Researching Health Risks

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Foreword

In everyday life, we evaluate the risks associated with various activities and make choices, considering such things as benefits, costs, convenience, and past experience. As a society, we must make similar choices. The process of health risk assessment can help guide the decisions necessary for living in a world full of chemicals, radiation, and fibers, both natural and manufactured.

Risk assessment illuminates the hazards that result from exposure to a substance and the magnitude of the risk associated with different levels of exposure. Results of health risk assessments are used as one of the inputs in formulating regulatory decisions. Those decisions affect expenditures for regulatory compliance or treating exposure-related diseases that can total billions of dollars.

Because of the public health and economic implications of risk assessments, Congress has grown increasingly interested in the accuracy and scientific underpinning of risk assessment. An indication of this interest was the request by the House Energy and Commerce Committee and the House Science, Space, and Technology Committee to the Office of Technology Assessment (OTA) to analyze the nature, organization, and management of federally supported research on health risk assessment. This focus is important because such research provides the scientific foundation for health risk assessments.

In this report, OTA describes the Federal Government's research activities that are intended to improve health risk assessments. One of the findings of this Report is that the attention and resources allotted to health risk assessment research are not commensurate with its national impact, A particular problem is that research is fragmented within and across the Federal agencies, greatly complicating setting research priorities. Consequently, the agencies are not focusing on areas of research likely to have the most far-reaching effect on policy+ specially risk assessment methodology-and they are unable to harness fully the rapid advances in the basic biological and biomedical sciences.

Many individuals and institutions contributed their time and expertise to this project. Experts from government, industry and academia served on the project's advisory panel and workshop on research structure and organization and reviewed drafts of chapters and the full report. OTA gratefully acknowledges their contributions and assistance. As with all OTA analysis, however, responsibility for the content is OTA's alone.



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NOTE: OTA appreciates and is grateful for the valuable assistance and thoughtful critiques provided by the advisory panel members. The panel does not, however, necessarily approve, disapprove, or endorse this report. OTA assumes full responsibility for the report and the accuracy of its contents.

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Summary, Issues and Options 1

Health risk assessment provides a systematic approach to evaluating and estimating risks to human life and well-being. Risk, as it pertains to the health effects of toxic substances, is the probability of injury, disease, or death for individuals or populations who undertake certain activities or are exposed to hazardous agents. It is sometimes expressed numerically (e.g., one excess cancer death in 1 million exposed people is termed a 10^{-6} risk of cancer). If quantification is not possible or necessary, risk may be expressed in qualitative terms such as low, medium, or high risk. Health risk assessment is a synthesis of the following four steps: hazard identification, dose-response analysis, exposure assessment, and risk characterization (figure l-l).

The primary sources of data for assessing risks to human health are from epidemiologic, toxicological, structure-activity relationship, and exposure studies. But those data are usually incomplete, failing to describe the risk from the exposure being considered. The incompleteness of the data requires the use of extrapolations to make predictions. Common extrapolations are from measured effects in people exposed to high concentrations of substance to the effects expected at lower exposures, from the results of animal tests to predictions of effects in humans, and from observations of effects from one route of exposure to estimates of effects from another route.

To perform those extrapolations, Federal agencies use assumptions or science policy choices to bridge gaps in data or knowledge. Because assumptions and policy positions contain value judgments and a substantial measure of scientific uncertainty, they are the main areas of controversy in risk assessment.

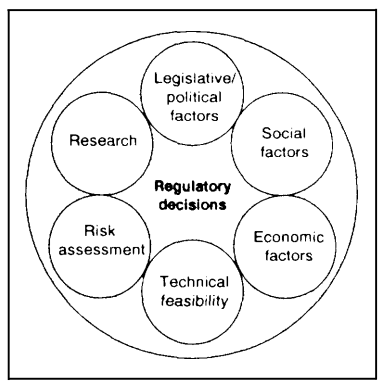
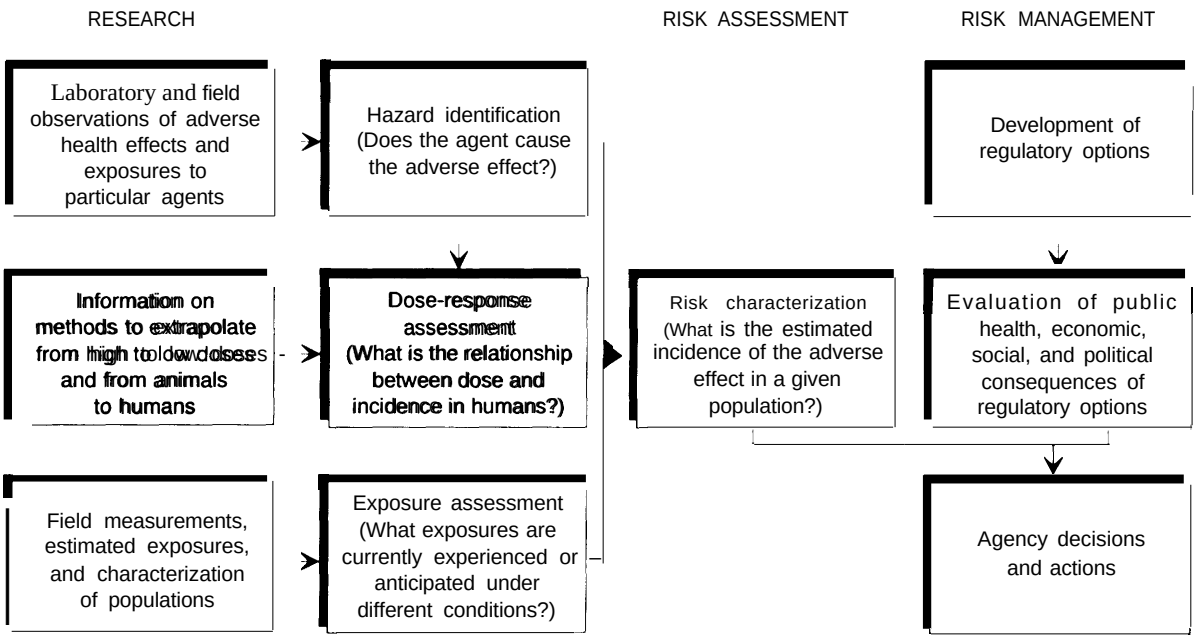


Figure I-I—Elements of Risk Assessment and Risk Management



SOURCE: National Research Council, *Risk* Assessment *in the Federal Government: Managing the Process, 1993.*

But, however uncertain the results of health risk assessments may be, they provide the foundation for health risk-based decisions (e.g., emission standards for incinerators). Those decisions affect expenditures for complying with regulations and medical expenses for exposure-related diseases that can total billions of dollars.

With so much at stake, it seems fitting to seize opportunities to use scientific research to narrow the scope of uncertainty in health risk assessment. In its landmark 1983 report, the National Research Council (NRC) concluded that improving the quality and comprehensiveness of knowledge is by far the most effective way to improve risk assessment. The decade following the publication of the NRC report saw impressive advances in the biological and biomedical sciences and provided regulatory agencies with considerable experience in conducting risk assessments and applying risk assessment methods. This report reviews Federal research efforts to harness those advances and experiences and develop abetter knowledge base for health risk assessment.

In this study, the Office of Technology Assessment (OTA) analyzed the nature and organization of federally supported research on health risk assessment and examined whether such research was adequately supported and managed. The first section of the report summmizes the results of the survey OTA conducted of Federal programs and identifies the resources, research priorities, trends, and gaps of current research in this area Subsequent sections describe the linkage of research to decisionmaking and the limits of research-based information in making social decisions, using management of the risks associated with radon exposure as a case study. A final section describes prospects for the future, including promising areas of research on risk assessment and factors to enhance the chances of success in the endeavor.

Table l-l-Categories of Health Risk Research

Methods Development

Method and model development-Developing tests and structure-activity analysis for identifying toxicants; developing models for predicting human exposures; developing methods for extrapolating effects, dose, and dose-response from laboratory study results to humans. Activities for method and model development include:

- Toxic effects identification and extrapolation
- Exposure extrapolations
- Dose-response extrapolations
- Uncertainty analysis

Methods *evacuation and validation--The* iterative process for validating new methods by comparisons to methods of known and established veracity. When validated, methods can be applied to risk assessments.

Basic Research

Toxicity mechanisms--Research to determine the nature, sequence, and combinations of events that result from exposure of test animals or humans to toxicants. This includes the study of the concentration of the toxicant or its metabolize that reaches the site **of action,** the rates and nature of the reactions with target organs or tissue that are causally linked to disease or the development of toxic effects, and an understanding of how the toxic effect comes about.

Biological and biomedical--Research on the structure and function of molecules, ceils, organs, physiological systems, and organisms. The resulting knowledge of comparative genetics, biochemistry, and physiology can be used to guide studies on toxicity mechanisms or reduce uncertainty in effects, dose, and **dose-response extrapolations.**

Chemical and physical sciences--Research on physical and chemical properties that govern absorption, distribution, fate, transport, and transformation in the environment and in biological systems.

Chemical-Specific Data Development

Toxic effects--Research designed to identify the toxic effects of agents and the nature of dose-response relationships under defined conditions of exposure. Activities include:

- Human studies
- Whole-animal studies
- Mammalian tissue, organ, and cellular studies
- Microorganism and other studies

Human exposure data--Measuring toxicant levels in different media or commodities and biological materials to test predictive models and to validate measurement methods.

SOURCE: Office of Technology Assessment, 1993.

HEALTH RISK ASSESSMENT RESEARCH AT FEDERAL AGENCIES

OTA surveyed Federal programs that conduct research on the toxicity of environmental pollutants, occupational toxicants, and toxic contaminants in food. It collected information through written requests for data, following up those requests with interviews of agency representatives and visits to agency laboratories.

Survey of Federal Research Activities

To narrow its range of inquiry, OTA restricts risk assessment research **to two types** of activities: 1) generalizable research to improve methods for assessing the risks of adverse health effects from food contaminants and environmental and workplace exposures, and 2) research to improve estimates of risks from exposure to specific agents. Because of the controversies that surround the methods for evaluating and estimating risks from exposure to agents suspected of causing cancer, this report frequently uses research to improve the assessment of risk from potential carcinogens to illustrate the directions and needs of research on health risk assessment in general.

Given that framework, OTA divided health risk assessment research into three key areas (table l-l). Two of the areas encompass more general research, and the third encompasses chemical-specific research. Methodological research, the first area, is specifically aimed at

improving the approaches and methods used for assessing risks. The second, basic research, contributes to an understanding of how environmental agents perturb normal biological functioning. The third category involves research that expands the database about specific chemicals for use in risk assessments. The results of all three types of research are crucial; inadequate development in any one area could impede progress toward the overarching objective of making risk assessment more credible and its results more widely accepted. For instance, the models developed in methodological research depend on the results of basic research and chemical-specific data development.

RESEARCH TO IMPROVE HEALTH RISK ASSESSMENT METHODS

OTA sees the goal of research on health risk methodology as development of better methods for extrapolating results: from animal models to humans, from high to low exposures, and from emission data to predictions of population or individual exposure. It also encompasses efforts to estimate uncertainty and develop new methods for toxicity testing. An important and often overlooked part of methods research is evaluating and validating the methods with experimental data.

Many scientists argue that methodological research holds the most immediate promise for substantive improvement of risk assessments. To begin with, generic methodology research, in contrast to chemical-specific studies, can have considerable impact on assessing the risks from exposure to many different chemicals and radiation. Moreover, when the methods are directed at the most uncertain aspects of risk assessments (extrapolations from high to low doses and from animal models to human populations and predicting the risk of chemicals for which few or no toxicity data exist), they can reduce the range of uncertainties in current risk assessment approaches. Because of a number of characteristics, methodological research falls in between basic and chemical-specific research, making it a bridge between basic and applied efforts. In other respects, however, this research is sufficiently unique that its practitioners refer to it as "risk science.

BASIC RESEARCH TO SUPPORT RISK ASSESSMENT

For the purposes of this report, basic research is separated into two types: basic health risk research and basic sciences research. Basic health risk research investigates the mechanisms of disease associated with exposure to toxic agents. These studies examine the fate and transport of chemicals and physical agents, the avenues of exposure, and interactions with living systems and biological tissues, all of which feed into health risk assessment research. The focus of basic health risk research on the application of results to risk assessment problems and opportunities sets it apart from the basic sciences.

Basic sciences research encompasses the basic biological and biomedical, chemical and physical sciences. Although some research in the basic sciences contributes to risk assessment research, basic sciences research is a very broad endeavor, and it is not included in OTA's analysis of relevant research. These studies examine the structure and function of molecules, cells, organs, and physiological systems and their relationship to the functioning organism, as well as the properties of chemicals and physical agents.

Of the three types of health risk assessment research, findings from basic research usually require the most time to be incorporated into decisionmaking. The research has also been generally characterized as having the lowest probability of success. Nevertheless, it can serve as the foundation for developing new methods in generating or applying primary data for health risk assessment and affect risk assessment in a far-reaching way, as it does other applications of science. Recently, techniques and findings from basic research have been rapidly incorporated into health risk research. Within the past several

years, for example, many molecular biological principles and techniques have proliferated throughout the field of toxicology.

CHEMICAL-SPECIFIC DATA DEVELOPMENT

Chemical-specific data development identifies the toxic effects of agents and characterizes dose-response relationships under defined conditions of exposure. Efforts to identify toxicants probably constitute the broadest and most diverse type of data development. Usually, they involve testing agents in laboratory animals, sometimes complemented by results from epidemiologic studies. This type of research also includes collecting data on exposure of humans to environmental agents. Some scientists dismiss the idea that collecting or gathering data using "routine" tests or monitoring methods is research. In contrast, the majority of scientists who advised OTA in the study and who reviewed drafts of this report voiced the opinion that such activities are properly classified as research. In OTA's evaluation of research funding, only two Federal agencies reported collection of exposure data as a research activity, but many included toxicity testing in research activities. The programs that carry out toxicity tests do more than provide the basic information for risk assessments, they also do research that leads to better tests and basic research on mechanisms of disease causation.

Resources and Priorities for Research

The Federal Government's support of research on health risk assessment extends from basic studies in the biological and biomedical sciences to toxicity testing and methods for extrapolating observations from one setting to another. That breadth was evident during OTA's attempts to evaluate the funding devoted to improving health risk assessments. Under the broadest definition of research that affects health risk assessment, a significant portion of the Federal Government's obligations in health research and development (R&D) generally can be considered as contributing to the effort.

