Delaney Clause may well be modified.

This report has stressed on several occasions the likelihood that scientific research will raise new and unexpected questions about former decisions and regulatory choices. This new science—old decision question is a major perturbing factor in what otherwise might be a reasonably stable system. In many cases, the information which may be of interest to regulatory decision-makers comes from recent experiments and, hence, is often not confirmed or thoroughly understood. The challenge in such cases is to exercise reasonable prudence in regulatory action so as to afford responsible protection of health and yet not to act capriciously.

The achievement of these combined goals would often be best accommodated by a temporary restriction on the use or distribution of the material in question while the newly generated scientific results are confirmed, extended and their significance evaluated. This concept was noted by a previous PSAC Panel in the case of pesticides. That Panel recommended that, ". . . a mechanism should be established for restricting the use of a registered pesticide temporarily on the basis of information which implicates the chemical as a possible health hazard pending the collection of more definitive information."[1] That report noted that a pesticide registration could be held in obeyance only through the actions of cancellation or suspension. Both of these were viewed as definitive and serious actions. There was no corresponding avenue for temporary withdrawal.

New scientific findings will frequently make it evident that the Government should change its mind from time to time on past regulatory decisions. The regulatory laws should permit responsible flexibility to allow prior decisions to be changed. For example, the present version of the amendments to the Federal Insecticide, Fungicide, and Rodenticide Act would permit reclassifying a pesticide from a category of general use to one of restricted or controlled use.

Regulatory laws dealing with chemicals and human health should be amended to accommodate explicitly temporary limitations on manufacture, sale or use on the basis of information which implicates the chemical as a possible health hazard pending the collection of more definitive information.

Elsewhere in this report (Chapter 11) the Panel took note of the widely scattered Federal programs of environmental health research, and recommended a strong and permanent mechanism of coordination. The finding above, urging flexibility in the regulatory laws to accommodate the acquisition and review of additional scientific data, should be considered in association with the previous finding concerning coordination. This represents the very type of contingency to which reference was made earlier and for which accommodation was felt needed.

Whenever a temporary restriction is invoked on the manufacture or use

of a chemical agent for reasons of implied hazard to human health, full use should be made of the high-level coordinating body mentioned in Chapter 11 to review the research underway and to make the best use of the Federal research resources.

3. PROS AND CONS OF ADDITIONAL CRITERIA FOR INTRODUCTION OF MATERIALS

Regulatory laws dealing with chemical and physical products (pesticides, foodstuffs, radioisotopes, etc.) treat the producers of the commodities as types of public utilities and the commodities as having a public utilitarian function. Implicit in each case is a specific benefit or utility which might be expected from the use of the product. Pharmaceutical products treat disease and promote individual well-being. Insecticides reduce numbers of insects and increase productivity of other investments in the agricultural enterprise. Authority to regulate reflects certain items which, it is thought, might detract or add to the utilitarian function of the products (safety, human health, purity, etc.). The rigidity with which criteria are imposed as obligations on a manufacturer before permitting him to market a product is a function of how important these utilitarian functions seem.

Historically, in the case of regulated chemical materials, purity or absence of adulteration is the item on which a regulatory law seeks assurance first. In the evolution of pesticide and food and drug laws, purity of these materials was the original preoccupation. Usually later, purity was joined by assurance of suitable analytic techniques, reasonable freedom from side effects, and safety.

In addition to the simple enumeration of criteria, there arises also the matter of the degree to which each criterion is applied. The subject of human health and safety is illustrative. The evolution of scientific understanding of the biological effects of exogenous chemicals and of the mechanisms of various disease processes led to an increasing scope and complexity of questions asked about pesticidal chemicals and their effects on human health. These same comments about the relative importance of criteria can be applied to others as well.

Reduction of Diversity?

It is sometimes held that one purpose of registration or approval is to reduce the diversity of chemicals to which humans and the environment are exposed. Those who hold this view tend to ask that additional criteria be used in registration, mainly to reduce diversity. There seems to be no valid basis for this position. Our knowledge background and our study techniques always improve, faster or slower. As a result, our testing of new chemical entities becomes more and more searching and insightful.

Testing, both in animals and in humans, has one set of limitations; studying experience with human exposures to a chemical has another set. When all considerations are brought together, it is our judgment that under our present schemes of regulation for safety, it is reasonable to anticipate that the new will be at least as safe as the old.

Three general arguments speak out for encouraging the development and use of alternative substances. First and foremost, the development and use of two or more substances make it easier to take vigorous action when one becomes suspect or is known to have even a very small risk, since action implies only shifting to the other substances, without giving up the benefit. Second, and often very important, both people and situations differ in many ways, and the substance that is more effective or lower in undesired effects often differs from one to another. People do vary in responsiveness to drugs. There are several examples available showing that one member of a class of drugs is useful for some patients while another is required to achieve the same result in other patients being treated for the same condition. This argues in favor of some degree of diversity. Third, there are well-known cases—as with some of the early sulfa drugs—where exposure to mixtures leads to smaller side effects than exposures to equivalent amounts of either substance alone. In general, then, we are better off to have several substances discovered, developed, checked for safety, and in use for a given purpose than to have only one.

Betterment

The additional criterion most often called for is betterment. For example, it has been suggested that a new pesticide should not be registered unless it has been demonstrated to have desired characteristics not now possesed by other materials on the market. A further evolution is to allow new and demonstrably better products to displace (by regulation) older and less desirable substances. The practice in the United Kingdom is to oblige users of food additives to demonstrate in a test situation that a proposed food additive has advantages over existing substances.

Betterment is not a criterion for regulatory consideration at the present time for any of the regulated chemical substances. Thus, for the most closely regulated of the items, prescription drugs, the Food and Drug Administration approves *effective* drugs—not better drugs. Since the use of betterment as a criterion would both reduce diversity and tend to keep up prices, its effects would be unfavorable.

Improvement or betterment in intended effects over substances already known is NOT a desirable basis for regulation.

Efficacy

Proposals to extend requirements of efficacy beyond the classes of

use—human and animal medicines, pesticides—where it is now required are often supported either by the sort of argument that has just been discussed for betterment or by an argument that unless we require efficacy data with registration petitions we will never get around to learning about it. If this position is not just a concealed version of the former—or an argument that efficacy needs measurement to protect the consumer's pocketbook, one that applies equally to many things other than chemicals—then it is hard to see exactly how it is to be supported.

In those areas where efficacy is a subjective matter—for instance, food additives used for flavor or appearance—the difficulties with efficacy measurement make requirements for efficacy testing especially counterproductive.

Regulations for the purpose of health and safety should not call for establishment of efficacy outside the classes of use—human and animal medicines and pesticides—where it is now required.

4. STAGED INTRODUCTION OF CHEMICALS

When marketing should begin, and when manufacturer's surveillance should stop raises difficult problems. If something is to come into close contact with very many people, is there virtue in staged or phased introduction? Where along this line should marketing begin? Should we do more in the way of "geographically" limited trial, and open marketing earlier? Should other substances receive the intensive post-marketing surveillance required of some prescription drugs?

In the abstract, there appears to be merit in a system which permits phased or gradual introduction of new products accompanied by a system of surveillance for unexpected adverse side-effects.

The ideal safety test progresses sequentially from crude estimates of effect in small groups of laboratory animals to more and more refined questions on larger and larger groups of animals and finally to man. This last step should obviously only be taken when considerable confidence in the laboratory data has been secured, and then the move should be made cautiously and first on a small number of persons.

This staged progression in human exposure is a well established tradition with drugs but has had limited application in respect to consumer chemicals.

Starting with the premise that the degree of assurance of safety required should be tempered by consideration of the benefit sought, two practical issues arise. These are very different philosophically and relate in varying ways to different chemical uses: 1) costs, i.e., the necessity of keeping the cost of testing commensurate with the social benefit (and in some instances market value) of the chemical, and 2) the scientific and ethical problems of progressing through stages of expanded human trials.

A. Costs

Although there are no circumstances in which a chemical should be released for uses where reasonably anticipatable hazards have not been eliminated, there always remain elements of uncertainty. To carry out very elaborate investigations of all chemicals is an impracticality, not only because of cost, but simply because of a built in lack of attainable testing resources. Accordingly, a selection must be made as to what chemicals should be studied and to what extent.

The considerations entering into such choices must include those of extent of use, number and age of persons exposed, reversibility or irreversibility of effects suspected and other considerations.

There are sometimes sound arguments for moving into controlled and limited human usage without having run through the complete range of laboratory studies. In such instances it will be appropriate to continue and extend the laboratory studies as the human use expands.

One might consider as one guide (but only one, and not always the predominant one) that as sales increase, further tests in the laboratory and additional human surveillance might both progress in parallel pace. This could be done by imposing a tax on sales or by requiring that a certain fraction of sales income be applied to further studies along lines defined by the regulatory agency.

B. Scientific and Ethical Factors in Human Studies

A staged approach is a well established practice in testing for drug safety. Normally after laboratory studies on animals, careful clinical trials, first on a few patients and later on larger and larger groups, are undertaken. With drugs, at least in the very early stages, the physician responsible for the clinical studies systematically undertakes the follow-up of the patient to determine whether side effects do or do not occur. However, as the drug passes into a later stage of extended distribution, the same careful controls are not necessarily available. When the drug reaches general availability to the medical profession the present pattern for reporting adverse side effects is, as is noted elsewhere in this report, very poor, and adverse drug reactions are very inefficiently reported.

It seems probable that the safety evaluation of drugs could be improved by more systematic use of the technique of limited introduction at the later stages of drug introduction. Thus, one could consider the utility of moving in the later stages of drug trial to limited introduction based on such restrictions as to hospitals only, or to teaching hospitals only. Other approaches might involve distribution to physicians certified for relevant specialties or distributions based on a well established "medical

group" system, e.g., Kaiser Permanent Hospital Insurance Plan. This would not alter the philosophy currently operative, but would introduce additional graded steps in the path toward general distribution. In all such trials, "informed consent" of the patient is now required in this country.

Clearly one can justify human trials on substances such as drugs which may confer substantial benefits on the test subjects, and where the understanding and consent of the subject are obtained. But whenever the possibility of significant benefit to the test subject is low, or difficult to determine then the only basis for human testing is the use of volunteers who, for any sufficient reasons, accept whatever small risks there may be in a carefully monitored test in order to be of service to society.

With substances other than medicines, the risks in actual use should be so low and infrequently encountered as to render them very difficult to detect. To provide reasonable assurance of detection would require large groups of many thousands and detailed surveillance, two mutually contradictory requirements. And, as we have just observed, there is no ethical basis for asking anyone to take part in a test and assume a risk greater than a minimal and irreducible one, if the possibility of more than offsetting personal benefit is absent, except as a fully informed volunteer, and with the protection of careful monitoring to assure timely intervention in the event of any ill effects. And such close and detailed monitoring cannot practically be provided on the massive scale required even if the volunteers could be recruited.

On the other hand, a relatively small number of volunteer human subjects can be of irreplaceable value in establishing the metabolism of a substance, and the relevance of previous or future animal studies. Such small-scale studies often are practical, and their wider use should be encouraged.

1. The use of human subjects for the detection of adverse effects should be restricted to those tests which (a) can be closely monitored and (b) where the risks are either trivial and transient, or involve substances, usually medicines, where the possibility of personal benefit is judged to exceed the probable risk.

2. Large-scale testing of the sort implied in staged introductions is not ordinarily defensible for substances other than medicines because the possibility of benefit is not sufficiently clear, personal, informed consent is less likely, and adequate monitoring is virtually impossible.

Because we do not propose intentionally to test by a staged introduction a substance such as a food additive or a detergent component does not mean we should go to the other extreme of ignoring or failing to observe whatever consequences can be detected.

C. Population Studies

Population studies aimed at a general surveillance for possible adverse effects of chemicals in general (as opposed to limited studies focused at specific chemicals as suggested above) are currently minimal, and indeed are very difficult. The difficulty relates largely to the frequent inability to correlate observed disorders with specific exposures. A person encounters almost an infinity of stresses in a lifetime; the reliable association of a specific exposure with a specific effect in the general population is thus always difficult and sometimes impossible.

There are techniques for selecting groups on the basis of more intense exposure than the general population: use of occupational groups, selection of the basis of dietary habits (heavy fish consumers, groups showing evidence of heavy exposure from tissue analysis as for example mercury, arsenic, body fat content of chlorinated hydrocarbons) and so on. These have been very inadequately used and should be systematically extended.

There remains the need for national alert and surveillance systems to detect a possible perturbation of national disease patterns arising from chemicals. There appear to be practical ways of doing this in limited fields. For example, suggestions have made for developing national alert systems for teratologic disorders and mutagenic defects.[5]

Surveillance of prescription drug experience including the monitoring of adverse reactions deserves to be vigorously pursued. In practicality, there are great difficulties attendant on the systematic surveillance of human use of most chemical products other than prescription drugs and a general policy of staged introduction does not appear to be warranted.

5. ISSUES RELATED TO HUMAN TESTING

The principal issue raised here is that of timing. For those chemical substances where purposeful human exposure is to be expected and where humans are used in evaluation and testing before marketing, when in the course of evaluation should human testing begin? How much preliminary information should one have in hand before initiating human studies?

By definition this discussion is almost exclusively concerned with therapeutic drugs. Chemicals used to secure some desired effect in man, the prophylactic and therapeutic drugs being prime examples, and chemicals used as pesticides, food additives, and household products, present fundamentally different testing problems.

A pesticide designed to control an insect, or a food additive designed to maintain the texture of bread, can be thoroughly tried for effectiveness without exposing humans in any degree. However, most of the information on effectiveness of a drug

must be gathered from experience in humans. Clinical trials in both normal humans and in patients are heavily used to gather data on mechanisms of action, absorption, metabolism and toxicity in the case of drugs. In some instances, where appropriate animal models of a disease are available for study, some confidence with respect to the safety and efficacy of a new drug may be gained through experimentation on animals. Unfortunately, reliable animal models of human diseases are by no means generally achievable, and thus, except in rare instances, it is impossible to screen new drugs reliably for efficacy without administration to humans. Further, for drugs used specifically for human exposure it is clearly necessary to engage in investigations on human subjects in order to achieve a full and adequate understanding of absorption, metabolism, excretion, and other elements of biological activity which contribute to toxicity and side effects as well as intended action.

The present rules for evaluation of new drug candidates derive from amendments to the Food, Drug and Cosmetic Act published after 1962. These direct the sponsor of a potential drug to supply the Food and Drug Administration with the results of a number of investigations according to a fixed sequence. A new drug developer petitions the FDA for permission to examine a chemical entity in humans as an experimental or investigational drug. In his petition, he is obliged to supply ". . . adequate information about the preclinical investigations, including studies made on laboratory animals, on the basis of which the sponsor has concluded that it is reasonably safe to initiate clinical investigations of the drug."[2] The regulations then proceed to outline the stages of investigation of the drug as an investigational entity. This schedule of investigation is divided into three phases. Phase 1 begins with the introduction of the drug into man (normal human subjects) and is used to gather data on human toxicity, metabolism, absorption, elimination, other pharmacologic action, preferred route of administration, and safe dosage range. Phase 2 is a period of initial trials on a limited number of patients. The first two phases may overlap and additional animal data may be called before Phase 3. Phase 3 represents a full-scale but controlled clinical trial in patients.

The economic pressure to proceed as rapidly as possible to human trials is very strong in the case of drugs. The conduct of elaborate toxicity testing on candidate drugs prior to human trials for efficacy would customarily involve the costly safety testing of many compounds which would eventually be discarded as not effective. More importantly, it would also lead to a considerable loss of time which in some cases could lead to delay in the introduction of an effective drug with a consequent possibility of permitting avoidable human suffering.

There seems to be no single easy resolution to this dilemma. The range of considerations varies greatly depending on circumstances. Much less animal toxicity is required for a chemotherapeutic agent for a normally fatal malignancy, than for an antihistaminic analgesic or tranquilizer which are used for relatively mild conditions. In the former instance, one could move on to human trials while some measure of uncertainty as to safety is still present. In the latter instance, there would seem to be no defensible reason for not undertaking a meticulous preexamination aimed at assuring that chronic irreversible lesions such as cancer are very unlikely to occur before proceeding to the exposure of a significant number of humans.

Again, there is a distinction in the kinds of safety tests to be used. Those tests aimed at acute and reversible functional effects, on the one hand, can often be realistically studied in animals and, on the other, where one is concerned only with reversible functional side effects, human testing is practicable. It is in respect to chronic effects, such as cancer, that major difficulties arise. These tests are lengthy, normally requiring a large part of the life span of an animal, e.g., two years in the case of rodents, seven to ten years in the case of dogs, and similar periods in the case of primates.

Increased concern has developed about the carcinogenic risk of new drugs in man. A requirement that all new drugs be evaluated for their carcinogenic potential before human testing would have a serious impact on the development of new drugs. As has been pointed out, the need for initial efficacy studies in man is obvious in view of the inadequacy of animal models for disease and of the frequently encountered species differences in drug response. Interruption of drug investigation for two to three years, which would be needed for carrying out carcinogenic testing in rodents, would seriously impede the validation in man of pharmaceutical data obtained in animals with new chemicals. However, there are enough examples of chemicals known to be carcinogenic for both humans and laboratory animals that one cannot disregard a positive laboratory animal test for cancer. A number of scientific groups are studying this problem in an attempt to formulate a way of performing drug testing without placing human subjects at risk but still allowing drug development to proceed.

It is clear as a minimum that drugs cannot be dealt with in a single category, as is sometimes the tendency. Decisions as to the amount of safety testing needed must be judged in the light of the benefit sought and, as well, in the number of persons likely to be exposed. These are matters about which general and categorical statements cannot be made, but which in the last analysis must be decided on an ad hoc basis, judging the issue in the light of good scientific information and prudence keeping in mind both the qualitative

and quantitative consequences of a wrong guess.

*When should animal studies for new drugs give way to controlled evaluation in humans is a question that demands an understanding of the potential benefit to be derived from the drug in each case and its probable biological behavior.**

6. PROPRIETARY NATURE OF SCIENTIFIC INFORMATION

Much of the scientific information, including that on toxicology, which is submitted to FDA and EPA by industry has been considered proprietary. This information has not been generally available to the scientific community and the general public. The proprietary nature of toxicological information is a stumbling block to improving the quality and usefulness of safety investigations. Failure to share this biological information in the past has prevented scrutiny of it by much of the scientific community—a matter recognized by a previous PSAC Panel.[3] In the interim since that PSAC Panel report, the Government agency responsible for the registration of pesticides (now the Environmental Protection Agency) has moved to make available to the toxicological data for those pesticides whose registration applications were approved. The National Library of Medicine has proceeded to assemble these data systematically and in a form useful to scientific investigators. Similarly, the Food and Drug Administration has recently proposed to make available to the public most of the scientific data collected by that agency and formerly held as proprietary.[4] The Panel finds this a highly desirable trend. With passage of some form of a Toxic Substances Control Act, the Environmental Protection Agency will again be faced with decisions on the release of large amounts of scientific information provided to it by the industries it regulates.

We have tried to encourage pluralism among our options by trying to support R&D, both through our patent system and through protection of proprietary information, and to encourage pluralism among our producers by antitrust regulations. As a result we have accepted, as part of the necessary costs, the costs of parallel research and development. As we continue with this policy, we need to be careful about extending it to situations where loose analogy suggests that it fits, but careful study shows its effects are not what we want.

Information about the safety of chemical-use combinations, whether toxicological or environmental, is of great public importance. Obtaining the same information several times is wasteful of money and of scarce resources in skilled people and special laboratories. Not allowing the academic research community access to the detailed results of safety testing can do much to slow our progress in the understanding of the presence or absence of unfortunate effects of chemicals on people, domestic animals, domestic plants, and the environment at large.

When clearance for marketing a chemical-use combination is applied for, significant amounts of safety-testing data will be required as part of the application. Once the application is either approved or finally rejected, this information should become part of the public record.

The release of safety-test data to the public record, and thereby to competitors, deserves to be excluded from the provisions of all antitrust controls. While it may promote competition, keeping knowledge of safety information secret cannot help society.

There is no overriding reason for maintaining the privacy of toxicological information for products—both for successful and unsuccessful developments. In the case of petitions for permission to market which are approved, the background scientific information should be made available without further encumbrance. For petitions which are rejected, the background data have economic value and may represent a sizable investment on the part of the developer. Such toxicological information should, however, be made available after a fixed delay such as two years from time of the rejection of a petition for registration.

7. REGULATORY DECISION-MAKING IN BEHALF OF CHEMICAL AGENTS

It has been the clear intent of Congress over the past several years to set apart the protective functions of regulatory agencies from those aspects which most would consider relate to promotion. Thus, the Food and Drug Administration was established and its jurisdiction grew in incremental steps over foods, drugs, cosmetics, and consumer products. Interestingly, the increments typically reflected a crisis atmosphere of a discovered toxic contaminant in a drug or a hazardous food additive. The spirit behind each successive amendment of the Food, Drug, and Cosmetic Act was the separation of this protective function of the government from all others. The more recent evolution of the Environmental Protection Agency is illustrative of the same philosophy of separation of protection from promotion.

The separate administration of protective regulations, as brought about with the creation of the FDA and EPA, and has been the clear Congressional intent over the past several years, is in the national interest. At the same time, appropriate regulatory decisions in the best national interest must include a balancing of a broad series

* The Panel is pleased to note that the Food and Drug Administration has moved to expedite the review of drugs with very high expected benefits while insisting on exhaustive examination of other classes.

of considerations and issues. It is clear that, in the past, this has been difficult to achieve in the face of the narrow constituency of regulatory agencies. Ways should be explored for deriving balanced judgments and decisions while preserving the integrity and separation of protective function agencies.

The present pattern, then, is for Congress to delegate to an administrative agency (personified by its chief administrator) the dual responsibility of assessing the seriousness of danger and the determination of the detailed actions needed to respond to it.* There is evident virtue in effecting this separation of protective functions. The legislative history of the laws which give the FDA and the EPA its jurisdiction clearly reflect a Congressional awareness of this problem: an agency should not be or even appear to be a captive of the very groups it is supposed to regulate. The separation of the protective functions means, in essence, that the protective agency has a constituency of its own which generally feels more strongly and often more emotionally about the needs for stopping certain actions or trends. It is to this constituency that the protective agencies look for support.

Regulatory agencies including those which focus on the protection of human health, must attempt to arrive at balanced decisions. As was pointed out in the section on risks and benefits, it is impossible to achieve a perfect solution to all of the various considerations when reaching a regulatory decision of the sort being considered here. Rather, the process is inevitably one of a reconciliation of a number of desires—often seemingly in conflict with one another—but with a primary criterion of human safety or health or environmental integrity. Balancing should be performed among the several kinds of considerations which are inevitably raised with every major regulatory decision. The setting of national standards for ambient air quality must balance the health of our more susceptible fellow citizens against the costs of rearranging the transportation habits of many of our largest metropolitan areas. The demand for the control of a polluting effluent by way of a standard must necessarily be accompanied by a corresponding technology capable of achieving control. Regulatory decisions made in the name of human health which implicate large expenditures (and many do) should be accompanied by an analysis of such a question as, "Can the implied expenditure purchase even greater health if spent in a different way?"

In this connection, the panel notes with approval the recent tendency of appellate courts, when dealing with statutes designed to protect human health and environmental integrity, to stress the legitimacy and wisdom of a broad balancing of the competing considerations by each agency empowered to take regulatory action. In the pesticide area, for example, although the underlying statutory mandate might have been interpreted more narrowly, the United States Court of Appeals for the District of Columbia held in 1971 that the ultimate decision to cancel a pesticide's registration should not "turn on a scientific assessment of the hazard alone" but should, in light of the legislative history, reflect an effort by the responsible agency "to balance the benefits of a pesticide against its risks."[6] We look forward to extension of this attitude.

Finally, there should be, in the balancing process, a systematic consideration of the effect of each regulatory decision on other government programs and policies. Regulatory decisions of any consequence (such as the banning of a heavily used product, the proposal of a standard for exposure to an environmental contaminant or for the use of a drug) invariably impinge on other government business. (Obviously, in some circumstances, it is the protective regulatory purpose to achieve this very end.) It appears clearly desirable that the architects of protective agency decisions be fully aware of the consequences of their intended actions for the rest of the government's business.

The panel, therefore, is deeply concerned with the necessity of deriving balanced regulatory decisions aimed at preservation of human health and safety in a setting where the regulatory agency's constituency was comprised of somewhat narrower interests. There were other considerations also. One is the credibility of the decisions. Credibility, by its nature, resides in the eyes of the beholder. It is essential that all of the interested segments of the public have the fullest confidence in the decisions taken by the government. The health-related regulatory arena is a particularly difficult one, since scientifically based regulatory decisions almost never reflect clear-cut, totally identifiable issues. The area of uncertainty and, hence, judgment usually looms very large. What is important, then, is that the public enjoy full confidence that all of the available pieces of information have been obtained and analyzed and that both the facts and the uncertainties have been submitted to the best judgments possible.

The credibility of the Federal Government in regulatory matters appears to have been severely strained in recent years. It appears essential that confidence should be restored.

Elsewhere in this report it was noted that Congress reserved for itself in some cases the right to make the "social" decision concerning how much of a particular hazard the

* The various laws under which FDA and EPA have jurisdiction represent a wide spectrum of degrees of discretion. At one extreme, for example, Congress has written into the law governing air pollution standards the levels of exhaust emission which the administrator shall permit. In this case he has essentially no discretion. In other cases, the administrator is afforded discretion as to both levels of contamination and time of imposition of standards or rules.

American public should be willing to suffer. (This is as opposed to the narrower consideration of how much of a risk to human health is represented by exposure to a particular environmental agent.) Examples of the Congressional preemption include the Delaney amendment dealing with carcinogenic food additives, and the more recently mandated airborne emissions standards for automobiles. The trend seems to be one in which Congress is more apt to assume this role in the absence of scientific information than when scientific understanding is available.

In general, the Executive branch regulatory agencies have responsibilities for both narrow technical judgments and broad social decisions dictated by the various laws governing their regulatory activities. They inevitably make both findings of fact and judgments about appropriate social hazards.

Opportunities for appeal and adjudication have themselves become important vehicles for decisions in recent years. Regulatory laws vary but virtually all of them provide for avenues of appeal either through administrative or judicial mechanisms or both. For decisions relating to pesticide registrations made originally by the Administrator of the Environmental Protection Agency, for example, an aggrieved party to a decision may solicit additional and sometimes broader reviews through a public hearing or through the calling of a scientific advisory committee. Appeal of the outcome of this process can then be taken through the courts.

There has developed, in recent years, some tendency to look to the appeals processes as the principal forum for important decisions—rendering the administrator's decisions almost academic in some cases. One may reasonably ask, to what extent should the several appeal mechanisms be looked upon as the setting for major decisions, and to what extent should these follow-on devices be allowed to supplant the administrator's actions. One of the important aspects of appeal mechanisms, of course, is that they often tend to enlarge the informed and participating audience, and, hence, the constituency.

Finally, there exists the question of timeliness of decisions. Developers of a product for manufacture commonly complain that decisions leading to registration or approval are characteristically dilatory. On the other hand, decisions to ban a product or control an effluent are seen as being taken too hastily.

It is the Panel's considered view that the original decision process should remain as the major factor in regulatory decisions. In order to achieve this, however, the original decision process must entertain a broad menu of considerations. It must explicitly include some of the elements now found in appeal proceedings such as public hearings when necessary, and the frank and timely publication of the ingredients of the decision and the details of how the decision was reached. Avenues of appeal are essential and should always be provided. However, a sound decision process should make their use unusual rather than common.

Avenues of administrative and judicial appeal of administrators' decisions are essential and should be available. However, avenues of appeal should be considered as supplemental to the major decisions of the Government agency, not supplanting these decisions. In order to assure the strength of the original decision process it must take into account a suitable breadth of issues which correspond to the variety of important interests of the parties to the decision in each case.

The Panel believes that the major regulatory decision-making task in the broad sense should continue to be in Executive Branch agencies. It is here that the best technical competence resides. Other forums for infusing such considerations with the relevant technical and scientifically based judgments appear to the Panel to be far inferior and to run the risk of serious distortion or compromise or misunderstanding. In this same spirit, it would be the Panel's strong hope that Congress would, in its legislative initiatives dealing with health-related regulatory patterns, provide the administrative bodies with suitable discretion in the exercise of their regulatory authorities. It has been emphasized several times throughout the course of this report that mandated standards and non-discretionary regulatory laws are more often than not in conflict with what both scientific judgment and a sound weighing of affected social values would dictate. Flexibility and room for the exercise of competent judgment rather than severe restriction of action are urged.

Within the Executive Branch, the Panel feels (and agrees with past Congressional views) that regulatory decision-making should be the clear responsibility of the agency to which that task is delegated by the regulatory law. The decision process should not be escalated upward into the Executive Office of the President, for example. At the same time, therefore, the agency with this decision-making responsibility should be adequately and fully equipped with the various resources needed to make broad analyses and sound judgments. Adequate information of high quality is essential. First and foremost, the regulatory decisions considered here require sound science, and the regulatory agencies must be well equipped with adequate scientific resources. (This subject is considered fully in Chapter 11.)

At the same time, in order to render broad decisions of high quality, the agencies must also have access to other types of data, such as economic information, data on the flow of materials through the environment, and knowledge of a variety of other factors bearing on fair and sensitive evaluation of the public issues presented in each case. They all require

resources for information which have not been traditional for these regulatory agencies. Although to satisfy these needs may at first appear expensive, the cost of injudicious decision-making because of their absence would far exceed these costs.

It is the Panel's strong view that the decision process for which the administrative agency is responsible should be so strengthened and so broadly based that resort to or need for appeal would become unusual. Vehicles for administrative and judicial appeals can serve not only to assure fair process and conformity with Congressional mandates but also as a catalyst for needed regulatory change. While these vehicles for appeal should be available in every case, the trend toward original decisions being regularly supplanted or set aside by later appeal is unfortunate. In essence, this means that many of the elements now characteristic of the appeals processes should be included in the original decision process. These include opportunities for public input from a variety of interested parties as through public hearings where needed, and, again, explicit consideration of a broad rather than a narrow set of issues with each decision.

Credibility is highly important. The decision process in the public's interest must be designed and carried out so as to assure the perception as well as the fact of integrity. Public information and a sense of participation are necessary ingredients.

On the question of timeliness of decisions, the Panel feels that, in general, deliberate and well considered actions are always in the best national interest. Thus, the optimum time for a regulatory decision is that duration required to assemble the facts and to analyze them appropriately and fully.

For each of the health-related regulatory agencies there needs to be provided to the chief administrator an Advisory Board of Review to offer him assistance and advice in reaching sound decisions. In each case, this Advisory Board should be composed of persons representative of a breadth of interests and not be limited to persons expert in specialized scientific disciplines. No Board seat should ever "belong" to a particular constituency (consumers, science, universities, etc.). Rather, members should be chosen for their breadth of view and orientation as well as their expert qualifications. Longevity of membership should be sufficiently long (at least five years) in order to assure continuity of judgment. The Board's activities should not be an *ad hoc* or occasional exercise but should represent a continued dedication; each advisory board should be frequently and regularly called upon.

The Board should be empowered to call forth a variety of different kinds of evidence, to call for a breadth of background studies and analyses, and to solicit public comment through public hearings where desirable. The Board should be in a position to be able to judge the relationship between a proposed regulatory action and other Government programs and policies.

The product of the Board's studies and deliberations would be advice and recommendation. The chief administrator would reserve the right to make a final decision in every case. However, there would inevitably result a certain collectivization of the decision process which, in the Panel's view, would be to the public's benefit. It would be expected that the Board of Review would be viewed by the public with respect due a body of reputed experts and with the esteem afforded the best of the judicial process. To the extent that it can be called precedent, the Panel has been impressed with the success of similar systems of regulatory decision-making in other industrialized nations such as Great Britain and Sweden.

Finally, the Panel believes that it is important in the case of the activities of the Advisory Board of Review to make available to the public a written document which describes the information considered and the rationale for reaching the recommended positions. This "white paper" would go far toward supplying both information and a sense of candor which are necessary in maintaining the credibility of the decision process.