OTA used the research objectives and the three categories of risk assessment research discussed above, which parallel the categories used by the executive branch,[1] as the framework for the analysis of the research funding. OTA's call for information from the various Federal agencies resulted in estimates of resources that were highly dependent on how the responder classified agency research activities. OTA concluded that reliable estimates of expenditures for health risk assessment research had not been obtained; nonetheless, OTA was able to discern some general trends and directions.

using Summary data issued between 1981 and 1991 from the National Toxicology Program (NTP) review of research related to toxicology as a surrogate for health risk R&D,[3] OTA determined that total support of health risk assessment research increased from $336 to $520 million, a 55 percent increase before adjusting for inflation. During the same period, Federal obligations for health R&D, as reported in the National Institutes of Health data book, increased from $5.0 to $10.7 billion, a 123 percent increase before adjusting for inflation (figure 1-2).

Using the above data, OTA estimated health risk R&D's share of total Federal health R&D dropped from 6.8 percent in 1981 to 4.9 percent in 1991. Moreover, this relative decline in health risk R&D took place during a period of expanding Federal legislation and responsibilities to protect

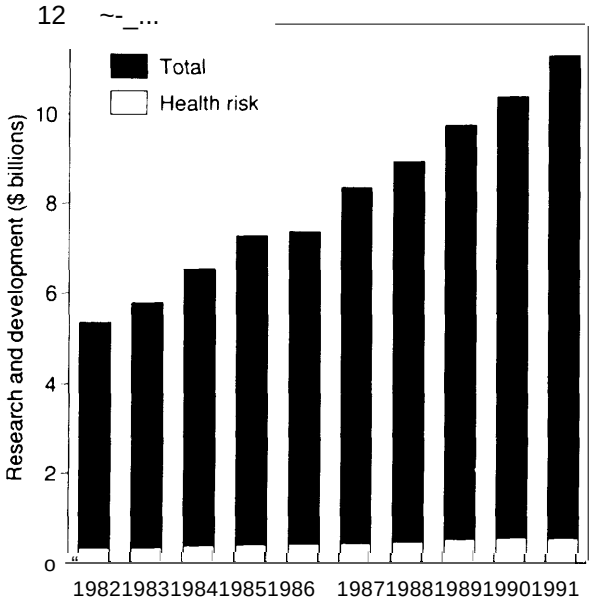
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[1] The NTP Reviews of DHHS, DOE, and EPA Research Related to Toxicology compiles data 011 agency programs in the categories of Basic Toxicology Research, Toxicology Testing, and Toxicology Methods Development.

[2] The NTP review also includes human studies as research related to toxicology.

[3] OTA's survey in 1993 indicates health risk research is also carried out by the Department of Defense, Department of Agriculture, the consumer Product Safety Commission and Nuclear Regulatory Commission. NTP data did not cover resources for those agencies. However, their contributions are small relative to the agencies covered in the review.

Figure 1-2-Funding fo Federal Health Research and Development, Fiscal Years 1982-1991

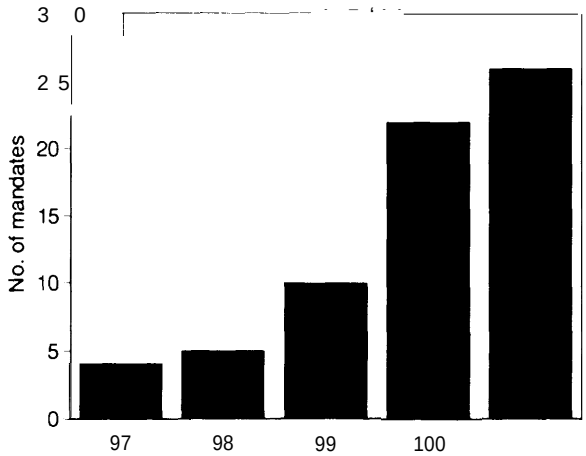


SOURCES: National Institute of Health Data Book, 1992; Review of Current DHHS, DOE and EPA Research Related to Toxicology, Fiscal Years 1982 through 1991, National Toxicology Program, U.S. Department of Health and Human Services.

human health from environmental pollutants. During that period, the number of environmental legislative mandates increased with each successive Congress-horn 4 in the 97th Congress (1981 and 1982) to 26 in the 101st Congress (1989 and 1990) (figure 1-3).

In addition the NTP data also illuminated trends in how the various agencies apportioned support and resources for methods development, basic toxicology, and testing (data development) (figure 1-4). In general, over the 1980-92 period, research agencies such as the National Institute of Environmental Health Sciences (NIEHS) and the National Cancer Institute increased the percentage of basic toxicological research that they conducted. In contrast, regulatory agencies such as EPA and the Food and Drug Administration (FDA) devoted a larger proportion of their health R&D to methods research than did the research institutes.

Figure I-3-Environmental Legislative Mandates



SOURCE: Office of Technology Assessment, 1993.

The personnel figures, in full-time equivalents (FTEs), devoted to this research reflect the size of the intramural program. In general, the regulatory agencies have sizeable intramural programs compared to their R&D budgets, while the research agencies support relatively larger extramural programs. For example, these data show that NIEHS devotes the most resources, in both dollars and FTEs, to health risk research. EPA, in contrast, has FTEs nearly equivalent to NIEHS, but only about one-third of the R&D budget.

Based on fiscal year 1993 estimates in the OTA survey of research (table 1-2), less than 11 percent ($65 million) of the total R&D budget of $600 million for environmental and occupational health and food safety is devoted to research on methods. It is possible only to estimate roughly the total amount that was actually spent on methods research during the period, because of the difficulties in categorizing the research. Nevertheless, the small size of the risk research analysis programs at the National Center for Toxicological Research of FDA and the National Institute of Environmental Health Sciences, and the reported part-time participation of researchers at the regulatory agencies, support a conclusion that methodological research is underfunded.

Table 1-2—Health Risk Research and Development Estimates, 1993 **(In millions of dollars)**

Agency	Health risk research*		Agency total: health or biomedical research**
	Total	Methods	
National Institute of Environmental Health Sciences.	129.0	14,0	251.2
Department of Energy	10.0[a]	3.0[a]	90.0"
Department of Defense	19.6	2 . 5[b]	300,0'
U.S. Department of Agriculture . . . . . .,	11.5	0.5	11 .5[nd]
Agency for Toxic Substances and Disease Registry	16.9	0.0	16.9[nd]
Environmental Protection Agency	32.0	21.3[d]	49.0[e]
Food and Drug Administration (other than NCTR)	13.0[a]	3.5a	1 3 .[nd]
National Center for Toxicological Research	33.6	7.6	38.9*
National Institute for Occupational Safety and Health.	49.0	6.1	49.0*
National Cancer Institute ., ...	82.0[a]	4.4[a]	1,981.4
Other NIH	140.oa	2.2[a]	6,929.9
Alcohol, Drug Abuse, and Mental Health Administration . .	64.0[a]	0.0[a]	1,164.1
Total	600.6	65.1	10,894.5

a Estimat,based on agency's 1992 funding for research on toxicology as reported in the National Toxicology Program Review of current DHHS, DOE, and EPA Research Related to Toxicology, Fiscal Year 1992.
b Calculated as 13 percent of agency R&D for health.
c Steinberg, 1993. *Journal of NIH Research* 5:35. Data on biomedical research, which excludes $210 million for breast cancer research.
d Research t. Improve Health Risk Assessment program estimated to be $5 million; $21.3 million is sum of funding for human exposure, health effects, and risk assessment methods.
e Figure represents Health Effects Research Laboratory total budget: EPA-wide data are not available.
nd No data (research related to toxicology was used).
● Based on data from the OTA survey of agency resources.
● "U.S. Congress, CRS, 1993. Research and development funding; fiscal year 1993; issue brief (IB2062).

SOURCE: Office of Technology Assessment, 1993.

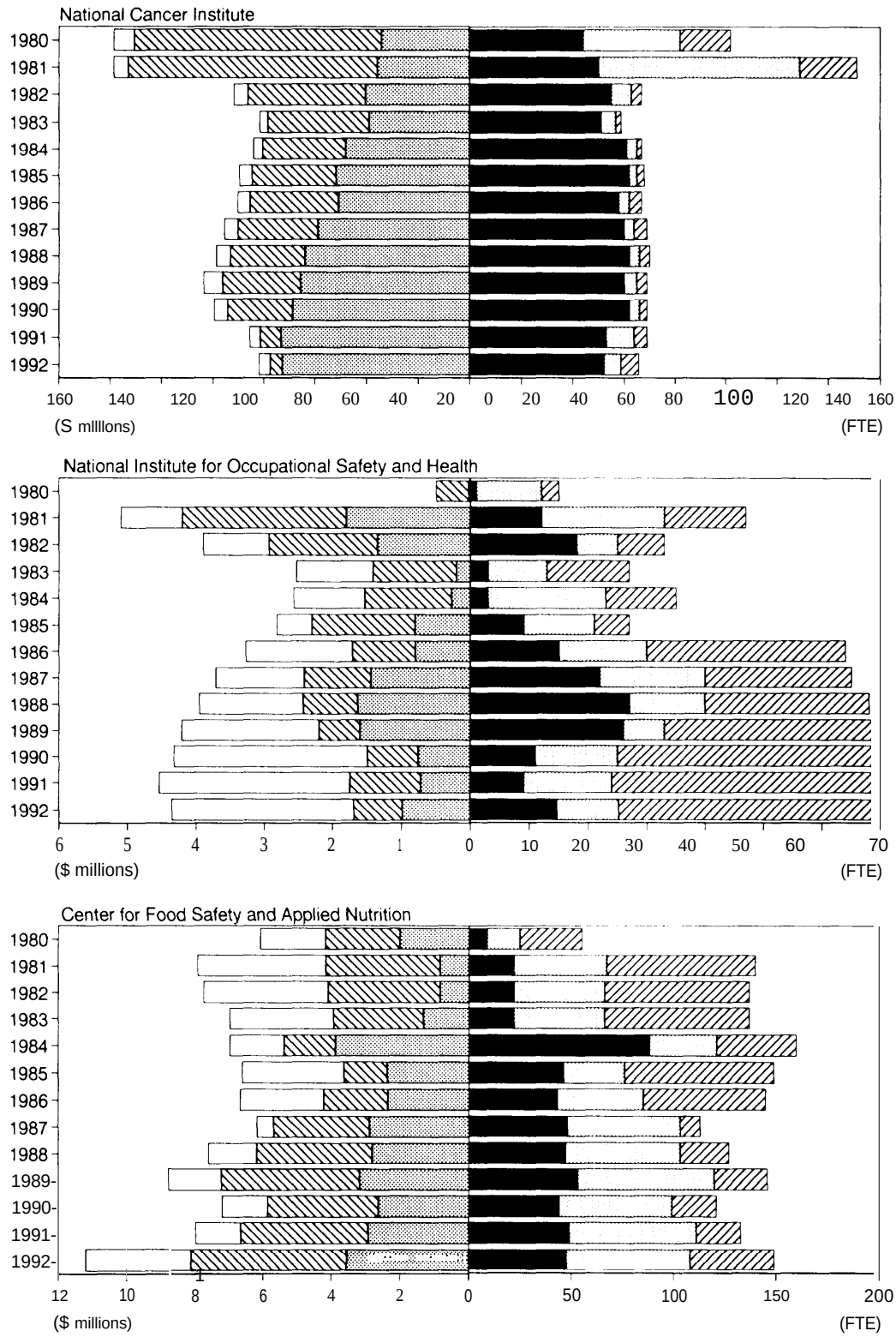
As would be expected for activities as broad as risk assessment research, some fields of inquiry have received more funds, some fewer. However, environmental health research funding has neither kept up with the increase in health research nor increases in environmental mandates that depends on that research for decisionmaking. Methodological research, in particular, seems inadequately supported, despite the most immediate promise that OTA sees for this research to improve risk assessment.

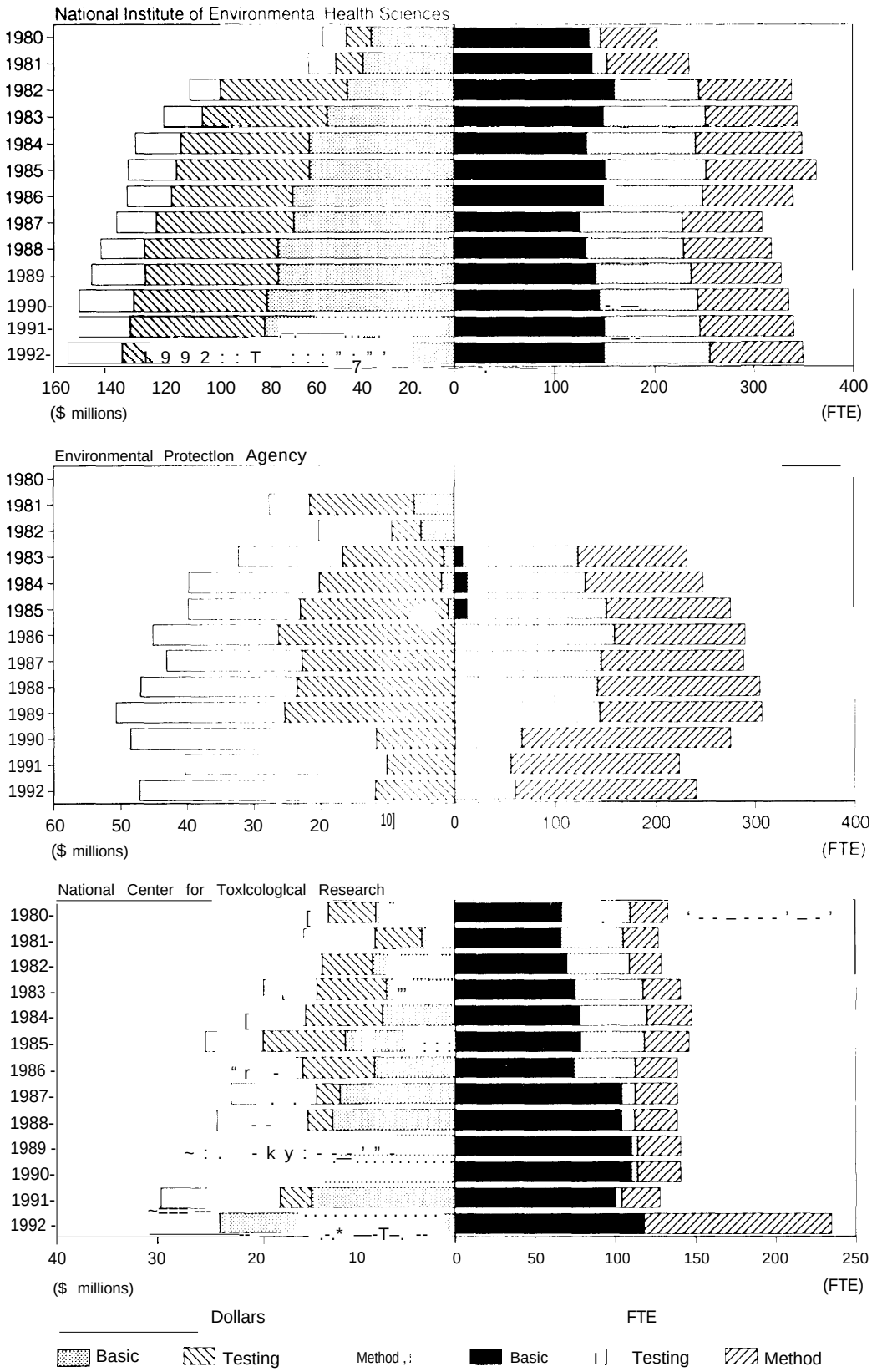
Setting Priorities for Research

Charting a course for improving risk assessment research requires Federal agencies to work at several organizational levels. OTA examined the priority-setting process for such research at three different levels: national, agency, and program. Each level uses different processes and methods. OTA's analysis indicated that priority-setting at the program level uses the most formalized, systematic processes; the national level, the least. In addition, OTA identified various factors that influenced the choice of one type of research over another.

National priorities for research, based on national needs and goals, are influenced by prevailing economic, social, and political conditions. Federal research to improve risk assessment is largely decentralized and uncoordinated. The work of Federal researchers is almost entirely in support of the agencies and departments that sponsor the research. Except for the NTP, which sets priorities for toxicity testing, OTA observed few national priority setting efforts. One of those is the Federal Coordinating Council on Science, Engineering, and Technology (FCCSET), an interagency body within the Executive Office of the President (EOP). However, participants and nonparticipants alike displayed little enthusiasm for or optimism about the recent FCCSET process as it relates to risk assessment or risk assessment

Figure 1-4--Federal Research Related to Chemical Toxicology, 1980-1992
(In millions of dollars and full-time equivalents)





SOURCE: ***Review*** *of Current DHHS, DOE and EPA* **Research** *Related to Toxicology,* Fiscal Years 1980 through 1992, National Toxicology Program, U.S. Department of Health and Human Services.

research. In any case, the Clinton Administration plans on eliminating FCCSET and creating a National Science and Technology Council.

The priorities for risk assessment research vary with the mission and function of an agency—especially whether or not the agency's responsibilities include risk management. The research conducted by the regulatory agencies, and the Departments of Defense and Energy, is mostly chemical-specific data development; the research agencies, by and large, conduct basic research.

Setting priorities at the program level is generalIy a more developed—that is, both a more systematic and a more formal-process than priority-setting at the agency or national levels. One of two distinct types of management methods is used to determine priorities for individual research projects. The style termed ''bottom up' depends on researchers to develop research ideas and priorities and to communicate those ideas and requests for research support to their superiors or to grant managers. In contrast, ' 'top-down' management has the most senior decisionmakers in an agency deciding the priorities for research. OTA observed both styles of management used separately or in combination in its survey of risk assessment research. In general, research priorities for programs at the regulatory agencies are more frequently decided by top-down management, whereas program priorities at the research agencies are determined through a bottom-up process. EPA and DOE have used a combination of these styles in managing their research programs.

Trends and Gaps

Over the course of this study, OTA observed several major trends in Federal research activities that support health risk assessment. To begin with, agencies are expanding their research horizons to include not only cancer but other adverse effects on health. Many scientists interviewed by OTA expressed the belief that research on health effects other than cancer has the potential to influence regulatory policy significantly. But they also believe that the current science base is not sufficient for adequate assessments of noncarcinogenic health effects. One reason that such research may have a great impact on policy is that health risk issues about noncarcinogens do not usually lead to the acrimonious policy debates associated with carcinogens.

Many agency research programs, along with expanding the breadth of their research, have been restructuring. In most of those cases, the restructuring reflects a greater emphasis on social relevance. As agencies link their research activities more closely to social needs, their research becomes, by necessity, increasingly multidisciplinary. No one field of academic training or research encompasses all aspects of health risk research, which ranges from basic biomedical research to computer modeling. The increasing complexities of the science involved and the need to incorporate more science into rulemaking have made it clear that multidisciplinary research is required to provide the requisite scientific underpinning for future risk assessments.

Yet overall, few incentives exist for long-term multiagency, multidisciplinary research on health risks, and very few resources are allocated to this work. Scientists from all of the environmental health disciplines, such as toxicology, epidemiology, biostatistics, environmental chemistry, and clinical studies, make contributions to health risk assessments and are the mainstay of agency research to improve the risk assessment process. Nonetheless, those fields remain disparate, and collaborative studies remain the exception rather than the rule.

Without more incentive to collaborate, disciplinary myopia may continue and grow more pronounced and entrenched. Compartmentalization by agency or discipline can only hinder progress and retard the infusion into risk assessment research of newly developed techniques and knowledge arising out of the rapid advances now occurring in the biomedical sciences. Ironically,

dwindling agency resources may actually be spurring some collaboration: evidence indicates that decreasing budgets have catalyzed some interaction as the need for cooperation becomes apparent. Setting aside turf battles, Federal agencies are beginning piecemeal approaches to promoting multiagency, multidisciplinary research.

Today, Federal Government risk assessment research support is spread out across at least 12 different agencies. That dispersion has both positive and negative consequences. On the one hand, agencies can monitor their agency-specific research without having to overcome additional hurdles, and they can target their activities to the areas they consider of highest priority. On the other hand, work is fragmented and diffuse. Those characteristics may hinder progress with risk assessment problems that are common to several agencies.

OTA finds a particular lack of emphasis on collaborative research to evaluate and validate new methods and models, especially in the important area of corroborating experimental results from animal studies with studies in humans. Admittedly, this is a most difficult undertaking, but it is critical to elevating the level of confidence to be accorded to risk assessment results. OTA also found little research under way to examine or attempt to validate extrapolation models for general use or for use with specific chemicals.

The basic building block for much of the critical research-chemical-specific toxic effects data—is generally obtainable, although the Federal Government supports fewer toxicology tests than in years past. The number of tests carried out by industry is uncertain. Regardless of the number of tests, what is missing is funding for studies to use those data in combination with expanding knowledge in toxicity mechanisms and biomedical sciences to examine various extrapolation models in order to learn which models are more predictive. With additional resources, Federal agencies could conduct those bridging studies. For instance, the Federal Government has collected toxicity information in response to mandates for registering or approving drugs and pesticides. Both animal and human data have been collected in those efforts, and they could be used in attempts to evaluate and validate existing models as well as develop new ones. However, such research requires better collaboration between and among agencies and research disciplines. Although it remains to be seen how much such analyses would cost, gathering of data is typically the largest cost, and that has already been accomplished.

The past decade has witnessed nearly revolutionary developments in the biological sciences. Researchers are poised to use those advances to improve health risk assessments. Yet despite the potential for progress, the present Federal risk assessment R&D infrastructure maybe an impediment to moving forward. Many scientists interviewed by OTA claim that the research system is "broke." Resources, they argue, are squandered on a system that is incapable of setting priorities. Consequently, the perception exists that the areas of research of highest priority-those most likely to improve risk assessment approaches—are not being funded or studied, to the benefit of lower priority or even irrelevant research. Even the $65 million spent on methods research may not be targeted correctly. Instead, according to some scientists, there is a tendency to fund projects that may yield improvements on current methods but that are unlikely to open new avenues of research or application.

The absence of an identified central leader in risk assessment research contributes to the pessimistic viewpoint and to the current level of funding and disciplinary and agency fragmentation in the effort to improve health risk assessments. A nationally recognized leader could provide leadership and assurances about political support for research, promote multiagency collaborations, and provide incentives for overcoming bureaucratic hurdles and turf battles. A national leader in the White House in a position equivalent to the "Drug Czar" or "AIDS Czar,"

could bring national visibility and unify and coordinate research activities across agencies, in addition to articulating the needs of the field to Congress and the President. Furthermore, this central figure could instill a sense of common purpose among researchers and program managers.

LINKING HEALTH RISK RESEARCH TO DECISIONMAKING

The complex relationship between research and decisionmaking demonstrated in figure 1-5 deviates from the conventional representation of a unidirectional flow of information from risk assessment to risk management. It is, however, a reasonable evolution of the conventional model put forward in a 1983 report by the National Research Council. Part of the reason for the unidirectional information flow was the desirability of the compartmentalization of the risk assessment process from risk management. In the 10 years since the publication of the report, the importance of information sharing to increase the efficiency of research for decisionmaking has become apparent. Thus, OTA's figure highlights the bidirectional flow of information as well as the integration of the various disciplines and types of research. In addition, it shows that evaluating and validating methods can be the focal point for integrating different lines of health risk research, since anew model or method should be examined and compared with methods of known and established veracity. The figure also indicates OTA's stress on the interdependency of research activities, the risk assessment process, and policymaking.

Moreover, the interdependence of health risk research and decisionmaking limits the capacity of agencies to structure long-term solutions to problems posed by toxic substances. As research identifies potentially adverse health effects of an agent, the public conveys its concern to Congress, and Congress considers and passes laws to address those concerns. By necessity, agencies' addressing those more immediate concerns restricts their opportunities to continue research to decrease the reliance on science policy assumptions in risk assessments.

The Impact of Research

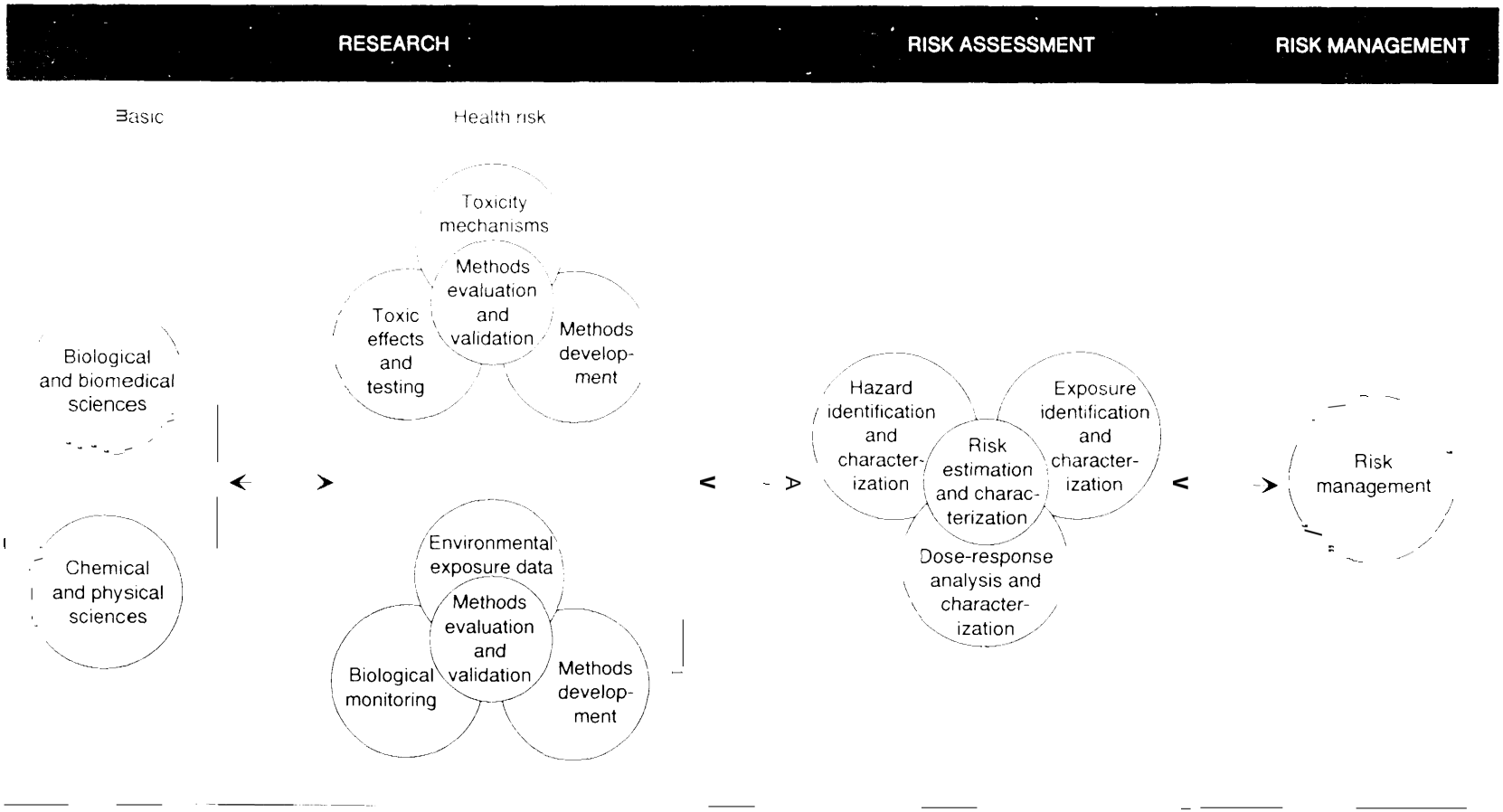
Science and policymaking are uneasy partners. Nevertheless, the primary criterion for health risk assessment research is that it be useful for decisionmaking. OTA examined three questions about the relationship of research to decisionmaking:

1. How has research influenced Federal risk assessment guidelines and risk assessment practices?
2. What impact has research had on decisionmaking?
3. How can research be designed to make risk assessment more useful in decisionmaking?

To answer those questions, OTA reviewed the evolution of Federal risk assessment guidelines and risk assessment practices and some of the comments and criticisms made about them.