Each major regulatory decision should be accompanied by a "White Paper" which will be a brief but complete description of the basis on which the action was taken. This summary should be prepared in language understandable by laymen. It should, however, be completely referenced to the more complete technical and scientific reports which provide the factual basis on which the decisions were taken. These technical and scientific data should be accessible to the public.

The panel views the questions of supplying, interpreting and supporting the advice for regulatory decision-making as being of primary importance. The use of *ad hoc* scientific panels or advisory groups has become common in many government agencies. Outside advisors are employed more in some cases than in others. The Panel believes that a greater use of expert scientific advisors would be of assistance to agency reviewers who are faced with tasks of evaluating scientific evidence of various types and qualities in regulatory matters.

The Panel has been aware of delays in the development and approval of new therapeutic agents—delays occasioned by the mechanisms of the petition review process but not necessarily related to substantial scientific issues. Also, it was noted that the duration of the process of drug review is often long. Continuity of review is difficult to assure with repeated changes in viewpoint or in personnel and protocols.

In the case of therapeutic drugs, the Food and Drug Administration should adopt a series of ad hoc scientific panels that include outside

advisors—one panel for each distinctively new chemical entity or unique combination. Each panel would assist in the formulation of the scientific questions related to safety and efficacy which would be posed experimentally for the chemical. Each panel would remain in force through the period of the performance of this testing and would assist in the review of its results for the purpose of expediting and for passing on the adequacy of the petition.

8. PUBLIC INFORMATION, SCIENCE, AND THE REGULATORY PROCESS

Several times in the course of this report the subjects of information, explanation and candor have been emphasized. In the case of each reference, a plea was made for an increasing public understanding of the details of scientific-regulatory business. The general view of the Panel is that the process of public information and education should complement the process of regulation.

Many environmental problems and the corresponding Government responses are viewed by the public with a combination of fear and skepticism. For many, announcements of environmental insults or hazards are interpreted with exceptional fear. Yet there is reluctance at times to accept fully the explanations and the details offered as background for regulatory responses. There has been, admittedly, a tendency of some parts of the press to favor dramatic news and those portions of environmental incidents which evoke particular attention. A balanced view is not always the result. Generally, there has been less than a systematic attempt to reflect the scientific details of either the environmental hazard or of the response to it. What often stands out is a reflection of recently performed piece of experimental work, unconfirmed and without critical interpretation by any of the rest of the scientific community. Both the press and the scientists appear to owe responsibilities here. The former, in its zeal to seek a newsworthy or even sensational story, pursues or readily accepts tentative scientific information. The latter, on occasion, make available to the press the results of their work, however tentative, creating an exaggerated impression of an implied threat to human health and well-being. A fair assessment would also include, in this list, agencies of the Government whose spokesmen from time to time have appeared to "play" to their constituents by espousing tentative scientific findings in the name of prudent regulatory action.

The Panel is persuaded that there are true opportunities for education and information. Informing should be complementary to the regulatory process. They are not mutually exclusive. To realize these opportunities will require a variety of bold, active moves to make information available and to make it understood.

First of all, there appear to be some major areas and concepts where public re-education is needed. For example, a general pattern of evaluation of the hazard to human health of an environmental agent or a commercial product has been thought of popularly as leading to a sort of certification of proof of safety. Except when understood in the narrow sense of scientific proof (tentative demonstration of a scientific phenomenon) this idea of proof is a misnomer. Assurance of safety is never guaranteed by the process of scientific fact-finding and interpretation. If experimentation and review have been exercised appropriately, if science has been squeezed for understanding and evaluation to the extent that it can be on any particular question, then it can be said that according to the present level of understanding, the probability of hazard is low. There are two important implications of this type in interpretation. First of all, it recognizes that the assignment of low probability of risk is based on an area of uncertainty as well as on scientific understanding. The problem, of course, is that it is never possible to ascertain fully the extent of this uncertainty. Secondly, the tentative nature of the finding of safety or hazard should be stressed. Often, although improperly, a statement to the public about a particular hazard is interpreted as immutable. Demonstration or "proof" of safety is viewed as proof for all times. Likewise, implication of a hazard is seen not as a temporary interpretation but as a permanent one. In fact, science would dictate a different view. Science is a dynamic affair and continually tends to raise new questions and offer new interpretations. New scientific information should be expected to alter our regulatory minds from time to time. We should neither be surprised nor frightened by the advent of new and unexpected findings. Rather, a more accurate public view would include an element of tentativeness.

There is an additional and special task of public interpretation and information which should be mentioned. Scientific information which is reflected in environmental decisions comes both from the established body of science and from recently completed investigations. In recent years, this latter category has often been the data around which an environmental decision has been taken. An examination of most any sample of recent crisis-laden decisions reveals a heavy contribution of scientific data from recently completed experimentation.

Data such as these are, by definition, unconfirmed, are not always fully explained or interpreted as to meaning, and may or may not be consistent with previous observations in the same area. In brief, they may point toward an *implied* hazard but not a *demonstrated* one. Yet such tentative data are exceedingly common in environmental decision-making and require exceptional care in public interpretation.

There are several parties to this process and each possesses a particular responsibility:

A. Scientific investigators

Traditionally, members of the scientific fraternity tend to be conservative in drawing inferences from the raw data of their experiments. Scientists generally present their ideas and interpretations to a forum of their peers. Scientific meetings and scientific journals are the vehicles for testing and establishing new scientific information. This conservatism has great merit and the deliberate nature of scientific judgment serves both science and society well. The bulk of "established" scientific information has been subjected to this process.

There is, however, a clear need for a reconciliation between the traditional scientific conservatism and deliberateness in judgment and the need for interpretation of scientific information for public and social understanding. The public or the Congress or a regulatory agency is bound to pose broad questions on what the scientific data mean for the public's health. Since there is a technical or scientific base for these questions, they deserve a sound scientific judgment. Clearly a regulatory agency needs to react appropriately and soon in the face of new scientific findings clearly implicating a hazard to human health. Few would argue with the judgments taken in behalf of thalidomide. Yet, there is perhaps an equally strong need to preserve the deliberate quality of review and interpretation in order to assure the quality of interpretation.

Because of the scientific and technical nature of these decisions, scientists must be engaged actively in the process of interpretation. In the past some well qualified scientists have fled from this task because of the hazards of public buffeting and controversy. It is clear that where the scientific community shuns this obligation, others will step in their place.

The scientific community should take an active role in interpreting the results of scientific investigation in ways which are meaningful to the public and to those agencies responsible for regulatory decisions.

Bold and aggressive steps should be taken during the course of scientific meetings and through special background sessions to brief members of the press on factual material and on the results of interpretation.

Regulatory decisions will inevitably reflect a large segment of scientific data from recently performed experiments. The scientists involved should act to preserve the deliberate review of these data in behalf of both the public press and the regulatory decision-makers. This will often require special efforts on the part of all three, scientists, the press and the government. Premature statements by scientists before deliberation in the company of their peers should be avoided.

Professional scientific societies must take an active role in public education. They are uniquely equipped to do this because, a) they usually draw their membership from academic, governmental and industrial sources and have available inputs from all, b) they are free from the taint of special pleading attached to single agencies or industries.

B. The press

It has been common to attack the press as irresponsible and encouraging sensationalism in regulatory matters. Newsworthi-ness is clearly a criterion of success. At the same time the Panel is satisfied that the press has some special opportunities or even obligations for educating as well as informing.

For example, the press would serve the public interest well by aiding in the public understanding of certain special issues. One is the dynamic nature of science and the changing character of scientific understanding. This would properly foster expectation of rather than surprise over occasional re-evaluation of past decisions. Another is the inevitable element of uncertainty in all regulatory decisions. A third is the probabilistic rather than clear cut, definitive character of scientific judgments.

In addition to simply providing information, the press should undertake special efforts at public education on the scientific basis for regulation and on certain special issues surrounding it.

The initial publication in the lay press of tentative, unreviewed scientific findings, because of the zeal of either a scientist or a journalist is highly undesirable.

The press, as it meets its responsibility for balanced coverage, can do much by combining any publication of tentative, unreviewed scientific findings with a significant representation of the views of other scientists competent to make comments.

C. Government agencies

Regulatory decisions are inevitably the result of judgment about a broad series of factors some of which reflect scientific findings. In the spirit of candor and public disclosure, the interests of all parties would be best served by the provision, in the case of each decision, of a well documented background paper. This paper should describe the kinds of information used in considering the decision, and the reasoning and judgments employed in arriving at the final decision point.

Government regulatory agencies should make publicly available a "white paper" at the time of each decision in which the several kinds of considerations, the scientific data and the rationale are all clearly laid out and described in a way which is understandable to the public.

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Chapter 14

Judgments about Risks and Benefits

CHAPTER 14

JUDGMENTS ABOUT RISKS AND BENEFITS

INTRODUCTION

The phrase, risk-benefit analysis, has achieved its place as a household expression in the past few years. As the nation has turned its attention increasingly toward matters related to the quality of life of its populace such as environmental integrity and human health and safety, so has come national attention to the costs of the various enterprises designed to bring about quality. Intuitively, it has pleased all of us, more or less, to hear that a comparison of risks and of benefits was made when decisions were taken affecting the quality of life. With this phrase comes a certain amount of at least public confidence that the decisions being made are accompanied by some sort of balance sheet of desirable and undesirable consequences—a carefully formulated pro and con statement. Indeed, the term, analysis, suggests a certain rigor of examination and a strong effort to put matters into numerical terms.

Risk-benefit analysis means different things to different groups of people depending upon their particular frame of reference. Each is worthy of discussion. One concern, for example, is the development of analytic methodologies for performing risk-benefit analysis. Another is the aggregate of observations about public attitudes and public behavior toward risk taking and perceived benefits. Questions whose answers are sought here are what are public expectations of risk, what is the pattern of spontaneous risk-taking among members of the general population, and what are public perceptions of risks and benefits? A third concern is with the specific scientific aspects of risks or benefits, that is with the quantity and quality of information for making judgments about risks and benefits. The list of considerations up to now has mainly revolved around the scientific and technical aspects of risks and benefits. Apart from these (but in the eyes of some, of greater importance) are a series of relevant political and social judgments. For example, having defined the character of the risks involved in administering a therapeutic drug, what is the degree of risk which society is or should be willing to experience? This, in turn, raises the question of how such answers are to be obtained, what are the opportunities for public participation, what is the role of surrogates (such as physicians or regulatory agencies) and what are the relevant roles of various parts of the Government particularly the legislative and executive branches.

Informal balancing of risks and benefits is widely practiced. As we have made clear elsewhere, it can be made both more effective and more credible by the preparation and publication of appropriate background documents, setting out as clearly as may be the relevant considerations and the state of our knowledge about them. (Most of the difficult balancing problems involve either "a risk of a risk" rather than a clear risk or the uncertainty, sometimes because of its subjective character, of a benefit, or both.) In this chapter we discuss the present status of formal methods for interrelating—and hopefully balancing—risks and benefits.

During the course of the Panel's deliberations, the National Academy of Engineering held a symposium on benefit-risk decision-making, whose papers have been useful here.[1]

FORMAL METHODS FOR RISK-BENEFIT ANALYSIS

Models in the various sciences, including economics, are exactly what the dictionary says they are: miniature or abstract representations of real things. The world is much too complicated for our minds to deal with photographic reproductions of entire societies or firms or machines. Hence, one must abstract from much of reality—hopefully retaining the most significant portions—when he tries to figure out how something works or might work. Women try to perceive how a dress would work by looking at it on a mannikin; engineers try to see how a proposed airplane would function by observing a model in a wind tunnel; and we can try to set up formal structures within which one might gauge risks and benefits of chemicals, or perceive what an "optimal" arrangement would be. To do this, we must do two things: (1) We must devise algebraic or numerical models and (2) we must choose what it is we are to make as large (new reward)—or as small (net loss)—as the model permits.*

Conditions for optimality, however, depend on the "objective or welfare function" that is to be maximized. Hence, an arrangement or set of policies can be "optimal" only in terms of a specified criterion. One such criterion is maximum value to total output (which in principle should include such products as beauty, safety, pollution abatement, peace of mind, and friendliness) with outputs valued at whatever consum-

* Work has recently been done to develop risk-benefit methods in the absence of any single objective function.[2,3] These approaches at least narrow the range of reasonable choices and deserve reasonable attention.

ers would voluntarily pay for marginal or extra units of such output.**

A model showing the conditions for this kind of optimality would say that risks should be reduced as long as consumers value the incremental safety more than they value the benefits foregone. What one might like to know, therefore, is (1) the various risks to lives and health (plus any other disadvantages) attributable to each use of a substance, (2) the beneficial consequences attributable to each use, and (3) the (negative) values of the risks and the (positive) values of the beneficial products.

There have been relatively few serious attempts to develop true analytic methodologies as models useful for doing risk-benefit analysis. In one of the best known, Starr has suggested that a ratio of risk (some number reflecting at least one dimension of risk) to benefit can help us judge what should be done about automobiles, chemicals, or other phenomena in which risk is a prominent feature.[4] [5] Starr selected "fatalities per person-hour of exposure" as the indicator of risk and some estimate of the "value to the individual" as the denominator. The denominator (benefit) in most cases is described by the perceived benefit and represented as the monetary investment consumers are willing to make. In discussing air transportation, for example, the denominator was the price paid by travelers plus the estimated value of the time saved by air travel in comparison with its closest competitor, the automobile. For an occupational hazard, Starr considers as the proxy benefit the dollar earnings of the occupational worker for each of several occupations. In describing the risk value (fatalities per person - hour at risk), Starr offers as comparison the observed fatality rate for the total population due to diseases other than accidents.

Starr concludes that there is some clustering among the various risk/benefit ratios, that for a variety of activities (voluntary, involuntary, avocational, occupational), they fall along a curve where risk is approximately equal to the value of benefit cubed. Further, the location on such a curve (where the risk value falls above or below the average fatality rate due to disease) is a reasonably accurate portrayal of human expectations of risk and judgments about risk-taking. Finally, having offered these historical observations about human risk-taking, Starr suggests that the general patterns gleaned from such an analysis can be useful in arriving at societal judgments for new or previously unassessed risks.

Carl Muehlhause has developed a more formal, theoretical analysis.[6] In the simplest form, the benefit or utility of an item is taken as adequately represented by the price a consumer is willing to pay for it. To the extent that there is a hazard or risk associated with its use, the value (still represented by the price) is correspondingly reduced. The addition of features to the product in order to "build in" safety (or compensate for the original risk) correspondingly adds to its cost and this is reflected in its price (termed, by the author, a compensating variation).

Classically, as suggested above, it has been assumed that costs associated with assurances of safety (reduction of hazard) can be increased to the point where consumers no longer value the benefits of the product. It is Muehlhause's contention, however, that there is an additional "non-pecuniary" component to risk. There is a threshold of risk, he insists, beyond which no amount of benefit from the product will compensate and the general public will refuse to purchase the product or engage in the activity.* He has developed a formal mathematical treatment of this idea for situations both where consumers are fully informed of the nature of the risks and benefits and for those where a surrogate or intermediary is commissioned to pronounce on risks. It is Muehlhause's view that the more usual form of risk-benefit analysis involving the assessment of marginal increment of risk reduction provided by a marginal expenditure in behalf of safety be properly entitled cost-benefit analysis and that the phrase, risk-benefit analysis be reserved for the addition of this second, non-pecuniary limiting risk judgment.

It is, perhaps, in the realm of accidents such as automobile accidents where there has been most attention given to rigorous analysis. The reasons are perhaps evident. Accidental injuries and deaths can be enumerated and more easily quantified than can the consequences of environmental chemicals, for example. Furthermore, alterations in the risk involved (accident rate) associated with specific interventions (lap belts in automobiles) can be determined with enough precision to choose among several possible strategies.[7]

There are a few generalizations which one can offer concerning the methodologies which have been offered up to now. All of these depend on some knowledge about how people actually behave in the face of risks—known or implied. They generally tend to assume that perceptions of benefit as seen in the market place are accurate representations of true benefit (utility, effectiveness, etc.). Thus, benefit of a product or activity is never questioned but rather simply described by whatever people are willing to pay for the item. By contrast, those who have constructed numerical models have assumed some inaccuracy in the public's view of risk and suggest that public perception of risk may have to be modified or combined with information concerning true risk. ("If

** More precisely, a pareto-optimal situation is one in which no affected person could be made better off without another affected person being made worse off.

* A more general argument, designed to show that both individual and social preference orderings display numerous "threshold" characteristics that adequate policy analyses must reflect, has been advanced in Tribe, L. H., Policy Science: Analysis or Ideology?, *Philosophy and Public Affairs*, Vol. 2, No. 1 (Fall 1972).

the public really understood the hazard to health and life of cigarette smoking that pattern of risk taking would be quite different".) Thus, it is the view of some students of risks-benefits that by combining experimentally derived information about risk with public perceptions of benefit (willingness to pay), one can arrive at a suitable and useful analysis of how risks and benefits relate. It is their ultimate hope that insight into such relationships can be useful in guiding appropriate social behavior.

At the present time there seem to be a number of severe limitations of the usefulness of the existing methodologies of risk-benefit analysis. First and foremost, these models (by definition) are abstractions of reality. In their present state of evolution, their "distance" from reality is probably very large, rendering it difficult to convert or extrapolate their intended lessons into practice. Thus, these models tend to be highly simplified representations and may not adequately account for all of the factors operating in the real environment. Since they are simplifications, they necessarily rest on a large number of assumptions which are loosely formulated but are very important in the final analysis. First, to approve "pareto optimality" (or any other criterion) is itself a value judgment, and most of us frequently vote for departures from this sort of optimality. Thus its use does not necessarily settle anything even conceptually. Second, while such models can help one think in an orderly fashion about resource use, they can rarely give unambiguous operational guidance. For example, the "theory of second best" tells us that, unless *all* of the *other* conditions for optimality are fulfilled, it is uncertain whether fulfilling a particular condition makes us better off or worse off. Yet many of the conditions are *always* unfulfilled. As another example, government intervention nearly always applies compulsion to some persons, and in these circumstances we do not understand, even in principle, how to measure certain costs and gains.

As for operational guidance in a practical sense, unless one can estimate the magnitudes of the incremental risks, costs, and benefits associated with different drugs and policies, there is essentially no guidance. There are two kinds of problems here. One concerns a quantitative estimate of the magnitude of the risk (and benefit). What is the probability that cancer will result from exposure to a food additive? What is the biological consequence of a pesticide residue in human adipose tissue? As will be described later, in practice the degree of ignorance or uncertainty is typically much greater than the knowledge of both risks and benefits. This lack of sufficient information emerges as one of the most severe limitations to any attempt at formal risk-benefit analysis.

Typically, then, proxy measures are used to represent risks and benefits and these proxies are usually exceedingly crude. Starr represents risk in terms of death.[5] This gives no guidance concerning substances which may produce eczema, enteritis, brain damage, or years of painful invalidism before death. More importantly, however, fatalities per exposure-hour depends crucially on what one counts as exposure. For floods, Starr assumes that people are exposed 24 hours a day. What should the exposure-hours be for penicillin—the few seconds it takes to get a shot or take a pill, the duration of infections, or again 24 hours per day? What are the exposure-hours for air pollution—24 hours a day for urban dwellers only or for the entire population? The point is that the resulting indicators of risk for different substances may contain an arbitrary element that makes the final ratios exceedingly difficult to interpret. Moreover, as Starr says, the benefit indicators may be even shakier.[5]

Furthermore, risks and benefits of various items and actions do not usually come in single pairs. Rather, in each case, there is a diversity of risks and benefits.

With respect to a single chemical or drug, there is not just one well-defined hazard (such as a 1 in 10 chance of causing 1,000 deaths per year). There are numerous different kinds of hazards, with some probability distribution rather than a single probability associated with each kind of undesirable event. Each type of hazard differs in significance; for example, an expected 1,000 cases of mild eczema would not be as important as an expected 1,000 cases of lung cancer in the same age bracket. Similarly, benefits are characteristically plural in number and are distributed in a complex fashion.

Another kind of problem involves the marginal values attached to the risks and benefits once they are recognized and assessed. The issues about chemicals and health are largely about effects, such as risks, that do not pass through direct markets for those effects. Therefore, we cannot directly observe what individuals would be willing to pay, e.g., to save other people's lives, to reduce other people's illness, to achieve specific reductions in the probability of their own deaths, to have the extra knowledge that basic research might yield. Personal judgments or "guesstimates" have to be made; this rather than the formal theory is a chief bottleneck.

One can derive some clues to what some individuals have paid for life insurance or have paid to save family-members' lives, and such calculations can be helpful. But with no direct market for lives, people are usually buying such things as an unspecified reduction in the probability of death in combination with something else. For example, when people buy medical treatment or an annual physical check-up, they are buying some (perhaps unknown) reduction in the probability of death, the probability of painful illness, the probability of minor complications. If someone buys a safer automobile, he is buying such reduced risks plus a

package of other features. Thus it is almost impossible to sort out, with much confidence, the values that individuals attach to a *particular* risk reduction.

Far more important, though, without a direct market, there is no mechanism to bring people's marginal evaluations into equivalence. With a market, there is a mechanism that causes all consumers of a product to value the marginal unit at approximately the same amount. If oranges sell for $1 a pound, but someone values an extra pound per month at $5, he will simply increase his consumption until he does value an extra pound per month at about $1. If he values the marginal pound at only 10 cents, he will simply decrease his purchases until the marginal pound that he buys *is* worth $1 to him. Thus everyone ends up valuing an incremental unit of marketed products at approximately the observed price. With no direct way for individuals or government agencies to exchange such commodities as "lives saved," however, their marginal evaluations can be expected to differ greatly. And, as far as one can observe, this seems to be the case: different individuals, highway programs, Defense Department programs, and health programs spend widely varying amounts to save lives. One ends up at best with a wide range of values to choose from.

Risk benefit analysis for environmental chemicals (or for automobile accidents for that matter) is colored by the fact that the risks are generally low-probability events. Thus, while their consequences may be quite serious (e.g. birth defects, chronic degenerative disease) their likelihood of occurrence is typically very low.

On the one hand, environmental agents that pose risks of minor troubles are simply not of major concern. On the other hand, agents that kill or seriously injure 10 percent or more of those exposed are easily detected, and it is not difficult to decide what governmental action one prefers. But agents that kill or seriously injure one in a thousand to one in ten thousand of those exposed may often lack sure identification. Moreover, given the uncertainties about how to interpret animal tests, massively used substances such as cyclamates or oral contraceptives may have low or very low probabilities of causing near-disasters many years hence. It is extremely hard to decide what weights should be assigned to such risks. At any given time, individuals seem to be unclear about how they evaluate low chances of their own immediate demise, so it is far from clear how policy-makers should evaluate low risks of serious consequences a decade or a generation later.

A particular limitation of risk-benefit ratios is the limitation that goes with almost any ratio. One should use ratios carefully, for they submerge everything in one number, concealing for instance the sizes of the numerators and denominators. It is important, therefore, not to conclude that a larger risk-benefit ratio implies a greater urgency for action. A chemical that yields benefits of $1,000,000 per year, but is expected to kill 1,000 persons between ages 30 and 40, is surely a more serious matter than a chemical that produces benefits of $1,000 per year and is expected to kill 2 persons between the ages of 60 and 70.

WHAT ARE THE SPONTANEOUS PATTERNS OF HUMAN RISK-TAKING?

As suggested above, most students of risk-benefit analysis have assumed that there are useful lessons to be learned by observing how members of the general population view risks and benefits and how they behave in the face of these perceptions.

> Clearly, we do have functioning social technical systems which over a period of many years have developed an empirically acceptable balance between utility and social cost.[3]

Observations of how the public behaves towards risks and benefits reveal a variety of complex patterns with some generalizations discernible. First, there are clear differences in the public's view between those situations where risks are assumed voluntarily and those in which they are imposed or assumed involuntarily.

Students of risk-benefit behavior have universally commented on the striking differences between what the public seems to be willing to put up with voluntarily and what it claims to accept when it leaves the decision to others.

> As one would expect, we are loathe to let others do unto us what we happily do to ourselves.[4]

The public seems to be clearly willing to suffer a much larger risk (or higher probability of hazard) if that choice is in the individual's hands than if a surrogate decisionmaker arrives at the decision for him. The choice of whether or not to drive an automobile, to fasten a seat belt, or to smoke a cigarette are the common examples offered of individual or personal choices. Starr has observed that the public appears willing to accept voluntary risks roughly 1,000 times greater than involuntary risks.[5] To offer some perspective, natural disasters, such as floods, earthquakes, tornadoes cause five to ten deaths in the United States per million population per year.

Another example of voluntary acceptance of high risk is the field of occupational exposures. Some occupations can represent very high probability of death and injury when compared to other involuntary activities. Of course, it can be argued that voluntarism does not completely describe occupational choices.

A second method of categorizing risks when describing human risk-taking behavior is in terms of the collective nature of risk-taking. The larger the aggregate of people included in risk-taking, generally, the lower the risk society is willing to assume.

A special (but very common) problem arises in those cases where risks and benefits accrue to different groups or individuals. This is the situation for environmental pollutants. The pattern of choice which

seems to be emerging here is one of general unwillingness to accept risks.

Related to this latter is the fact that risk-taking appears to vary with the benefits to be expected. The greater the perceived benefit, the larger the acceptable risk. A life-saving therapeutic drug may be expected to carry with it undesirable side-effects which themselves could be expected to compromise health.

It has been suggested that public preferences be examined in terms of a factor termed a "protection ratio" which is:

$$\frac{\text{The exposure people seem to be willing to bear}}{\text{The exposure that is known to produce designated ill effects}}$$

For drugs used in serious illnesses, we may often have to be content with a ratio of 1:2. (When employing radiation therapy for acute cancer we may go to ratios of 2 or 3.) For routine insults, such as pesticide residues, we appear to accept ratios of perhaps 1:100. For known carcinogens in important substances, such as radium in tap water or radium in household salt, we seem to be content with ratios of perhaps

$$\frac{1}{1{,}000{,}000} \quad \text{or} \quad \frac{1}{1{,}000{,}000{,}000}$$

Finally, it has been observed that, in considering environmental agents which may provoke insults to human health, the public's view toward risk-taking leads to a kind of a rank-ordering of various outcomes and effects such as:

carcinogenesis
teratogenesis
death
serious illness
less serious illness
miscarriage

As was pointed out above, there is a school of thought which, having reviewed the patterns of public behavior toward risks, finds these patterns irrational.[1] They cite, for example, the relatively prudent course (large investments in safety with low resulting risk) in the case of nuclear power production alongside the much riskier course (small expenditures in safety with higher resulting risks) in the case of natural disasters such as earthquakes. It is in part these very inconsistencies which have led some to advocate or even insist upon departures from *caveat emptor* through the intermediary of third-party, government regulation.[8]

RISKS OF PRODUCTS VERSUS COSTS OF POLICIES

It is, perhaps, useful to pause in this discussion in order to make a distinction between two concepts which are commonly confused. One is the concept of a risk or hazard associated with the use of a therapeutic drug or exposure to a pesticide residue or with the driving of an automobile, etc. This is the negative value attached to the particular piece of technology under consideration. The other concept is that of the cost (usually in or reducible to monetary terms) of adopting any of several policies. Examples here are decisions to abate air pollution emissions from power plants or automobiles (which may have costs associated with unemployment, higher costs of electricity and automobiles, etc.), decisions to delay environmental actions, etc. The particular biological risk to health of a chemical, for example, is one of the costs associated with exposure to the chemical. The concept of the cost of a policy is a much broader one than is that of the particular risk or hazard to human health. In the present example, the cost to society of depriving it of the chemical, the cost of substitutes for it, etc., are illustrative of this second category. Both risks, in the narrow sense, and costs in the broader sense, have on the other sides of their equations factors of benefit or of positive values.

The risks and benefits associated with a drug are not as directly relevant to our choices as the costs and benefits associated with a policy. To judge or know how the risks attributable to DDT compare (low or high) to DDT's benefits is relevant information, and yet to decide what to do, one would prefer to know or to know such things as what happens to costs (including the negative value of expected deaths and illness) and benefits, if we (1) cut usage of DDT in half, (2) limit DDT to certain places and modes of application, (3) tax DDT heavily, (4) limit its use and at the same time adopt other precautionary measures or limit the use of other drugs. Information about total risks and benefits from a chemical is pertinent mainly to the question, "should the chemical be banned completely?" This information does not pertain directly to other possible policies regarding that chemical. Nor does it tell one anything about the consequences of requiring more tests of new drugs or the consequences of modifying the future R&D or production environment.

Hence, as a framework for thinking about decisions or recommendations, cost-benefit analysis applied to alternative policies is in many ways more suitable than risk-benefit analysis. Clearly, however, information about particular risks and benefits is an essential ingredient in arriving at any appropriate form of a cost-benefit judgment.

There have been a few attempts at cost-benefit analyses for various program and policy decisions. They are generally limited severely by a lack of basic information to describe the elementary parameters of risks and beneficial values. Again because data are more available, cost-benefit studies have been most prominent in behalf of vehicular accidents and choices of safety features for vehicles.[7 9 10 11 12]

A few recent attempts have been made to treat the subject of air pollution in a similar fashion. Ridker[13] discussed in theoretical terms the consequences of various possible strategies toward air pollutants. These included the costs of accepting air pollutants versus the costs of abatement versus the costs of a delay in

making a decision. Lave and Seskind[14] using data available from the biological literature dealing with the known biological effects of various air pollutants attempted to characterize the dollar penalty associated with exposure to various patterns of air pollution. It is interesting that this analysis became a key argument in the legislative history of the current air pollution legislation[15] (and also a recent review of this subject by the Office of Science and Technology.[12]) Serious limitations have been recognized in the original analysis by Lave such as the failure to take into account the biasing effect of cigarette smoking.[16] Nevertheless, in the face of a scarcity of other comparable analyses, this one remained as a strong argument.

INFORMATION FOR RISK-BENEFIT ANALYSES

From what has been described above it should be apparent that the success of any risk-benefit analysis exercise is very much dependent upon the quality of the data used. In spite of the most rigorous and the sophisticated of methodologies, an analysis is worth no more than the information used in the analysis.

In practice, it appears to be lack of good data (in many cases of any data) which has inhibited the systematic performance of risk-benefit analyses. At a recent symposium on risk-benefit analysis it was noted on several occasions that sufficient data simply do not exist to provide a suitable basis for the evaluation of risks in most cases. For environmental chemicals, the magnitude of hazards involved is typically obscure and the area of uncertainty in each case is enormous. What usually emerges is a possible threat to health rather than a definite explicit one. The measures which analysts fall back on are characteristically crude proxies of the ones which they would like to have and, in many cases, even these are not available. If uncertainty truly exists, to fasten onto spuriously precise estimates and pretend the uncertainty is not there, is unlikely to produce good decisions. Such a procedure is like the drunk searching for his lost door key under the street lamp instead of where he lost it "because the light was better under the lamp." On the other hand, this admonition should not dictate a spirit of resignation to no information. With an appropriate understanding of the underlying qualifications, data should be used and alternate assumptions should be tried.

Surprisingly, perhaps, indicators of benefit may be even shakier than those of risk.[5] Again proxies are generally accepted and there are usually reflections of behavior in the market place. Thus, the price of a product or the cost of air travel or the wages paid to workers are the usual indices used. The assumption underlying each of these is that the public perception of benefit as seen in its monetary choices are true reflections of benefit.

The results of the recent study on the efficacy of therapeutic drugs represent an example in which true utility and perceived benefit were distinguished.[17] There is a special case which is worth singling out since it is somewhat simpler than the others. This is the case of a product whose nature approaches essentiality or upon which a degree of dependence has developed. This quality was considered in a recent Government analysis of the risks and benefits of the chemical, polychlorinated biphenyls.[18]

GOVERNMENT PREEMPTION WHO DECIDES?

There remain two questions whose answers have profound implications for public policy making. One concerns the separation between technical analysis of risks and benefits and the social question of how much of a hazard should the public suffer. The question which arises is to what extent should that latter judgment be removed from the public's own hands and be made for it by a surrogate. The second question follows the first, assumes that the Federal Government will assume some of this surrogate activity (as it has historically and increasingly) and asks which part of the government should enjoy (or suffer) that role.