Research findings from many scientific fields provide the basic data for health risk assessment. But those data are never extensive enough for answering questions about exposure, effect, and the people who are likely to be affected. Agencies frequently confront questions that science cannot answer, and in order to make decisions they have adopted so-called science policy assumptions to bridge the gaps in the available information. The assumptions have some grounding in science-they don't contradict accepted scientific conclusions and opinions at the time they are adopted—but they necessarily incorporate other ideas that are based on policy rather than science. For instance, choosing the risks of the maximally-exposed individuals as a basis for regulatory decision is a policy decision, as is the decision to include 24-hours/day exposure for 70 years in calculating maximum exposure. Those decisions

Figure 5—Linking Research on Health Risks to Decisionmaking



SOURCE: Office of Technology Assessment, 1993.

can be set aside, but as matters of policy, not science.

The assumptions that are used in health risk assessments can be divided into two general types: those that bridge gaps in scientific knowledge and those that compensate for a lack of agent-specific data.

After reviewing the evolution of EPA's risk assessment guidelines, OTA concluded that research has had only a modest effect on the agency's efforts to revise the science policy assumptions adopted in its risk assessment guidelines. The controversary generated by EPA's current efforts to revise its 1986 cancer risk assessment guidelines underlines the importance of policy-based decisions. Research has, however, had a substantial impact on chemical-specific risk assessments and consequently on regulatory actions,

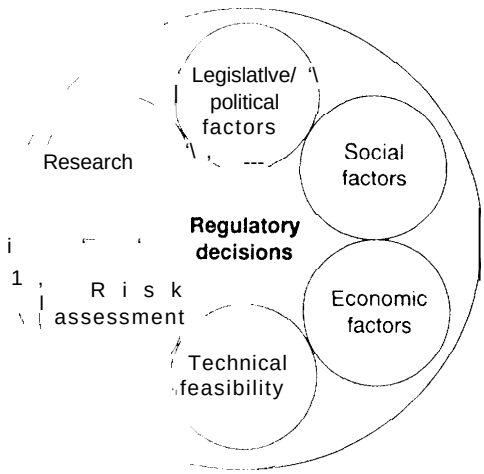
Three interacting factors account for the limited impact of new scientific research on EPA's science policy assumptions: the nature of the assumptions, the importance of the assumptions to regulatory approaches, and the policy reverberation from changing specific default assumptions.

The Limits of Science

Whatever is expected of risk assessment in any given circumstance, it is only one of the elements in formulating regulatory actions. Legislative mandates, social values, technical feasibility, and economic factors may take a more prominent role than expert assessments of risk (figure ***1-6).***

The limits of science are manifest at different levels. Uncertainty in measurements and observations constrains science at the most fundamental level, and the scientific underpinnings of risk assessment are more subject to those limitations than the experimental sciences. At a higher level of complexity, the interpretation of data and observations to predict outcomes introduces other unknowns. And risk management actions can themselves produce uncertainty. Solving the problems in health risk assessment goes beyond more and better science; it also requires building trust among government, industry, and citizens.

Figure 1-6-Research as an Element of Decisionmaking



SOURCE: Off Ice of Technology Assessment, 1993.

Radon as a Case Study of Research and Decisionmaking

The controversy developed around EPA's proposed regulation of radon in drinking water illustrates some of the interplay between science and decisionmaking. When radon gas, which originates in the Earth's crust, is emitted into an open space such as outdoor air, it is rapidly diluted to the low "background" or "outside" levels found around the world. But when it is emitted into a home, a school, or another type of building, dilution is slower. As a result, the concentrations of radon inside structures are usually higher than the concentrations outside. These higher levels raise concerns about health because studies have revealed higher rates of lung cancer among miners and other workers exposed to radon on the job than are found in the general public. (All estimates of risk from indoor radon are based on extrapolations from the results of studies of miners.)

Responding to those concerns, Congress and EPA have considered ways to reduce the risks posed by indoor radon. Most indoor radon enters buildings directly from the soil, and efforts to lessen those exposures have included EPA programs to inform homeowners about the risks from radon and about methods to reduce radon inflow into buildings. The private sector has also acted on the problem by imposing requirements for measuring and, if it is deemed necessary, reducing indoor radon as a condition in real estate contracts in some localities.

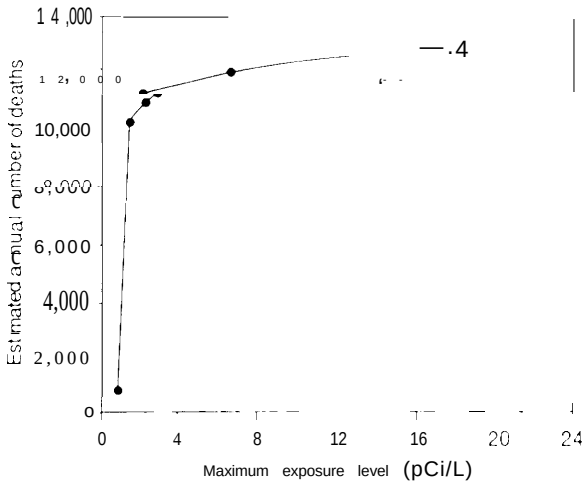
EPA cannot, of course, regulate radon from the soil because radon from that source enters homes directly, without passing through any entity that can be regulated. Some radon, however, enters buildings through the water supply, and the agency can regulate radon in water just as it regulates other contaminants under the Safe Drinking Water Act (P.L. 93-523 and P.L. 99-339).

Some Members of Congress, including the Chairman of the House Committee on Science, Space, and Technology, asked OTA to examine an ''inconsistency'' in EPA's approach to radon. That request arrived at OTA after this study to examine health risk assessment research was in progress. OTA officials decided to include the office's response to the request as a case study in this report.

REGULATORY APPROACHES

EPA divides its regulatory programs along media lines: air, water, industrial wastes, and so forth. It has approached the issue of indoor radon as a media problem, and has different policies toward radon entering buildings directly from the soil and through water. The agency has not proposed regulating radon emitted directly from the soil, but it has proposed regulating water suppliers. Some scientists, Members of Congress, and other policymakers have recognized that indoor radon is only a single part of the larger issue of indoor air pollution. The question of risks to health from indoor exposures presents assessment, remediation, and regulatory difficulties that differ from those associated with pollutants in outside air.

Figure 1-7—Estimates of Deaths From Lung Cancer at Different Levels of Radon Exposure

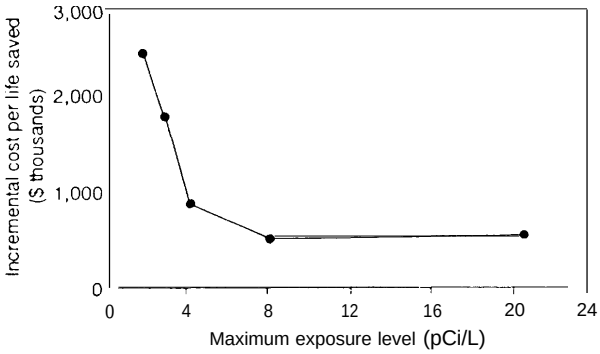


SOURCES: Office of Technology Assessment, 1993, based on Environmental Protection Agency, 1992. Technical Support Document for the 1992 Citizen's Guide to Radon. M. Reimer, U.S. Geological Survey.

Air—Based on its National Residential Radon Survey, EPA estimates that about 5.8 million homes (6 percent of all U.S. homes) have concentrations of radon in air above 4 pico curies per liter (pCi/L), the level at which EPA would recommend remedial action. The agency estimates that the average home has a concentration of around 1.25 pCi/L.

As figure 1-7 shows, the bulk of cancers that are associated with exposures to radon occur in the population exposed to low levels, below 2 pCi/L. The primary reason is that many more people are exposed to those levels than to higher levels, Given EPA's conclusion that it is impossible to reduce levels below 2 pCi/L in some houses, the practical lower limit on the number of deaths associated with radon may be as high as 10,500. That estimate is based on extrapolations from studies of miners who were exposed to radon. Refining those extrapolations might re-

Figure 1-8-Cost-Effectiveness of Different Action Levels for Reducing Indoor Radon Exposures



SOURCE: Office of Technology Assessment, 1993.

duce or increase the estimate of the number of cancers.

Because radon is present in all air, both inside and outside, it is impossible to have zero exposure to radon. Thus, some risk of death from radon-associated lung cancer is always present, if one assumes that there is no threshold for radon-associated lung cancer deaths. Exposures to radon in outside air is estimated to be associated with about 500 deaths from lung cancer annually.

EPA's ***Technical Support Document for the 1992 Citizen's Guide to Radon*** provides the agency's reasoning behind choosing 4 pCi/L as the level at which homeowners should obtain more information about exposure and take steps to bring the level of radon in their homes below that concentration. But because EPA does not regulate radon in air, the Federal Government is not required to provide an administrative forum to debate whether the projected benefits of reaching 4 pCi/L of radon justified the associated costs. Figure 1-8 summarizes EPA's cost-effectiveness analysis for reducing concentrations of indoor radon to various levels. Reducing exposures to 8 pCi/L is expected to save lives at a cost of less than $0.5 million per life; the cost per life saved just about doubles (to a little less than $1.0 million) at 4 pCi/L and increases further at lower action levels.

Water—The Safe Drinking Water Act (SDWA) Amendments of 1986 require EPA to develop regulations for toxic chemicals in water. The agency has decided to regulate radon like any other waterborne carcinogen; it calculates that radon in water is associated with 30 to 600 cancer deaths a year. That single radioactive element accounts for most of the total risk from radiation in water, and the upper bound on its risk exceeds the total risk from all chemicals in water (table 1-3). The regulatory process can be considered in two time periods. Before the summer of 1992, EPA was developing the regulation under its usual procedures, but at that time Congress intervened in the process and mandated that EPA reassess its estimates of risks and costs in relation to radon in water and imposed a one-year moratorium on any regulation of radon in water.

The SDWA imposes a goal of zero for concentrations of carcinogens in water, which is unattainable for radon. Extensive aeration of radon-bearing water would discharge the radon into the air, but there would always be radon at least at the concentration found in outside air. EPA determined that the lowest "practical quantification level" for radon in water was 150 pCi/L, and in 1991 it set the regulatory maximum contaminant level at that value in its proposed rule. Because of the decay of radon over time, the "quantification level" translates to a concentration of 300 pCi/L. Differences in the procedures for measuring radon in air and water account for the fact that measurements of 2 pCi/L or less of radon in air are routinely obtained, whereas EPA contends that measurements below 150 pCi/L in water are not practical.

Scientists generally agree that 10,000 pCi/L of radon in groundwater results in 1 pCi/L of radon in air from volatilization. Therefore, if the 300 pCi/L limit on radon in water were imposed, it would mean that no more than 0.03 pCi/L of radon in indoor air would result from the waterborne radon. That concentration is 10 percent or less of the radon in outdoor air, and it would contribute about 5 percent to total indoor expo-

Table 1-3-Cancer Risks From Water

Source of risk	Estimated annual cancer mortality
Radiation in drinking water	37 to 730'
All chemicals in drinking water.	215 to 430

a her EPA estimates vary within this range.

SOURCES: Office of Technology Assessment, 1993, based on M. Gough, 1989. Estimating cancer mortality. *Environmental Science and Technology* 23 S25-930, based on USEPA. 1987. Unfinished Business. Washington, DC: USEPA.

sures. EPA has carefully examined such things as how much radon is released into the air from water during showering, laundering, and flushing the toilet in order to estimate the contribution of radon from water to indoor air.

"Inconsistency" in EPA's Approach to Radon

The letter that requested this OTA examination of indoor radon cited the concerns expressed in 1992 by EPA's Science Advisory Board about inconsistencies in the agency's approach to reducing risks from radon. It contrasted the goals of the Indoor Radon Abatement Act (IRAA) with EPA's action level for indoor radon and its proposed level for regulating radon in water under SDWA. The IRAA goal is to bring indoor radon levels down to those commonly found outdoors (0.1 to 0.5 pCi/L). EPA, however, urges that remediation be undertaken to reduce concentrations of radon in homes to 4 pCi/L or less and acknowledges that it is infeasible to reduce concentrations below 2 pCi/L in some homes. In contrast, EPA's proposed regulation under SDWA would set 300 pCi/L radon in drinking water as the highest permitted level, limiting radon in indoor air to 0.03 pCi/L from this source. Clearly, the goal, the action level, and the proposed regulation set different exposures as acceptable levels of risk (box l-A).

These inconsistencies are not surprising, given the way that the goal, the action level, and the regulation were derived. Congress in the IRAA acknowledged that the level of radon in outdoor air is unavoidable and that concentrations cannot be reduced below it. At the same time, it maintained that reducing concentrations indoors to that level would be as protective of health as possible.

EPA, in setting the 4 pCi/L action level for indoor radon, accepted a risk of cancer from radon that is far higher than the 1 X 10^{-6} (one excess cancer per million people) that the agency routinely uses as a goal in regulating exposure to toxic chemicals. A 10^{-6} cancer risk is equivalent to about three excess cancer deaths annually; thus, the risk of 7,900 excess cancer deaths at exposures of 1.25 pCi/L, which is the national average for indoor exposures, is about 2,600 x 10^{-6} or 3 X 10^{-3}. ***The Citizen's Guide to Radon,*** a publication issued jointly by EPA and DHHS, provides some examples of comparative risk; for instance, the risk that a nonsmoker bears from constant exposure to radon at 4 pCi/L is roughly the same as that person's risk of drowning,

The level of 300 pCi/L of radon in water, set at what EPA had determined was the practical limit on quantification, was projected to reduce risks to about 2 X 10^{-4}. In its preamble to the proposed rule, EPA raised the question of the significance of waterborne radon to total exposure to radon: "In evaluating the various alternatives for proposing a radon MCL [maximum contaminant level, which is the regulatory standard], EPA considered the critical policy questions of whether radon in water should be regulated like other drinking water contaminants, or whether it should be regulated more in accord with its importance compared to overall radon exposure. EPA decided to regulate radon as it does other waterborne contaminants, but its Science Advisory Board in 1992 criticized that action because of the small contribution that waterborne radon makes to overall exposure to radon.

As a result of Congress's mandating the multimedia risk assessment in 1992, EPA's risk and cost assessment changed slightly, but whether it will make a difference in regulation remains to be seen. The risk estimate of about 200 cancer

Box I-A–Reducing Exposures to Radon: A Goal, an Action Level, and a Regulatory Standard

Nazaroff and Teichman (1990)[1] calculate that current exposures to radon are associated with about 15,700 lung cancerdeaths annually. They estimate that 97 percentof those deaths are expected in smokers with 3 percent in nonsmokers. Concentrations of indoor radon are higher than those outdoors, and the Federal Government has directed several initiatives at reducing indoor exposures. As a result, there is a goal for the reduction of indoor concentrations of radon, an action level to guide voluntary reductions, and a proposed regulation to reduce concentrations of radon in water.

A Goal

The indoor Radon Abatement Act sets the goal of reducing indoor concentrations of radon to the concentrations found outdoors-that is, 0.4 pCi/L. Currently, the average indoor concentration is about 1.5 pCi/L, with about 6 percent of all houses having concentrations greater than 4 pCi/L. EPA states that it is difficult to reduce indoor levels below 2 pCi/L (apparently for houses with current levels greater than 4 pCi/L). if, however, the goal of 0.4 pCi/L could be reached, it would reduce EPA's estimated annual number of radon-associated lung cancer deaths to about 3,100 (a reduction of about 80 percent).

An Action Level

EPA recommends that indoor radon concentrations be reduced to 4 pCi/L or below, a level considered technologically feasible for all houses. Reducing ail indoor radon concentrations that are now greater than 4 to 2.7 pCi/L is expected to eliminate about 3,500 deaths (a reduction of about 17 percent). (The 2.7 pCi/L figure is the mean between the national average of 1.5 and the action level of 4 pCi/L.)

A Regulatory Standard

Under the provisions of the Safe Drinking Water Act, EPA proposes regulating radon in drinking water so that the concentration of radon in air that is the result of the volatilization of radon from drinking water is no more than 0.03 pCi/L. According to EPA, reducing all higher concentrations of radon in water to this level would eliminate 80 radon-associated lung cancer deaths annually (a reduction of about 0.5 percent).

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1 W.W. Nazaroff and K. Teichman, Indoor radon. *Erw/romnenta/Science and Technology* 34:774-782, 1990.

SOURCE: Office of Technology Assessment, 1993.

deaths expected from waterborne radon changed hardly at all, and radon in water remains associated with a risk greater than 10^{-4}, which is the usual upper limit on the risk that EPA finds tolerable.

Despite EPA's revisiting its risk assessment and making only small changes, there is little consensus about the certainty of the estimate of risks or the costs of addressing them. As the Science Advisory Board of the EPA pointed out in its review of the multimedia risk assessment, substantial questions remain about the validity of EPA's estimate of the risk from ingested radon, about the number of water suppliers that will exceed the regulatory limit, and the costs of regulation. As of October 1993, EPA's multimedia risk assessment had not been released, pending the agency's development of responses to the Science Advisory Board critiques. Congress in 1993 again intervened in the regulatory process and imposed an additional one year moratorium on any regulation of radon in water.

The specific questions raised by radon maybe answered by congressional or EPA decisions that impose new regulations or leave the current approaches intact. New epidemiologic results may inform those decisions by revealing more certain evidence of the level of risk posed by

indoor radon. And it is possible that research into mechanisms of carcinogenesis may shed some light on such risks. More generally, however, radon is a case that illustrates the difficulties posed by an environmental risk of uncertain size that reaches human beings through different media.

PROSPECTS FOR THE FUTURE

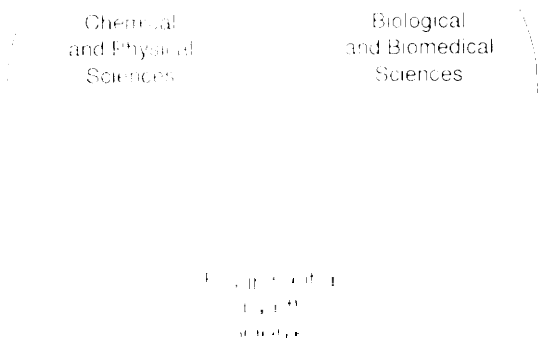
In its study, OTA noted several qualities that characterize common to high-quality research programs that should be considered in structuring the future of health risk assessment research. These include leadership, well-defined objectives, investigator initiation of projects, competitive awards and peer review, planning and criteria for evaluating success, collaboration and coordination, training, and advisory input.

OTA also identified several areas of research that promise to advance health risk assessment: new methods for toxicity studies, biomedical and molecular epidemiology, mechanistically bawd dose-response extrapolation methods, improved methods for measuring or estimating human exposures, mechanistic studies, data development and management to support toxicity evaluation and methods evaluation and validation.

The exploration of the many promising areas for research requires establishing linkages not only among various scientific disciplines but also with decisionmakers. No one category of research can be classified as the most useful for decisionmaking. Instead, risk assessments will increasingly require multidisciplinary approaches and analyses of available information. The nature of the health risk being addressed, the nature of the information already at hand, and the other factors that affect decisionmaking should all be considered when structuring a research program for health risk assessment.

Research linkages and collaborations offer enduring benefits to all participants. They bring together researchers with different strengths and expertise, foster the dissemination of knowledge,

Figure 1-9--Linking Scientific Disciplines in Health Risk Research



SOURCE: Office of Technology Assessment, 1993

and permit the sharing of resources. Research linkages also allow researchers to undertake projects that might otherwise not be possible. Linkages can occur within and between Federal agencies as well as between Federal and nonfederal institutions.

The link between health effects research and basic biological, chemical, and physical sciences has often been neglected (figure 1-9). More recently, however, bridges are being constructed between basic and health risk research in response to calls from Congress and the private sector to link science to social needs. Although basic scientists may respond grudgingly at first, some may actually find it rewarding to modify and redirect their research to serve the requirements of health risk assessments.

Analogous to the Human Genome Project, in which collaborations have been formed among scientists working to sequence the human genome, researchers from a plethora of disciplines could work together to improve health risk assessments as a desirable social and scientific goal.

In addition to scientists' collaborating to improve risk assessments, researchers who study

health risks can transfer knowledge to the private sector to foster economic growth, now a vital part of the mission of many research agencies. Revenue raised in technology transfer could be used to bolster research in this area. Such a contribution would be an important source of funds since, as this report describes, few resources are allotted for long-term funding of research to improve risk assessments despite the amounts of money involved in decisions that depend on risk assessment.

Risk assessment involves the analysis and synthesis of the entire knowledge base on the risk at hand, such as a specific chemical or class of chemicals. A substantial amount of reasoning and judgment is required in determining g whether the composite data on toxic effects, exposure, and dose-response characteristics as a whole make the hypotheses of risk tenable. This line of questioning and reasoning weighed against scientific principles and data is an iterative process, not unlike conducting experiments. It is a process different from the frequent practice of summing up the data that indicate risk and downplaying or ignoring contradictory information. When applied, questioning and reasoning can reveal the strengths and weaknesses of the evidence for risk and identify additional research needs.

Health risk assessments, by their very nature, require extrapolations from current information to estimates of effects under different circumstances. Scientists contribute to those extrapolations, but the science policy decisions that guide the choices of models include assumptions with embedded value judgments. The process of selecting the science policy assumptions (e.g., extrapolation models) may benefit from involving practitioners of disciplines other than the biological, chemical, or physical sciences. In this, OTA agrees with analyst Sheila Jasanoff, who argues for ‘‘bridging the two cultures of risk analysis’—the “hard” quantitative sciences and the soft’ nonquantitative disciplines such as the behavioral and political sciences.

The objectives of this OTA report are more limited. They are to describe current research, how research contributes to decisionmaking, and the limits of research and science in decisionmaking. Accepting those limits, it remains clear that improvements in scientific understanding from research will produce better risk assessments, which are mighty contributors to decisions about how much society will pay to cleanup pollution, how many resources will be expended on pollution prevention, and judgments about the extent of environmentally related illnesses.

INTRODUCTION TO ISSUES AND OPTIONS

This OTA study finds that health risk assessment research is itself ‘‘at risk:

- The attention and resources allotted to health risk assessment research are not commensurate with its impact on public health and the economy. Moreover, the proportion of funds devoted to environmental health R&D relative to health R&D declined from 6.8 to 4.9 percent in the decade from 1982 to 1991, despite expanded congressional mandates for Federal environmental responsibilities. The research being conducted is fragmented within and across at least 12 Federal agencies, resulting in the inefficient and ineffective use of resources.
- Inadequate resources are devoted to research on risk assessment methodology, the area likely to have the most far-reaching effect on policy. Methodological research receives about $65 million in 1993-only about 11 percent of the $600 million of Federal spending on risk assessment research.
- Not enough attention is given to linking research to decisionmaking.
- Opportunities to link government, university, and industry research are not being exploited.

OTA raises six issues related to health risk assessment research (box l-B). Four interrelated

Box I-B-Summary **of Issues and Options**

HEALTH RISK RESEARCH, STRUCTURE AND FUNDING

ISSUE 1: Given what is at stake, inappropriate attention being paid to health risk assessment research?
- . Option A-Continue with present policies.
- . Option B-Create a national initiative for health risk assessment research.
- . Option &Expand resources for health risk assessment research by redirecting funds, raising tax revenues, collecting user fees, or increasing funds.

ISSUE 2: How can Congress foster research on risk assessment methodology?
- • Option A--Continue with **present policies.**
- • **Option B--Promote or mandate** more interagency coordination of methodological research.
- . Option C-Establish a risk assessment research agency.

ISSUE 3: Should Congress mandate more targeted research to improve risk assessment?
- . Option A-Continue with present policies.
- . Option B-Mandate programs of targeted research at some Federal agencies.
- • Option C-Provide incentives for programs of targeted research.
- * Option D--Support research priority-setting based on level of risk.

ISSUE 4: How can Congress promote research linkages and technology transfer among the Federal Government, universities, and Industry?
- . Option A--Continue with present policies.
- • Option B-Establish more academic centers for health risk assessment research.
- . Option &Promote technology transfer from health risk assessment research.
- . Option D-Encourage industry support of health risk assessment research.
- • Option E—Provide incentives for collaborative research.

LINKING RESEARCH *TO* DECIS1ONMAK1NG *(RADON* AS A CASE STUDY)

ISSUE 5: Can epidemiologic studies confirm, reject, or sharpen estimates of the risk posed by indoor radon?
- . Option A--Accept the results of a meta-analysis as sufficient to answer questions about the level of risk posed by exposure to indoor radon.
- . Option B-Convene a planning group to consider a study to answer questions about risks from exposure to indoor radon.

ISSUE 6: Can there be a consistent approach to reducing radon exposures?
- . Option A—Accept the inconsistency and let the Environmental Protection Agency (EPA) deal with exposures to radon under existing laws.
- . Option B-Use the reauthorization of the Indoor Radon Abatement Act to direct EPA to integrate all routes of exposure in considering activities to reduce exposure to indoor radon,
- . Option C-include radon in a comprehensive law for regulating indoor air.

issues address the Federal research infrastructure: 1) deciding on the appropriate level of health risk assessment research; 2) fostering research on health risk assessment methodology; 3) targeting research to improve health risk assessment; and 4) promoting research linkages and technology transfer among and between Government, universities, and industry.

Two issues are related to understanding risks from exposures to radon and controlling them. They involve research, risk assessment, and regulatory decisionmaking. This example typifies

the issues relating to the limitations of science for resolving policy questions. The issues for radon are: 1) using epidemiologic studies to confirm, reject, or sharpen the estimates of risk posed by indoor radon, and 2) developing a consistent approach to reducing radon exposures.

OTA has provided options for congressional consideration for each of the issues raised in the OTA report. The options are not mutually exclusive; in many cases, they are complementary and can be integrated to improve health risk assessment research.

ISSUES IN HEALTH RISK RESEARCH, STRUCTURE AND FUNDING

ISSUE 1: Given what is at stake, is appropriate attention being paid to health risk assessment research?

Health risk assessment research provides the scientific foundation for health risk-based regulatory decisions (e.g., emission standards for incineration). Those decisions affect expenditures for complying with regulations, cleaning up contaminated sites, and treating exposure-related diseases that can run into the billions of dollars.

EPA estimates that complying with its regulations costs more than $150 billion annually. Compliance with FDA and Consumer Products Safety Commission regulation of food and product safety adds to the above estimate as does compliance with Occupational Safety and Health Administration regulations. Moreover, although estimates of the total health costs from environmental exposures are not available, a number of studies suggest that the costs of some environmentally related illnesses-such as lead poisoning and pollution-related respiratory conditions -could reach well into the billions of dollars.

Yet OTA finds that health risk assessment research is not high on the national research agenda. To elevate this research to a priority level consistent with its impact on health and the economy, requires leadership from higher reaches of government, strategic initiatives that incorporate and respond to the needs of many Federal agencies, and funding commensurate with the magnitude of the problem. Currently, health risk assessment research, according to this OTA study, has none of those hallmarks. Only about $600 million-less than one-half of 1 percent of the costs of complying with EPA regulations alone-is spent annually on health risk assessment research.

With adequate support, research can develop informative, cost-effective toxicity testing, better evaluations of human exposure, and health risks. The results will improve health risk-based decisionmaking and strengthen public confidence in environmental decisionmaking.

The expected health, environmental, and economic benefits from health risk assessment research warrants the consideration of raising it to a higher level of research priority. OTA explored several options for improving leadership and providing additional funding.

Option A: Continue with present policies.

If Congress takes no action, the present piecemeal approach will probably yield slow, incremental progress in health risk assessment research. In the absence of congressional action, Federal health risk assessment research is likely to remain focused on carrying out individual agency priorities, responding to specific legislative mandates, or being based on the culture and talents of agency researchers. This is not a completely undesirable outcome, Research by its very nature is a foray into the unknown, making progress difficult to predict.

However, continuing with present policies means that advances in research on health risk assessment are left very much to chance. In particular, little research is devoted to finding solutions to problems with overarching impact or tailoring solutions to meet risk assessment needs that cut across the boundaries of discipline, agency, or risk assessment issue.

Risk assessment research has not kept abreast of the needs of our modern society. It is estimated

that more than 1,500 new chemicals are introduced into U.S. commerce each year, adding to the more than 62,000 chemicals already in use. Studies suggest that only 10 percent of chemicals existing worldwide have adequate toxicity data. New insights from research can produce better tools to decide which chemicals require more investigation and which require regulation. But without better tools, Government agencies and private companies will never eliminate the backlog of chemicals needing testing or unanswered questions about their risk to human health.