TECHNICAL ANALYSIS VERSUS SOCIAL JUDGMENT

With a tradition of relative freedom of choice and activity which is characteristic of this notion one may well ask why shouldn't consumer sovereignty include his right to make his own mistakes. In fact, this question has been raised by some of those preoccupied with risks and benefits.[19] Yet in many instances, surrogate or third-party agents have obviously assumed the role of both analysis and judgment in behalf of the public benefit and its collective risk. The usual explanation of this preemption relates to a growing complexity of commerce, a proliferation of products, to the extent that the individual citizen is unable to evaluate on his own the consequences of various items of technology.[6] What has emerged, then is a pattern of increasing governmental involvement in judgment making and regulation of some products (foods, drugs, pesticides) and of materials which exist in the public domain (radioactive emissions, chemical and particulate air pollutants, etc.).

One observer has pointed out that:

> The emphasis on freedom which characterizes our society brings caution to any legislative attempt to restrict choices and innovations. Our history demonstrates the value (for national vigor and growth) of risk-taking. The present development of chemical regulation seems not to impose a pattern of behavior, but rather to make certain that we know as much as possible about risks and benefits when a decision is made.[6]

This author suggests that it has been Congress' intent that the government should analyze and in-

form. In fact, the government's role in judgment is compelling in certain areas (including certain classes of chemical substances).

If one is content to separate the question of technical analysis from social judgment, then one is perhaps justified in inquiring as to which part of the government has the latter responsibility, the Executive branch or the Legislative. One school of thought has urged that the Executive branch be given only the responsibility of technical analysis leaving social judgments to the Congress.[20] In fact, the pattern up to now has been a mixed one. In some cases, clearly the Congress has assumed the role of judge of social issues concerning how safe is safe enough. The amendment to the Food, Drug and Cosmetic Act which determines the destiny of food additives found to be carcinogenic in animals or man (Delaney amendment) is perhaps the best known example. The Clean Air Act which determines the degree of reduction of automobile emissions is another. It is interesting to note that it seems to be the very lack of sufficient information plus an implied threat in each case which has led Congress to take social judgment-making into their own hands. In most regulatory activities dealing with chemical agents, the administrator of the law enjoys some discretion either as to time of regulation or as to degree of regulation. Thus, in most cases, both the Executive and Legislative branches have opportunities for offering surrogate judgments in the public's name.

A great deal of effort has been expended in behalf of trying to determine "appropriate" patterns of social decisions. Characteristically, this has assumed the form of inquiries about how members of the general population value health, ill-health and death.[19] The "principles" which emerge, again, are a combination of observation of how people seem to behave plus some judgments as to how they should behave. In general, it may be said that the more people who are exposed to a given risk, the more society is justified in imposing controls on the degree or choice of risk (keeping in mind that the factor of voluntarism versus involuntarism is even more important).

SUMMARY OF FINDINGS

The Panel views systematic attempts at risk-benefit analysis with great interest. Despite an evolving analytic methodology, it is clear that there are a number of severe limitations to the use of any formal models and methods. They are highly abstract. They lean heavily on assumptions which themselves are often debatable. They can be no better than the original data used to describe the risks and the benefits. This lack of basic information is probably the most severe limitation to the use of these models. In addition, there are no agreed upon ways of valuing in meaningful terms the increments of health and safety under consideration. In summary, then, we should not be deceived by falsely high expectations of formal risk-benefit analysis, though development and refinement of methodologies should be continued and encouraged.

Observations about how people do behave and how they perceive risks and benefits are useful. Again, there are limitations. Inaccuracies in perception of both risks and benefits should be recognized. Correction obviously comes from education.

While formal risk-benefit analysis in a rigorous sense may not be possible yet, systematic review and balanced decisions are possible. How to perform these and how to accommodate them within a political setting is the subject of a further chapter.

Finally, regardless of the type of review and analysis mechanisms chosen, the Panel finds great virtue in explicit explanation to the public as to how decisions are arrived at, what assumptions are included and what information is used.

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APPENDIX A

CAUSES OF DEATH WITH INCREASING RATES IN THE 1960's

George B. Hutchinson
Department of Epidemiology
Harvard School of Public Health

A long term fall in overall death rates in the first half of the twentieth century was interrupted in the decade of the 1950's by a flattening off. It has recently become apparent that this flattening represented the beginning of a trend of an increasing slope of death rate per unit time, with the slope for males passing from negative through zero to positive in the 1960's. For females the same trend is suggested by a change from a negative to a zero slope, though a positive slope has not yet been observed.

The National Center for Health Statistics has investigated these trends by age, sex, race, and cause of death and has identified ten causal categories in the standard List of 60 Selected Causes of Death which are responsible for major parts of the rise for white males.[1] Causes identified are those which satisfy at least one of two criteria—

1. an increase over a ten year period of at least 15 per 100,000 in the annual mortality in any 5-year age group.

2. at least 10 per cent of the increase in all causes in any 5-year age group.

Two causal categories identified by the above rule showed increases satisfying the criteria in only limited age groups and had decreases for the total experience of all age groups combined. One of these, arteriosclerotic heart disease, showed a decrease in 10 of 13 five-year age groups and satisfied the criteria of a rise only in the single age group 70 to 74. The other category, suicide, showed a decrease in 9 of 14 five-year age groups, and the rise was confined to ages below 45 years.

For the other eight categories the increase was seen in each five-year age group for each cause except for four age groups for the category cirrhosis of liver. There was a small decrease in cirrhosis at age 20 to 24 and at all ages above 70 years. Rates rose in all intermediate ages, 25 to 69, and the overall result was an increase. The eight categories showing overall increases are—

Carcinoma of the lung
Carcinoma, other and unspecified
Other circulatory diseases
Bronchitis
Other bronchopulmonic diseases
Cirrhosis of liver
Motor vehicle accidents
Homicide

In table A-1, numbers of "extra" deaths in 1967 as compared with 1960 are shown for the eight categories listed above by 5-year age groups. These theoretical numbers are obtained by applying the difference in cause- and age-specific death rates between 1960 and 1967 for white males to the entire 1967 male population of the United States for the age groups indicated in the table.

It is felt that these changes in death rates over a short period of years represent environmental changes in a broad sense. No change in the classification rules has occurred in this interval, and no major change in the composition of the population is thought to have occurred. More significantly, the causes identified as contributing to the increase are categories known to be heavily related to two groups of environmental factors, smoking and other forms of air pollution and alcohol use. It may be supposed that major changes in smoking and other air pollution are responsible for a substantial part of the rise in death rates in the categories carcinoma of lung, bronchitis, and other bronchopulmonic diseases, while they are to a lesser degree associated with the categories of carcinoma other and unspecified and other circulatory disease. Alcohol use may be presumed to be similarly related to the last three categories, cirrhosis of liver, motor vehicle accidents, and homicide.

By age the greatest numbers of extra deaths occur in the ages of heaviest mortality from all causes, with the exception of the two oldest groups, age 75 and over, where the numbers of extra deaths fall off. In tabulations of deaths from all causes these are the ages with greatest numbers of deaths, since the rapid rise in rates more than counter-balances the fall in population at risk in these age groups.

By cause of death, two of the respiratory disease categories, carcinoma of lung and other bronchopulmonic diseases, dominate the picture. These two categories contribute 20,139.2 extra deaths, or over half the total extra deaths tabulated.

The age distributation of extra deaths demonstrates two sharply varying patterns by cause. The respiratory and circulatory deaths have an old age pattern, with the modal number of extra deaths coming in the age group 65-69, 70-74, or 75-79 for each of the five categories. A young age pattern is found

for the violent deaths, motor vehicle accidents and homicide, with modal ages of 15-19 and 20-24, respectively. The category of cirrhosis is intermediate, shows a mode in the middle years, 60-64, and shows an absolute fall in death rates in the oldest and youngest ages, where the other categories are most concentrated.

While the causes of death shown in the table contribute in total 36,171.5 estimated extra deaths, many other categories have shown decreases in this period, and the overall extra deaths for all causes, a balance between positive and negative computed numbers, is only 10,235.7 deaths, or 1.09 per cent of all male deaths in 1967. For each of the selected causes the number of extra deaths comprises more than 10 per cent of total deaths from that cause. These percentages are as follows—

	Percent
Carcinoma lung	22.9
Carcinoma, other, unspec.	14.2
Circulatory, other	17.0
Bronchitis	39.3
Bronchopulmonic, other	39.4
Cirrhosis	15.3
Motor vehicle accidents	14.6
Homicide	30.1

It is seen that the rise in the benign respiratory diseases is the greatest proportionate rise, amounting to almost 40 percent of the total 1967 deaths for these groups.

The time trend over the years, as has been mentioned, has been one of a fall in death rates until 1950, followed by a leveling off and a current rise. This has also been the pattern in most individual age groups. For the individual causes of death this pattern has not been seen in most cases. Carcinoma of the lung has risen steadily in most age groups in the past 15 years, though for the younger ages, with very low absolute rates, there has been little change, and in some age groups a fall in rates. The patterns are similar for bronchitis and for other circulatory diseases. For cirrhosis there is also an essentially steady rise for the ages at which this category is currently demonstrating an excess. For motor vehicle accidents and homicide the time trend has been similar to that for the total group of all causes, an early fall-off, followed by a recent and disappointing rise.

It would appear in general that certain categories of disease have never

EXHIBIT A-1

NUMBER OF EXTRA DEATHS, 1967, MALES, UNITED STATES

AGE	CA[1] LUNG	CA[1] OTHER UNSP.	CVS,[1] OTHER	BRONCH,[1]	BRONCH.-[1] PULM., OTHER	CIRRHO-[1] SIS	MOTOR[1] VEH.	HOMIC.[1]	TOTAL
15-19			18.1				1,525.8	154.4	1,698.3
20-24			7.7			-7.7[2]	942.8	245.3	1,188.1
25-29			0			36.2	531.1	222.9	790.2
30-34	5.4		16.3		16.3	48.9	407.8	163.1	657.8
35-39	91.4		5.7		0	234.2	279.9	160.0	771.2
40-44	247.4		36.2		12.1	271.5	235.3	169.0	971.5
45-49	373.4	138.8	74.7	23.0	51.7	327.5	327.5	74.7	1,391.3
50-54	559.0	125.4	99.3	36.6	125.4	386.6	240.3	57.5	1,630.1
55-59	869.1	324.8	173.8	146.4	594.6	626.6	114.4	59.4	2,909.1
60-64	1,511.6	387.4	319.0	193.7	1,036.9	706.4	186.1	34.2	4,375.3
65-69	2,259.9	408.2	245.5	237.4	1,659.4	168.6	109.4	41.4	5,129.8
70-74	2,231.5	610.4	713.3	351.1	2,204.7	-11.2	87.2	40.2	6,227.2
75-79	1,907.6	311.1	628.5	363.4	1,942.5	-76.2	42.8	15.9	5,135.6
80 AND OVER	933.2	37.0	561.0	291.7	1,506.1	-92.4	54.1	5.3	3,296.0
ALL AGES	10,989.5	2,343.1	2,899.1	1,643.3	9,149.7	2,619.0	5,084.5	1,443.3	36,171.5

[1] CA LUNG. Malignant neoplasm of respiratory system, not specified as secondary (160-164)
CA OTHER, UNSP. Malignant neoplasm of other and unspecified sites (156B, 165, 190-199)
CVS OTHER Other diseases of circulatory system (451-468)
BRONCH Bronchitis (500-502)
BRONCH.- PULM., OTHER Other bronchopulmonic diseases (525-527)
CIRRHOSIS Cirrhosis of liver (581)
MOTOR VEH. ACC. Motor vehicle accidents (E810-E835)
HOMIC. Homicide (E964, E980-E985)

[2] A negative sign implies a fall in death rates

participated in the overall downward trend, and that these diseases are now predominating the mortality experience. These are principally respiratory diseases, malignant and non-malignant.

To the extent that the rise in cigarette smoking is responsible for increases in mortality rates, a leveling off and a subsequent fall may be anticipated. While per capita consumption of cigarettes in the United States more than doubled in each decade from 1900 to 1930, the rate of rise subsequently decreased, so that there was only a 17 percent rise between 1950 and 1960, and the single year 1961 saw a fall (Table A-2).[2]

The pattern of cigarette use has been studied in detail in two major investigations in the 1950's and 1960's.[3,4] Both reports showed a fall in smoking by men and a rise in women, but with a clear male excess persisting. Two features of the male cigarette use pattern are particularly pertinent to the present discussion. First, the proportionate fall in numbers of cigarette users is greatest is the younger ages, where the lung cancer death rates are presently constant or falling. Second, the fall in cigarette use has occurred in the light or moderate smoking males, while the heavy smokers have remained constant or increased. If the decreased smoking in the younger groups represents a cohort trend to less smoking, a similar decrease in older ages may be anticipated in future decades. The resistence to change of the heavy smoking groups may have the unfortunate consequence that disease trends are only marginally influenced by major changes in total numbers of smokers. This would be expected if cigarette smoking behaved like a threshold phenomenon with little or no effect in small doses.

EXHIBIT A-2

CONSUMPTION OF CIGARETTES PER PERSON AGED 15 YEARS AND OVER IN THE UNITED STATES FOR SELECTED YEARS 1900-1962[2]

Year	Cigarettes Number
1900	49
1910	138
1920	611
1930	1,365
1940	1,828
1950	3,322
1960	3,888
1961	3,986
1962	3,958

Source: Smoking and Health. Report of the Advisory Committee to the Surgeon General, 1964.

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APPENDIX B

OTHER PERSPECTIVES ON HEALTH

In Chapter 5 we have looked at what linked deaths can tell us about threats to health when the linked deaths are looked at as a percentage of all deaths. We recognized that this measure did not give adequate attention to the greater seriousness of early deaths, and gave, in addition, some figures for "adjusted percentages" of deaths. We now look at linked deaths from a different aspect—how many people "might be alive"—which also helps to explain how these adjustments were made.

We then go on to consider long-term changes in survival, and what can be learned by comparing long-term changes in women with those in men.

As we will see in Section 2, the details of exactly what "might be alive in 1967" are mildly complex, just as are the details of "1967 expectation of life at birth." For all this, the reader who takes the "number who might be alive" as a reasonable pointer to the number who really might be alive is, we feel, being as well guided as is presently possible. (The uncertainties in "linking" almost certainly outweigh any that are added.)

1. Number who might be alive

Let us compare two quite hypothetical situations: one in which people continue to die, year after year, in the same numbers at each age that died in 1967; another in which every death linked to a particular threat is postponed, so postponed that the distribution of continued life is the same for all linked deaths postponed from a given age as it is for all those who reached that age without dying. We next calculate the number that "might be alive," that is how many more people would be alive in the second hypothetical situation than in the first. (The concept is discussed further in Section 6 below. Details of the calculation are given in Appendix C.)

Exhibit B-1 sets out the numbers that result. Let us look at the first line, that for cigarette smoking, in some detail. If we ask for those who "might be alive" at all ages, we find 3,700 thousand—about 3 3/4 millions of people. This does NOT mean that had no one born in the last eight or nine decades smoked cigarettes, that 3 3/4 million more would be alive. It DOES mean, though, that thinking about 3 3/4 million more now alive is a reasonable way to grasp the importance of deaths linked to cigarette smoking.

Moving to the right, if we only consider those under 85, about 3,100 thousands "might be alive." Similarly about 2,000 thousand under 75 and 900 thousand (about 1 million) under 65. On the right-hand part of the exhibit we take these numbers apart, and reach, as something to give us a feeling for the impact of cigarette smoking.

0.9 million who *might be alive* under 65

1.1 million who might be alive between 65 and 75

1.1 million who might be alive between 75 and 85

0.6 million who *might be alive* above 85

This is to be compared, for example, with the corresponding figures for alcohol abuse.

1.2 million who might be alive under 65

0.3 million who *might be alive* between 65 and 75

0.2 million who *might be alive* between 75 and 85

0.1 million who *might be alive* above 85

Clearly the impact of these two threats is about the same (alcohol abuse is in fact somewhat larger) if we only look at ages under 65. The greater impact of cigarette smoking occurs at the ages beyond 65.

Exhibit B-1 allows one to gain similar impressions for the other threats considered above, except for those that are either too uncertain or too small to be worth such treatment.

Clearly we are talking of large numbers "who might be alive"—something like six million for cigarette smoking and alcohol abuse, perhaps twice this number if we include both choice of diet composition and unknown chemical initiators or promoters of cancer and if these two turn out to be very important.

2. Adjusted percent of deaths

We can now calculate an adjusted percent of deaths—either for all ages or for ages up to a given limit—as:

$$\text{adjusted percent of deaths} = \frac{\text{No. who might be alive (linked to given threat)}}{\text{No. who might be alive (all causes)}}$$

The adjustments used in Chapter 5 were:

Adjustment A: all ages included.
Adjustment B: only ages up to 65.

3. Long term changes

We said earlier that a significant fraction of the improvement in health in this century could be credited to

chemicals. What does this mean in terms of those who might, or might not, be alive?

If the 1901 death rates had continued throughout the lifetimes of those now alive, nearly 50 million people now alive would have died. If the 1967 death rates had applied instead, nearly 20 million people now dead would still be alive. The probable impact of today's large chemical threats, say 6 to 12 million who might be alive, may well not be as large as the benefit we have already had from chemicals, but it is at least a large fraction.

For those who want a little more detailed feel, we give age breakdowns for what 1901 and 1967 death rates would mean. If 1901 death rates had been in existence (with no allowance for children born of parents who would have died before having the children):

- about 40 million people under 65 would not now be alive.
- about 4 million people between 65 and 75 would not now be alive.
- about 2.5 million people between 75 and 85 would not now be alive.
- about 1 million people over 85 would not now be alive.

If the opposite had happened, if 1967 death rates had applied in the past:

- about 10 million more people under 65 would be alive.
- about 4 million people between 65 and 75 would be alive.
- about 3 million more people between 75 and 85 would be alive.
- about 1.5 million more people over 80 would be alive.

These figures offer a more detailed feeling for what the differences in death rates—(1) as they were in 1901, (2) as they changed through this century, (3) as they were in 1967—mean in terms of our present population.

4. Effects on average lengths of life

Rather than think of how many might still be with us, some wish to think about what impact these threats are likely to make on one's own life. Careful calculation here is a little more complicated, so we will content ourselves with a very rough approximation, namely:

1 year of extra life for every
2 million who *might be alive*

1 month of extra life for every
160 thousand who *might be alive*

1 week of extra life for every
40 thousand who *might be alive*

1 day of extra life for every
5 thousand who *might be alive*

1 hour of extra life for every
230 who *might be alive*

1 minute of extra life for every
4 who *might be alive*

With these rules of thumb the figures of the left-most column of Exhibit B-1

EXHIBIT B-1

"NUMBERS WHO MIGHT BE ALIVE" = DIFFERENCE BETWEEN: (1) RESULT OF CONTINUING ALL 1967 DEATHS IN SUCCEEDING YEARS AND, (2) SAME EXCEPT THAT EACH LINKED DEATH IS REPLACED BY THE AVERAGE CONTINUATION OF LIFE FROM THAT AGE.

Cumulative (thousands)					Separated[1] (thousands)			
all ages	up to 85	up to 75	up to 65	Linked to[2]	to 65	66 to 75	76 to 85	86 up
3700	3100	2000	900	cigarette smoking	900	1100	1100	600
1800	1700	1500	1200	alcohol abuse	1200	300	200	80
?	?	?	?	dietary composition ..	?	?	?	?
?	?	?	?	unknown cancer	?	?	?	?
390	370	330	270	illicit drug abuse	270	70	40	20
375	?	?	?	adverse reactions to medication	?	?	?	?
150	120	75	30	airborne particles	30	45	40	30
130	120	100	75	suicides with chemicals	75	30	20	5
110	100	65	30	air pollution	30	35	35	10
75	70	65	50	accidents with chemicals	50	15	5	5
30	25	15	5	coffee	5	10	10	5
7	7	6	5	oral contraceptives ...	5	1	1	0.3

[1] Rounded further.
[2] Note that the numbers given "who might now be alive" are calculated as though current risks had been in effect throughout the life of our present population.

have a different, useful (and still more approximate) interpretation.

The conversion applies to "the average person." So far as risks due to the choice of others go, the result is roughly correct for anyone. But where it is a matter of own choice, we need to allow for how many choose. We have taken the fraction of cigarette smokers to be about 3/8 (1/2 for men, 1/4 for women). Accordingly, while removing deaths linked to cigarette smoking would give an average of two years of extra life, non-smokers would gain nothing and the average smoker would gain about 2/(3/8) = about 5 years.

Similar, but often much more extreme, adjustments would be appropriate for other self-chosen threats.

5. Females vs. males

We have noticed how much more the expectation of continued life has been improved for females as compared to that for males. Two major reasons for this are clear: More men than women smoke cigarettes. (Indeed our estimates link about 140,000 more male deaths than female to cigarette smoking.) More men than women die from accidents, homicides and suicides. This raises such questions as: How much faster do men die? How much of this is due to these two major effects? How rapidly has the pattern changed?

Exhibit B-2 sets out the ratios comparing death rates for men to those for women for various ages, as it used to be in 1901, and as it was in 1968. The ratios are the relative number of deaths among equal numbers of men and women at a given age. In 1901, males died about 1.1 times as fast as females. In 1968, males died more nearly 1.8 times as fast as females. In large measure, this came about from the removal of causes of death that affected both sexes more or less equally. In almost equally large measure this came about from the increasing importance of threats that were more important for males than for females.

As a first step in understanding the implications of Exhibit B-2, we can look at the corresponding ratios when we set aside all deaths due to accidents, homicides, and suicides. The result is shown in Exhibit B-3. We see that in 1901, removing all deaths due to external causes leaves men dying slower than women between 10 and 40 years of age, and, except for the first year of life, never dying more than 1.1 times as fast. In 1967, the omission of deaths from external causes has reduced the first peak in the ratio—the one falling in the late teens—from 2.9 to 1.3. (The small peak that remains would be accounted for if about 10 percent of those dying because of external causes do so from complications, one of which is then entered on the death certificate as the cause of death.) The second peak—the one falling in the early 60's, is not appreciably reduced.

EXHIBIT B-2

RELATIVE DEATH RATE—FRACTION OF MEN DYING AS A MULTIPLE OF FRACTION OF WOMEN DYING—FOR VARIOUS AGES, BOTH IN 1901 AND 1967

Age	Ratio in 1901	Ratio in 1967
0-1	1.20	1.29
1-5	1.07	1.25
5-9	1.06	1.39
10-14	1.04	1.75
15-19	1.00	2.50
20-24	1.07	2.80
25-29	1.04	2.26
30-34	1.06	1.81
35-39	1.12	1.69
40-44	1.17	1.70
45-49	1.17	1.78
50-54	1.13	1.99
55-59	1.13	2.03
60-64	1.13	2.07
65-69	1.12	1.82
70-74	1.08	1.70
75-79	1.08	1.46
80-84	1.08	1.24
(median)		

It is natural to try to go somewhat further by excluding both deaths from external causes and deaths linked to cigarette smoking. The fourth column of Exhibit B-3 shows that the peak in the early 60's is reduced from 2.05 to 1.67. This leaves us with the impression that differences in frequency of cigarette smoking accounts for a sizable fraction of the excess death rate for men, as compared to women, but probably for less than half this excess. (The last column (all in parentheses) shows the effect of removing twice as many deaths as we have linked to cigarette smoking. After this hypothetical adjustment, the mean ratio is still 7 percent greater than in 1901. Our impression is confirmed.)

What about the remainder? Some will believe that a large part of the remaining excess is due to environmental exposures of some sort or other. Others will believe that the stresses of working life are the major cause. As yet there is no clear answer.

We can say, however:

- that men die at a rate almost twice that of women between 50 and 70 years of age.
- this direction is consistent with more men smoking cigarettes.
- the estimates we have made of deaths linked to cigarette smoking are not large enough to account for quite half the difference.

Looking at the comparison of men and women does nothing to contradict our earlier analyses; indeed it offers a small amount of indirect support.

6. Measures of life and death

Human life terminating in death is a lengthy process, yet the world we live in changes rather rapidly. As a result, measures of health based on how and when we die tend to be somewhat less than straightforward in their interpretation, not for mali-

cious reasons but rather because making the best use of current information is not a trivial task.

COUNTING DEATHS

One thing we can do is just to count deaths according to a standard set of causes. This throws some light on the situation: a cause of 500,000 deaths a year is almost certainly more serious than one that causes only 5,000. Besides the absence of a natural reference, two considerations weaken a mere death count: First, all we can do is to postpone death—the total number of deaths is essentially fixed by the total number of births. Second, death of a younger person is almost universally agreed to be more serious than that of an older one.

To get around some of the difficulties, we can compare official causes in terms of the percent of all deaths. In 1967, for example, we have such results as those shown in Exhibit B-4, where numbers are in one column and percents in the other.

Most readers will agree that they can get a clearer picture from the percent column than from the count column.

EXPECTED YEARS OF LIFE

Expected years of life is a measure that sounds easier to understand than it is. What would probably be most meaningful would be some measure of how long an average individual born at a given date lives. If average is meant in the technical sense—as an arithmetic mean—we do not yet know the answer for any group born in this century, since it is not until almost all have died that we will know enough to find an average. (If we really meant "median" we know the answer for those born in the early and middle 1890's, where we cannot yet be sure of the average.) Such "cohort" figures—quite relevant for individuals—are of little help in watching changes in current public health. After all they combine what has happened to each cohort (at various ages) over some eight or nine decades.

As a result, most expectation of life figures refer to some brief period of time—often one year, sometimes three years. What they tell us, for instance, is the average age of death of a composite person who spent all his or her life in the short period. If the period were January to December 1967, for example, this imaginary person would be born on 1 January and, if he or she lived to 31 December, would reappear again, 12 months earlier, at 1 January of the same year, aged exactly one year old, and so on, each year of life being lived—or terminating in death—in exactly the same calendar year. Clearly this measure makes it easier to watch public health from year to year, since it is calculated from observed deaths in that year and that year alone. (Events that were the underlying causes of some of these deaths happened a decade or more earlier.) Equally clearly, it is at least correspondingly harder to explain just what we are talking about. (This seems to be characteristic of measuring life and death: the more useful the measure, the harder it is to explain.)

PROFESSIONAL MEASURES

Demographers and epidemiologists need to know about deaths in greater detail than we will really need here. They are likely to use death-rates for, say, given age and sex. This means, of a hypothetical 100,000 people, all of the given sex and all having their nth—say

EXHIBIT B-3

RELATIVE DEATH RATE—FRACTION OF MEN DYING AS A FRACTION OF WOMEN DYING—WHEN DEATHS FROM EXTERNAL CAUSES (ACCIDENTS, HOMICIDES, SUICIDES, ETC.) ARE EXCLUDED

Age	Ratio in 1901	Ratio in 1967	1967 further adjusted[1]	1967 hypothetical adjustment[2]
0-1	1.20	1.29	1.29	(1.29)
1-4	1.07	1.17	1.17	(1.17)
5-9	1.01	1.11		
10-14	.86	1.14	1.14	(1.14)
15-19	.85	1.27		
20-24	.91	1.18	1.18	(1.07)
25-29	.90	1.13		
30-34	.97	1.13	(1.02)	(0.89)
35-39	.98	1.31		
40-44	1.01	1.49	(1.28)	1.00
45-49	1.04	1.66		
50-54	1.05	1.92	(1.59)	(1.14)
55-59	1.08	1.98		
60-64	1.09	2.05	(1.67)	(1.18)
65-69	1.09	1.80		
70-74	1.08	1.70	(1.43)	(1.11)
75-79	1.10	1.46		
80-84	1.10	1.24	(1.11)	(0.99)
(Median) ..	(1.04)	(1.30)	(1.23)	(1.12)

[1] With both deaths linked to cigarette smoking and deaths assigned to external causes removed.

[2] With deaths due to external causes and twice as many deaths as linked to cigarette smoking removed.

their—58th—birthday on 1 January of the year in question, how many will die—or die of a given cause during that year. (In practice results are quoted for ages spread out to some reasonable degree.) There is no substitute for the use of death rates by age if we need a detailed look at what is happening. Fortunately we will need to make only limited use of death rates here.

Fortunately, also, if death rates at *all* ages go up, the corresponding expected years of life goes down, while if death at *all* ages go down, the corresponding expected years of life goes up. Thus, it is usually safe to use "live longer" as a shorthand for "all death rates coming down" and "live shorter" as a shorthand for "all death rates going up."

IMPACT OF DEATHS

We said above that the difficulty with merely counting deaths was that it took no account of at what age they occurred. There are various ways to try to take account of this. Some try to do it by assigning an "economic value" to death at a given age, often considering both what society has spent (education, etc.) and what the future return may be in the absence of death (useful work, etc.). We find none of these satisfactory for our purposes here. Our considerations are health considerations, and we resist mixing in economic ones.

Our concern with causes of death is to ask what would be the impact if they were weakened or removed, thus postponing some or all of the related deaths. What would this mean in health terms?

The *simplest—and most optimistic* way of valuing not dying at a specific age is to calculate as if, were death to be postponed at a given age, those for whom it would be postponed would live as long as the average person of that age and sex. If the cause of death that might be postponed has little connection with general healthiness—as we would expect for accidents, homicides, and being struck by lightning, for example—this calculation should come close to corresponding to the truth. For other causes of death it may be optimistic. But it is a well defined calculation in any event, and probably does quite well in making a relatively satisfactory allowance for the importance of death at different ages.

To value each death from a given cause in terms of the expected years of life at that age and sex and to add these values up to find a total value associated with all the deaths is numerically the same as to find an average value, here an average years of expected life for all the deaths, and multiply the number of deaths by this factor. We will often find it useful to speak and think in this latter way.

Average years of expected life for a cause of death, then, grade down from largest values for causes of early deaths to smallish values for causes of late deaths. Some examples are:

Cause of death	Average years
deaths from oral contraceptives	50
motor vehicle accidents	33
cancer of the lung	17
cardiovascular disease	11
adverse reaction to medication in hospital	5

In the last example, we have made a rough (judgment-based) correction for the fact that many deaths in hospital linked to adverse reaction to medication involve patients who were, in any case, near death. So far, this is the only case where such a judgment-based assumption seems justified.

NUMBER WHO MIGHT BE ALIVE

If our optimism were correct, and if nothing changed—death rates and population size remaining constant—for many years, then the number of people who would be alive if deaths associated with a cause of death were eliminated, but who would not be alive if these deaths were not eliminated would just be this product of annual number of deaths by average years of expected life at death. Accordingly, we refer to this product as the "number of people

EXHIBIT B-4

COMPARISON OF NUMBER OF DEATHS WITH PERCENT OF DEATHS IN 1967 (FOR SELECTED CAUSES)

(1,852,000)	(Total deaths)	(100.0%)
575,540	arteriosclerotic heart disease	31.0%
315,996	cancer (all forms)	17.0%
202,940	vascular lesions affecting central nervous system	11.0%
108,940	all accidents	5.9%
53,140	motor vehicle accidents	2.9%
27,410	cirrhosis of liver	1.5%
14,120	rheumatic fever	0.76%
6,560	tuberculosis	0.35%
3,136	cancer of the liver	0.17%
1,450	influenza	0.078%
710	infectious hepatitis	0.038%
369	complications of pregnancy	0.020%
110	syphilis and sequelae	9.006%
40	whooping cough	0.002%
20	diptheria	0.001%

who might be alive." We would be more concerned about the difficulties of giving a precise and relevant interpretation to this measure, and about the approximations it involves, were it not true that other measures have, to greater or lesser degree, the same difficulties. Expected years of life, for example, as we have explained, refers to hypothetical people living all their life in one single calendar year. Indeed, careful analysis shows that the calculation of "number who might be alive" also makes assumptions about how large a fraction of less generally healthy people have died in comparison with more healthy ones.

Once we are prepared to assign an "expected years of life" to a death specified by age (and often, also, by sex) we have only the arithmetic to change when we want to use "expected years of life before age 75"—or before any other specified age—in its place.

CHOSEN MEASURES

The result of these considerations is thus two-fold. When, as we usually should, we want to give early deaths a higher value, we use—and recommend the use of—number who might be alive (before age—). When we feel that we must use as measure tied as close to observation as we can, we use—and recommend the use of percent of all deaths.

APPENDIX C

DEATHS LINKED TO VARIOUS CAUSES

1. Introduction

Data from which we infer links between exposures to various chemicals and health come essentially from systematic observations of associations between known exposures and the sickness experience (including deaths) of the people exposed. Death is nearly always accompanied by the filing of a death certificate and death certificates almost always include expert judgments of cause of death. The latter are by no means perfect. Nevertheless, they are reasonably consistent. Fashions in diagnostic nomenclature have changed over time, but much is known about these changes and standardization has been increasingly imposed in recent years.

The quality of associations between known exposures and causes of death vary somewhat—both in strength of association and in quality of data. Some associations are well established and result from multiple independent observations (e.g., cigarette smoking and lung cancer). Other possible linkages are best classified as still emerging (e.g., dietary composition and cardiovascular disease). While some associations suggest major linkages (contribution of alcohol to automobile accident deaths), others are seen as almost overwhelmed in the "noise" of more powerful factors. (For example, any association between urban residence, which includes air pollution effects, with diseases of the lung, is almost overwhelmed by the association of these diseases with cigarette smoking.) Finally, while associations that involve both only a small fraction of the deaths from a specified cause and death for a very small fraction of those exposed are often important in human terms, they may not be recognizable, just because both fractions are small.

2. What has been the general mortality experience of the United States?

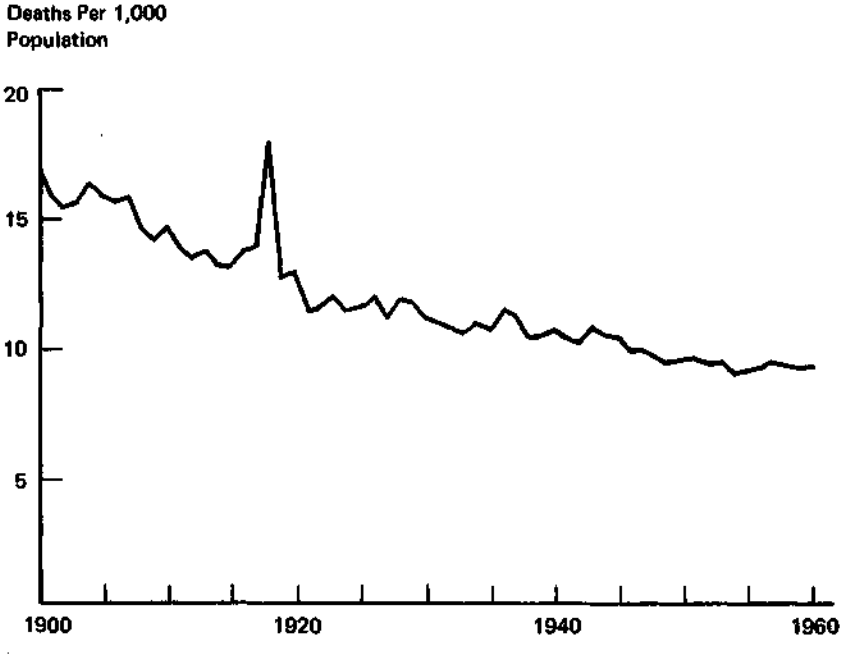
The 1900 crude death rate for the U.S. of 17.2 per 1,000 population fell fairly consistently until the sixth decade of this century. Various deviations from this trend can be traced to epidemics of infectious disease which occurred from time to time before the 1940's.

Between 1900 and 1960, large relative declines in mortality took place during infancy and childhood. In absolute terms, however, the declines in mortality at older ages are also substantial.

What is important for the present discussion is to examine the changes that have taken place in the rank ordering of causes of death by disease category:

These figures suggest several messages. For the present purposes, perhaps the most important are the relative decline in importance of infectious diseases as compared to chronic degenerative diseases (cancer, diseases of the heart, arterio-

EXHIBIT C-1



Source: Various reports of the National Office of Vital Statistics.

sclerosis, cirrhosis). In 1900, diseases of the heart caused eight percent of the deaths in the United States and cancer caused less than four percent. By 1960 influenza and pneumonia were the only infectious diseases ranking in the top 10 causes of death (together less than four percent in 1969), while diseases of the heart were responsible for over 38 percent of all deaths and cancer for over 15 percent. These increases were substantially greater than could be accounted for by the decreases in deaths from infectious diseases and the increased fraction of the population reaching advanced ages.

Exhibit C-3 illustrates the rise in cancer mortality with time. This suggests to some, perhaps, that cancer has simply "taken the place" of other causes of death. However, as Exhibit C-4 illustrates, a large part of the absolute increase in cancer deaths since 1900 cannot be explained by the increase in the size and age of the population.

3. Deaths linked to various specific causes

a. Deaths linked to cigarette smoking

There is by now considerable quantitative evidence linking the smoking of cigarettes to excess deaths by various causes. This is so while the mechanisms by which smoking causes excess early deaths are uncertain and though some experts continue to doubt that relationship.

We have adopted figures published in the World Health Organization's Chronicle for 1970 as a basis of calculation. We have also taken the fraction of smokers to be half of all adult males and a quarter of all adult females. (The correct period over which such fractions should apply would be some years before the date (1967) of our death information. A Bureau of the Census Study in 1955 gave 49.8 percent of males and 23.6 percent of females as cigarette smokers.)

The proportion of deaths attributable to smoking were obtained from Table 5, page 349, of the W.H.O. Chronicle, Vol. 24, No. 8, 1970.

Only causes with a mortality ratio of 1.3 or more have been included. Other causes mentioned in the article corresponded to very low proportions of linked deaths (for a population of whom 50 percent smoke; 17 percent of deaths by accidents, suicides or violence, 10 percent of nephritis deaths, six percent of rheumatic heart disease deaths, and two percent or less for certain other forms of cancer).

Since the seven prospective studies summarized in the WHO article involved primarily males, two exhibits have been prepared, one for males only and one for total deaths assuming the proportions computed from Exhibit C-5 also apply to females.

Neither the WHO article nor the two exhibits presented here take age into account. All of the estimates should therefore be viewed as approximations only.

Exhibit C-5 illustrates the effects of smoking calculated for different assumptions about the proportion of smokers in the population. The proportion of deaths linked to smoking is reduced as the assumed number of smokers in the population is decreased.

Exhibits C-6 and C-7 present the numbers of linked deaths in the U.S.

EXHIBIT C-2

LEADING CAUSES OF DEATH IN THE U.S. 1900 AND 1960

Rank	Cause of death	Deaths per 100,000 pop.	Percent of all deaths
	1900		
	(All Causes)	(1,719)	(100)
1	Pneumonia and influenza	202.2	11.8
2	Tuberculosis (all forms)	194.4	11.3
3	Gastritis, etc.	142.7	8.3
4	Diseases of the heart	137.4	8.0
5	Vascular lesions affecting the CNS	106.9	6.2
6	Chronic nephritis	81.0	4.7
7	All accidents[1]	72.3	4.2
8	Malignant neoplasms (cancer)	64.0	3.7
9	Certain diseases of early infancy	62.6	3.6
10	Diphtheria	40.3	2.3
	(TOTAL)		(64%)

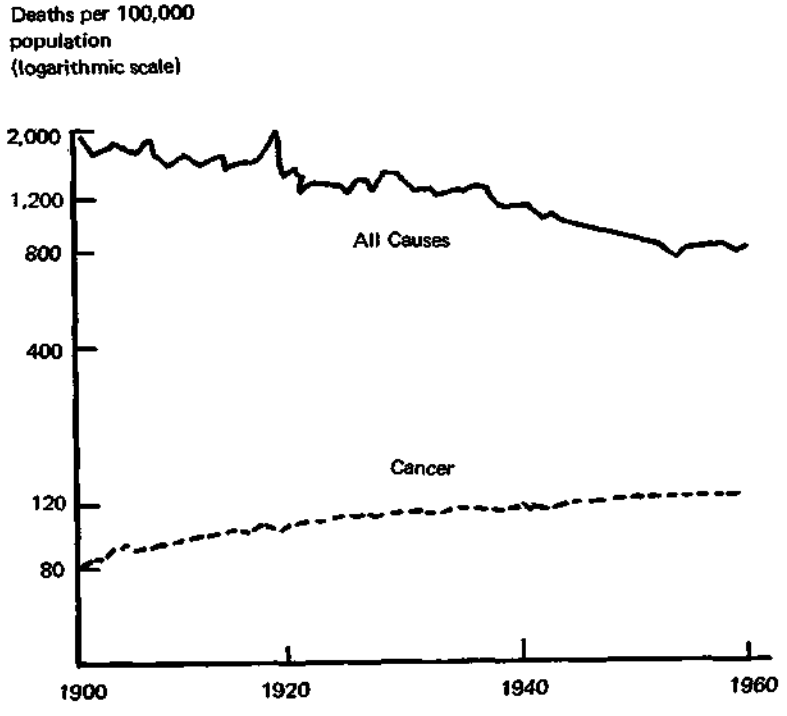
[1] violence would add 1.4%; horse, vehicle and railroad accidents provide 0.8%.

	1960		
	(All Causes)	(946)	(100)
1	Diseases of the heart	366.4	38.7
2	Malignant neoplasms (cancer)	147.4	15.6
3	Vascular lesions affecting the CNS	107.3	11.3
4	All accidents[1]	51.9	5.5
5	Certain diseases of early infancy	37.0	3.9
6	Pneumonia and influenza	36.0	3.5
7	General arteriosclerosis	20.3	2.1
8	Diabetes mellitus	17.1	1.8
9	Congenital malformations	12.0	1.3
10	Cirrhosis of the liver	11.2	1.2
	(TOTAL)		(85%)

[1] violence would add 1.5%; motor vehicle accidents provide 2.3%; railroad accidents provide less than 0.1%.

EXHIBIT C-3

Mortality from all Causes and from Cancer, United States, 1900-1960

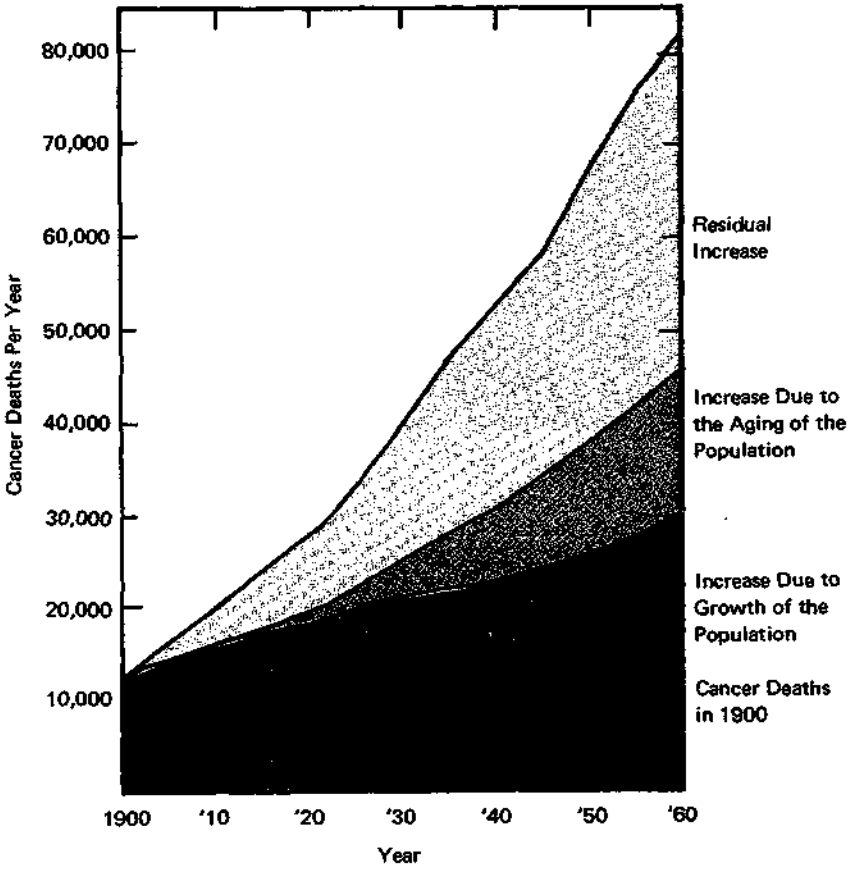


Source: Various reports of the National Office of Vital Statistics.

(Rates since 1949 have been adjusted to the Fifth Revision of the International List of Diseases and Causes of Death).

EXHIBIT C-4

NUMBER OF DEATHS FROM CANCER OF ALL SITES,
U.S. DEATH REGISTRATION
AREA OF 1900, 1909-60



Source: Cancer Rates and Risks, Public Health Service Publication No. 1148

in 1967, based on the 50 percent and 25 percent proportions mentioned above.

b. Deaths linked to alcohol abuse

Exhibit C-8 shows the number of 1967 deaths that can be attributed to abuse of alcohol. Over 13,000 deaths occurred from diseases directly linked to alcoholism (mainly cirrhosis of the liver and chronic alcoholism). About twice as many deaths are attributable to driving a motor vehicle under the influence of alcohol. These deaths include not only single vehicle accidents in which the driver was fatally injured while under the influence, but also deaths of other occupants, either of the single vehicle or of other vehicles when the drunken driver was at fault. They also include pedestrians killed when the driver of the vehicle was under the influence. Numerous studies have shown that overuse of alcohol is a significant factor in approximately half of accidental deaths associated with motor vehicles.

The proportions of other deaths (other accidents, suicide, homicide) linked to abuse of alcohol are estimates based on judgment, not yet supported by systematic epidemiologic studies.

c. Deaths linked to dietary composition

The best available opinion is that a fair proportion of "heart" deaths (those classified as cardiovascular) are linked to long-term dietary composition. The long-term studies needed to establish what fraction is actually linked to which dietary components are barely begun. (These studies may not yet include the possible effects of carbohydrates in general, and sucrose in particular, in addition to the central issues of cholesterol and fats of various degrees of saturation.)

It must be stressed that we are not yet clear what to do to reduce whatever amount of early deaths come from this cause.

With an average of about 11 years of expected life at the time of death from coronary heart disease, an estimate of about 400,000 linked deaths leads us to a possible four or five million persons who would perhaps be alive today, if we had known what they should avoid, if we had told them, and if they had chosen to avoid what they were told to avoid—each of these three if's all through this century.

d. Cancer deaths possibly linked to chemicals

This is a very large question mark, as indicated in Chapter 5. There are many opinions and no hard data.

e. Deaths linked to "adverse drug reactions"

The most rigorous studies on deaths from "adverse reactions to therapeutic drugs" that have been so conducted as to give a reasonable estimate of rates have been conducted in medical wards of teaching hospitals. They show one such death for each few hundred admissions. The best available judgment is that rates are somewhat higher on surgical wards and in nonteaching hospitals. With 20 million hospital admissions per year, this amounts to nearly 100 thousand deaths.

In thinking about this figure it is important to recognize that it includes deaths from overloaded circulation. Such deaths make up a significant share of those included,

EXHIBIT C-5

THE PROPORTION OF ALL DEATHS FROM THE INDICATED CAUSE LINKED TO SMOKING AS A FUNCTION OF THE PROPORTION OF THOSE IN THE POPULATION WHO SMOKE[1]

Cause of Death	Proportion Smoking			
	100%	75%	50%	25%
Cancer of lung	.91	.90	.86	.72
larynx	.81	.76	.68	.52
oral cavity	.76	.71	.61	.44
esophagus	.70	.64	.54	.37
bladder	.48	.41	.32	.19
kidney	.34	.28	.20	.11
stomach	.31	.25	.18	.10
prostate	.20	.16	.11	.059
other (excluding rectum and intestine)	.30	.24	.18	.097
Vascular lesions	.21	.17	.12	.06
Arteriosclerotic heart disease	.42	.35	.27	.15
Other heart	.39	.32	.24	.14
Hypertensive heart disease	.35	.29	.21	.12
General arteriosclerosis	.32	.26	.19	.11
Other circulatory	.61	.54	.44	.28
Bronchitis and emphysema	.84	.80	.72	.57
Stomach and duodenal ulcers	.64	.57	.47	.31
Cirrhosis of the liver	.55	.48	.40	.23
Influenza and pneumonia	.27	.22	.16	.085

[1] If the risk of death from the indicated cause is R times as great for each smoker as for each nonsmoker, and a fraction f of the population smoke, then the number of excess deaths linked to smoking is proportional to (R-1)f and the fraction of all deaths from the indicated cause linked to smoking is

$$\frac{(R-1)f}{(1-f)+Rf} = \frac{(R-1)f}{1+(R-1)f}$$

EXHIBIT C-6

NUMBER OF MALE DEATHS IN 1967 LINKED WITH SMOKING FOR VARIOUS PROPORTIONS OF SMOKERS

Cause of Death	Proportion Smoking		
	75%	50%	25%
Cancer of lung	40,845	39,029	32,676
larynx	1,876	1,678	1,283
oral cavity	3,559	3,058	2,206
esophagus	2,756	2,325	1,593
bladder	2,468	1,926	1,144
kidney	1,034	739	406
stomach	2,599	1,871	1,040
prostate	2,615	1,798	964
other*	12,992	9,744	5,251
Total Cancer	70,744	62,168	46,563
Vascular lesions	15,822	11,169	5,584
Arteriosclerotic heart disease	120,804	93,192	51,773
Other heart	13,815	10,361	6,044
Hypertensive heart disease	4,828	3,496	1,998
General arteriosclerosis	4,313	3,152	1,825
Other circulatory	9,586	7,811	4,971
Total cardiovascular	169,168	129,181	72,195
Bronchitis and emphysema	17,206	15,485	12,259
Stomach and duodenal ulcers	3,872	3,193	2,106
Cirrhosis of liver	8,593	7,161	4,118
Influenza and pneumonia	7,019	5,105	2,712
TOTAL	276,602	222,293	139,953

EXHIBIT C-7

DEATHS LINKED WITH SMOKING, 1967 ASSUMING 50% OF MALES AND 25% OF FEMALES SMOKE

Cause of Death	Males 50%	Females 25%	Total Deaths
Cancer of lung	39,029	6,497	45,526
larynx	1,678	171	1,849
oral cavity	3,058	750	3,808
esophagus	2,325	505	2,830
bladder	1,926	521	2,447
kidney	739	242	981
stomach	1,871	665	2,536
prostate	1,798	.....	1,798
other	9,744	4,234	13,978
Total Cancer	62,168	13,585	75,753
Vascular lesions	11,169	6,547	17,716
Arteriosclerotic heart disease	93,192	34,200	127,392
Other heart	10,361	5,711	16,072
Hypertensive heart disease	3,496	3,999	7,495
General arteriosclerosis	3,152	2,307	5,459
Other circulatory	7,811	3,414	11,225
Total cardiovascular	129,181	56,178	185,359
Bronchitis and emphysema	15,485	2,214	17,699
Stomach and duodenal ulcers	3,193	940	4,133
Cirrhosis of liver	7,161	2,280	9,441
Influenza and pneumonia	5,105	2,124	7,229
TOTAL	222,293	77,321	299,614

and should probably be considered cases of unsuccessful treatment rather than of untoward reaction toward medicine. They have been excluded from our considerations.

As a rough judgment, then, we have assigned 75 thousand deaths a year—the figure corresponding to the latest studies—to untoward or unsatisfactory reactions to medicines. This figure is unlikely to be twice too high. It might be twice too low. A large fraction, perhaps a half, of these deaths, appear to come from cases where very potent drugs were given in an attempt to treat very sick patients. (The official list of causes of death includes "therapeutic misadventures linked to drugs." In 1967 such deaths totaled 640. Clearly, we judge this figure to be very low, as the rules defining the official causes of death would lead us to expect.

f. Deaths linked to illicit drugs

This covers illicit use of narcotic and addicting substances—some of which are legally manufactured but wrongfully used (e.g. some uses of morphine) and some of which are illegal. The deaths associated with their use or abuse are of various sorts; direct action (as in accidental poisonings or suicides) or indirect but contributing influences (such as automobile accidents).

Reliable figures describing deaths due to narcotic drug use are generally not available. The recent experience of one U.S. city (as seen from figures compiled from death certificates for 1971) suggested that there were about 2 deaths with drug addiction as an indirect cause for each 5 deaths with it as a direct cause. Since about 80 percent of these indirect-cause deaths were homicides, and since at least an equal number of non-drugged victims of homicides by drug abusers were to be expected, we would expect at least 3.6 homicides linked to drug abuse for each 5 direct drug deaths. Linking 10 percent of all homicides matches this figure rather closely. Judgment-based factors were used for linkage of accidents and for suicides involving analgesic and soporific substances. Exhibit C-9 shows the results, totaling 6,141 linked deaths. This total number of deaths stated as linked to drugs, is, in our opinion, likely to be low. Accordingly, we have used 10,000 in Chapter 5 and Appendix B.

g. Deaths linked to air pollution

As Exhibit C-10 shows, deaths that could be specifically linked to air pollution in 1967 are estimated to be about 9 thousand. The proportion of deaths due to nonspecific lung diseases linked to air pollution is based on surveys of living persons in which careful smoking histories and occupational histories were obtained, so that pulmonary symptoms and impairment could be related to the relative risks of cigarette smoking, other tobacco smoking, occupational exposure, and community air pollution exposure. (No large scale study of deaths from these diseases thus far completed has been designed to permit separation of these factors.) Both for these diseases and for lung cancer it is known that cigarette smoking is far more important than community air pollution.

Although no epidemiologic study in this country has demonstrated an effect of community air pollution on lung cancer, we have used a proportion of five percent, since an "urban factor", which has to include any effect of air pollution, appears to play a role in lung cancer incidence.

h. Deaths linked to airborne particles (occupational lung diseases)

The gross inadequacy of reporting

EXHIBIT C-8

DEATHS LINKED TO ALCOHOL, 1967

Cause of deaths	Estimated proportion linked to alcohol	Male deaths	Linked deaths, male	All deaths both sexes	Linked deaths both sexes
alcoholic psychosis	1	552	552	599	599
alcoholism	1	2,300	2,300	2,982	2,982
cirrhosis with mention of alcoholism	1	6,528	6,528	9,555	9,555
cancer of esophagus	.1	4,306	400	5,627	600
cancer of oral cavity	.1	5,013	500	6,718	700
motor vehicle accidents	.5	38,133	19,100	52,924	26,500
other accidents	.2	39,746	7,900	60,245	12,000
suicide	.2	15,182	3,000	21,325	4,300
homicide	.2	10,228	2,000	13,425	2,700
TOTAL			42,300		59,900

EXHIBIT C-9
DEATHS LINKED TO ABUSE OF ILLICIT DRUGS FOR THE YEAR 1967

Cause of Death	Males	Females	Fraction linked	Number linked
Drug Addiction	153	49	1.0	202
Accidental poisonings linked to drugs	1,090	770	1.0	1,860
Suicide from poisonings linked to analgesic and soporific substances	985	1,794	0.4	1,076
Homicides	10,228	3,197	0.1	1,343
Motor vehicle accidents	38,133	14,791	0.02	1,058
Other accidents	39,746	20,499	0.01	602
Total				6,141

on occupational exposures as primary or contributory causes of death is well known. Numerous other sources of information must be used . . . prevalance surveys, studies of compensation claims where pulmonary disease is legally recognized to be caused by occupational exposure, and others. Chronic and potentially fatal lung disease is known to occur in many industries, from inhalation of specific particles, fumes, or vapors. Lung cancer, fibrosis, and other forms of lung disease may occur in response to inhalation of coal dust, silica, asbestos, cotton dust, beryllium, and many other chemicals. There are estimated currently to be 125,000 cases of coal miners' pneumoconiosis in this country, with an estimated 3 to 4 thousand deaths each year in which the pneumoconiosis was in fact either the underlying or a contributory cause of death. Over 2,000 new cases of silicosis are diagnosed each year, with about an equal number of deaths. Asbestos-linked deaths—including asbestosis, lung cancer, and mesothelioma—probably amount to a further 2,000 deaths a year.

From these kinds of admittedly incomplete information on various kinds of occupational lung disease, we estimate that at least 9,000 persons die each year with occupational lung disease as a primary or contributory cause of death.

i. Suicides linked to other chemicals

The following figures apply to suicides by chemical means (U.S. 1967, number linked to the nearest 10):

Suicides by	Males	Females	Fraction linked	Number linked
Analgesics and soporifics	815	1794	.6	1670
Solids and liquids	339	317	1.0	660
Gases and vapors	1715	635	1.0	2350
Round total				4700

j. Deaths linked to drinking coffee

Until recently coffee drinking did not receive much attention as a factor which might be causally linked with degenerative deseases, although the ingredient caffeine was known to be mutagenic in certain experimental systems. A recent study of bladder cancer, however, showed an unexpected role for coffee drinking and it now appears likely that his commonly used beverage will receive much attention as a possible source of adverse effects on health. Our estimates of deaths linked to coffee drinking—24 percent of male deaths and 49 percent of female deaths from cancer of the bladder, giving 1,445 and 1,344 = 2,800—are based on findings of the bladder cancer study and do not take into account other possible effects.

k. Accidental deaths linked to other chemicals

The following figures apply to accidental deaths from other chemical substances (U.S. 1967):

Accidents from	Males	Females	Total
Solids and liquids	416	230	646
Gases and vapors	1168	406	1574
Round total			2200

l. Deaths linked to oral contraceptives

We have taken the number of deaths linked to oral contraceptives as 10 percent of the deaths from phlebitis and thrombophlebitis combined. This gives about 150 deaths a year. We have made no attempt to express numerically the risk from not using contraceptives, which may well outweigh the risk assessed; it is also important to realize that there may be other risks, as yet unidentified, from taking them.

m. Deaths linked to recently public-noticed chemicals

Three chemicals recently subject to regulation for possible adverse effects on health are mercury, DDT, and diethylstilbesterol (DES). Each chemical has very important commercial uses, but each is unwanted as a contaminant of human food. Our only concern in this chapter is whether there was likely to be a health effect at the levels consumed.

In the case of methylmercury, swordfish was banned from our food supply because samples from swordfish frequently exceeded the tolerance for mercury in food. This might have constituted a hazard for people who depended on swordfish as their major source of protein, but it could hardly have had any importance to the occasional consumer.

With respect to DDT, no evidence thus far has been found that current levels of body storage have any effect on health. If there were an effect from DDT stored in our bodies, it would probably escape detection because of the universality of exposure. Much higher levels than those in the general population have occurred for years in persons occupationally exposed to DDT, with no overt sign of toxicity.

In regard to diethylstilbestrol, this synthetic estrogenic compound has long been known to produce cancer in animals. It apparently has also produced a small epidemic of vaginal cancer in young women due to the use of the compound twenty to thirty years ago in treating the mothers of these young women during pregnancy. The doses administered to these women were truly massive compared to the traces that might be derived from consumption of meat from farm animals treated with this compound.

4. A general caveat

The figures discussed in this appendix are clearly, from the discussion above, based on a mixture of epidemiological studies and professional judgment. They are not claimed to be either precise or accurate. Almost any single figure could be refined somewhat by careful study, and new knowledge is to be expected to make substantial changes in many if not in most of them.

It is easy to point out areas of significant uncertainty. We know, for example, that those who smoke heavily are more likely to drink heavily and consume much coffee. As a result of this sort of association, we are somewhat uncertain as to how to link many deaths—to smoking, to alcohol, to coffee drinking. Future studies will gather data in forms that will help to resolve such uncertainties.

Our calculations are made with seeming accuracy. But our displays, both in Chapter 5 and Appendix B, are only given to one or two figures. Our conclusions—and, we believe, the feelings and conclusions of our readers—would not be appreciably changed by doubling some figures and halving others. Accordingly, we feel that the figures presented are adequate to set the general perspectives so important to us all.

We hope that, as the years and decades pass, figures of these sorts will become more accurate, and thereby at least somewhat more useful.

A further warning has to be given concerning the figures, to be considered below, of "thousands who might be alive." Lacking other evidence, almost all calculations have had to be made as if the age distribution at death of those whose deaths are linked through a specified cause of death to some threat were the same as the age distribution of all deaths from that cause. (Where this approximation seemed likely to be poorest, i.e., deaths linked to oral contraceptives and adverse drug reactions, we have resorted to judgment estimates as undoubtedly more accurate.)

When the results of epidemiological studies begin to be reported in a form appropriate to such calculations, there will undoubtedly be moderately substantial changes in the numbers of thousands that might be alive. However, as in the case of linked deaths, we feel that the figures

EXHIBIT C-10

DEATHS LINKED WITH AIR POLLUTION, 1967

Cause of death	Estimated proportion linked with pollution	Deaths U.S., 1967	Linked deaths
Asthma	.15	4,137	620
Bronchitis	.15	6,264	940
Other bronchopulmonic			
Cancer of lung	.05	54,407	2,720
Total			8680=8700

presented are (a) somewhere near the best available and (b) good enough for the purposes of general perspective.

5. Comparing the three patterns of mortality

In Appendix B we discussed the differences in the numbers of people who might have been alive (say in 1970):

- given 1901 death rates throughout
- given actual death rates
- given 1967 death rates throughout.

The basic data for this calculation consists of:

- the 1901 and 1967 life tables
- a "cohort" life table (that gives survivorship for cohorts of people born on different round dates)
- the distribution of ages of the population in 1970.

The calculations required are simple, and almost straightforward. Let us look at age 40 (in 1970). The numbers surviving out of 100,000 white female births are:

67,935 (on the 1901 life table)

90,570 (on a cohort table for those born in 1930)

95,654 (on the 1967 life table).

The first of these is 75 percent of the second, so we conclude that 25 percent of white females 40 years old in 1970 would already have died had 1901 death rates continued. The third is 105.6 of the second, so we conclude that 5.6 percent more white females aged 40 (in 1970) would have been alive, had the 1967 death rates applied throughout their lives. The corresponding figures for age 50 (in 1970) are:

61,005 (on the 1901 life table)

84,738 (on a cohort table for those born in 1920)

92,757 (on the 1967 life table)

—28.0 percent

9.5 percent.

Simple interpolation now gives:

	1901 to cohort		cohort to 1967	
age 40	—25.0%		5.6%	
ages 40-45		—25.8%		6.6%
age 45	—26.5%		7.6%	
ages 45-50		—27.2%		8.6%
age 50	—28.0%		9.5%	

In 1970, the census estimated that there were 5,412,000 white females aged between 40 and 45. Had the 1901 death rates applied throughout instead of the cohort rates, 25.8 percent—or 1.40 million—of these would have already been dead. Had the 1967 death rates applied throughout, 6.6 percent—or 0.36 million more would have been alive.

Exhibit C-11 shows the full details of the calculation for white females. That for white males is similar. Since a convenient cohort table for nonwhites was not at hand, but 1901 and 1967 life tables were available for nonwhites of each sex, an approximate calculation was made, dividing each total change into two portions, one from 1901 to cohort and the other from cohort to 1967, in about the same proportions as for whites of the same sex. Exhibit C-12 shows the results both separately by sex and race, and combined, for various terminal ages.

6. Calculation of number who might be alive

The basic quantities used in calculating "the number who might be alive," in addition to the number of linked deaths discussed above, are the distribution of deaths by age, for each cause of death in question, and the expectation of life for that sex and age. Since deaths by cause were available by 5-year age groupings, the calculations were organized in their terms. Exhibit C-13 illustrates the detailed calculations for two cases: all male deaths and male motor-vehicle-accident deaths.

PRE-ADULT DEATHS

For many of the causes of death that concern us, almost all who die are adults. There are exceptions, however, and we need to notice how they ought to affect our calculations.

Bronchitis (chronic and unqualified) is a good extreme example, where female deaths in 1967 were 104 up to age 19 and 1,159 at age 20 and beyond. The corresponding contributions to the total expected years of life were 7,475 from those dying by 19 and 16,980 for those dying later. What figure ought we take for average expected years of life at death (particularly if we think early deaths are not linked to the threat)? Should it be

$$\frac{7475}{104}\ \frac{16980}{1159} = 19.36 \text{ years (females in 1967)}$$

as we could get by considering all ages, or

$$\frac{16980}{1159} = 14.65 \text{ years (females in 1967)}$$

as we would get by considering only those dying at or after age 20—or should it be something different from both of these?

Our concern with acute bronchitis deaths arises mainly in connection with community air pollution. The proper answer to what average expected years of life we should use depends upon just how the studies comparing deaths for polluted and unpolluted areas were done. If, as seems most likely, these studies concentrated on adult deaths only, the fraction of linked deaths drawn from these studies would most properly be applied to adult deaths.