Regulatory agencies attempt to protect the public's health by counterbalancing uncertainty and incomplete information with conservative assumptions. From the standpoint of those that must comply with Federal regulations (e.g., industry and government entities and utilities), that orientation leads to unnecessary costs that must be passed on to consumers and citizens. Although their points of view may differ in some respects, representatives from both regulatory agencies and the regulated entities would agree that resources are misspent if risks of greater magnitude are not handled earlier and with more resources than risks of lesser magnitude. Both would argue for adequate resources for health risk research to take advantage of progress made in science (e.g., cellular and molecular biology) to reduce uncertainty in health risk assessments.

Finally, without national leadership and a commitment to health risk assessment research, the public's support for environmental protection may erode.

Option B: Create a national initiative for health risk assessment research.

If the decision is reached that current activities in the area of health risk assessment are too fragmented, Congress can consider methods to centralize the planning and evaluation of Federal health risk assessment research. Some areas of health risk assessment research would benefit from a multiagency approach. A national initiative would focus attention on such research and make it more responsive to national needs. It would provide a forum to debate, develop, and plan research. In particular, it would identify problems in risk assessment that cut across the agencies and distinguish which of those problems are addressable by research and which remain essentially policy choices. It would also provide guidance of Federal policy that is open to scrutiny by the public and Congress, and its plans and operation would reflect the overall needs of the Nation. It can be accomplished by:

- setting up crossagency strategic planning,
- providing leadership from the White House, or
- directing the Department of Environmental Protection (should it be established) to develop a program.

CROSSAGENCY STRATEGIC PLANNING

Crossagency strategic planning can be designed to bring agencies together to establish common research goals-for the short, medium, and long terms. On paper, the benefits of crossagency strategic planning appear within reach, but formidable obstacles lie in the way of securing them. Most agencies have a deeply rooted commitment to their own priorities, based on historical or legislative imperatives. Their resistance to change can thwart the setting of national goals. The most typical forms of resistance are to set objectives that are so broad as to be meaningless or to repackage existing programs to make them appear to be meeting objectives for which they were not actually intended. The nature of health risk assessment research and the breadth of disciplines that support it lends itself to those kinds of deception.

One way to enlist agency cooperation in strategic planning is to offer financial incentives for participation, such as additional research resources that are earmarked for research tailored to meeting government-wide objectives. The Bush Administration used such a mechanism,

called a ‘‘crosscut,’’ to augment funding in priority areas of research under the auspices of the Office of Science and Technology Policy’s Federal Coordinating Council on Science, Engineering, and Technology. Given the currently tight Federal budgets, providing additional funding will be difficult. However, another way to enlist agency cooperation is through strong and well-respected leadership.

LEADERSHIP FROM THE WHITE HOUSE

Leadership at the pinnacle of the executive branch can provide accountability, authority, and responsibility for risk assessment research. Furthermore, a nationally recognized leader can elevate the stature of programs for health risk assessment research, instill a sense of common purpose, and persuade agencies to cooperate in attaining national objectives. Such a person within the Executive Office of the President (EOP), similar to the “Drug Czar” or the “AIDS czar,” would provide a focus for discussing research needs across agencies. The President’s Science Adviser might fill this role; he or she could certainly spearhead the important function of cross-agency strategic planning. Similarly, the Carnegie Commission recently proposed that the EOP become the focal point for developing environmental and risk-related policy and coordinating the activities of the Federal agencies. One potential pitfall, however, in assigning this responsibility to a political appointee in the White House is that it will engender fears, warranted or unwarranted, about the politicization of science.

In contrast to a designated leader, a Center for Research Policy could serve within the EOP, most likely in the Office of Science and Technology Policy, as a neutral forum for linking research to decisionmaking. Such a forum could assist Federal agencies in identifying important gaps in research, setting crosscutting research objectives, and monitoring whether those objectives are being met. Another of the center’s functions could be to distinguish issues of policy from issues of science. Those distinctions are necessary because the high stakes and commercial interests involved in health risk assessment research virtually guarantee controversies about the scope, interpretation, or application of research. The center could help to educate policymakers and the public about the nature and limitations of research; it could also help identify which areas of controversy involve unverifiable assumptions and which are amenable to resolutions by further research.

The center may well be unnecessary, however, because it would be performing the same functions that existing agencies could perform by working together.[4] However, as the center would evaluate the potential impact of research on policy, it would require an analysis of cultural and social factors as well as scientific merit. Commingling science and policy may be viewed unfavorably by some communities: keeping policy separate from research has been seen as essential to maintaining the credibility of scientific research. It may also be problematic to assign the job of developing and monitoring objectives to a center without also giving it the responsibility or the capacity to implement those objectives. All of these issues require a discussion of the scope and scale of the center and the source of its resources, which is not attempted here.

PROGRAM IN THE DEPARTMENT OF ENVIRONMENTAL PROTECTION (SHOULD IT BE ESTABLISHED)

As part of the responsibilities for a new department, the much discussed Department of Environmental Protection could be instructed to establish a high-level program in health risk assessment research. Such a program could be made to provide a collaborative atmosphere for Federal research and to include private sector initiatives.

[4] A working party under the auspices of FCCSET had been attempting to Identify government-wide gaps in health risk assessment research. However, the effort apparently has been abandoned before the release of its results.

Option C: Expand resources for health risk assessment research by redirecting funds, collecting user fees, raising tax revenues, or increasing appropriations.

Congress could increase the level of support for health risk assessment research through several mechanisms. For example, it could use any of the following approaches:

- redirecting funds to risk assessment research,
- collecting user fees,
- raising tax revenues, or
- increasing appropriations.

New legislation could channel special taxes or user fees to finance health risk assessment research. Unlike many areas of science, health risk assessment research is so closely linked to regulatory action that a strong argument can be made for the appropriateness of finding such research through charnels related to regulation.

REDIRECTING AGENCY FUNDS TO RISK ASSESSMENT RESEARCH

Congress could redirect existing Federal resources toward research programs with potentially high dividends for health risk assessment. The funds could be secured from Federal agencies that support health risk assessment research or from agencies whose programs depend critically on the results of such research. DOE, for example, relies on the results of research in its vast program of environmental cleanup, which is larger in scope than EPA's Superfund program. Yet DOE lacks a targeted, coordinated research program that could help it set priorities among cleanup sites on the basis of the risk to human health. Redirecting a portion of the funds appropriated for remediation of its sites would provide a substantial increase in research funding. Even a comparatively small 2 percent redirection of the $5.4 billion allocated to DOE's cleanup activities would expand risk assessment research by more than $100 million. That figure is substantially larger than the estimated $65 million this country spends on health risk assessment methodological research and is more than double the entire health effects research budget at EPA. Based on its research, OTA agrees with those who point out that DOE's own national laboratories have the expertise and laboratory capacity necessary to absorb an infusion of funds for methodological research. Given EPA's experience with the types of research necessary to improve policy decisions, Congress may want to consider joint EPA/DOE projects.

Redirected funds could be used either to bolster existing programs in health risk assessment research or to create a new program. They could be channeled within the agency or to another agency that is already supporting health risk assessment research. In any case, this approach is viable only if the redirected funds are sufficient to support a meaningful level of research.

RAISING TAX REVENUES

The Superfund law is an example of Federal legislation that provides funds for research from directed tax revenues—in this case, from a tax on the petrochemical industry.[5] The tax revenues are deposited in the Superfund trust fund, which finances cleanup, compliance, and research.[6] Research receives the smallest share of the funds, and the exact amount is not a fixed proportion or set-aside. Of the 1992 Superfund appropriation of $1.6 billion, Congress appropriated about $116 million for research, of which only a small portion was devoted to health risk research. In fiscal year 1994, Superfund research programs are being cut 13 percent.

At the State level, California has enacted a cigarette tax of 25 cents per pack that specifically

[5] The Comprehensive Environmental Response, Compensation and Liability Act of 1980.

[6] Superfund appropriations also come from general revenues. In 1992, for example, $250 million of the Superfund's appropriation of $1.6 billion came from general revenues.

sets aside a flat percentage of tax revenues for research. Proposition **99,** passed in 1988, earmarks 5 percent of collected revenues for research. As a result of this legislation, $30 million was set aside in 1989 for a competitively awarded grants program of research on tobacco at the University of California.

There are many arguments, pro and con, over the use of such 'sin' taxes. On the one hand, they can raise substantial revenues for desired programs and can promote socially desirable behavior, such as reducing pollution and reducing smoking. On the other hand, these taxes are often levied on those individuals who can least afford them. Moreover, the earmarking of tax revenues can be seen as a license for agencies to raise money for their own ends. Many in Congress adamantly oppose earmarking of tax revenues, insisting that collected money go into the general revenue.

COLLECTING USER FEES

To augment the resources available for research, Congress could enact legislation authorizing user fees for regulatory review of industry products. The money collected in fees could be earmarked for research on health risk assessment.

The concept behind a user fee is that the Government is entitled to charge for a service that directly benefits private individuals or entities. The idea of charging user fees for the regulatory review of drugs has been debated for many years on the grounds that industry is not the only direct beneficiary of a premarketing review; the public also stands to benefit from drugs being introduced into the market. In 1992, Congress passed groundbreaking legislation, the Prescription Drug User Fee Act (P.L. 102-57), requiring drug manufacturers to pay user fees for FDA's review of their product applications. Under the provisions of the act, FDA uses a portion of the funds it collects to improve the drug approval process.

Similarly, Congress could enact new legislation to allow EPA to collect user fees from individual manufacturers for reviewing industry-submitted information about pesticides and toxic substances. Although a sizable portion of EPA's regulatory activities involves industry-wide standard-setting, the agency also reviews the applications of individual manufacturers. Manufacturers or importers of new pesticides and new chemicals, in general, are required to obtain premarketing registration or submit premanufacturing notices, respectively. Fee levels would have to be set to approximate the costs of such reviews. Whether the fees would be sufficient to warrant creating and administering a user fee program would need analysis.

INCREASING FEDERAL APPROPRIATIONS

As another approach, Congress could appropriate more money for health risk research. Research is the source of new methods for improving the accuracy of risk assessment and new ways of preventing, treating, or remediating risks that have already been identified. The desired outcome of this area of research is to enable society to make informed decisions about which risks to reduce and which to tolerate.

Yet despite the advantages of increased resources, nondirected increases in funding can present problems. Chief among them is that little evidence exists to suggest that Federal agencies, if given more money, would direct the funds toward research of the highest national priority. In fact, existing priority-setting mechanisms may allocate resources ineffectively and inefficiently to agency programs. As a result, enhanced resources alone may not provide a commensurate improvement in the process of risk assessment because the most critical areas of research maybe neglected. In any case, substantial increases in appropriations are not likely.

ISSUE 2: How can Congress foster research on risk assessment methodology?

As defined in this report, methodological research is aimed at improving the methods for assessing risks to human health. Specific examples of such research include efforts to improve

the extrapolations from laboratory results to predictions of human effects; to explore new approaches to extrapolating results obtained at high doses in animals and at high exposure levels in workers to estimates of effects at low ‘ ‘environmental’ exposures; and to improve estimates of risks and methods for analyzing uncertainties.

OTA’s emphasis on methodological research does not imply that other research is not important to risk assessment. Rather, it recognizes that other kinds of risk assessment research have already benefited from substantial attention and support. For instance, research in chemical-specific data development for identifying toxicants has long been emphasized in Federal programs and undoubtedly that emphasis will continue. Today, however, methodological research seems to offer the best opportunity to move the field of risk assessment-forward. Yet it receives little attention and funding.

Optimism about methodological research springs from several sources, but two are especially important. The rapid advances in basic biological and biomedical research provide a wealth of information that further research may incorporate into health risk assessments and tools for toxicological research. In addition, generic methodological research provides results that can be applied to large numbers of chemicals. That kind of broad scope is particularly attractive given the enormous backlog of chemicals for which little or no information about risk is available and for which resolving questions about toxicity through traditional testing methods are impractical. Furthermore, new chemicals are being developed, many to replace older chemicals. Methodological research offers the possibility of developing methods for screening to prevent introducing new risks.

Option A: Continue with present policies.

A major conclusion of this study is that relatively meager resources are devoted to such research. In particular, of the $600 million that OTA estimates the Federal Government spent on health risk assessment research in fiscal year 1993, only $65 million (11 percent of the total) went toward improving risk assessment methodology. Some progress is likely under present policies, but the pace will be slow.

While methodological research holds the prospects for improving the accuracy of risk assessments, the controversies on health-risk based decisions are not entirely about the accuracy of risk assessments. They are about different viewpoints. There is not now and there may never be a consensus among those who hold the two major conflicting views in this area: the one, that human health is paramount and that costs and forgone benefits should not be weighed against it, and the other, that some threats to health are sufficiently small that they can be tolerated and that controlling them costs too much. The general conflict between the two perspectives may be intractable, but conflicting interpretations of toxicity data from scientists supporting either view help to fuel the discord. Research into specific areas of uncertainty can help to reduce some of this conflict.

Moreover, under present policies, any augmenting of the resources allocated to methodological research will involve shifting funds from other programs, a move that could cause new controversy. For instance, if the shift were made at the expense of toxicity testing in support of the identification of toxicants, it could be viewed as reducing research in an area of historical Federal emphasis and promoting research that is perceived by some as being the industry’s responsibility.

Still, there are arguments for such shifts. Continuing with present research policies will exacerbate problems in setting standards and undercut the confidence of the public in the standards (and government) because of questions raised about risk assessment results. While industry and taxpayers pay billions of dollars in control and cleanup costs, everyone is left uncertain about how much safety has been

purchased or how much risk has been left unaddressed.

Option B: Promote or mandate more interagency coordination of methodological research.

It is all too frequent a complaint that Federal research programs need to be better coordinated. But some areas of research labor under a greater disadvantage than others when coordination is lacking. Health risk assessment research and especially methodological research, which draws from diverse scientific disciplines, are such areas.

The linkage to regulatory decisions is a distinctive feature of health risk assessment research and a further reason for coordination. Many of these decisions pose problems common across agencies that can be addressed by targeted research. Such targeted research could be potentially better handled in a coordinated manner.