If we believe that deaths from bronchitis (chronic or unqualified) at ages up to 19:

- do not include any appreciable number of deaths that should be linked to air pollution;

EXHIBIT C-11

CALCULATION OF INCREASES OR DECREASES IN THE NUMBER OF WHITE FEMALES ALIVE IN 1970 IF EITHER 1901 OR 1967 LIFE TABLES HAD APPLIED THROUGHOUT (PARENTHETIC VALUES INTERPOLATED)

Age	Survivors of 100,000*			Change in %[2]		Same for 5-year blocks		Pop'n[3] in 1970	Numbers[3] changed	
	1901	cohort	1967	1901	1967					
0	100,000	100,000	100,000	0.0	0.0	-4.0	0.1	7.049	-.28	.01
				(-8.1)	(0.2)	-12.2	0.3	8.264	-1.00	.02
10	81,723	97,578	98,928	-16.2	(0.4	-16.7	0.5	8.647	-1.45	.04
				(-17.2)	(0.6)	-17.7	0.7	8.079	-1.43	.06
20	78,978	96,680	97,508	-18.3	0.9	-19.1	1.4	7.381	-1.40	.10
				(-19.9	(1.9)	-20.7	2.4	5.962	-1.24	.14
30	73,887	94,073	96,850	-21.5	3.0	-22.4	3.6	5.042	-1.13	.18
				(-23.2)	(-4.3)	-24.1	5.0	4.936	-1.19	.25
40	67,935	90,670	95,654	-25.0	5.6	-25.8	6.6	5.412	-1.40	.36
				(-26.6)	(7.6)	-27.2	8.6	5.558	-1.51	.48
50	61,005	84,738	92,751	-28.0	9.5	-28.6	11.8	5.169	-1.48	.61
				(-29.2)	(14.1)	-29.7	16.4	4.696	-1.39	.67
60	50,762	72,804	86,437	-30.4	18.7	-32.2	21.8	4.157	-1.34	.91
				(-33.8)	(24.9)	-35	28.0	3.491	-1.22	.98
70	35,200	55,890	73,286	-37.0	31.1	-40	37.6	2.874	-1.15	1.08
				(-42.5	(44.0)	-45	51	2.114	-.95	1.08
80	15,319	29,670	46,881	-48	58	-52	70	1.318	-.69	.93
		(16,200)		(-56)	82	-60	100	.890	-.62	1.06
90	2,322	6,414	29,303	-64		-70	120			
							Totals through 65		16.24	3.82
							Totals of all		20.87	8.95

[1] According to three life Tables: ("1901" from James W. Glover 1921, United States Life Tables 1890, 1901, 1910 and 1901. ("cohort" from Milbank Memorial Fund Quarterly ("1967" from Vital Statistics of the United States, 1967.

[2] From "cohort"

[3] In millions

• were excluded from the calculation of the linking factor,

the most appropriate total expected years of life at death linked to air pollution (=number who might be alive) is to be found from:

(linking factor) (total expected years after deaths at ≥ 20)

which can be written as

(linking factor) (total deaths at all ages)

as used earlier in this appendix, times

$$\frac{\text{total expected years after deaths at} \geq 20}{\text{(total deaths at all ages)}}$$

this last factor being

$$\frac{16980}{104 + 1159} = 13.44 \text{ years (females in 1967)}$$

in our example.

EXHIBIT C-12

COMPONENTS AND TOTAL INCREASES AND DECREASES IN NUMBERS ALIVE IN 1970 IF EITHER 1901 OR 1967 LIFE TABLES HAD APPLIED THROUGHOUT (IN MILLIONS OF PEOPLE)

All		White		Non-whites	
		Females	Males	Females	Males
If 1901 life tables had applied throughout (losses)					
39.74	Ages to 65	16.24	14.81	4.39	4.30
4.22	65 to 75	2.37	1.26	.35	.24
2.57	75 to 85	1.64	.68	.15	.10
.96	85 on	.62	.24	.06	0.4
47.49	All ages	20.87	16.99	4.95	4.68
If 1967 life tables had applied throughout (gains)					
9.59	Ages to 65	3.82	4.19	.83	.75
3.97	65 to 75	2.06	1.44	.26	.21
3.27	75 to 85	2.01	.96	.18	.12
1.55	85 on	1.06	.34	.10	.05
18.38	All ages	8.95	6.93	1.37	1.13

If we believed that the study had included deaths before 19, but that air pollution had not contributed to such deaths, we ought to use 14.65 years, instead of 13.44 years.

We have generally chosen to use average expected years of life of the form giving 13.44 years in the example, making exceptions for homicides and for all forms of accident, where the risks clearly fall upon all ages. The overall changes due to taking the other choice would be small (we have selected a rather extreme case as an example) and would increase the numbers who might be alive somewhat.

7. Details for specific threats

a. Cigarette smoking

Exhibit C-14 shows the details of the calculation for females and deaths linked to cigarette smoking. Exhibit C-15 summarizes the cigarette smoking picture.

b. Alcohol abuse

Exhibit C-16 summarizes the situation.

c. Dietary composition

No figures presented in view of uncertainty of total impact.

d. Cancer possibly linked to chemicals

Uncertainties even greater than for dietary composition, no figures presented.

e. Adverse reactions to medication

Here we have used a round, judgment-based figure of 5 years of expected life at death. An alternative approach would have been, for example, to assign zero years of expected life to one-third of the deaths, one year to another third, and normal expectation of life for age and sex to the remaining third. Doing this for the 23 deaths not from fluid overload in the latest published study, would have led to a line in exhibit B-1 reading

460 430 300 170 adverse reactions to medication 170 130 120 20

instead of the line given, namely

375 ? ? ? adverse reactions to medications ? ? ? ?

f. Illicit drug abuse

Exhibit C-17 summarizes the situation.

g. Community air pollution

Exhibit C-18 summarizes the situation.

h. Airborne particles (occupational)

Since the age distribution of deaths from pneumoconioses was not available, we have borrowed the age distribution of deaths for emphysema in males, as a rough approximation. For 10,000 males, this gives 32, 75, 123, and 147 thousand who might be alive up to ages 65, 75, and 85, and for all ages.

i. Suicides involving chemicals

Here the numbers of deaths, after transferring 40 percent of those with analgesic and soporific drugs to illicit drug abuse, were 2,590 males and 2,027 females. Applying the age distribution for all suicides involving chemicals (as had to be done with

EXHIBIT C-13

CALCULATION OF AVERAGE EXPECTED YEARS OF LIFE AT DEATH FOR: (A) ALL MALE DEATHS (B) ALL MALE MOTOR-VEHICLE-ACCIDENT DEATHS

ALL MALE DEATHS (1967)

		Total expected years of life at death			
Age Range	No. of Deaths	Years to 65	Years to 75	Years to 85	Years Ever
0	45442	2671989	2917376	3030981	3062790
1	2767	162146	177365	184282	186942
2	1917	110611	120963	125947	127097
3	1601	90937	99582	103585	104705
4	1366	76223	83599	87014	87970
5-9	5191	274604	302116	315613	319247
10-14	5170	248160	276078	289520	292622
15-19	13047	563630	634084	668006	677139
20-24	14138	545727	622072	658831	670141
25-29	11217	381378	441950	472236	480088
30-34	11701	341669	407195	438788	446978
35-39	17472	429811	527654	576576	587059
40-44	28273	565460	729443	808608	825572
45-49	42771	667228	919577	1043612	1073552
50-54	62592	701030	1089100	1276876	1326950
55-59	85994	584759	1169518	1444699	1513494
60-64	106492	255581	1054270	1448291	1544134
65-69	122632	0	760318	1299899	1434794
70-74	138250	0	331800	1092175	1299550
75-79	132744	0	0	690269	982306
80-84	103919	0	0	218230	581946
85-89	60651	0	0	0	248669
90-94	24084	0	0	0	77069
95-99	5400	0	0	0	7560
Totals	(1044831)	(8670943)	(12664062)	(16274038)	(17957376)
Years		8.30	12.12	15.58	17.19

Note: 8.30 = 8670943/1044831,. . ., 17.19 = 17957376/1044831.

MOTOR-VEHICLE-ACCIDENT DEATHS

Total expected years of life at death childhood included					
Age Range	No. of Deaths	Years to 65	Years to 75	Years to 85	Years Ever
0	159	9349	10208	10605	10717
1	201	11779	12884	13387	13507
2	275	15868	17353	18068	18233
3	293	16642	18225	18957	19162
4	258	14396	15790	16435	16615
5-9	1306	69087	76009	79405	80319
10-14	1177	56496	62852	65912	66618
15-19	5942	256694	288781	304230	308390
20-24	6227	240362	273968	290178	295160
25-29	3322	112948	130887	139856	142182
30-34	2367	69116	82372	88763	90419
35-39	2117	52078	63933	69861	71131
40-44	2140	42800	55212	61204	62488
45-49	2111	32932	45387	51508	52986
50-54	2033	22770	35374	41473	43100
55-59	1798	12226	24453	30206	31645
60-64	1669	4006	16523	22698	24201
65-69	1429	0	8860	15147	16719
70-74	1273	0	3055	10057	11966
75-79	1038	0	0	5398	7681
80-84	666	0	0	1399	3730
85-89	244	0	0	0	1000
90-94	60	0	0	0	192
95-99	8	0	0	0	11
Total	38113	1039550	1242144	1354746	1388171
Years Factor		27.28 3.287	32.59 2.689	35.55 2.282	36.42 2.119

Note: 27.28=1039550/38113, 3.287=27.28/8.30, 2.119=36.42/17.19

EXPECTED YEARS OF LIFE

	Males				Females			
Age Range	to 65	to 75	to 85	Ever	to 65	to 75	to 85	Ever
0	58.8	64.2	66.7	67.4	61.2	68.4	73.0	74.4
1	58.6	64.1	66.6	67.2	60.8	68.0	72.6	74.2
2	57.7	63.1	65.7	66.3	60.0	67.2	7.18	73.2
3	56.8	62.2	64.7	65.4	59.0	66.2	70.8	72.3
4	55.8	61.2	63.7	64.4	58.0	65.2	69.8	71.4
5-9	52.9	58.2	60.8	61.5	54.6	62.4	67.0	68.4
10-14	48.0	53.4	56.0	50.5	50.1	57.4	62.0	63.6
15-19	43.2	48.6	51.2	51.9	45.2	52.5	57.2	58.7
20-24	38.6	44.0	46.6	47.4	40.4	47.7	52.4	53.9
25-29	34.0	39.4	42.1	42.8	35.6	42.9	47.6	49.1
30-34	29.2	34.8	37.5	38.2	30.8	38.1	42.8	44.3
35-39	24.6	30.2	33.0	33.6	25.9	33.3	38.1	39.6
40-44	20.0	25.8	28.6	29.2	21.2	28.7	33.5	35.0
45-49	15.6	21.5	24.4	25.1	16.6	24.2	29.0	30.6
50-54	11.2	17.4	20.4	21.2	11.8	19.7	24.7	26.3
55-59	6.8	13.6	16.8	17.6	7.2	15.4	20.6	22.2
60-64	2.4	9.9	13.6	14.5	2.5	11.0	16.6	18.3
65-69	nil	6.2	10.6	11.7	nil	6.8	12.8	14.7
70-74	nil	2.4	7.9	9.4	nil	2.4	9.3	11.5
75-79	nil	nil	5.2	7.4	nil	nil	5.8	8.6
80-84	nil	nil	2.1	5.6	nil	nil	2.2	6.2
85-89	nil	nil	nil	4.1	nil	nil	nil	4.4
90-94	nil	nil	nil	3.2	nil	nil	nil	2.4
95-99	nil	nil	nil	1.4	nil	nil	nil	1.5
Totals Years								

those transferred, as well) yields the following thousands who might be alive:

Deaths in 1967	Up to 65	Up to 75	Up to 85	All ages
2590 males	42	56	64	66
2027 females	34	48	58	61
Total	76	104	122	127

j. Coffee drinking

Using the linked deaths stated in (j) of Section 3 yields the following figures for the thousands who might be alive:

Deaths in 1967	Up to 65	Up to 75	Up to 85	All ages
1445 males	2.5	7.2	12.8	15.4
1344 females	2.6	6.7	16.6	16.3
Total	5.1	13.1	25.4	31.7

k. Accidents with chemicals

Here the thousands who might be alive run as follows for accidents with gases and vapors:

Deaths in 1967	Up to 65	Up to 75	Up to 85	All ages
1168 males	25	32	35	36
406 females	10	13	14	15
Total	35	45	49	51

EXHIBIT C-14

CALCULATION OF NUMBER WHO MIGHT BE ALIVE
(FEMALES, CIGARETTE SMOKING)
(1967)

Cause	Linked deaths	Average expected years				Thousands who might be alive			
		to 65	to 75	to 85	all	to 65	to 75	to 85	all
Cancer of lung	6497	5.94	11.51	16.64	18.70	39	75	108	121
larynx	171	6.12	12.34	17.57	19.51	1	2	3	3
oral cavity	750	5.11	10.09	14.94	17.14	4	8	11	13
esophagus	505	4.23	8.97	13.86	16.15	2	5	7	8
bladder	521	1.79	4.80	9.22	11.12	1	2	5	6
kidney	242	3.45	7.59	12.39	14.51	1	2	3	4
stomach	665	2.78	6.28	10.96	13.53	2	4	7	9
other	4234	5.22	10.04	15.02	17.12	22	43	64	73
(TOTAL cancer)						(72)	(146)	(208)	(237)
Vascular lesion	6547	1.63	3.76	7.86	10.42	11	25	49	68
Arteriosclerosis ...	34,200	1.27	3.66	7.68	10.55	43	125	262	360
Other heart	5711	1.64	3.70	7.16	10.12	9	21	41	58
Hypertensive heart .	3999	1.92	4.62	8.71	11.52	8	18	35	46
General arteriosc...	2307	.20	.95	3.37	6.73	0	2	8	16
Other circulatory...	3414	4.58	8.25	12.70	15.22	15	27	43	52
(TOTAL circulatory)						(86)	(218)	(439)	(600)
Bronchitis and emphysema	2214	3.22	7.58	11.98	14.41	7	17	27	32
Ulcers	940	3.49	6.95	11.26	13.80	3	7	11	13
Cirrhosis of liver ...	2280	10.47	17.20	22.30	24.07	24	39	51	15
Influenza and pneumonia	2420	2.23	4.08	5.99	9.51	5	9	12	26
(TOTAL other)						(39)	(72)	(101)	(120)
(GRAND TOTAL)						(197)	(431)	(748)	(957)
Total by interval						197	234	317	203

For accidents with solids and liquids other than those classified under illicit drug abuse, the thousands that might be alive run as follows:

Deaths in 1967	Up to 65	Up to 75	Up to 85	All ages
410 males	11	14	15	16
230 females	6	7	8	9
Total	17	21	23	25

l. Oral contraceptives

In the absence of information on age distribution for these deaths, it seemed reasonable to assume a spread in ages similar to that over which oral contraceptives are likely to be used. (Greater use at lower ages may well balance greater incidence at higher ages, for example.) The average expected years of life for ages 20 to 34 or for ages 15 to 39 are found (see Exhibit C-13) to be the same as those for 25 to 34. We thus used 35.6, 42.9, 47.6 and 49.1 years, which for 150 deaths per year gives 5.3, 6.4, 7.1 and 7.4 thousands that may be alive.

EXHIBIT C-15

SUMMARY FOR DEATHS LINKED TO CIGARETTE SMOKING, 1967

Thousands who might be alive to 65	to 75	to 85	all	Linking Cause	Thousands who might be alive to 65	66-75	76-85	86-up
				---- (Males) ----				
161	352	505	555	lung cancer	161	191	153	50
83	172	256	284	other cancer	83	89	84	28
284	520	955	1120	arterioscler.	284	336	335	165
83	170	307	369	other circula.....	83	93	131	62
119	246	358	406	other	119	127	112	47
730	1566	2378	2735	TOTAL	730	836	812	357
				---- (Females) ----				
39	75	108	121	lung cancer	39	36	33	13
33	71	100	116	other cancer	33	38	29	16
43	125	262	360	arterioscler.	43	83	137	98
43	93	171	240	other circula.....	43	50	84	63
39	72	101	120	other	39	33	28	19
197	431	768	957	TOTAL	197	234	317	209
				---- (Both sexes) ----				
200	427	613	676	lung cancer	200	227	184	63
116	243	351	400	other cancer	116	122	114	43
227	745	1217	1480	arterioscler	227	518	472	263
126	269	484	609	other circula.....	126	143	215	125
158	318	459	525	other	158	160	141	66
927	1997	3126	3694	TOTAL	927	1070	1129	568

EXHIBIT C-16

SUMMARY FOR DEATHS LINKED TO ALCOHOL ABUSE, 1967

Thousands who might be alive to 65	to 75	to 85	all	Linking Cause	Thousands who might be alive to 65	66-75	76-85	86-up
				---- (Males) ----				
101	159	191	200	3 diseases	101	58	32	9
520	624	675	694	motor veh. acc.....	520	104	51	19
175	214	238	245	other accidents	175	39	24	7
15	27	37	41	suicide	15	12	10	4
42	52	57	59	homicide	42	10	5	1
4	8	12	12	2 cancers	4	4	4	0
857	1084	1209	1250	TOTAL	801	223	125	41
				---- (Females) ----				
49	76	95	102	3 diseases	49	27	19	7
200	245	282	246	motor veh. acc.....	200	45	37	14
63	78	94	105	other accidents	63	15	16	11
21	30	36	38	suicide	21	9	6	2
14	4	21	22	homicide	14	4	3	1
2	6	6	6	2 cancers	2	2	2	0
349	451	534	569	TOTAL	349	102	83	35
				---- (Both sexes) ----				
536	657	714	750	Involuntary	536	115	63	36
674	884	1029	1069	Voluntary	674	215	145	40
1210	1535	1743	1819	TOTAL	1210	325	208	76

EXHIBIT C-17

SUMMARY FOR DEATHS LINKED TO ILLICIT DRUG ABUSE

Thousands who might be alive to 65	to 75	to 85	all	Linking Cause	Thousands who might be alive to 65	66-75	76-85	86-up
				---- (Males) ----				
6	7	7	8	drug addiction[1]	6	1	0.4	0.2
23	28	30	31	acc. poisoning	23	5	2	1
21	28	31	32	suicides	21	7	3	1
27	33	36	36	homicides	27	6	3	0
20	25	27	28	motor veh. acc.	21	4	2	1
9	11	12	12	other accidents	9	2	1	1
107	132	143	147	TOTAL	101	25	11.4	4.2
				---- (Females) ----				
2	2	2	3	drug addiction[1]	2	0.3	0.2	0.1
15	20	23	24	acc. poisoning	15	5	3	1
20	27	33	35	suicides	20	7	6	2
9	11	13	14	homicides	9	2	2	1
8	10	11	12	motor veh. acc.	8	2	1	1
3	4	5	5	other accidents	3	1	1	0
57	74	87	93	TOTAL	57	17.3	13.2	5.1
				---- (Both sexes) ----				
56	69	77	78	Involuntary	56	13	8	1
108	139	153	162	Voluntary	108	29	16	7
164	206	230	240	TOTAL	164	42	24	8
267	334	372	390	TOTAL[2]	267	67	38	18

[1] Using 40, 46, 48 and 50 years of expected life at death.

[2] Scaled up from 6141 linked deaths to 10,000 linked deaths.

EXHIBIT C-18

SUMMARY FOR DEATHS LINKED TO AIR POLLUTION

Thousands who might be alive				Linking Cause	Thousands who might be alive			
to 65	to 75	to 85	all		to 65	66-75	76-85	86-up
				---- (Males) ----				
1.7	3.1	4.3	4.8	asthma	1.7	1.4	1.2	.5
1.6	3.8	6.2	7.3	bronchitis.....	1.6	2.2	2.4	1.1
7.1	20.0	33.7	39.5	other bro.-pul	7.1	12.9	13.7	5.8
9.4	20.5	29.4	32.4	cancer of lung	9.4	11.1	8.9	3.0
20	47	73	84	TOTAL	20	27	27	10
				---- (Females) ----				
2.4	3.9	5.3	5.8	asthma	2.4	1.5	1.4	.5
.8	1.6	2.5	3.0	bronchitis.....	.8	.8	.9	.5
2.8	6.2	9.7	11.6	other bro.-pul.	2.8	3.4	3.5	1.9
2.7	5.3	7.5	8.4	cancer of lung.....	2.7	2.6	2.2	.9
9	17	25	29	TOTAL	9	8	8	4
				---- (Both sexes) ----				
12.1	25.8	36.9	40.8	cancer of lung.....	12.1	13.7	11.1	3.9
6.7	18.7	31.6	37.1	emphysema	6.7	12.0	12.9	5.5
9.7	19.9	30.1	34.9	other lung.....	9.7	10.2	10.2	4.8
29	64	99	113	TOTAL	29	35	35	14

APPENDIX D

ECONOMIC DATA

GENERAL CHARACTER AND HEALTH OF THE REGULATED INDUSTRIES

1. Pharmaceutical industry

The Food and Drug Administration counts some 6,330 pharmaceutical manufacturers as subject to its regulatory activities.[1] Of these, in 1969, there were 1,129 firms primarily engaged in drug manufacturing.[2] Manufacturers of biological products and medicinal and botanical products together account for ten percent of drug industry shipments.

The major portion of primary manufacturers of pharmaceutical products, the pharmaceutical preparations industry, included 875 firms according to the 1967 Department of Commerce 5-year Census of Manufacturers.[2] Exhibit D-1 represents trends for the various segments of the pharmaceutical manufacturing industry. Note that there has been a decline in the total number of these manufacturers although the number of large manufacturers has remained almost constant since 1954.

Exhibit D-2 shows the value of manufacturers' shipments of drug products from 1939. Also included are projections for 1975 and 1980. In the 30-year period from 1939 to 1969, drug industry shipments increased over 1,600 percent. The pharmaceutical preparations industry consistently accounts for 90 percent of the value of manufacturers' shipments of drugs each year. Of the total value of manufacturers' shipments of pharmaceutical preparations in 1969 of $5 billion, $3.5 billion were prescription drugs. Pharmaceutical preparations ranked 15th among

EXHIBIT D-1
PRIMARY MANUFACTURING ESTABLISHMENTS

Year	Total	With 20 Employees or More
2831 Biological Product Industry		
1967 ..	128	44
1963 ..	113	40
1958 ..	116	35
1954 ..	93	43
1947 ..	84	NA
1939 ..	80	NA
2833 Medicinals and Botanical Products Industry		
1967 ..	126	45
1963 ..	138	42
1958 ..	129	50
1954 ..	115	40
2834 Pharmaceutical Preparations Industry		
1967 ..	875	316
1963 ..	1,011	319
1958 ..	1,114	318
1947 ..	1,163	NA

Source: U.S. Department of Commerce, Census of Manufacturers.

Note: Data are only for those firms primarily engaged in drug manufacturing.

Data on firms where drugs are not the primary source of revenue, as well as repackers, distributors are not included.

EXHIBIT D-2
MANUFACTURERS SHIPMENTS OF COMPONENT PARTS OF DRUG INDUSTRY
($'s Millions)

Year	(S.I.C. 283) Drug Industry	(S.I.C. 2834) Pharmaceutical Preparations Industry	(S.I.C. 2833) Medicinals and Botanicals Industry	(S.I.C. 2831) Biologicals Productions Industry
1939	$ 386	$ 338	$ 29	$ 19
1947	1,197	941	218	38
1954	2,048	1,700	281	67
1958	2,977	2,592	322	64
1959	3,129	2,692	369	68
1960	3,214	2,772	351	91
1961	3,312	2,927	284	101
1962	3,541	3,142	296	103
1963	3,716	3,314	306	96
1964	3,922	3,571	253	98
1965	4,403	4,050	256	97
1966	4,825	4,432	285	108
1967	5,301	4,696	445	160
1968	5,759	5,114	N.A.	N.A.
1969	6,335	N.A.	N.A.	N.A.
1970	7,000[1]	N.A.	N.A.	N.A.
1975	10,700[1]	--	--	--
1980	19,350[2]	--	--	--

Source: U.S. Department of Commerce, Census of Manufacturers

[1] Estimate by U.S. Department of Commerce, B.D.S.A. Outlook 1970

[2] Estimate based on 9 percent average annual growth rate.

Note: This data includes the value of both primary and small amounts of secondary products for each industry.

industries according to value of shipments and 41st according to number of employees in 1969.[3]

Exhibit D-3 reflects data from the Pharmaceutical Manufacturers Association for world-wide sales of all forms of pharmaceutical products by U.S. companies between 1951 and 1971. In recent years, foreign sales by U.S. manufacturers have increased more rapidly than have domestic sales. Foreign sales of all types of pharmaceutical preparations by U.S. firms increased at an annual rate of 12 percent between 1940 and 1960—twice the rate of growth of the domestic market.[4] In 1970, foreign sales amounted to $2.2 billion, or 16 percent over the corresponding figure for 1969, and one prediction suggested an additional increase for 1971.[5]

A great deal of controversy has arisen over past efforts to describe the various categories of expenditures by the drug industry aimed at marketed drugs. The HEW Task Force on Prescription Drugs offered the following accounting of the drug industry's sales dollars in 1968:[4]

Category	*Percentage of Sales Dollar*
Marketing, administration, and general expenses	35
Cost of goods	35
R&D	6.5
Taxes	10
Profit	13.5

EXHIBIT D-3

U.S. HEADQUARTERED FIRMS' SALES AND R&D EXPENDITURES, 1950-1971[1]

($'s millions)

Year	U.S. Sales[2]	Global Sales Human & Veterinary[3]	
	Human Dosage	Dosage Only	Dosage & Bulk
1971	$4,750[5]	$ n.a.	$7,592[4]
1970	4,322	6,442	6,853
1969	4,008	5,832	6,208
1968	3,655	5,280	5,666
1967	3,226	4,707	5,102
1966	3,011	4,256	4,660
1965	2,779	3,841	4,219
1964	2,479	3,405	3,717
1963	2,317	3,152	3,469
1962	2,199	2,932	3,236
1961	1,954	2,685	2,992
1960	1,905	2,600	n.a.
1959	1,850	2,500	n.a.
1958	1,802	2,400	n.a.
1957	1,742	2,200	n.a.
1956	1,676	1,900	n.a.
1955	1,457	1,650	n.a.
1954	1,252	1,500	n.a.
1953	1,213	1,450	n.a.
1952	1,175	1,400	n.a.
1951	1,148	1,350	n.a.

[1] Based on annual PMA surveys, Department of Commerce reports and other PMA sources.

[2] U.S. sales of finished prescription and "o-t-c ethical" pharmaceuticals for human use.

[3] Global sales are defined to include total ethical pharmaceutical sales within the United States, exports to non-affiliated firms, and sales abroad of U.S. affiliates.

[4] Global R&D includes all ethical pharmaceutical research and development financed or conducted by U.S. pharmaceutical companies in the United States and abroad.

EXHIBIT D-4

COMPANY FUNDS FOR R&D PERFORMANCE BY INDUSTRY 1957-1970 ($'s MILLION):

Industry	Year													
	1957	1958	1959	1960	1961	1962	1963	1964	1965	1966	1967	1968	1969	1970
Chemicals and Allied Products..	616	666	743	807	881	939	1004	1098	1195	1271	1357	1458	1560	1624
Industrial Chemicals	423	443	488	544	578	599	662	736	784	796	822	853	895	915
Drugs and Medicine	104	126	151	158	177	191	207	224	255	275	a	a	a	a
Other Chemicals	89	97	104	105	126	149	135	a	a	a	a	a	a	a

a: Not separately available from the NSF but included in the total.

Source: National Science Foundation.

Data published by the National Science Foundation and the Pharmaceutical Manufacturers Association reveal that the chemical industry as a whole is highly research intensive. Exhibit D-4, from the National Science Foundation, shows the amount of private investment in R&D for various categories of chemical industries. Exhibit D-5, using data from the Pharmaceutical Manufacturers Association, lists the company funded research and development for drugs through 1971. The chemical industries as a whole are equaled in their research investment by manufacturers of communication equipment and electronic components and exceeded only manufacturers of aircraft and missiles. This latter industry has received a large proportion of Federal funds in behalf of research and development. If only company-funded research and development is considered, no other industry surpasses the R&D investment fraction of pharmaceutical preparations. Exhibit D-6 illustrates the contribution of company to government funds (spent in industry) for R&D in the pharmaceutical industry.

As a percent of sales, the investment in R&D in the pharmaceutical industry has increased with time. Exhibit D-7, data from the NSF, shows this trend for several parts of the chemical industry.

Exhibit D-8 illustrates the number of new drugs marketed in the U.S. each year from 1950 to 1971. The total number, which includes new single chemical entities as well as duplicate products, compounded products, and new dosage forms, declined each year beginning in the 1950's. The number of new single chemical entities has fluctuated year by year, reached a peak in 1959 and has generally fallen since then. However, the number of significant new chemical entities developed year by year has remained fairly constant.

Joseph Jadlow has compared the R&D investment in the drug industry each year to the number of drug entities developed using expenditure data from both the NSF and the Pharmaceutical Manufacturers Association.[6] In both cases, the figures representing R&D expenditures have been adjusted to 1962 constant dollars. Exhibit D-9 lists these data in tabular form. These measures are somewhat crude and, in reality, the expenditure for research lags behind the emergence of a new marketed drug. The trend is clear. The doubling time for R&D expenditures per new drug seems to have been about 2 1/2 years (Exhibit D-10).

What have been the directions and character of this industrial research

EXHIBIT D-5

COMPANY-FUNDED RESEARCH AND DEVELOPMENT FOR VETERINARY- AND HUMAN-USE DRUGS - 1956-1971

($'s million)

Year	1956	1957	1958	1959	1960	1961	1962	1963
	110		170		212	238	251	282
Year	**1964**	**1965**	**1966**	**1967**	**1968**	**1969**	**1970**	**1971**
	298	351	402	448	486	540	611	674

Source: Pharmaceutical Manufacturers Association

EXHIBIT D-6

RESEARCH AND DEVELOPMENT EXPENDITURES BY THE PHARMACEUTICAL INDUSTRY – 1956-1971

($'s million)

Company funded R&D	Year													
	1956	1958	1960	1961	1962	1963	1964	1965	1966	1967	1968	1969	1970	1971
For human-use drugs	110	170	207	227	238	267	278	329	374	412	450	506	566	625
For veterinary drugs	--	--	5	11	14	15	20	23	28	35	36	34	45	49
Total company funded R&D	110	170	212	238	251	282	298	351	402	448	486	540	611	674
Government R&D expenditures in drug industry	--	--	4	7	8	9	12	14	14	13	10	10	8	7
Total R&D expenditures	110	170	216	245	259	292	310	365	416	461	496	550	619	681

Source: Pharmaceutical Manufacturers Association.

EXHIBIT D-7
COMPANY FUNDS FOR R&D PERFORMANCE AS PERCENT OF NET SALES BY INDUSTRY 1957-1970

Industry	Year													
	1957	1958	1959	1960	1961	1962	1963	1964	1965	1966	1967	1968	1969	1970
Chemicals and Allied Products. .	3.1	3.2	3.2	3.7	3.5	3.4	3.6	3.8	3.6	3.7	3.8	3.5	3.5	3.7
Industrial Chemicals	4.2	4.3	3.9	4.7	4.2	4.0	4.1	4.2	3.9	3.7	3.7	3.4	3.4	3.6
Drugs and Medicine	3.6	4.0	4.2	4.5	4.2	4.2	4.5	5.6	5.4	a	a	a	a	
Other Chemicals	1.2	1.3	1.5	1.6	1.6	1.8	1.8	1.9	2.0	a	a	a	a	

Source: National Science Foundation

a: Not separately available from the NSF but included in the total.

EXHIBIT D-8
NUMBER OF NEW DRUGS MARKETED IN UNITED STATES FROM 1950–1971.

	'50	'51	'52	'53	'54	'55	'56	'57	'58	'59	'60	'61	'62	'63	'64	'65	'66	'67	'68	'69	'70	'71	TOTAL
Total New Products	326	321	314	353	380	403	401	400	370	315	311	265	255	213	162	119	82	83	101	71	110	83	5,438
New Single Products	28	35	35	48	38	31	42	51	44	63	45	41	28	18	17	23	13	25	14	11	16	14	680
Duplicate Single Products	100	74	77	79	87	90	79	88	73	49	64	33	47	43	34	23	16	26	36	26	52	40	1,236
Combination Products	198	212	202	226	255	282	280	261	253	203	202	191	180	152	111	73	53	32	51	34	42	29	3,522
New Dosage Forms[1]	118	120	170	97	108	96	66	96	109	104	98	106	84	52	41	22	26	14	21	12	23	30	1,613

Source: Basic Data, Paul deHaen, Inc., New York, New York.

[1] Not included in Total New Products.

EXHIBIT D-9

ANNUAL R&D EXPENDITURES[1] IN THE DRUG INDUSTRY AND ANNUAL TOTALS OF NEW DRUGS INTRODUCED, 1956-1968

Year	(NSF Data) Drug Firms' Outlays for R&D (millions of dollars)	(PMA Data) Drug Firms' Outlays for R&D (millions of dollars)	New Single Chemical Entities Marketed	R&D Outlays Per New Single Entity[2] (millions of dollars)		Total Number of All New Products Marketed[3]	R&D Outlays Per New Ethical Drug[2] (millions of dollars)	
				(NSF Data)	(PMA Data)		(NSF Data)	(PMA Data)
1956....	$ 98.3	$109.8[4]	42	$ 2.3	$ 2.6	401	$0.2	$0.3
1957....	105.7	129.1[4]	51	2.1	2.5	400	0.3	0.3
1958....	126.3	170.3[4]	44	2.9	3.9	370	0.3	0.5
1959....	150.0	197.0[4]	63	2.4	3.1	315	0.5	0.6
1960....	165.8	205.8	45	3.7	4.6	306	0.5	0.7
1961....	178.5	227.7	39	4.6	5.8	260	0.7	0.9
1962....	194.0	238.0	27	7.2	8.8	250	0.8	1.0
1963....	209.7	267.8	16	13.1	16.7	199	1.1	1.3
1964....	224.2	278.3	17	13.2	16.4	157	1.4	1.8
1965....	255.2[5]	322.9	23	11.1	14.0	112	2.3	2.9
1966....	275.4[5]	355.2	12	23.0	29.6	80	3.4	4.4
1967....	n.a.	390.5	25	n.a.	15.6	82	n.a.	4.8
1968....	n.a.	436.6	11	n.a.	39.7	87	n.a.	5.0

n.a. Not available.

[1] R&D expenditures have been adjusted into 1962 constant dollars.

[2] Calculated from data from the sources listed below.

[3] This total includes new single entities, new duplicate single products, and new combinations.

[4] R&D outlays for veterinary drug products before 1960 are included in these totals.

[5] An approximation calculated from NSF data by multiplying the number of "full-time-equivalent" R&D scientists in the drug industry times the cost per R&D scientist in this industry. This exaggerates private R&D spending slightly because federal funds are included. R&D outlays for this industry have not been separately available from the NSF since 1964.

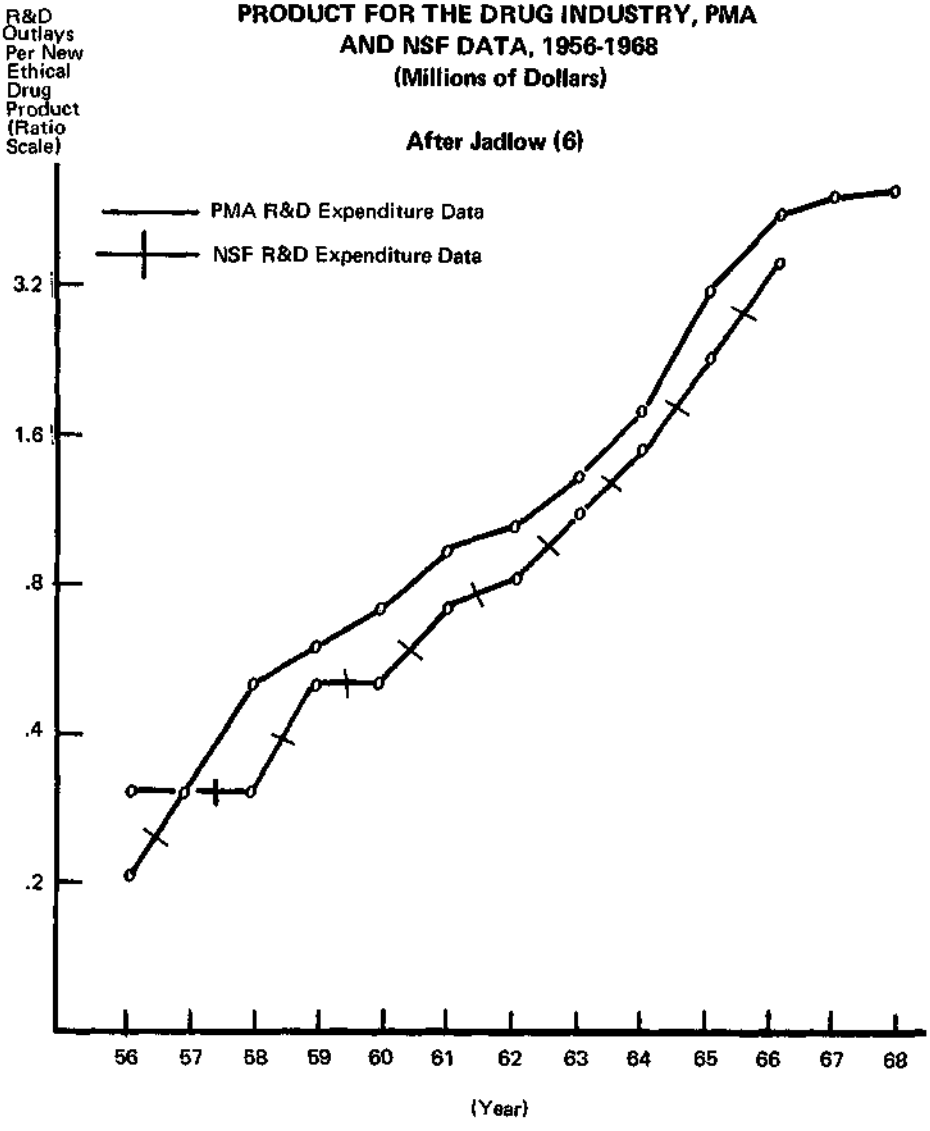
Sources: NSF; PMA; Paul deHaen, Inc.; and Economic Report of the President (1970), p. 229, After Jadlow[6].

effort? Among the members of the pharmaceutical industry, expenditures for basic research between 1960 and 1970 have ranged from 13 to 18 percent and averaged approximately 16 percent of total R&D expenditures.[7] Mansfield et al; who have examined the course of innovation in various industries, observed that increasingly in the drug industry intra-industry sources have risen in importance as sources of discovery and innovation.[8] His periods of comparison were 1935-1949 and 1950-1962. There is no comparable information for the period 1962-1972.

EXHIBIT D-10

AVERAGE R&D EXPENDITURES* PER NEW ETHICAL DRUG PRODUCT FOR THE DRUG INDUSTRY, PMA AND NSF DATA, 1956-1968
(Millions of Dollars)

After Jadlow (6)



*R&D expenditures have been adjusted into 1962 constant dollars.

Sources: See TABLE 5. NSF, Research and Development in Industry (years 1961-1968); PMA, Prescription Drug Industry FACT BOOK; PMA, Pharmaceutical Industry Research and Development Activity (years 1961-1968); deHaen, New Products Parade (years 1961-1969); and Economic Report of the President (1970), p. 229.

However, with continuously increasing R&D expenditures and with a relatively steady proportional private investment in basic research, it might be safely assumed that the rate of industrial discovery and innovation had been maintained. Drug research has undergone a very rapid evolution. Others have commented on the fact that 95 percent of all drug research has been carried out since 1930.[9] During the period since 1930, knowledge of biochemistry and pharmacology in the human organism have advanced enormously. However, very few major drug discoveries can be attributed to this knowledge.

Rather, the source of new drugs has overwhelmingly been as a result of empirical screening and random testing of synthesized compounds.[9] The evolution of improved techniques in the study of drug metabolism, of greater sophistication in the study of biological systems, and in clinical pharmacology have all been strong contributors.

It has been in the past clearly to the advantage of the drug industry to direct its innovative attention toward the development of molecular modification, duplicate single products and combination drugs. Their development, on the average, was much less expensive and required a shorter period of maturation than for newly synthesized products.[10]

With the advent of recent critical reviews of the proliferation of new drug products as from the National Academy of Sciences, this trend has been dampened markedly in recent years.

Perhaps not unexpectedly, drug industry research and development have been directed toward market opportunities. This fact has determined in no small part the areas of specific concentration of product-directed R&D. Thus, a review of the classes of 823 new single entities developed during the 26 years between 1942 and 1968 revealed a sizable concentration among anti-infective agents, cardiovascular drugs and anti-inflammatory drugs.[4] A

corresponding accounting for 1971 demonstrated somewhat similar areas of concentration.[11] Drugs for therapeutic intervention in the case of diseases of fatal or disabling prognosis but exhibiting low or rare incidence have been developed by drug firms under the category of "prestige drugs" as a sideline to their major line of endeavor. There is some suggestion that drug firms, faced with tighter reins on research expenditures, may find it increasingly less attractive to consider low-incidence diseases as appropriate areas for new drug development in the future.[12] Similarly, with increasing sophistication demanded of the drug research and development process and a consequent lengthening of that process has come a questioning within the industry over the attractiveness of development of drugs for chronic administration.[13]

There have been a few attempts at estimating the cost of development of a new drug to the point of marketing. Clymer in 1971, estimated that the development cost of a successful drug varied between $2.7 and $4.7 million and required 4.5 to 8.5 years.[14] The largest portion of these expenditures were made during the latter phases of clinical evaluation. Clymer's estimate of the combination of costs for successful and unsuccessful developments per success in 1971 was $10.5 million ($3.5 million for one success plus $7.0 million for eight unsuccessful projects). Steinberg in the same year estimated that the cost of development was from $2.3 to $6.7 million.[15]

Jerome Schnee analyzed 134 drug development projects conducted by one firm between 1950 and 1967.[10] 75 of the 134 were brought to the point of marketing. (All but 9 of the 75 were completed before 1960.) There was considerable variation in success among the three categories of drugs. 37 percent of new chemical entity developments were successful. Of new compounded products 60 percent were successful and 73 percent of alternate dosage forms were successful. The average development cost of a new chemical entity was $534 thousand and required an average of 2 years' development time. For compounded products, an average of $161 thousand and 16 months was required. For alternate dosage forms, the corresponding figures were $83 thousand and 15 months. By combining the costs of development of the 75 successful products with those of the unsuccessful ones, the following costs were incurred:

	Successful product (millions)
New chemical entities	$1.5
Compounded products	0.25
Alternate dosage forms	0.11

2. Agricultural Chemicals

The agricultural chemicals industry, according to Commerce Department figures, was among the 100 fastest growing industries in the period 1958 to 1969.[3] It ranked 46th in 1969 according to value of shipments and 84th according to number of employees.

According to the Department of Agriculture, in 1964 there were 106 firms operating 169 plants in the United States which produced nearly all of the basic pesticide chemicals.[16] In addition to producers of primary materials there were 1,542 plants engaged in formulation of pesticide mixtures and in distribution of products. The value of shipments of basic pesticide chemicals was estimated at $849 million in 1968,[16 17] $851 million in 1969, $870 million in 1970, and $979 million in 1971. Production and sales are given in Exhibit D-11.

In 1971, the National Agricultural Chemicals Association undertook a sample survey of 33 U. S. producers of pesticides which were said to represent a total aggregate share of 81 percent of the total pesticide sales in 1969.[18] This report reflected a percentage increase in sales among the sampled companies of 13 percent between 1967 and 1970 while research and development expenditures over the same period rose 33 percent.[18]

EXHIBIT D-11
U. S. PRODUCTION AND SALES OF PESTICIDE CHEMICALS, 1962-1971

	1962	1963	1964	1965	1966	1967	1968	1969	1970	1971
Production (millions of lbs)	730	763	783	877	1013	1050	1192	1104	1034	1136
Sales (millions of lbs)	634	651	692	764	822	897	960	929	881	946
Volume of sales ($'s million)	346	369	427	447	584	787	849	851	870	979

(Data from U. S. Tariff Commission)

(The investment of man-years in research and development was estimated to have risen by 17 percent during the same period.) The Department of Agriculture had offered a previous and not dissimilar estimate of the rate of change of R&D investment in the pesticide industry of 4.5 percent per year.[16]

In 1962, the Department of Agriculture estimated that it required an investment of $1 million to $1.5 million to achieve a successful and marketed pesticide product.[19] In 1969, "Chemical Week" estimated that it required $1.1 million on the average to develop each compound starting from the point of synthesis and initial screening.[20] If one takes into account the costs of the unsuccessful candidates as well, the average cost of development was $3.6 million. Adding to this figure the cost of "commercialization" raised the total cost of development to $5.6 million. The experience of one firm over a ten-year period between 1960 and 1970 was that, combining the costs attributed to both successes and non-successes, the average cost per success was $11 million.[21] Finally, the estimates offered by a group of pesticide manufacturers demonstrated a wide range of experience (Exhibit D-12).

Some have contended that regulatory restrictions have had a definite depressing effect on the economic climate in the pesticides industry, even to the extent of forcing some firms to discontinue at least part of their activities relative to pesticides. There is some evidence for this contention in that 11 firms have discontinued all or part of their pesticides business in the past several years[21] and a number of other firms have merged with other larger companies.

R&D costs to maintain the registration of existing products has risen sharply during the past five years. For 33 firms representing 80 percent of the pesticide sales these costs increased from $6.0 million in 1967 to an estimated $16.8 million in 1971 (Exhibit D-13). This was 13 percent and 23 percent respectively of the total R&D expenditures for these two years. Smaller firms are finding it difficult to support the size and sophistication of R&D teams necessary to obtain and maintain clearance of these chemicals. It is logical for such firms to seek firms, to seek merger opportunities or to get out of pesticides manufacture altogether.

The cost of discovery and commercialization of pesticides has increased markedly since 1967. An average cost of $7,430 per chemical was reported in 1970 compared to $5,481 in 1967.[18] Also, the time between discovery and commercialization increased from 60 to 77 months during the same period. These facts have economic implications for the industry.

It is difficult to ascertain the extent to which regulatory requirements have affected the economic climate of the pesticide industry. The reduction in the number of manufacturers has taken place during a time of general economic stress. The Panel has no evidence that firm mergers or the discontinuation of chemical manufacture by given firms is more pronounced than in any other seg-

EXHIBIT D-12

ESTIMATES OF THE LENGTH OF TIME AND THE TOTAL EXPENDITURES REQUIRED FOR THE DISCOVERY AND COMMERCIALIZATION OF AN AVERAGE PESTICIDE PRODUCT. THE FIGURES SHOW THE RANGES OF EXPERIENCE OR OF ESTIMATION OF A GROUP OF 33 PESTICIDE MANUFACTURERS SURVEYED

	1967			1970		
	High Est.	Low Est.	Average	High Est.	Low Est.	Average
Cost of Discovery & Commercialization ($'s million)	7.0	0.5	3.4	12.0	1.0	5.5
Elapsed time from discovery to marketing (months)	96	48	60	108	60	77
Number of compounds screened per successful product	20,000	500	5,481	20,000	531	7,430

(Data from National Agricultural Chemicals Association).

EXHIBIT D-13

COMPANY-FINANCED R&D EXPENDITURES FOR REGULATORY MAINTENANCE OF EXISTING PESTICIDE PRODUCTS 1967-1971

	'67	'68	'69	'70	% increase '67 - '70	Est '71
Expenditures ($'s million)	7.0	8.7	11.8	16.0	+129	16.8
Percent of total R&D expenditures	13.4	15.4	18.1	22.9		23.5

(Data show experience of pesticide manufacturers representing 80 percent of sales)

ment of the chemical industry during the past five years. Pesticide production figures would suggest no overall cutback, although production has definitely leveled off. The number of compounds being screened remains at about the same level in 1971 as in 1967[18] suggesting no marked change in efforts to seek new chemicals.

It would seem that a number of factors have combined to halt the rapid expansion in the pesticide industry which characterized the 1960's. The effect of these factors on the future of the industry is yet to be determined.

CANCELLATION AND RECALLS

It has been suggested in recent years that the threat of recall of chemical products has increased due to more frequent exercising of the regulatory machinery or, occasionally due only to exhortation by government spokesmen.* With increasing numbers of product recalls, it has been suggested that the economic risks of development are altered. The chance of foreshortening the expected period of commercialization or even of preventing marketing after most development had been completed have been seen by some industrial spokesmen as discouraging to further research and development or, in some cases, to further marketing.

It has appeared difficult to examine this question rigorously since sound data are very scarce. There does seem to be some evidence for some increase in the reversal of approvals previously given for manufacture and marketing of drugs and pesticides. As of December 31, 1971, there were 2,976 approved New Drug Applications (NDA's) on file with the FDA. 2,365 of these had been approved prior to 1962. From 1967 to 1971 there were 5,189 NDA's withdrawn by the FDA.[22] All but 50 of these were withdrawn during the past three years. The majority of these withdrawals were based on recommendations of the Drug Efficacy Study of the National Academy of Sciences.[23] On the basis of a recommendation that there was insufficient scientific evidence of effectiveness, the FDA offered the manufacturer of each drug an opportunity to supply additional data. Where the manufacturer failed to offer satisfactory new findings, the FDA removed the NDA from the approved list The accounting of additions and subtractions from the list of approved pesticides is more complicated than in the case of therapeutic drugs. The major problem in the case of pesticides is that the unit, termed registration by the Environmental Protection Agency (which is the registrar), reflects information both about numbers of products (formulations or mixtures of chemicals) and use patterns for the formulations. Many (or most) formulations have multiple registered uses. To the extent that these are represented on separate labels (it is the label information which is registered) they account for multiple registrations. The Environmental Protection Agency is not able to account for these separate factors in the registration figures.

A "balance sheet" of registrations and de-registrations of pesticides for the fiscal years, 1969-1972 can be seen in Exhibit D-14. From this table it can be seen that, while there were 35 to 45 thousand pesticide resgistrations outstanding in each year, these represented approximately 1,500 different chemical entities.

For the time period covered by this table, the number of registrations canceled was clearly balanced by the number of new registrations accepted (6,376 compared to 6,128). The overwhelming majority of registrations represent variations in the approved use pattern of the chemical substances. The total number of chemical entities has changed very little. The majority of cancellations are occasioned by withdrawals voluntarily made by manufacturers or by failures of manufacturers to re-register their products. Government actions to de-register pesticides ran at a higher rate than usual during 1970 and 1971 reflecting the recommendations of a National Academy of Sciences review of allowable pesticide residues on food crops.

The survey of the pesticide manufacturing industry by the National Agricultural Chemicals Association noted the following pattern of reported cancellations or suspensions of pesticides among the 33 companies polled:[18]

	1968	1969	1970
Products removed entirely from market	25	18	123
Total restrictions	717	388	376

Again, the overwhelming number of restrictions concern limitations on patterns of usage—not total bans. Unfortunately these figures do not discern between formulations and basic chemical entities. More important, perhaps, is the fact that the total number of pesticide products manufactured by these firms is not given and it is not possible for the reader to comtemplate the size or the importance of the fraction of products upon which restrictions were placed.

Finally, from the point of view of trying to understand the implication of cancellation and recall to the manufacturers, there is an additional piece of information which is not contained in any of these figures. Undoubtedly some chemical products are more meaningful economically to a manufacturer than are others (larger market, higher profit, longer period of commercialization, etc.). There is no way of distinguishing among the list of products canceled those which are of particularly high economic importance.

* Nitrilotriacetic acid (NTA), developed as a substitute for phosphate builders for household detergents, is not a member of any of the classes of chemicals over which the Federal agencies have clear regulatory control. The developers of this chemical were urged publicly by the Surgeon General in 1971 to delay its introduction into use until additional research could be performed in behalf of its biological properties.

EXHIBIT D-14

PATTERN OF ADDITIONS AND SUBTRACTIONS FROM REGISTRATIONS OF PESTICIDES FOR THE FISCAL YEARS 1969 TO 1972

	1	2	3	4	5		6	7	8
Fiscal Year	Total number registrations at beginning of each fiscal year	Number of registrations canceled during the fiscal year by government initiative[2]	Total number of registrations canceled during the fiscal year[3]	Number of new registrations added during the fiscal year	Total number of chemical entities registered[4]		Number of agricultural chemicals registered at beginning of fiscal year[5]	Total new chemical entities accepted during the fiscal year[6]	Total new agricultural chemicals accepted during the fiscal year[7]
					Families	Distinct chemical entities			
1969	45,121	688 (10 appeal)	3,544	3,437	900	1,500	I 156 H 85 F 77 Total 318	19	11
1970	45,014	2,105 [8] (49 appeal)	5,236	1,029	900	1,500	I 158 H 111 F 94 Total 363	7	4
1971	40,807	3,583 [8] (814 appeal)	7,005	1,662	900	1,500	I 160 H 122 F 111 Total 393	7	2
1972[1]	35,464	0	n/a		900	1,500	I 159 H 125 F 122 Total 406 I 159 H 126 F 122 Total 407	4 to 1/1/72	1 to 1/1/72

I: Insecticides
H: Herbicides and plant growth regulators
F: Fungicides, nematicides

Data from the Office of Pesticides, EPA.

References (Exhibit 14):

1. Through January 1, 1972.
2. These are the cancellation actions initiated by the Government.
3. These figures represent cancellations resulting from Government action plus those voluntary withdrawals by registrants or lapses in re-registration.
4. Estimates made by the Environmental Protection Agency. The smaller number ("families") reflects a grouping of related chemicals. 2, 4, 5-T, its salts and erters are all counted as one entity. The larger figure treats them as separate entities.
5. The Federal Insecticide, Fungicide, and Rodenticide Act under which pesticides are registered and regulated actually covers chemicals other than agricultural chemicals. This column separates agricultural chemicals from these other materials. The units correspond to the families figures in column 5.
6. Units correspond to the families in column 5.
7. That fraction of chemical entities in column 7 classed as agricultural chemicals.
8. The very large number of cancellations in these years reflected a revision of the concepts of permitted residues on food. This arose as a result of a National Academy of Sciences review of the concept of O-tolerance.

The threat of product banning or recall has been viewed as a significant perturbation in market outlook for some parts of the chemical product industry.[18 24] The banning of products and their recall from the market has undoubtedly caused perturbations from time to time. However, the effect seems to be variable and difficult to define. By themselves, threats of product banning and recall have not been the major determinants of economic risk for manufacturers except in a few instances. When added to other uncertainties and to altered obligations before marketing, however, the threat of "premature" removal from the market may have been additive.

RESEARCH AND DEVELOPMENT TOWARD NEW CHEMICAL PRODUCTS

R&D in the chemicals industries could vary as a result of several real forces in our society other than those that are embodied in Government regulation. In fact, all indications are that industrial R&D has increased rather than decreased in an era when Government regulation has become stiffened and broadened.

It has been suggested that R&D in the chemicals industry has been forced to become more "defensive" in recent years in order to maintain the existing product positions.[16 25] Part of the "defense" is against competitors' products which could displace earlier ones. In addition, it is said, the expenditures required to satisfy new Government obligations regarding both new and already marketed products are rising rapidly and are detracting from the efforts which might have otherwise been directed toward new innovations. First of all, it appears generally clear that the length of the development process from discovery to marketing of a new chemical product (e.g., agricultural chemical, industrial chemical, therapeutic drug) has increased as a function of new levels of public and regulatory agency questioning. There are, however, compensating factors which may maintain high industry profits, however. Of particular note among these is the genuine public demand for vital products whether they be new or old. This lends stability to the system. The slower pace of innovation will be common to all competing members of the industry. Thus, although the barriers to entry into the market may be increased, they are increased similarly for all members and the chance of displacement by competitors' products is similarly postponed. It seems likely that there will exist a threshold of length of development beyond which projects will not be attempted.[13]

In the case of pesticides, an increasing proportion of company funded R&D expenditures have apparently been directed toward "regulatory maintenance" of existing products (Exhibit D-13).

There appear to be no coresponding figures for other classes of chemical products. If the 1962 drug amendments to the Food, Drug, and Cosmetic Act and the results of the National Academy of Sciences Drug Efficacy Study have been "successful," however, it must be true that pharmaceutical manufacturers have been forced to undertake examination of some additional questions for already marketed products. This, of course, was one of the explicitly intended effects of certain of the regulatory statutes and the burden of costs of the evaluation of "new" questions has been placed on the private sector.

A related point of view frequently offered is that the combination of various regulatory actions have led to a much increased aggregate of obligations on the part of manufacturers to perform research and provide information before marketing is permitted. Manufacturers have been very forthright in recent years in supporting this notion with figures representing their experience.

The survey conducted by the National Agricultural Chemicals Association concluded that there had been an increase of 33 percent in pesticide R&D expenditures between 1967 and 1970 and a modest decline for 1971 (considering a five percent rate of inflation) (Exhibit D-15). The experience of one company has been that the direct costs involved in satisfying additional premarketing investigations of toxicology and environmental impact are not generally substantial. However, the delays occasioned by their performance are exceedingly costly—especially if the delays occur late in the course of development—mainly because of the cost of servicing the investment made in the product. Whether or not there has been an actual increase in the time required for development of a successful pesticide to the point of marketing is less clear. The opinions (as opposed to data) of the industries

EXHIBIT D-15

PESTICIDE R&D EXPENDITURES OF PARTICIPATING COMPANIES

Type of Expenditure	1967 $Million	1970 $Million	%Increase 1967-70	Est. 1971 $Million
Sythnesis & Screening	$17.7	$22.0	24%	$21.3
Field Testing & Development	15.9	22.3	40%	22.7
Toxicology & Metabolism	6.9	9.1	32%	10.5
Formulation & Chemical Development	8.9	12.3	38%	12.8
Registration & Other	2.9	4.2	46%	4.3
TOTAL R&D EXPENSE	$52.4	$69.9	33%	$71.6

Source: National Agricuttural Chemicals Association.

EXHIBIT D-16
PESTICIDE R & D COST

	1968	1969	1970
No. cpds. synthesized per product	4,000	36,000	5,000
Time: cpd. discovery to product	5-8 yrs.	.....	5 yrs.
R&D Cost	$4M*	$6M**	$4M***

*Includes cost of chemical process and pilot plant studies
**Does not include cost of chemical process and pilot plant studies
***Does not include cost of chemical process and pilot plant studies or "losers"

1968 = N.A.C. News and Pesticide Rev., Vol. 27, No. 2, Dec. 1968, p. 3
1969 = Chemical Week, April 26, 1969, p. 38
1970 = Bioscience, Vol. 20, No. 18, p. 1006

polled by the National Agricultural Chemicals Association was that there had been an increase in the average elapsed time from discovery to marketing of 28 percent (60 months to 77 months) between 1967 and 1970.[18] However, these estimates varied widely among those surveyed (Exhibit D-12). Previous estimates of experience in the manufacture of pesticides has revealed a similarly wide variation in the time for development and unclear trends (Exhibit D-16). What perhaps is important is the fact that for most major chemical companies which manufacture pesticides, the pesticide portion represents only a small portion of the total corporate operation and one which is perceived as increasingly risky.

Mansfield *et al.*, in studying the process of innovation and industrial research concluded that the average time interval between discovery and innovation (marketing) for pharmaceuticals (5.0 years in the period 1935 to 1962) was shorter and less variable than for all other industries for which data are available.[6] For the petroleum industry, for example, the corresponding average lag was 14 years.

Mansfield reported on the average costs (in dollars and time) of development of a successful pharmaceutical product in the 1950's and early 1960's.[28] The average monetary cost of development of a drug in his study was $534 thousand. The average cost of a successful drug was 57 percent of the combined costs of success and non-successes bringing the total cost of development to $1.1 million per success. The total development time was 25 months on the average. In 1968, Clymer presented data referring to costs of drug development in that year (Exhibit D-17).

Acceptance of these figures would indicate a sixfold increase in the cost of a successful project, a threefold increase in the length of time required for the project, and a halving of the probability that a given project would be successful. Djerassi's prediction has been that a male antifertility agent would require 12 to 20 years and more than $6 million to develop and a luteolytic or abortifacient female contraceptive would take 17 to 18 years and over $18 million.[13]

It is of interest to determine the contribution to the time duration of the FDA's review process for new drugs. Exhibit D-18 is the FDA's own estimate of the average length of time from the date of original filing of a New Drug Application to its approval for the years 1958 to 1967. These figures by definition should reflect both the period of FDA review and the time required for additional studies because of inadequate data with the original submission.

EXHIBIT D-18
The average length of time from the date of original filing of a New Drug Application to the time of approval (1958-1967)*

Year	*Average length of time (months)*
1958	3
1961	11
1962	7
1964	14
1965	24
1966	24
1967	23*

Data from the FDA published in Jadlow [6]

* According to the FDA, this period included on the average about eight months of additional research by the firm (because of inadequate data in the original submission) and about fifteen months of review of the various submissions by the FDA.

EXHIBIT D-17
COSTS AND TIME OF DEVELOPING A NEW PHARMACEUTICAL CHEMICAL ENTITY

Item	1950's & early 1960's (one firm)	1968 (one firm)
Average development costs	$534,000	$2.5-4.5 million
Standard deviation	500,000	
Total development time	25 months	51-105 months
Standard deviation	13 months	
Average cost of success plus non-success	$1.1 million	$10.5 million

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APPENDIX E

ECONOMIC TRENDS IN CHEMICAL PRODUCTION

C. O. Muehlhause

GROWTH AND TRENDS

Basic economic data are collected by the Bureau of Domestic Commerce of the Department of Commerce via a full census every five years with annual sampling in between. These data[1,2] reveal key chemical industries to be both substantial and growing at a respectable rate. "Pharmaceutical Preparations" ranks among the 100 largest industries both by "value of shipments" and by "number of employees."

In a total of over 400 four digit industries this group ranks 15th according to "value of shipments" and 41st according to the "number of employees," this being for the year 1969. "Agricultural Chemicals" is among the 100 fastest growing industries in the period 1958 to 1969. It ranks 46th according to "value of shipments" and 84th according to the "number of employees." A related but less relevant four digit industry, "Biological Products," also ranks among the 100 fastest growing industries. Its rank is 24th according to "value of shipments" and 21st according to the "number of employees." "Pharmaceutical Preparations" also displays a respectable growth rate, however.

Data published by the National Science Foundation and the Pharmaceutical Manufacturers Association reveal these industries to be highly research intensive. They are in fact equaled only by the industry group termed "Communication Equipment and Electronic Components" and exceeded only by "Aircraft and Missiles." This latter industry group, unlike the chemical industries of interest, however, receives a very large fraction of Federal funds. If only company R&D is considered, no industry group surpasses the R&D investment fraction of "Pharmaceutical Preparations." (See Exhibits E-1, E-2, and E-3.)

NSF data[3] are available for "Drugs" over the period 1958-1969. Shown in Exhibit E-4 are the company invested R&D both in dollars and as a percent of sales. In these data the ratio of applied to basic research is about 6:1. Further characterization of the nature of the R&D is given by certain PMA data,[4] and shown in Exhibits E-5 and E-6. These are: human use vs. veterinary drugs, the R&D breakdown into research activities, and R&D expenditures for domestic vs. foreign investments covering the years 1968 to 1971. Other NSF data disclose that both the number of R&D scientists per 1,000 employees and the company invested funds for R&D per employee are highest for the category "Pharmaceutical Preparations." High talent and investment in R&D presumably correlate also with high profitability.

In a report by I. N. Fisher et al.[5] of the Rand Corporation a study of the effect of risk, defined as the inability to anticipate profits by company management, was made for 88 firms representing various industry groups, including "Drugs". The analysis was performed fundamentally by examining the dispersion of profits from year to year and by eliminating temporal trends, skewness, and autocorrelated firms. About half of the fluctuations could be accounted for. This, as well as some other methods of statistical analysis, consistently ranked "Drugs" as having the highest "risk-adjusted rate" of return. In addition "Drugs" enjoy the highest "rate of return on net worth," the latter being the usual accounting basis for computing profit.