Improving the coordination of research efforts, both within and across agencies, has been seen as important to improving risk assessment for more than a decade. And some efforts have been undertaken. At the national level, the National Toxicology Program was created in 1978 to coordinate Federal programs in toxicological testing. At the program level, EPA's Research to Improve Health Risk Assessment program coordinates research by providing funds to offices within EPA's Office of Research and Development to address problems that cut across research disciplines and issues in improving health risk assessments.

Yet despite those and other efforts, research programs are separated by more than the barriers of organization and location existing among and between agencies, programs, and disciplines. Power struggles over budgetary and bureaucratic turf are common, according to many agency scientists and managers interviewed by OTA. In addition, fragmentation within and across agencies has impeded effective communication, created unnecessary duplication, and stymied research progress toward overarching goals.

Some coordination can occur as a result of leadership at different levels of management—within, between, and among agencies and within programs and laboratories. Perhaps perversely, dwindling resources may provide momentum to these voluntary efforts as program and laboratory managers have no choice but to enter into collaborative efforts to complete research that previously they might have accomplished alone.

A major drawback to taking no action to promote or mandate more interagency coordination is the opportunities that may be lost for large-scale integration of programs. More comprehensive efforts at coordination can lead to synergistic advances in research and more efficient uses of resources-provided that strong leadership is exercised to prevent agencies from transforming coordination efforts into mere paper exercises.

To coordinate research on health risk assessment methodology research, Congress could promote central coordination or establish a lead agency.

PROMOTING CENTRAL COORDINATION

Congress could mandate that research on risk assessment methodology be coordinated centrally through the Executive Office of the President (EOP) to enhance its visibility and promote better communication. Because Federal agencies spend only about $65 million for research on health risk assessment methodology, coordinating such a program would require only modest resources. In fact, the Federal Government's investment in this type of research is so small that some might argue that coordination is unnecessary. The other side of that argument holds that scarce resources deserve the greatest of care.

One possible mechanism has been established: the Federal Coordinating Council on Science, Engineering, and Technology (FCCSET), which is chaired by the President's Science Adviser, is a cabinet-level interagency group charged with coordinating the Federal Government's activities in science and technology.

FCCSET in 1991 and 1992 had some focus on health risk assessment research: its Subcommittee on Risk Assessment of the Committee on Life Sciences began effort to identify future health risk assessment research needs. Although this activity was not aimed at coordinating research projects, the activities of the subcommittee were a first step in creating an inventory of ongoing research activities, which could be useful in future coordinating efforts. A research inventory would have allowed FCCSET members to identify redundant research, areas of little or no activity, and research efforts that could be usefully integrated across agencies. However, this project apparently has been put quietly to rest with the transition to the Clinton Administration.

Even with an active effort, there are limits to the effectiveness of FCCSET or an organization like it. First, FCCSET members were typically policymakers so highly placed in each Federal agency that they were unfamiliar with the technical aspects of research, which impaired their credibility among researchers. Second, the FCCSET staff was quite small; often one staff member was assigned to more than one committee, leaving the bulk of the staff work to agency personnel. Unless FCCSET (or a like organization) were given more staff, it will lack the capacity to coordinate government-wide research efforts. Third, any FCCSET-like activity, however worthy the cause, will inevitably raise the specter among researchers of political tampering, because of the committee's proximity to the President.

ESTABLISHING A LEAD AGENCY

A lead agency could be assigned responsibility for developing and maintaining an inventory of ongoing projects; spearheading cross-agency planning of research to meet the most pressing needs of risk assessors; encouraging collaborative research across Federal agencies and possibly with industry and academia; and offering centralized resources, technical assistance, and public information.

A lead agency to coordinate research offers several advantages. It can draw on its own experience, staff, and resources—although additional resources would be needed for its increased responsibilities. No legislative changes would be necessary if it were located in an existing department or an agency. Also, the creation of a Department of Environmental Protection could provide an administrative location for a lead agency. A lead agency also has an operational investment in the success of efforts at coordination because of its own responsibilities for research or risk management (or both). In addition, using a lead agency instead of the EOP for coordination can ameliorate concerns about the politicization of research.

Yet such an undertaking as coordinating all research on health risk assessment methods may drain the resources of a lead agency. A further problem is the resentment such a designation—and the additional resources to be provided-may foster among other agencies. That outcome could conceivably undermine the very purpose of the action.

Were Congress to proceed with this option, a key factor in selecting a lead research agency would be whether to choose a research or a regulatory body. A regulatory agency would help to ensure greater relevance in selecting research directions aimed at meeting the immediate needs of regulation. A research agency, in contrast, would help to ensure proximity to scientific advances, but its link to regulation would be more remote.

Option C: Establish a risk assessment research agency.

Congress could establish a small agency to administer funds for health risk assessment methodology research. A small but highly visible source of funding for research on health risk assessment methods could focus Federal efforts, draw attention to the promise of the research, attract qualified investigators, provide a forum for review and guidance of the research from all

interested parties, and, if it were structured appropriately, include built-in mechanisms for judging its success. Such a Risk Assessment Research Agency (RARA) could review applications for research funds from inside and outside the Federal Government, evaluating them in the light of whether they would improve risk assessment. Funding for RARA could be secured by tapping the resources of Federal research agencies, which would raise problems, or by new appropriations, also problematic.

Any tap on a Federal agency, however, is likely to encounter stiff resistance. It is to be expected that each of the agencies that currently funds risk assessment research will be reluctant to part with its funds. Somewhat counterbalancing that tendency will be the knowledge that money spent by RARA will be directed at risk assessment methodology. Managers in other agencies who support such research may favor its being performed by the new agency, since, as this report documents, it is currently being done on the margins at the agencies. By contributing agency funds and individual guidance, they will earn credit for successes and dilute responsibility for approaches or programs that do not work.

To ensure that each agency currently involved in risk assessment is treated fairly, RARA could be governed by aboard of directors consisting of the head of each agency that contributes to it. The board could designate an executive officer to oversee the day-to-day operation of RARA and later decide between a permanent executive (the model for most grants and contracts officers at the National Institutes of Health and EPA) and a rotating executive who would serve a fixed 1- or 2-year term (as is done in some programs at the National Science Foundation). RARA would also benefit from a board of nonfederal expert advisers on the direction of its research and panels of experts to review proposals that it is considering funding.

RARA could be located administratively in any Federal organization that supports health risk assessment research, but at least two reasons can be advanced for placing it within the National Institute of Environmental Health Sciences (NIEHS). NIEHS has more than a decade of experience hosting the National Toxicology Program, which pools the resources of a number of agencies to address cooperatively government-wide needs for toxicological research and testing. Moreover, NIEHS has mechanisms in place to administer grants, and it would need few additional resources to administer the RARA programs. An argument can also be developed to support EPA's housing such a program based on that agencys experience in its Research to Improve Health Risk Assessment program and its administration and funding of competitive cooperative agreements. Establishing RARA within a new organization, such as the proposed Department of Environmental Protection or the National Institute of the Environment, would allow the program to develop in an environment without pre-established barriers.

Regardless of where RARA is placed, it may be criticized as duplicating or being unresponsive to the functions of existing agencies. An active board of directors, with an interest in the coordination of research as well as the concerns of their own agencies, could dampen such criticisms.

One of the most significant aspects of RARA is that it would provide a mechanism for evaluation if it commanded all (or a major part) of the funds allocated for risk assessment methodology research. The agency could be established with a sunset provision that required a thorough review of its activities at the end of some set period. Eight years might be appropriate. Two years could be used to establish RARA, solicit proposals, and make the first funding decisions. Most grants would be made for 3 years, provided that the agency's funding pattern parallels other Federal research activities. With 3-year grants, the scientists who received the earliest grants would be able to apply for continuation grants during the 8-year period.

During those years, the board of directors, in consultation with researchers, policymakers, and

users of risk assessment results, could be required to set forth the objectives of the methodological research supported by RARA. The primary criterion for success might be whether RARA-supported research had made a perceptible difference in risk assessment policies. At the end of the 8 years, RARA's board of directors, along with other agency managers and appropriate congressional committees, would evaluate the agency's success. Its future would depend on the outcome of the evaluation.

ISSUE 3: Should Congress mandate more targeted research to improve risk assessment ?

In broad terms, targeted research is designed to solve a specific problem or meet an objective set in advance by an agency or by congressional imperative. In the context of this report, research can be targeted to areas likely to have the greatest impact on policy and decisionmaking. Targeted research is a tool that can be used to link research to the decisionmaking process,

Targeted research on health risks is especially appropriate for regulatory agencies that use risk assessment to develop standards, guidelines, and regulations. It is also appropriate for agencies like DOD and DOE that have research capability as well as an operational investment in the outcome of research-in the form of cleanup programs designed to reduce risk.

Targeted research is especially useful for filling gaps in the data required for specific risk assessments and, more generically, for developing new methods of performing risk assessment. It should not be confused with "mandated" or ''manager-directed' research, in which the scope and methods of a research project are dictated in advance by the managers of an agency. Such projects are less likely to undergo peer review and be awarded competitively. Pertinent examples of targeted research programs are EPA's Research to Improve Health Risk Assessment program and methodological programs at FDA's National Center for Toxicological Research (NCTR).

Frequently people think of targeted research as synonymous with applied research, but targeted research can be either basic or applied, as long as its goal is to meet an agency's established objective. The Human Genome Project of the National Institutes of Health/Department of Energy is an example of targeted research that is basic in orientation. As defined by OTA in this report, targeted research is linked to a specific goal; thus, terms such as "directed," "identified," or "prioritized" research are also appropriate. Any of those terms expands the concept of targeted research beyond the narrow connotation of applied research.

The most familiar method for Federal agencies to target research is Requests for Proposals issued to the scientific community to solicit research intended to address a specific problem. Scientists inside or outside the agency prepare competitive applications detailing how they would study the problem. After a process involving peer review and ranking of the proposals, funds are awarded to scientists whose applications appear most likely or best suited to yield an answer.

Option A: Continue with present policies.

More targeted research may not be necessary. Programs at EPA and FDA's NCTR are already moving in the direction of more targeted research. In addition, establishing more targeted research programs may discourage highly productive researchers, who would rather pursue projects of their own design and interest. Another advantage of no congressional action at this time is that increased targeting may be perceived as leading to lower-quality science. (One way of overcoming such a perception is by using a properly designed procedure for competitive awards.) A final advantage to inaction is that the efficacy of programs of targeted research-in health risk assessment specifically-has not been evaluated. It may be too soon to assess the achievements of EPA's prototype for that kind of research, the RIHRA program. RIHRA was established in 1988 to support targeted, long-term research to

reduce uncertainties in risk assessment. Such programs take at least 5 years-and usually longer—to mature.

Option B: Mandate programs of targeted research at some Federal agencies.

Congress could mandate more programs of targeted health risk assessment research at Federal agencies with responsibilities for risk management. In its mandate, Congress could stipulate broad objectives (e.g., ''improve risk assessment methodology' yet permit agencies enough flexibility to set and revise their own discrete goals to meet those objectives.

An example of possible targeted risk research comes from an OTA study that stated that DOE cleanup of contaminated nuclear sites is proceeding haphazardly, without an adequate understanding of the risks to human health. A program of targeted research in health risk assessment at DOE might improve the process. It could focus on those substances and combinations of substances at cleanup sites, such as complex mixtures of solvents and radioactive materials to which people are likely to be exposed. Furthermore, by redirecting some resources from remediation to research, strategies for cleaning up the sites could be underpinned by research results based on the conditions for a particular site, such as soil, geography, climate, and the number and types of exposure conditions. These efforts could direct DOE's remediation efforts to those areas of highest priority and set levels for remediation that are appropriate for that site.

Option C: Support setting research priorities based on risk.

Congress could support risk-based priority-setting for health risk assessment research as a less prescriptive way of encouraging agencies to establish their own programs of targeted studies.

In the simplest terms, risk-based priorities constitute a "worst-first" strategy: priorities for research are established on the basis of the degree of risk that a substance or situation represents. The degree of risk, in turn, is determined by risk assessment. In recent years, this kind of prioritization has received endorsements from several sources. For example, EPA managers, responding to concerns that EPA's agenda is set more by public and political perceptions than by expert-based judgment about risks, issued a landmark report in 1987 that ranked and compared environmental problems on the basis of the managers' risk estimates. The report's message was that EPA should set priorities for its programs-and its resources-according to the ranking of risks. EPA's Science Advisory Board reviewed and endorsed the report and in so doing expanded the concept of risk-based priorities for research. Two other advisory committees of nationally recognized scientists have also recommended risk-based research priorities. Such a priority for research does not dictate priorities for regulation, which are set inconsideration of many other factors in addition to the level of risk.

Not everyone endorses setting research priorities on the basis of risk. Those who object cite several arguments, for example:

- risk assessment itself is so fraught with uncertainties that it should not be used to set directions for research programs;
- agencies will use risk-based priorities to ignore environmental problems that are of concern to the public or to ignore environmental problems that have few data on which to base risk assessments;
- rankings of environmental problems tend to be problem-specific and fail to recognize the need for research that can cut across many risk assessment issues and affect many problem-specific needs; and
- using risk to set priorities will skew research in the direction of existing problems rather than anticipating those that may crop up over the long term.

Supporters of using risk-based research priorities acknowledge that the approach has problems,

but they contend that it ensures a role for science in a process that historically has been dominated by political and budgetary concerns. Supporters also point out that the vast majority of EPA's research is driven by legislative mandates and would not be affected.

Similarly, Congress could support a "value-of-information" approach to resource allocation that bases priorities for research on whether its results can improve risk management. Most research aims for a greater degree of scientific certainty. In contrast, a value-of-information approach gives higher priority to research based on utility for risk management, channeling resources to research that will have the most impact on decisionmaking. That kind of decision framework "point[s] decisionmakers towards the most valuable improvements in information, enabling them to better evaluate the ever changing tradeoff between more analysis and more action. This type of analysis could be appropriately conducted in the Center for Research Policy discussed in issue 1, option B, under Central Coordination.

ISSUE 4: How can Congress promote research linkages and technology transfer among the Federal Government, universities, and industry?