It should be observed from Exhibit E-7 which displays this information that the so called "risk premium" was not high for the drug category. Perhaps the high talent characteristic of the R&D of sophisticated high technology companies tends to appear risk averse in the sense that other factors than risk limit profitability more so than with the average firm. In any event when the data have been adjusted for risk the drug companies still persist in exhibiting a high profitability relative to other industries. Hence, other factors are presumably important in determining the rate of return on investment, e.g. innovation and high technology.

BARRIERS TO INNOVATION

Professor E. Mansfield[6,7] and his students have modeled management's decision-making with respect to the determination of its forthcoming year's R&D budget relative to previous expenditures and management's expectation for profit. In this model, which Mansfield attempted to keep as simple as possible, the key profitability parameter appeared as follows:

$$\bar{p} / \dot{\bar{p}} - p^*$$

wherein $\bar{p}$ was the average return and p^* the minimum return required for acceptance of an R&D project. A fractional change in $\bar{p}$, e.g. due to new tax laws or, in this context a change in regulation, effected a fractional change in the R&D which was equal to the change in $\bar{p}$ multiplied by the above parameter. In the period around 1958 to 1962 this parameter had a value ~ 3.4 for "chemical industry." Thus if profits had been averaging 15 percent and were to fall to 14 percent

EXHIBIT E-1

SIC: 2A CHEMICALS AND ALLIED PRODUCTS

NUMBER OF ESTABLISHMENTS (1967): 11,799 BOOK VALUE OF ASSETS PER EMPLOYEE (1964): $27,679

Year	All Employees		Production Workers		Wages (SMIL.)	Value Added (SMIL.)	Cost of Materials (SMIL.)	Value of Shipments (SMIL.)	Capital Expenditures (SMIL.)	End-of-Year Inventories (SMIL.)
	Number (000)	Payroll (SMIL.)	Number (000)	Man-Hours (MIL.)						
1958	698.3	3,940.5	453.1	908.4	2,242.1	12,308.0	10,776.1	23,129.5	1,243.9	3,003.4
1959	717.7	4,233.4	470.9	949.0	2,409.5	14,335.7	12,099.8	26,327.8	1,102.7	3,238.9
1960	725.6	4,421.7	469.6	943.5	2,473.2	14,415.2	12,337.2	26,548.0	1,285.3	3,375.5
1961	712.9	4,523.6	460.4	932.1	2,520.6	14,804.5	12,544.1	27,242.1	1,500.2	3,463.1
1962	727.3	4,755.0	470.1	953.0	2,647.2	16,009.1	13,400.3	29,365.3	1,381.8	3,702.2
1963	737.4	4,969.8	474.1	963.4	2,779.9	17,586.1	14,255.1	31,772.7	1,545.7	3,285.8
1964	749.2	5,244.3	479.9	986.0	2,927.5	19,165.8	15,218.4	34,268.1	1,862.2	4,003.9
1965	780.3	5,594.4	502.4	1,022.5	3,104.8	20,955.6	16,804.5	37,478.8	2,482.0	4,438.1
1966	822.4	6,129.3	528.5	1,077.4	3,400.2	22,655.6	18,516.8	40,780.4	2,898.6	5,040.4
1967	841.4	6,443.0	541.4	1,086.1	3,555.2	23,550.1	18,821.2	42,148.3	2,936.1	5,348.7
1968	856.3	6,938.5	550.8	1,116.0	3,845.4	25,810.4	19,984.0	45,622.4	2,788.7	5,564.6
1969	882.9	7,585.0	574.9	1,143.5	4,160.4	27,176.7	21,138.3	48,164.6	2,846.8	6,164.4
% Change 1968-69	3.1	9.3	4.4	2.5	8.2	5.3	5.8	5.6	2.1	10.4
Avg. Rate 1958-69	2.2	6.1	2.2	2.1	5.8	7.5	6.3	6.9	7.8	6.8

Year	Ratio of Value Added to Shipments	Ratio of Inventories to Shipments	Ratio of Payroll to Value Added	Value of Shipments Per Prod. Worker ($000)	Manhours Per Production Worker (000)	Wage Per Production Worker Manhour ($)	Value Added Per Prod. Worker Manhour ($)	Index of Employment (1967=100)	Index of Value Added (1967=100)	Index of Shipments (1967=100)
1958	.532	.130	.320	51.0	2.005	2.468	13.55	82.99	52.26	54.88
1959	.545	.123	.295	55.9	2.015	2.539	15.11	85.30	60.87	62.46
1960	.543	.127	.307	56.5	2.009	2.621	15.28	86.24	61.21	62.99
1961	.543	.127	.306	59.2	2.025	2.704	15.88	84.73	62.86	64.63
1962	.545	.126	.297	62.5	2.027	2.778	16.80	86.44	67.98	69.67
1963	.553	.103	.283	67.0	2.032	2.886	18.25	86.64	74.68	75.38
1964	.559	.117	.274	71.4	2.055	2.969	19.44	89.04	81.38	81.30
1965	.569	.118	.267	74.6	2.035	3.036	20.49	92.74	88.98	88.92
1966	.556	.124	.271	77.2	2.039	3.156	21.03	97.74	96.20	96.75
1967	.559	.127	.274	77.9	2.006	3.273	21.68	100.00	100.00	100.00
1968	.566	.122	.269	82.8	2.026	3.446	23.13	101.77	109.60	108.24
1969	.564	.128	.279	83.8	1.989	3.638	23.77	104.93	115.40	114.27
% Change 1968-69	-0.3	4.6	3.8	1.1	−1.8	5.6	2.8	3.1	5.3	5.6
Avg. Rate 1958-69	0.5	−0.1	−1.2	4.6	−0.1	3.6	5.2	2.2	7.6	6.9

Source: Department of Commerce

EXHIBIT E-2

SIC: 283 DRUGS

NUMBER OF ESTABLISHMENTS (1967): 1,129 BOOK VALUE OF ASSETS PER EMPLOYEE (1964): $14,959

Year	All Employees		Production Workers		Wages	Value Added	Cost of Materials	Value of Shipments	Capital Expenditures	End-of-Year Inventories
	Number (000)	Payroll ($MIL.)	Number (000)	Man-Hours (MIL.)	($MIL.)	($MIL.)	($MIL.)	($MIL.)	($MIL.)	($MIL.)
1958	95.9	545.7	54.9	110.2	250.7	2,096.2	874.4	2,977.9	111.8	440.8
1959	99.8	594.3	56.1	111.3	262.7	2,274.5	875.2	3,129.6	N.A.	365.4
1960	103.8	623.6	56.3	111.0	267.7	2,354.4	861.7	3,214.2	115.7	457.9
1961	102.3	635.1	55.7	109.7	271.8	2,445.9	872.5	3,311.4	107.0	471.3
1962	106.2	684.2	58.3	113.7	291.5	2,636.0	928.7	3,540.9	95.0	501.4
1963	99.0	673.8	54.9	110.0	296.6	2,807.3	930.3	3,715.9	113.3	530.2
1964	101.6	718.1	56.4	113.5	312.9	2,943.3	985.3	3,921.[illegible]	118.2	548.8
1965	105.0	777.4	57.9	115.5	336.7	3,364.2	1,069.8	4,402.[illegible]	138.2	597.5
1966	109.1	842.5	60.4	122.2	368.5	3,674.8	1,196.4	4,826.0	162.5	671.0
1967	117.9	942.3	65.6	128.2	405.1	4,072.9	1,276.2	5,301.6	217.9	741.5
1968	118.9	1,001.2	65.7	130.7	437.1	4,355.3	1,324.1	5,645.3	228.4	781.2
1969	125.5	1,142.5	79.7	139.1	489.6	4,752.8	1,400.8	6,227.8	286.8	919.2
% Change 1968-69	5.6	14.1	21.3	6.4	12.0	9.1	5.8	10.3	25.6	17.7
Avg. Rate 1958-69	2.5	6.9	3.4	2.1	6.3	7.7	4.4	6.9	8.9	6.9

Year	Ratio of Value Added to Shipments	Ratio of Inventories to Shipments	Ratio of Payroll to Value Added	Value of Shipments Per Prod. Worker ($000)	Per Production Worker	Wage Per Production Worker Manhour ($)	Value Added Per Prod. Worker Manhour ($)	Index of Employment (1967=100)	Index of Value Added (1967=100)	Index of Shipments (1967=100)
1958	.704	.148	.260	54.2	2,007	2.275	19.02	81.34	51.47	56.17
1959	.727	.117	.261	55.8	1,994	2.360	20.44	84.65	55.84	59.03
1960	.732	.142	.265	57.1	1,972	2.412	21.21	88.04	57.81	60.63
1961	.739	.142	.260	59.5	1,969	2.478	22.30	86.77	60.05	62.46
1962	.744	.142	.260	60.7	1,950	2.584	23.18	90.08	64.72	66.79
1963	.755	.143	.240	67.7	2,004	2.696	25.52	83.97	68.93	70.09
1964	.751	.140	.244	69.5	2,012	2.757	25.93	86.17	72.27	73.97
1965	.764	.136	.231	76.0	1,995	2.915	29.13	89.06	82.60	83.04
1966	.761	.139	.229	79.9	2,023	3.016	30.07	92.54	90.23	91.03
1967	.768	.140	.231	80.8	1,954	3.160	31.77	100.00	100.00	100.00
1968	.771	.138	.230	85.9	1,989	3.344	33.32	100.85	106.93	106.48
1969	.763	.148	.240	78.1	1,745	3.520	34.17	106.45	116.69	117.47
% Change 1968-69	–1.1	6.7	4.6	–9.1	–12.3	5.2	2.5	5.6	9.1	10.3
Avg. Rate 1958-69	0.7	–0.0	–0.7	0.4	–1.3	4.0	5.5	2.5	7.7	6.9

Source: Department of Commerce

EXHIBIT E-2 Continued

SIC: 2834 PHARMACEUTICAL PREPARATIONS

NUMBER OF ESTABLISHMENTS (1967): 875 BOOK VALUE OF ASSETS PER EMPLOYEE (1964): $13,765
SPECIALIZATION RATIO (1967): 87% COVERAGE RATIO (1967): 97% CONCENTRATION RATION

Year	All Employees		Production Workers		Wages	Value Added	Cost of Materials	Value of Shipments	Capital Expenditures	End-of-Year Inventories
	Number (000)	Payroll ($MIL.)	Number (000)	Man-Hours (MIL.)	($MIL.)	($MIL.)	($MIL.)	($MIL.)	($MIL.)	($MIL.)
1958	82.0	466.6	45.7	91.4	205.5	1,881.5	700.6	2,591.8	72.4	365.8
1959	83.7	495.9	45.6	89.4	209.1	2,015.5	685.2	2,692.2	82.8	274.7
1960	86.7	517.6	45.6	88.9	212.9	2,085.2	675.3	2,772.1	85.1	357.2
1961	88.0	549.1	46.5	91.1	225.2	2,223.7	698.6	2,926.6	86.4	383.2
1962	91.2	588.7	48.8	94.2	240.7	2,413.5	734.2	3,142.2	71.5	403.5
1963	85.1	560.6	45.9	91.7	246.0	2,595.7	736.5	3,314.3	89.3	428.3
1964	90.2	639.8	49.4	99.3	273.8	2,766.2	815.2	3,571.1	102.7	469.0
1965	94.6	701.6	51.4	102.1	299.4	3,172.8	907.4	4,049.7	122.6	521.6
1966	98.3	761.1	53.6	107.9	327.9	3,446.9	1,018.0	4,432.4	133.8	582.3
1967	102.0	821.4	55.2	107.2	338.6	3,720.4	1,013.7	4,696.4	169.6	611.9
1968	102.3	868.7	54.9	109.1	364.6	3,979.2	1,043.2	5,008.3	185.3	630.7
1969	107.9	995.8	68.2	116.4	408.1	4,343.4	1,171.1	5,529.0	247.5	763.6
% Change 1968-69	5.5	14.6	24.2	6.7	11.9	9.2	12.3	10.4	33.6	21.1
Avg. Rate 1958-69	2.5	7.1	3.7	2.2	6.4	7.9	4.8	7.1	11.8	6.9

Year	Ratio of Value Added to Shipments	Ratio of Inventories to Shipments	Ratio of Payroll to Value Added	Value of Shipments Per Prod. Worker ($000)	Manhours Per Production Worker (000)	Wage Per Production Worker Manhour ($)	Value Added Per Prod. Worker Manhour ($)	Index of Employment (1967=100)	Index of Value Added (1967=100)	Index of Shipments (1967=100)
1958	.726	.141	.248	56.7	2.000	2.248	20.59	80.39	50.57	55.19
1959	.749	.102	.246	59.0	1.961	2.339	22.52	82.06	54.17	57.32
1960	.752	.129	.248	60.8	1.950	2.395	23.46	85.00	56.05	59.03
1961	.760	.131	.247	62.9	1.959	2.472	24.41	86.27	59.77	62.32
1962	.768	.128	.244	64.4	1.930	2.555	25.62	89.41	64.87	66.91
1963	.783	.129	.224	72.2	1.998	2.683	28.31	83.43	69.77	70.57
1964	.775	.131	.231	72.3	2.010	2.757	27.86	88.43	74.35	76.04
1965	.783	.129	.221	78.8	1.986	2.932	31.08	92.75	85.28	86.23
1966	.778	.131	.221	82.7	2.013	2.013	31.95	96.37	92.65	94.38
1967	.792	.130	.221	85.1	1.942	3.159	34.71	100.00	100.00	100.00
1968	.795	.126	.218	91.2	1.987	3.342	36.47	100.29	106.96	106.64
1969	.786	.138	.229	81.1	1.707	3.506	37.31	105.78	116.75	117.73
% Change 1968-69	−1.1	9.7	5.0	−11.1	−14.1	4.9	2.3	5.5	9.2	10.4
Avg. Rate 1958-69	0.7	−0.2	−0.7	3.3	−1.4	4.1	5.6	2.5	7.9	7.1

Source: Department of Commerce.

EXHIBIT E-3

SIC: 287 AGRICULTURAL CHEMICALS

NUMBER OF ESTABLISHMENTS (1967): 1,278 BOOK VALUE OF ASSETS PER EMPLOYEE (1964): $22,042

Year	All Employees		Production Workers		Wages ($MIL.)	Value Added ($MIL.)	Cost of Materials ($MIL.)	Value of Shipments ($MIL.)	Capital Expenditures ($MIL.)	End-of-Year Inventories ($MIL.)
	Number (000)	Payroll ($MIL.)	Number (000)	Man-Hours (MIL.)						
1958	38.7	160.4	27.3	54.4	99.5	414.7	962.7	1,376.9	40.0	232.2
1959	41.9	177.3	29.7	59.7	110.4	494.9	1,073.1	1,549.1	42.9	251.9
1960	42.8	186.6	30.0	60.8	112.6	528.5	1,105.7	1,608.7	57.1	281.1
1961	41.9	188.0	29.6	60.4	113.4	497.6	1,153.4	1,628.9	110.6	304.8
1962	41.8	197.6	29.1	59.7	118.5	532.9	1,240.5	1,762.7	74.9	332.4
1963	42.8	213.1	29.5	61.2	128.9	626.3	1,349.8	1,968.9	66.5	350.4
1964	43.6	224.9	29.7	61.9	132.9	713.3	1,453.0	2,142.8	111.3*	383.1
1965	45.0	238.1	30.8	62.0	141.1	800.6	1,560.3	2,335.9	192.5	426.0
1966	47.4	265.6	31.9	65.0	156.2	908.9	1,739.8	2,594.6	129.6	505.6
1967	45.7	280.5	31.0	63.6	162.6	1,005.8	1,780.2	2,745.0	205.1	524.0
1968	44.6	287.0	29.6	60.1	161.2	990.0	1,787.2	2,798.7	116.8*	497.4
1969	41.9	293.3	27.4	55.7	162.4	996.7	1,748.9	2,749.7	144.1	484.2
% Change 1968-69	−6.1	2.2	−7.4	−7.3	0.7	0.7	−2.1	−1.8	23.4	−2.7
Avg. Rate 1958-69	0.7	5.6	0.0	0.2	4.6	8.3	5.6	6.5	12.4	6.9

Year	Ratio of Value Added to Shipments	Ratio of Inventories to Shipments	Ratio of Payroll to Value Added	Value of Shipments Per Prod. Worker ($000)	Manhours Per Production Worker (000)	Wage Per Production Worker Manhour ($)	Value Added Per Prod. Worker Manhour ($)	Index of Employment (1967=100)	Index of Value Added (1967=100)	Index of Shipments (1967=100)
1958	.301	.169	.387	50.4	1.993	1.829	7.62	84.68	41.23	50.16
1959	.319	.163	.358	52.2	2.010	1.849	8.29	91.68	49.20	56.43
1960	.329	.175	.353	53.6	2.027	*1.852*	*8.69*	93.65	52.55	*58.60*
1961	.305	.187	.378	55.0	2.041	1.877	8.24	91.68	49.47	59.34
1962	.302	.189	.371	60.6	2.052	1.985	8.93	91.47	52.98	64.21
1963	.318	.178	.340	66.7	2.075	2.106	10.23	93.65	62.27	71.73
1964	.333	.179	.315	72.1	2.084	2.147	11.52	95.40	70.92	78.06
1965	.343	.182	.297	75.8	2.013	2.276	12.91	98.47	79.60	85.10
1966	.350	.195	.292	81.3	2.038	2.403	13.98	90.37	90.37	94.52
1967	.366	.191	.279	88.5	2.052	2.557	15.81	100.00	100.00	100.00
1968	.354	.178	.290	94.6	2.030	2.682	16.47	97.59	98.43	101.96
1969	.362	.176	.294	100.4	2.033	2.916	17.89	91.68	99.10	100.17
% Change 1968-69	2.5	−0.9	1.5	6.1	0.1	8.7	8.6	−6.1	0.7	−1.8
Avg. Rate 1958-69	1.7	0.4	−2.5	6.5	0.2	4.3	8.1	0.7	8.3	6.5

EXHIBIT E-3 Continued

SIC: 2879 AGRICULTURAL CHEMICALS, NEC

NUMBER OF ESTABLISHMENTS (1967): 364 BOOK VALUE OF ASSETS PER EMPLOYEE (1964): $15,919
SPECIALIZATION RATIO (1967): 87% COVERAGE RATIO (1967): 72% CONCENTRATION RATIO (1967): 4 LARGE 39% 8 LARGE 61%

Year	All Employees		Production Workers		Wages	Value Added	Cost of Materials	Value of Shipments	Capital Expenditures	End-of-Year Inventories
	Number (000)	Payroll ($MIL.)	Number (000)	Man-Hours (MIL.)	($MIL.)	($MIL.)	($MIL.)	($MIL.)	($MIL.)	($MIL.)
1958	7.8	37.8	4.9	9.5	18.6	111.0	223.2	333.1	7.0	62.5
1959	8.5	41.2	5.1	9.5	19.2	127.5	243.2	364.1	7.9	65.2
1960	8.9	45.0	5.3	10.1	20.0	142.4	262.8	398.0	7.8	68.1
1961	8.4	43.6	5.1	10.1	20.2	137.2	275.8	406.7	5.6	70.7
1962	8.7	46.3	5.1	10.2	20.9	146.4	292.7	431.7	7.5	76.8
1963	9.1	51.5	5.3	10.6	24.4	176.3	307.0	476.7	9.1	93.3
1964	9.0	52.8	5.3	10.8	24.1	181.5	302.6	478.6	12.4	96.5
1965	10.2	60.5	5.9	11.0	28.5	229.3	351.4	588.3	19.0	110.7
1966	11.0	72.8	6.2	12.1	32.5	277.6	425.2	692.7	25.4	137.8
1967	11.5	80.7	6.9	13.6	39.0	376.3	460.8	817.0	54.0	145.6
1968	12.1	85.2	7.4	13.8	41.4	414.0	488.6	902.4	64.7*	147.1
1969	12.1	93.0	7.2	14.4	44.1	472.6	509.4	957.7	75.9	166.6
% Change 1968-69	0.0	9.2	–2.7	4.3	6.5	14.2	4.3	6.1	17.3	13.3
Avg. Rate 1958-69	4.1	8.5	3.6	3.9	8.2	14.1	7.8	10.1	24.2	9.3

Year	Ratio of Value Added to Shipments	Ratio of Inventories to Shipments	Ratio of Payroll to Value Added	Value of Shipments Per Prod. Worker ($000)	Manhours Per Production Worker (000)	Wage Per Production Worker Manhour ($)	Value Added Per Prod. Worker Manhour ($)	Index of Employment (1967=100)	Index of Value Added (1967=100)	Index of Shipments (1967=100)
1958	.333	.188	.341	68.0	1.939	1.958	11.68	67.83	29.50	40.77
1959	.350	.179	.323	71.4	1.863	2.021	13.42	73.91	33.88	44.57
1960	.358	.171	.316	75.1	1.906	1.980	14.10	77.39	37.84	48.71
1961	.337	.174	.318	79.7	1.980	2.000	13.58	73.04	36.46	49.78
1962	.339	.178	.316	84.6	2.000	2.049	14.35	75.65	38.91	52.84
1963	.370	.196	.292	89.9	2.000	2.302	16.63	79.13	46.85	58.35
1964	.379	.202	.291	90.3	2.038	2.231	16.81	78.26	48.23	58.58
1965	.390	.188	.264	99.7	1.864	2.591	20.85	88.70	60.94	72.01
1966	.401	.199	.262	111.7	1.952	2.686	22.94	95.65	73.77	84.79
1967	.461	.178	.214	118.4	1.971	2.868	27.67	100.00	100.00	100.00
1968	.459	.163	.206	121.9	1.865	2.000	30.00	105.22	110.02	110.45
1969	.493	.174	.197	133.0	2.000	3.063	32.82	105.22	125.59	117.22
% Change 1968-69	7.6	6.7	–4.4	9.1	7.2	2.1	9.4	0.0	14.2	6.1
Avg. Rate 1958-69	3.6	–0.7	–4.9	6.3	0.3	4.2	9.8	4.1	14.1	10.1

Source: Department of Commerce

EXHIBIT E-4

COMPANY FUNDS FOR R&D PERFORMANCE BY INDUSTRY 1956-1969 ($'s MILLION)

Industry	Year													
	1956	1957	1958	1959	1960	1961	1962	1963	1964	1965	1966	1967	1968	1969
Chemicals and Allied Products. .		616	666	743	807	881	939	1004	1098	1195	1271	1357	1458	1560
Drugs and Medicine		104	126	151	158	177	191	207	224	255	275			

COMPANY FUNDS FOR R&D PERFORMANCE AS PERCENT OF NET SALES BY INDUSTRY 1957-1969

Industry	1957	1958	1959	1960	1961	1962	1963	1964	1965	1966	1967	1968	1969	1970
Chemicals and Allied Products. .	3.1	3.2	3.2	3.7	3.5	3.4	3.6	3.8	3.6	3.7	3.8	3.5	3.5	
Drugs and Medicine	3.6	4.0	4.2	4.5	4.2	4.2	4.5	5.6	5.4	a	a	a	a	

a. - not separately available but included in total from National Science Foundation Data, Reference 3

Source: National Science Foundation.

EXHIBIT E-5

EXPENDITURES BY DRUG FIRMS FOR R&D ON HUMAN-USE DRUGS ACCORDING TO LOCATION OF RESEARCH (U.S. OR FOREIGN)

	1968 Actual		1969 Actual		1970 Actual		1971 Budgeted	
	$ Million	%	$ Million	%	$ Million	%	$ Million	%
Amount spent in U.S.	410.4	91.3	464.1	81.7	518.6	91.6	569.4	91.3
Amount spent in foreign countries	39.1	8.7	41.7	8.3	47.2	8.4	54.1	8.7
Total	449.5	100	505.8	100	565.8	100	623.5	100

Source: Pharmaceutical Manufacturers Association.

management would, according to the model, reduce its R&D by about 22 percent. This should be regarded only as an example, but one which is in accord with data fitted to the model around the beginning of the decade of the 60's. The larger the value of the parameter cited, the stronger is the coupling between changes in profitability and management response. This is so because the larger this profitability parameter is the closer management's expectation is to the actual result and hence the less its margin for error.

COMPANY FINANCED R&D – PHARMACEUTICAL INDUSTRY ($'S MILLION)

	1968	1969	1970	1971 (Budgeted)
Human-use drugs	449.5	505.8	565.8	625.3
Veterinary drugs	35.7	33.8	45.1	49.0
Total	485.2	539.6	610.9	674.3

Source: Pharmaceutical Manufacturers Association.

From yet other considerations if the risk or uncertainty in anticipating profits or success becomes too large management could not undertake the venture, as it may not be possible to absorb the magnitude of a possible loss even if the statistical expectation or mean value were favorable.

As an aid to judging some of the effects discussed above, namely that of stretched out R&D and other costs or barriers to marketing, a type of cash flow calculation was performed which purports to be "typical" of an industry, e.g. pharmaceutical or agricultural-chemical. Having established the typical case, perturbations were then introduced into the model from which one may calculate either the change in net present value or the adjustment in sales or return on investment needed to compensate the perturbation. This served as a measure of the seriousness of the perturbation. For example, if a one year delay in marketing resulted in a loss in investment return of one percent out of say 15 percent, one would then be in a position to further speculate on the consequences. The application of Mansfield's model, for example, would predict a drop in next year's R&D allocation as previously cited.

In operating with cash flows over time a more convenient definition of "return on investment" was used than was employed in the discussion of risk-adjusted return. This is the so-called "discount factor" or rate used to evaluate future cash flows with respect to present ones. The practice is in accord with cost-benefit and other project analyses in which the stream of future costs and benefits are discounted to present value.

Two principal models were developed: one for pesticides and one for ethical drugs. The parameters for these model calculations were determined from a number of sources[8] and ultimately by dialogue and exchange with persons[9 10 11] in the industry who were able to pass judgment on their appropriateness. In some companies these actually served as a management tool for making judgments of the type sought here.

The two standard cases considered representative of pesticides and ethical drugs are given as follows:

Pesticides

12M$ Sales
6M$ R&D
12M$ Capital Investment
  Direct Plant 3M$, 10 year life
  Allocated Fixed 6.6M$, 14 year life
  Working Capital 2.4M$, fully recoverable
5 year R&D time
10 year commercialization
40 percent Return on Sales before Taxes
~10 percent Discount Rate, but adjusted to above
Operating costs: 50 percent fixed, 50 percent variable

Time pattern for R&D expenditures and sales are shown in the cash flow standard examples, AC 1 and 2 (Exhibits E-8 and E-9)

52 percent Tax Rate

Ethical Drugs

12M$ Sales
8M$ R&D

EXHIBIT E-6

COMPANY-FINANCED R&D EXPENDITURES FOR HUMAN-USE DRUGS ($'S MILLION)

	Year			
	1968 Actual	1969 Actual	1970 Actual	1971 Budgeted
Basic research	64.0			
Chemical research	101.5			
Funds spent in quest of new products	165.5			
Animal safety and toxicology	38.8			
Other pharmacologic animal testing	60.6			
Funds spent in evaluation of products and new products	99.4			
Total company funded R&D expenditures for human-use drugs	472.4	549.2	565.8	625.3

From — Pharmaceutical Manufacturers Association Annual Reports

"DEFENSIVE" & "OFFENSIVE" EXPENDITURES FOR HUMAN-USE DRUGS (AS % OF TOTAL COMPANY-FINANCED R&D EXPENDITURES FOR HUMAN-USE DRUGS)

	1968	1969	1970	1971
Funds spent in quest of new products	35.1%			
Funds spent in evaluation of products and new products	21.0%			

Source: Pharmaceutical Manufactuters Association.

3.36M$ Capital Investment
Direct Plant 300K$—15 yr. life
Allocated Fixed 660K$—15 yr. life
Working Capital 2400K$, fully recoverable
6 year R&D time
15 year commercialization
30 percent Return on Sales before Taxes
∿12 percent Discount Rate, but adjusted to above
Operating costs: 50 percent fixed, 50 percent variable

Time pattern for R&D expenditures and sales are shown in the cash flow standard examples, ED 1 and 2 (Exhibits E-13 and E-14)

52 percent Tax Rate

The cash flows for these two cases are shown for two discount rates each. This was to determine the rate which yielded a net present value of zero. This rate then becomes the expected return consistent with the model. They are 9.8 percent and 11.4 percent respectively for *pesticides* and *ethical* drugs.

EXHIBIT E-7

INDUSTRY PROFIT RANK ADJUSTED FOR RISK

Industry Group	Average Observed Rate of Return	Rank	Risk-Adjusted Rate of Return	Rank	Average Risk Premium
Drugs	.1832	1	.1664	1	.0168
Aerospace	.1570	2	.1335	2	.0245
Chemicals	.1409	4	.1131	3	.0278
Petroleum	.1147	7	.1026	4	.0121
Rubber	.1096	8	.1021	5	.0075
Food	.1072	9	.0915	6	.0157
Electrical mach.	.1195	6	.0857	7	.0338
Automotive	.1477	3	.0754	8	.0723
Office mach.	.1408	5	.0724	9	.0684
Steel	.0825	10	.0703	10	.0122
Textiles	.0789	11	.0594	11	.0195

Source: The Rand Corporation. [5]

The first set of perturbations and calculations were performed on the standard pesticide case. It was assumed that if delays in getting to market occurred, it did not affect sales or the period of commercialization. These assumptions will be criticized later and alternative perturbations examined; however, for the first set three different perturbations were introduced: (1) a one year delay to market, but no

EXHIBIT E-8

AC 1 - STANDARD CASE

Year	Sales,S K$	R&D Costs,C K$	S-C K$	S-C Net of Taxes K$	Dep. Allow. K$	Capital Costs K$	Net Cash Flow K$	Discount Factor	Net Present Value K$
0-1		-600		-312			-312	.9516	-297
1-2		-1200		-624			-624	.8611	-537
2-3		-1200		-624			-624	.7791	-486
3-4		-1800		-936		-3000	-3936	.7050	-2775
4-5		-1200		-624		-6600	-7224	.6379	-4608
5-6	3000	4007	-1007	-524	757	-2400	-2167	.5772	-1251
6-7	6000	4809	1191	619	629		1248	.5223	652
7-8	9000	5610	3390	1763	523		2286	.4726	1080
8-9	12000	6412	5588	2906	436		3342	.4276	1429
9-10	12000	6412	5588	2906	363		3269	.3869	1265
10-11	12000	6412	5588	2906	304		3210	.3501	1124
11-12	12000	6412	5588	2906	276		3183	.3168	1008
12-13	12000	6412	5588	2906	253		3159	.2866	905
13-14	12000	6412	5588	2906	253		3159	.2593	819
14-15	12000	6412	5588	2906	253		3159	.2347	742
				Residue 1166 undep. alloc. fixed cap.				.2231	260
				Residue 2400 working cap.				.2231	535
									-135

EXHIBIT E-9

AC 2 - VARIOUS DISCOUNT RATES

Year	Net Cash Flow K$	9% Rate	Net Present Value K$	10% Rate	Net Present Value K$
0-1	-312	.9560	-298	.9516	-297
1-2	-624	.8737	-545	.8611	-537
2-3	-624	.7985	-498	.7791	-486
3-4	-3936	.7298	-2872	.7050	-2775
4-5	-7224	.6670	-4818	.6379	-4608
5-6	-2167	.6096	-1321	.5772	-1251
6-7	1248	.5571	695	.5223	652
7-8	2286	.5092	1164	.4726	1080
8-9	3342	.4653	1555	.4276	1429
9-10	3269	.4253	1390	.3869	1265
10-11	3210	.3837	1232	.3501	1124
11-12	3182	.3552	1130	.3168	1008
12-13	3159	.3247	1026	.2866	905
13-14	3159	.2967	937	.2593	819
14-15	3159	.2712	857	.2347	742
15-16	2400	.2593	925	.2231	795
	1166				
16-17			+560		-135

9.81%
for NPV = 0

additional costs, (2) a two year delay to market, again with no additional costs, and (3) a two year delay to market accompanied by a one year premature construction of the production plant. In the first two cases it was assumed the delay to market was foreseen in time to avoid premature construction whereas in the third case it was assumed the delays also resulted in plant construction at a disadvantageous point in time, i.e. too early by one year.

These results are indicated in Exhibit E-10. Two measures of the perturbation are presented. The first is the adjustment in discount rate required to reestablish a net present value of zero. The second is the loss in net present value on the basis of having adhered to the original, i.e. standard case, rate of return.

From Exhibit E-10 it can be seen that the general magnitude of the perturbation is 2500K$ and/or 2/3 percent loss in rate of return depending to an important extent on whether the plant was appreciably displaced in time. Though it is easy to claim that larger uncertainties than this are encountered in management's decision for each of its projects, it is still true that further losses will bias against R&D investment. Before concluding that delays of the magnitude considered actually result in losses, however, a different set of perturbations was performed.

If one regards that delays in a given area of public demand do not alter that demand, it would be more consistent to assume that unless new competition appears, delays have the effect also of extending the period of commercialization. This would allow the public to continue consumption at its original rate. A particular company would then enjoy an extended period of commercialization and hence higher profits provided this situation did not attract new entries into the field. All of this also presumes constant effort on the part of a given company.

This general idea was first explored by further perturbing the second case above, i.e. by assuming that a one year delay to market generated an extra two years of commercialization. This is on the basis cited, namely that at fixed R&D effort the rate of new entries was slowed by the factor 5/6; hence the period of commercialization must be extended by 6/5 or from 10 to 12 years. The perturbation calculation discloses this now to be an advantage rather than a loss, inasmuch as the discount factor had to be adjusted upward from 9.81 percent to 10.87 percent to accommodate the change. One could say that a certain amount of destructive product obsolescence had been eliminated by the maneuver.

To investigate the above in greater detail the standard sales volume was first adjusted to fix the rate of return at 10 percent. This determined the sales to be $12,274 thousand/year.

EXHIBIT E-10

Case	Discount Rate Percent	Loss in NPV K$
Standard	9.81	--
1 year delay	9.46	222
2 year delay	9.13	483
2 year delay + 1 year "plant"	8.19	1,096

EXHIBIT E-11

(no new competition)

Case	Sales K$/year	Discount Rate Percent
New Standard		
10 year market	12,274	10.00
1 year delay		
12 year market	12,274	10.61
2 year delay		
14 year market	12,274	10.82
3 year delay		
16 year market	12,274	10.77

Next it was assumed that this sales volume held constant for three cases: 1 year, 2 years, and 3 years delay to marketing. In these calculations the discount rate was adjusted to effect a net present value of zero in each case. The results are shown in Exhibit E-11. It will be observed that the rate first rises then drops, its maximum value being ∿10.85 percent. It can thus not be claimed that such delays are in fact detrimental to a profit seeking management. An incentive to invest more R&D could result. Whether or not these extra returns can be realized could depend on the possibility of new competition. This is investigated in the next set of calculations.

In this set it was assumed that an additional peer type company would enter the field if it could realize the 10 percent return, otherwise not. This can be examined by fixing the discount factor at 10 percent and adjusting sales to yield net present value of zero for the various time to market delays. This is shown in Exhibit E-12 wherein it may be observed that the sales volume drops and then rises again, the minimum value being ∼ $11,060 thousand/year. Whether or not a new competitive company at the same average sales volume of the original companies could enter the field under these conditions would depend on the number N of companies already in the field. Thus if: 12,274N = 11,060 (N+1) the public demand would permit one more competitor at 10 percent return. For this equation to hold in the instance cited N ≃ 9. In the presentation to the Panel by one company, the market fraction assumed was one-third. Thus nine companies in a given pesticide field or class would appear high. If so, no new entries would occur and the delays cited would have a beneficial effect on profits.

EXHIBIT E-12

(with new competition)

Case	Sales K$/year	Discount Rate Percent
New standard		
10 year market	12,274	10.00
1 year delay		
1 year market	11,458	10.00
2 year delay		
	11,093	10.00
3 year delay		
16 year market	11,125	10.00

In the above no allowance was made for patent limitations on the period of commercialization, as these were only slightly exceeded, and moreover it is not clear the field is open to non-peer type companies in any event.

The next group of calculations deal with the ethical drug case. These are characterized by smaller investment in plant but somewhat greater investment in R&D time and money. Also the period of commercialization is longer so that patent limitations may more readily limit the period of profitability. (See Exhibits E-13 and E-14).

The first set of perturbations were similar to those in the agricultural chemical case except that the effect of displacing in time the smaller plant was not investigated. Instead the effect of one and two year delays were calculated with no other changes and for a fixed, i.e. 15 year period of commercialization. (See Exhibit E-15).

Next a test similar to the one used in the case of agricultural chemicals was applied here. A calculation was made wherein the period of commercialization was allowed to increase in proportion to the delay in R&D. The case chosen was for a two year additional delay in time to marketing with a 20 year period of commercialization. The discount factor adjusted to effect a new present value of zero was 11.13 percent, only slightly below the initial value for the standard case, and a whole percent above the two year delay restricted to 15 years of commercialization. Without pursuing this further it was assumed that the same general result would obtain; namely, that if the total demand is regarded as fixed there is little if any detrimental effect of delay.

Finally the possible effect of patent period limitation was investigated. In this study the standard case was restructured to limit sales to a 13 year

EXHIBIT E-13

ED 1 - STANDARD CASE

Year	Sales, S K$	R&D Costs, C K$	S-C K$	S-C Net of Taxes K$	Dep. Allow. K$	Capital Costs K$	Net Cash Flow K$	Discount Factor	Net Present Value K$
0-1		-800		-416			-416	0.9516	-396
1-2		-1600		-832			-832	.8611	-716
2-3		-1600		-832			-832	.7791	-648
3-4		-2000		-1040			-1040	.7050	-733
4-5		-1200		-624		-300	-924	.6379	-589
5-6		-800		-416		-660	-1076	.5772	-621
6-7	3000	5210	-2210	-1149	128	-2400	-3421	.5223	-1787
7-8	6000	5252	-252	-131	111		-20	.4726	-9
8-9	9000	7294	1706	887	96		933	.4276	420
9-10	12000	8336	3664	1905	83		1988	.3869	769
10-11	12000	8336	3664	1905	72		1977	.3501	692
11-12	12000	8336	3664	1905	63		1968	.3168	623
12-13	12000	8336	3664	1905	54		1959	.2866	561
13-14	12000	8336	3664	1905	47		1952	.2593	506
14-15	12000	8336	3664	1905	44		1949	.2347	457
15-16	12000	8336	3664	1905	44		1949	.2125	414
16-17	12000	8336	3664	1905	44		1949	.1923	375
17-18	12000	8336	3664	1905	44		1949	.1740	339
18-19	12000	8336	3664	1905	44		1949	.1574	307
19-20	12000	8336	3664	1905	43		1948	.1424	277
20-21	12000	8336	3664	1905	43		1948	.1289	251
		2400 W.C.						.12245	294
									+787

period following issue of a patent in the second year of product development. A 12 percent discount rate was assumed and sales were adjusted accordingly. This was then compared with a further delay of commercialization of only 12 years. Sales were again adjusted to see what greater market was required to yield the 12 percent return.

Exhibit E-16 reveals the need for $\sim$17 percent greater sales.

CONCLUSION

1. The two health related chemical industries examined here have up to the present been strong, profitable and highly research intensive.

2. Though barriers may be erected, either through a genuine need to effect more sophisticated research or for additional public demand for proof of safety and efficacy, there are compensating factors which may maintain high industry profits. Of

EXHIBIT E-14

ED 2 - VARIOUS DISCOUNT RATES

Year	Net Cash Flow K$	11%	Net Present Value K$	12%	Net Present Value K$	13%	Net Present Value K$
0-1	-416	.9465	-394	.9418	-392	.9371	-390
1-2	-832	.8479	-705	.8353	-695	.8228	-685
2-3	-832	.7596	-632	.7408	-616	.7225	-601
3-4	-1040	.6805	-708	.6570	-683	.6344	-660
4-5	-924	.6096	-563	.5827	-538	.5571	-515
5-6	-1076	.5461	-528	.5169	-556	.4892	-526
6-7	-3421	.4892	-1674	.4584	-1568	.4296	-1470
7-8	-20	.4382	-9	.4066	-8	.3772	-8
8-9	933	.3926	386	.3606	354	.3312	326
9-10	1988	.3517	699	.3198	636	.2908	578
10-11	1977	.3150	623	.2837	561	.2554	505
11-12	1968	.2822	555	.2516	495	.2243	441
12-13	1959	.2528	495	.2231	437	.1969	386
13-14	1952	.2265	442	.1979	386	.1729	337
14-15	1949	.2029	395	.1755	342	.1518	296
15-16	1949	.1818	354	.1557	303	.1333	260
16-17	1949	.1628	317	.1381	269	.1171	228
17-18	1949	.1459	284	.1225	239	.1028	200
18-19	1949	.1307	255	.1086	212	.09027	176
19-20	1948	.1171	228	.0963	188	.07927	154
20-21	1948	.1049	204	.0854	166	.06960	136
W.C.	2400	.09936	238	.08046	193	.06522	157
			+202		-275		-695

particular note among these is the genuine public demand for some vital product whether it be new or old. This lends stability and inertia to the system.

3. If the high talent capable of innovating new chemical entities is still required to maintain the slower pace, one might expect profits to remain high in order to sustain that talent even though it has been somewhat redirected to the maintenance of a status quo.

4. In any case the public pays for the result, the only trade-off being perhaps the one in which the barriers were exchanged for new products. Whether that exchange is in the public interest cannot be analyzed by the methods and data of this section.

5. If the barriers become too high at some point certain type projects are not attempted even at the slow pace.

EXHIBIT E-15

Case	Discount Rate Percent	Loss in NPV K$
Standard	11.43	--
1 year delay	10.73	338
2 year delay	10.11	(extrapolated) 630

EXHIBIT E-16

Case	Discount Rate Percent	Sales K$/Year
New standard		
13 year commercialization	12.00	13,821
1 year delay		
12 year commercialization	12.00	15,944

Exhibit E-16 reveals the need for $\sim$ 17 percent greater sales.

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APPENDIX F

I. REGULATORY PRACTICES ABROAD*

The basis for policy determinations in the chemicals and health area is a composite of scientific understanding and relevant information of other types. The policies adopted are implemented through legislation and regulatory practices. They influence the ways in which pharmaceuticals, pesticides, and other chemicals are used, scientific and informational inputs to policy makers are provided, and public understandings of policy are fostered. They influence both human health and the political and emotional climate in which current policy decisions are reached, and future ones deliberated.

The governmental mechanisms established to secure the requisite insight and information, communicate it to policy makers, blend it with non-scientific considerations, use it to apply existing standards or set new rules, and communicate it to the public all contribute to influence the physical and emotional health of citizens.

Practices in the United States are discussed at length in other sections of this document. The ways in which four European nations handle policy and policy implementation in the chemicals and health area have been researched and reviewed in an effort to recognize similarities and differences that may be informative and helpful. The four are England, the Federal Republic of Germany, the Netherlands, and Sweden. Among them there are sufficient differences in population, wealth, health statistics, and 20th Century history to insure that no too-narrow basis for comparisons would be erected. The few numbers gathered on the following page provide a sketchy outline of important statistical parameters for the United States and these four European countries.

Experimental data necessary for reaching sound regulatory decisions are done by a variety of organizations.

Industrial concerns wishing to gain registration for a new pharmaceutical or pesticide or food additive must supply data supporting claims of safety and efficacy.

University and governmental research institutes maintaining programs in related disciplines such as toxicology, plant protection, and food science provide two essential resources: scientific data on a range of topics including some but not restricted only to those having immediate practical import, and scientifically active and acute individuals, able to evaluate data and arguments presented by industrial firms to gain registration for their chemical formulations.

The precise pattern varies from country to country, but this basic pattern is constant: the large majority of product-specific, applied research is done by industry.

Swedish authorities, for instance, estimate that research and related costs for the introduction of one new agricultural chemical are $5 million for the firm. The National Poisons and Pesticides Board, responsible for acting on all petitions for registration of new agricultural chemicals, has an annual budget of $300,000 for everything, including outside consultants: in the course of one year they handle applications for about 10 new active chemicals and 100 new formulations of previous approved chemicals.

Fuller state-sponsored testing is done in the Netherlands: state institutes test pesticides for performance, as well as toxicity and side effects. But these tests are few and limited, relative to those performed by a company prior to application for registration.

The funding for state-supported research institutes may be estimated through a few examples. In the Netherlands, the total government spending for medical and public health research in 1969 was $13.5 million. Germany spent $4 million for all environmental research in universities in 1970. All environmental research in Sweden is currently estimated to cost $4.6 million a year. In the United Kingdom, the Medical Research Council was budgeted at $48.4 million in 1971.

Precise comparisons among these figures and the costs of similar enterprises here are difficult at best. Perhaps it is sufficient to note that Federal programs in these areas in the United States are more splendidly funded, absolutely and on a per capita basis.

Research directed toward a more fundamental understanding of biological responses to chemical agents is conducted in laboratories of every description: independent yet government-supported laboratories, such as the German Gesellschaft für Strahlen-und Umweltforschung or the Swedish National Veterinary Institute; universities, medical schools,

* During the course of the deliberations of the PSAC Panel on Chemicals and Health, two delegations were sent to three countries of Western Europe and to the United Kingdom to observe the regulatory practices in those countries. The following pages represent summary remarks which followed on these visits.

hospitals, and agricultural colleges; governmental laboratories with a well-focused responsibility, such as Plant Protection Service of the Netherlands, or the Toxicology Research Unit of the Medical Research Council at Carshalton, England; industrial laboratories; and in some facilities jointly supported and controlled by industry and the government, such as the Netherlands Organization for Applied Scientific Research (TNO) or the British Research Associations, including the British Industrial Biological Research Association (BIBRA).

While the quality of the basic research done in these establishments is often excellent, limitations on resources and manpower are such that great reliance must be placed on larger and wealthier lands, and on the published literature: however outstanding the basic science done, especially in the Netherlands (13 million population) and Sweden (8 million), these countries will never be self-sufficient providers of all their basic research needs. They strive, then, to make sure that what science is funded is good enough to count.

In all four European countries, petitions for registration of new pesticides, drugs, and food additives are evaluated by the staff members of the appropriate governmental agency, and decisions are reached by an advisory board or committee, composed of civil servants, university scientists, and other professionals. These are individuals of experience and tested judgment, some with specialized scientific competence, others having broader and/or different special strengths.

For solid scientific findings to have a positive influence on policy, good science must first be done (requiring support in a steady fashion) and it must be appreciated by the policy makers. The normal European practice of having men and women from scientific and non-scientific professional backgrounds on regulatory boards aids in achieving this needed appreciation: whether such boards are making a judgment on a new drug application for registration or considering a new legislative proposal suggested by a governmental ministry, they can deal effectively with the scientific aspects, including the recommendations of any scientific advisory panels that may have contributed an opinion, since board members understanding the science may be under-

EXHIBIT F-1

COMPARATIVE STATISTICS, FOUR EUROPEAN LANDS AND THE UNITED STATES VITAL STATISTICS, FOOD CONSUMPTION, HEALTH SERVICES, DOMESTIC PRODUCT

	England[1]	Germany[2]	Netherlands	Sweden	United States
Population (millions)	49	60	13	8	205
Population Increase (%)/year	0.6	1.0	1.2	0.8	1.2
Population Density (per km²)	324	240	319	18	22
Expectation of Life at Birth					
Male	68.7	67.6	71.0	71.9	66.6
Female	74.9	73.6	76.4	76.4	74.0
Expectation of Life at 50					
Male	22.9	23.0	24.9	25.7	22.8
Female	28.2	27.8	29.2	29.2	28.2
Infant Death Rate (per 1000 live births)	17.9	23.5	12.7	13.1	19.8
Food Consumption Per Capita					
calories/day	3180	2960	3030	2990	3240
g protein/day	88	81	84	83	96
Population Divided by					
Hospital beds	100	90	190	70	120
Physicians	860	580	840	800	650
Nursing personnel	332	336	255	235	210
Gross Domestic Product					
thousand $ per capita	2.3	3.3	2.6	3.6	4.6

[1] "England" in some listings should read "England and Wales", in others "United Kingdom".

[2] Federal Republic of Germany.

Source: "Demographic Yearbook 1970" and "Statistical Yearbook 1970"

stood by their non-scientific colleagues: they know one another through usually long-standing service on the board.

This is not the common practice in the United States. Scientific advisory mechanisms are considered more as one level of input in a complex decision-making process than as one component to be considered at every level as policy alternatives are weighed.

Better integration of the results of good science with the decision-making activities of governmental agencies having responsibilities in the chemicals and health area might be achieved, and better professionals recruited for such service, through maintaining a concern for the facts of the matter at every stage of decision-making deliberations.

The extent to which the deliberations of the review committees are final or merely advisory to a minister, and are public or private, is not uniform. The national boards and regulatory agencies in Sweden have the final say, and make publically available their decisions and reasons. Company-supplied data are held in confidence, but all correspondence into, out of, or within such a board is available for public inspection. In England, by contrast, the review committees make recommendations to a departmental administrator which are neither final nor public. The Netherlands and Germany fall between these extremes.

A close link between universities and governmental regulatory agencies is aided by many joint appointments: a prestigious university chair is often coupled with a directorship of a state-sponsored non-basic research institute. Thus practical issues and basic science are urged to illuminate and orient one another.

Public opportunity for participation in specific regulatory decisions is very small, while there is wide scope for public inputs on new legislation. Special interest groups and private citizens have fair opportunity for presenting their criticisms and suggestions on draft legislation, and for making their opinions felt. But they have no immediate way to control whether or not DDT will be permitted in the forests to protect tree seedlings.

A governmental agency faced with responsibility for a particular decision may need information of a specific sort. It may go after such information through in-house efforts, contracted studies, and short-term narrowly-defined research projects. All these tactics are used. In Sweden, for instance, the Naturvårdsverk maintains a program of water and air sampling needed to make and enforce pollution standards; the National Veterinary Laboratory analyzes fish and small mammals collected from throughout the country to monitor pesticide residues and metal ion concentrations in wildlife and indirectly in the environment. The TNO Committee in the Netherlands can commission research or study efforts it sees may be necessary. The Ministry of Science and Education of the Federal Republic of Germany has the authority and funds needed for special continuing as well as ad hoc study and experimental efforts.

Such short-term informational needs are recognized as important and absolutely necessary; in the European lands visited, they are fulfilled by the agencies in need, acting through governmental laboratories or independent contractors. They are not directly competitive with long-term scientific undertakings for manpower and funds. For instance, in Germany funds for fundamental research are appropriated by the Ministry of Science and Education to the German Research Foundation, which then distributes them to research institutes and projects throughout the country according to some scientific priority system. The Ministry also offers matching grant funds to industries, to attempt to stimulate new technological developments leading to cleaner production methods, and lets contracts to research centers for highly applied information-gathering projects. The decision as to the proper proportion in financial support between short-term studies and long-term scientific investigations is made by a politically responsible cabinet; no agency having a regulatory function and a primarily short-term focus is entrusted with funds to be spent at its own discretion for both short-term and long-term research projects, and no agency charged with long-term responsibilities for fostering creative scientific thought and experimentation is entrusted with authority over funds to be spent either for science or for information-gathering efforts that may help a regulatory body with its work immediately.

Detailed policy, for instance pesticide residue tolerances for foods or registration of a food additive, is typically made in Europe at a working-group level. A board or commission charged with responsibility for the topic deliberates, renders a decision, and makes it public. High public officials responsible for national policy goals are not directly involved, nor can they second-guess the board or commission and reverse its judgment. The system, then, tends to keep whatever controversies that arise more limited to factual and judgmental disputes; the political convictions or style or ambitions of the Minister of Health are irrelevant. Appeal of decisions made by boards and commissions may be made in orderly ways, much as court decisions in this country may be appealed. Regulatory decisions, then, are not so sensitive to the tides of political pressures and opinions.

The European countries manifest an increasing awareness of the issues related to chemicals and health, by the public, civil servants, and politicians. This awareness is reflected in journalistic rhetoric and more importantly in new legislative proposals and increased appropriations. The voluntary system controlling therapeutic drugs in

England is now being supplanted by one based on explicit statutory authority. Within the last year Sweden and the Netherlands have changed the structures of ministries and administrative agencies to improve and augment governmental control of chemicals. In Germany, interministerial working groups have, for the first time, been formed to face the environmental pollution problem in all its ramifications, and a constitutional amendment to give the Federal government more authority over environmental chemicals has been proposed. In Europe, as in America, the problems are seen and governments are attempting to provide improved health and safety through new programs and priorities.

Current legislative authority is full of loopholes. In Germany there is authority over pesticide residues on food derived from plants, but not when it is of animal origin. In Sweden, food additives are controlled by agencies given authority over substances in foods that are "toxic or damaging in any other way." Challenges through the courts of rules set by the Department of Food Hygiene as they exercise this authority could reveal the fragility of such a vague legal base. The Dutch parliament has asked for a new law requiring better information on the use of pesticides. In England, no statutory regulations govern pesticides!

The international aspects of regulations and practices are more acutely sensed in Europe. Air and water pollution from neighboring countries is a constant and deeply resented occurrence and national boundaries may be a serious barrier to agricultural produce, dairy products, and meats. Cooperation with the countries of Eastern Europe on environmental and public health matters is still a fond hope, a worthy enterprise for some future year.

Increased concern over the environment and human health has focused attention on the importance of long-range land-use planning. The location of industrial facilities and the development of new residential districts are seen to be related to problems in water and air pollution, and planning efforts commensurate with the task are being contemplated.

The participation of the press and special interest groups in the environmental and health-care debates are similar in character and extent to what has evolved in the United States over the past few years. Public confidence in the ability and objectivity of those making regulatory decisions may be slightly higher in Europe than in America, but there are still more than a few wishing to ban all "synthetic chemicals" and imagining that all regulatory boards are cat's-paws of rapacious chemical industries.

The four European countries visited have balanced the allocation of resources between better understanding and better control of chemicals in quite different ways. In the Netherlands, very thorough food inspection programs, public health consciousness, and preventative medicine are stressed to achieve a maximum beneficial return from currently available knowledge at the same time as long-term health research programs are maintained at a significant but not massive level. Sweden has not yet felt the need for a national center for long-term toxicological testing to be worth the cost, but spends heavily on public information efforts. In Germany, the opposite option is being pursued, a choice partly forced by the circumstances of federal-state relationships: the federal authority can invest in a new laboratory complex for the toxicological evaluation of chemicals in microorganisms, single cells, cell cultures and test animals (90,000 mice and several hundred dogs), to give special emphasis to persistent and potentially dangerous substances, but the government in Bonn may not sample foodstuffs in the market place or water from rivers in the Länder.

Neither advisory bodies nor regulatory agencies in England, Germany, the Netherlands, and Sweden are failing to cope with their responsibilities in spite of modest funding and imperfect knowledge. Though smaller in size and financial resources, the Netherlands and Sweden especially have achieved particularly impressive health statistics. Through the use of boards, concentrating the maximum possible information and authority and accountability at the lowest possible level, comparatively effective structuring of the scientific-administrative interface and sound regulatory decisions have been obtained. The division of resources between short-term studies and long-term basic science is not placed in the hands of an administrator of a regulatory agency or a basic science foundation. The resource allocation is argued and made by politically responsible and accountable groups in cabinets and parliaments. Full application of existing knowledge is attempted: deeper understanding of chemistry and biology is recognized as necessary for the future, but it is not accepted as the sole element limiting the health and well being of men and women today.

These three points seem the most pertinent. All three involve decision-making (regulatory actions, standards, and laws; research funding priorities; the balance between using and getting (greater knowledge) at the heart of public policy issues in the chemicals and health area.

Regulatory decisions on chemicals having an impact on human health in England, Germany, Sweden, and The Netherlands are typically made by groups of experts to whom this responsibility has been entrusted. The decisions are reached in nearly complete insulation from transient political pressures, and are generally accepted to be probably as wise and sane as could be acheived.

In the United Kingdom, regulatory decisions on drugs, food additives, and pesticides are made by committees composed of academic scien-

tists and outside professionals, aided by civil servants handling preliminary evaluations and informal business with the petitioning industries before decisions are rendered. The Committees do their work in private, and do not generally provide justifications for their decisions to the public.

The drug-control authority is exercised by the Committee on Safety of Drugs. It is a group of experts, not a representative body, which scrutinizes new drugs proposed for clinical trials, those performing well in clinical trials and proposed for marketing, and drugs on the market. Its subcommittee structure reflects these three aspects of medicines; there are subcommittees on Toxicity, on Clinical Trials and Therapeutic Efficacy, and on Adverse Reactions. A Vaccine Advisory Group of distinguished experts gives recommendations to the Committee on the safety of new vaccines prior to clinical trials.

Independent experts serve on the subcommittees together with members of the Committee on Safety of Drugs. They meet monthly, and their advice and recommendations are presented at the monthly meetings of the Main Committee.

The full-time professional staff for the Committee, seven physicians and two pharmacists, are civil servants working for and under the direction of the independent experts. They are widely experienced in drug evaluation, and work efficiently and responsibly. Their staff work on new drug submissions leads to a report sent to committee members, together with a copy of the full submission, within a period of three to four months. Submissions for reformulations are assessed within a few weeks.

The Committee does not specify rigid pre-clinical testing requirements for new drugs; the manufacturer has the responsibility for planning the appropriate assessments of a compound's chemistry, pharmacodynamics, metabolism, acute and intermediate term toxicity, teratology, and interactions with other common established drugs.

Informal contact with the Committee is maintained by the physician responsible for the clinical trials for the pharmaceutical company.

To get marketing approval, adequate evidence of efficacy in relation to safety must be presented. The quality of work done is more important than the quantity; the question is simply, "Do the clinical trial data provide proper support for the use of the new drug in the proposed clinical indications?"

Occassionally a "monitored" release or limited marketing approval is granted.

The Committee on Safety of Drugs exists to provide an authoritative and independent second opinion at each stage of a drug's development, thus attempting to achieve vigilant safety monitoring and yet to impose no unnecessary impediments to the emergence of important new drugs.

The Committee on Safety of Drugs assesses some 60 new drug applications, 800 reformulations, and 3,000 adverse drug reaction reports each year.

The Committee is not concerned with where clinical studies were conducted, as long as the documentation is satisfactory and the quality of the work high. There is no approved list of clinical investigators. No attempt is made to judge the comparative efficacy of safe drugs in the same therapeutic category.

A report on the work and decisions of the Committee is published annually by Her Majesty's Stationery Office.

In the Federal Republic of Germany, regulatory decisions on applications for registrations of new agricultural chemicals are made by the Federal Biological Institute after adequate testing.

The chemical formulation must prove effective for the intended applications, comply with trade regulations, and have no injurious effects on human or animal health, when used according to prescribed techniques of application.

The professional staff of the Institute's toxicology section analyze the data submitted with applications for registrations, and conduct additional research with the formulations, both in the laboratory and through field trials. These professionals are also engaged in the long term research programs of the Institute, dealing with the toxicology of the especially persistent and widely used agricultural chemicals, and on substances suspected of being carcinogenic.

A rough analogy would be for research scientists at an NIH laboratory to be responsible both for their toxicological investigations and for the decisions on agricultural chemicals now made by the EPA administrator. The expert group making the regulatory decisions is within the civil service and it is scientifically active and competent. The expert committee includes participants from several testing centers and laboratories, and representative public health authorities.

A similar reliance on in-house expert opinion is in evidence in The Netherlands. The regulatory mechanisms are closely structured into the governmental ministries.

A firm petitioning for registration of a new drug in The Netherlands, for instance, must send with the application all data obtained in their testing programs and must supply a sample for chemical control testing by governmental laboratories.

The petition is considered by three groups within the Ministry of Public Health and Environmental Hygiene. Clinical data are analyzed by a pharmacological therapy group; experimental data for animal tests by a pharmacy group; and chemical data by the chemical control laboratory. Throughout the review process, questions or concerns may be raised informally with the petitioning firm for clarification.

The bureaucratic divisions for the Registration of Pharmaceuticals may

and often does seek the counsel of outside experts, but the decisions are made internally, within the Ministry.

About 70 new drug applications are received and processed each year. Judgments on petitions for registrations must be rendered within certain time limits.

Clinical testing of a new pharmaceutical is possible whenever a doctor is willing to undertake the test program. An adverse drug reactions bureau is maintained, but it has not been wholly successful.

Although the State may recognize needs for certain new drugs, such as anti-cancer agents or a substitute for digitalis for treating various heart conditions, it feels no responsibility toward the development of new drugs. They only ask that people get what the firm marketing the drug claims, and that the benefit/risk ratio of the preparation is reasonable. The relative efficacy issue is not addressed through science at the reviewing stage, but later in the market place.

An Advisory Commission on Pharmaceutical Compounds advises the Ministry on which substances may be sold with or without prescription. A State Institute is maintained which tests for toxicity of pharmaceuticals to supplement the results coming from private laboratories.

The execution of policy in the chemicals and health area in Sweden rests with administrative boards, such as the National Board of Health and Welfare, the National Veterinary Board, and the National Poisons and Pesticides Board. The board members serve 3-or 4-year appointments.

These boards are remarkably independent of political influence. Ministers, including the Prime Minister, may not give orders or any binding directives to a Board, nor can questions concerning individual administrative decisions made by the Boards be raised in the Riksdag, the Swedish parliament.

All documents received by or sent from public institutions such as these boards are open to public inspection at once: the few exceptions, such as military and diplomatic secrets, and information on the private circumstances of individuals, are stipulated by specific legislation.

An example of such a regulatory agency is the National Poisons and Pesticides Board, responsible for the registration of pesticides. Staff work for the Board is done by seven or eight professionals and an equal number of clerks and typists. Administratively, the Board comes under the Ministry of Health and Welfare; it has an annual budget of about $300,000, everything included—staff, clerical help, and two inspectors of chemical manufacturing plants.

Firms wishing to register a new pesticide submit an application and supporting documentation, attesting to the efficacy and safety of the product. A staff member of the Poisons and Pesticides Board examines the documents; he may and usually does use the mails or telephone to seek additional information, from the firm or from other knowledgeable people in the governmental agencies, universities and research institutes, agricultural colleges, the Plant Protection Institute, or elsewhere.

When an adequate basis for a decision has been obtained, the petition for registration is presented before the Board at one of their monthly meetings. The staff member responsible for examining the application and documentation answers questions and participates in the Board's consideration of the merits of the case. The Board makes the decision to approve, reject, or defer action on the application.

The Board itself is composed of eleven members and eleven alternates. The Chairman is a full-time staff member of the agency; and others come to the monthly meetings bringing expert opinion and perspectives based on diverse professional activities. Among the Board members there are four professors, two members of the Riksdag, a pharmacist, a consulting physician, the director of the Food Additives section of the Ministry of Commerce, an engineer, and the technical director of a chemical firm. The professors are affiliated with the National Veterinary Institute, the National Plant Protection Institute, the National Medical Advisory Council and the Toxicological Institute of the Karolinska Hospital, and the National Institute of Public Health. Among the alternates there are men associated with the Veterinary Colleges, the National Board of Industrial Safety, Lund University, the National Pharmaceutical Laboratory, the Provincial Physicians Organization, and the National Office for Technical Development. Thus both broad experience and interagency communication on a person-to-person basis is focused as the Board renders its judgments.

The Poisons and Pesticides Board handles applications for about 10 new active chemicals and 100 new formulations of previously approved chemicals each year. Registration is granted if the Board considers the preparation both safe and effective; the material need not be more effective than products already on the market.

Test results submitted by the manufacturer and the research of the National Plant Protection Institute, the Swedish Agricultural Colleges, field research institutes in other northwestern European countries, and laboratory research findings in the published literature will all be weighed as the application is considered.

Whenever the Board makes a decision, it outlines the scientific basis for that decision. Usually the decisions are communicated only to the firm seeking registration. When public interest requires a broader publicity, the Board cooperates with the press and TV in an attempt to inform the citizenry. Policy changes regarding DDT and 2,4,5-T offer recent examples.

The two members of the Swedish

parliament on the Board were earlier a farmer and an electrician. They are expected to represent both political viewpoints and the interests of producers and consumers. When the board has business to conduct with the Riksdag or the Ministries, they do so directly, not through their two Riksdagmen.

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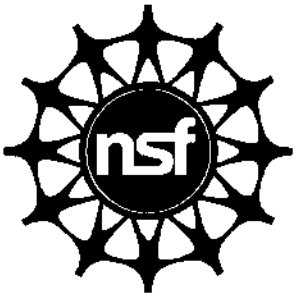
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