In times of limited, even declining Federal budgets, research linkages among the Federal Government, industry, and universities are critical for advancing health risk assessment research. These linkages could be important for at least three reasons: they infuse more resources into the field; they bring together researchers with different backgrounds, expertise, and interests; and they increase the trust between the public and private sectors. Congress could consider ways to promote research collaborations. Not all areas of health risk assessment research lend themselves to industry linkages because of inherent conflicts of interest, but many areas would benefit from Federal collaborations with researchers from academia and industry.

One way to foster such linkages and provide incentives for industry involvement is through the commercialization of products developed by health risk assessment research. In addition, product development and commercialization could provide incentives for the private sector to invest even more in this research, given the enhanced prospects for commercial success.

In addition to the growing demands for research in the United States, the other industrialized countries are increasingly interested in using these risk assessment methods for making their regulatory decisions. As quantitative risk assessment (QRA) methodologies were being developed by the United States in the 1980s, the international use of QRA was limited or nonexistent. That pattern, however, may be changing. The overwhelming need, for example, for environmental cleanup in the former communist countries in Central and Eastern Europe has spurred interest in U.S. risk assessment methodologies. In particular, the potential usefulness of QRA in setting priorities for those massive cleanup efforts has prompted ever greater demands from those countries for environmental health information.

As the world leader in health risk assessment research [see app. A of the full report], the United States can set the pace in research and product development:

- equipment and supplies for toxicological testing;
- equipment and supplies for monitoring exposure, both in the environment and inside the body; and
- computer software for estimating risks and their associated uncertainties and for providing options for decisionmaking.

Other types of products, which are beyond the scope of this report, include pollution prevention devices and technologies for environmental remediation.

Specifically, Congress can act to encourage the academic foundation of research and set the stage

for commercializing products invented by Federal scientists or university scientists who receive Federal support. In particular, Congress could develop programs at the Department of Commerce for transferring technologies that arise from health risk assessment research. The National Institute for Standards and Technology could play an important role in such transfers.

Option A: Continue with present policies.

If Congress takes no action, opportunities may be lost for cultivating U.S. preeminence in health risk assessment research and assisting in the commercialization of products. That market is not limited to the U. S., and it is likely to expand as Central and Eastern Europe begins to confront decades of environmental contamination. Those market pressures will probably lead to commercialization regardless of Federal support of such efforts.

Domestically, the need for information about the toxicity of the new chemicals added annually to U.S. chemical registers increasingly outpaces the ability of researchers to produce it. Furthermore, new methods are needed to provide decisionmakers with sufficient data on large numbers of chemicals for regulatory decisions. Those new methods will come from new investigators entering the field. Congressional support could enhance opportunities for collaboration that might otherwise be lost as declining resources and incentives discourage researchers from conducting health risk assessment research.

Option B: Establish academic centers for health risk assessment research.

Congress could establish academic centers that support health risk assessment research and training. It could also supplement the existing support for center grants funded by the National Institute of Environmental Health Sciences and the National Institute for Occupational Safety and Health. To stimulate support for research by industry, the grant awards for centers could be contingent on attracting matching levels of industry support. (The element of matching support is an essential feature of National Science Foundation center grants to universities in other areas of scientific and technological research.)

Even though academic centers are more likely to concentrate on research at the beginning of the ''pipeline' of commercialization, industry might well be interested in investing in research at this early stage, provided that the Federal Government offers encouragement through such mechanisms as tax incentives. Industry also has a stake in ensuring that training of environmental health professionals continues at academic centers, especially since some analysts predict a shortage of trained professionals in the field.

Option C: Promote technology transfer of innovations from health risk assessment research.

Congress could build on existing legislation and take steps to encourage the transfer of ideas and innovative technologies derived from health risk assessment research-for example, improved toxicological tests and technologies for exposure monitoring.

Legislation enacted over the past decade promotes the commercialization of research by permitting Federal grantee institutions, contractors, and laboratories to retain the rights to inventions they develop with Federal funding.[7] Scientists at those institutions can collect a portion of the royalties attached to the inventions; in addition, the legislation authorizes Federal agencies to enter into research efforts with the private sector through cooperative research and development agreements (CRADAs). Such agreements can be in place early in the research process—well before an invention has been developed.

The United States is currently the world leader in the kind of research discussed in this report, but

[7] The Bayh-Dole Act of 1980 (P.L. %517) and the Federal Technology Transfer Act of 1986 (P.L. 99-502) set out these principles.

it may be flittering away opportunities to transfer the technology to the private sector. The burgeoning national and international demand for these products offers a promising prospect for commercial ventures. But even more relevant to this report are the research opportunities that might be created if more resources were infused into the field. Some of the steps Congress could take to expand Federal efforts to transfer technology from health risk assessment research to the private sector include the following:

- Educational efforts----Congress could encourage Federal agencies to be more vigorous in educating their scientists about the personal financial advantages of patenting inventions. Agencies can also be encouraged to market their scientists' inventions more aggressively to private investors. The National Institutes of Health, for example, maintains an online database, available to the private sector at no charge, that lists by research topic inventions developed by Federal scientists. Similar initiatives could be fostered in other agencies.
- Grants or contracts to universities--Research grants and contracts to universities can be targeted toward the development of health risk assessment technology. They could also be structured to require matching industry funds for commercializing research products.
- Government programs for technology transfer----congress could create or strengthen programs at EPA and the Department of Commerce to promote the transfer of technology developed by health risk assessment research to industry. EPA's Office of Science, Planning and Regulatory Support administers the agency's responsibilities for the Federal Technology Transfer Act of 1986 and tries to find additional users for the agency's research products. The primary role of the Commerce Department is to develop and promote new inventions and technologies, and it could be directed to establish a program to promote the products of health risk research. The internal research programs of the department are conducted within the National Institute for Standards and Technology, which would appear to be the logical location for such a program.

Option D: Encourage industry support of health risk assessment research.

Chemical industry organizations, like the American Industrial Health Council, have long called for increasing the use of research results in decisionmaking. Their rationale is that these results would support enlightened regulatory policies. With such a tangible investment in the outcome of research, industry is ripe for encouragement to expand its commitment to health risk assessment research. Congress could seek ways to increase industry's investment in research through tax credits, joint sponsorship of projects, or regulatory incentives.

INCENTIVES FOR RESEARCH INVESTMENT OR PUBLIC-PRIVATE PARTNERSHIPS

There are two existing models of partnerships in industry-sponsored research in health risk assessment: industry consortia and private-public partnerships. The Chemical Industry Institute of Toxicology represents a consortium of industries that sponsors toxicological research. In contrast, a model of public-private partnership is the Health Effects Institute, a nonprofit research organization created by Congress in 1980. Its $6-million budget, which is jointly supported by EPA and automobile manufacturers, is directed toward determining the effects of auto emissions on health. In both cases, the designers of these programs devoted extensive efforts to ensuring high-quality, unbiased research and avoiding possible conflicts of interest. Such efforts are vital considering that even the perception of a conflict of interest can doom research results to obscurity.

Conflict of interest in public-private collaborations can be averted by judiciously selecting the

research projects to be conducted and by carefully reviewing the results of the research, perhaps by using an external review board. At least two areas of research are less likely to provoke controversy because public and private interests converge: research to prevent or reduce risks, and research on methods of toxicological testing aimed at developing cheaper, more cost-effective means of hazard identification.

REGULATORY INCENTIVES

Regulation can also encourage industry-sponsored research. Existing regulations can be revised and new regulations formulated to include incentives-rather than requirements-for scientific innovation. FDA, for example, responded to the plight of patients with acquired immunodeficiency syndrome (AIDS) by developing regulations that urged manufacturers to establish a drug's efficacy by faster means through new, clinical ''surrogate endpoints. ' Those endpoints replaced the standard clinical endpoint-mortality-and are used to predict more quickly whether a drug is actually working. This kind of regulation is purposefully intended to encourage innovation in clinical research.

Congress could foster industry-sponsored research by mandating or encouraging Federal regulatory agencies to review existing regulations more frequently than they now do and to update them with the latest scientific and technological advances. But health advocates may argue that because that approach merely sets forth a process and does not require regulatory changes, and because most regulations are oriented toward protecting health, a review of that kind could create a climate favoring less protection, which would force the advocates to defend the status quo. In contrast, industry may favor more frequent reviews and updating, given its opinion that, in general, most risk-related regulations are too burdensome and often obsolete scientifically. Another difficulty with this approach is that experts usually disagree about whether and when the science is ready to be incorporated into regulations. Debates over the strength of the science, however, can sometimes be a smoke screen for insoluble differences in regulatory philosophy.

A further obstacle to government-industry partnerships has been the protection of industry's proprietary information. Industry-government collaborations are unlikely unless industry is guaranteed that there will be no punitive reprisals or loss of control over proprietary material.

Option E: Provide incentives for collaborative research.

Congress could provide or designate discretionary funds to agencies to promote multidisciplinary collaborative research. The agencies could award the funds competitively, through a process of peer review, to investigators who are collaborating within or across agencies, with academia, or with industry. Funding could be administered through existing mechanisms; however, criteria would have to be developed for what constitutes collaborative research, because the intent of this option is to stimulate new collaborations that might not have otherwise occurred. Its advantages are that health risk assessment research would become broader and more responsive to diverse needs. Its disadvantage is the length of time required for establishing interdisciplinary communication.

ISSUES IN LINKING RESEARCH TO DECISIONMAKING (RADON AS A CASE STUDY)

The original request for this analysis asked for an examination of risk assessment research and not for a study of any particular issue in risk assessment. A subsequent request, however, specifically asked OTA to analyze an ' 'inconsistency' in EPA's approaches to reducing exposures to "indoor' radon, under the provisions of the Indoor Radon Abatement Act and the Safe Drinking Water Act. The request also asked OTA to provide policy options for developing a con-

sistent approach to reducing risks from indoor radon.

Radon is a radioactive gas. It originates from minerals in the Earth, and it has increased cancer rates in miners exposed to high levels. Typically, concentrations of radon are higher inside buildings than they are outdoors because the building partially "traps" the gas, making indoor radon the greater risk.

Radon in water poses a risk, in part because a fraction of waterborne radon volatilizes into indoor air, and, in part, because of ingestion of waterborne radon. EPA has proposed regulating radon in water based on its responsibilities under the Safe Drinking Water Act and the risks it associates with inhalation of airborne radon that comes from water and risks from ingesting water that contains radon. The proposed regulation is opposed by many utilities that provide drinking water. They claim that EPA has overestimated the number of cases of cancer that can be expected from radon in water and that the regulation will cost more than EPA estimates. The resulting controversy over the expected benefits and costs of the regulation resulted in Congress's directing EPA to revisit its estimates of benefits and costs and to submit the revised estimates to EPA's Science Advisory Board for review. That review concluded that the estimate of neither benefits nor costs is certain, and EPA has not yet released its report (November, 1993).

The indoor radon issue is a case study of the interplay between risk assessment and risk management. It is discussed here in two parts. The first part examines the opportunities to derive a more certain estimate of the risks from indoor radon; the second presents options for addressing the inconsistency in Federal approaches to reducing exposures to indoor radon.

RADON EPIDEMIOLOGY AND RISK FROM RADON IN WATER

Extrapolating from the results of animal tests to estimate the risks to humans complicates most risk assessments. It does not complicate the issue of risk from radon, however, because information about radon comes from studies of exposed humans. Nevertheless, no direct information exists to associate exposure to indoor radon with the risk of cancer. Instead, information has been culled from studies of miners. Miners in the past were exposed to radiation levels well above those experienced in most dwellings and, indeed, well above the levels experienced in today's regulated mines and other nuclear workplaces. Moreover, the miners were exposed to other toxic substances in the workplace, and almost all of them smoked. (Smokers are much more likely than nonsmokers to develop lung cancer as a result of radon exposure.)

Estimating the risk posed by radon in homes, therefore, involves an extrapolation from the effects seen at high levels of exposure and under mining conditions to estimates of the cancer rates that may be associated with the lower levels of radiation encountered in homes. Although some of the specifics differ, radon is typical of all assessments that depend on using risk data from high exposures in the workplace as the basis for estimating environmental risks. The options that follow focus on epidemiologic studies that might better inform estimates of risk from radon. In addition to those, it is possible that laboratory studies of the mechanisms of carcinogenesis and of the chemistry and molecular biology of repairing radiation-caused damage will be instrumental in Confirming or altering risk estimates.

There is no requirement for direct evidence of risk to justify environmental regulations. In fact, for many regulated chemicals, the evidence of cancer risks comes from animal toxicity testings. The projected risks for some of these chemicals are so small (risks of 10^{-6} to 10^{-5}, which are equivalent to between 3 and 30 excess cancer deaths per year in the United States), that no epidemiologic study can detect them. The risks of lung cancer deaths from indoor radon, however, are sufficiently large-EPA calculates them as between 7,000 and 30,000 deaths annually, with upwards of 90 percent of those deaths

occurring among smokers—that they might be verified, falsified, or sharpened by epidemiologic study. Studies to date do not answer the question of whether the risk estimate is correct, but ongoing or future studies may provide an answer. Such information could improve public health decisions regarding exposures to radon and provide researchers with invaluable experience through an investigation designed to test the accuracy of a risk assessment.

ISSUE 5: Can epidemiologic studies confirm, reject, or sharpen the estimates of the risk posed by indoor radon?

According to EPA and DOE, scientists around the world are conducting some 18 epidemiologic studies to determine quantitative relationships between exposure to different levels of indoor radon and rates of cancer. The studies share certain characteristics: all involve locating people with lung cancer or the records of people who have died from lung cancer and comparing their exposures to radon and other risk factors with the exposures of people who do not and have not had lung cancer. The frost group of people are called "cases," the second, "controls"; the studies are called ''case-control studies. ' Ideally, exposures to indoor radon are determined by measuring the levels of radon in all of the houses in which each case and control lived. (In practice, houses sometimes have been torn down or are no longer available for such measurements.)

The studies can differ from one another in a number of ways. Some studies question both cases and controls (or their surviving next of kin) about diet. All of them include questions about smoking, and some may obtain more complete information than others about radon exposure. Such differences complicate the interpretation of all of the studies taken together. For example, studies that do not ask about diet cannot supply information about that issue, and the rigor with which questions about smoking habits are asked provides more or less certain information about that risk factor. Such difficulties in comparison and interpretation can be at least partly overcome by the technique of meta-analysis.

Option A: Accept the results of a meta-analysis as sufficient to answer questions about the level or risk posed by exposures to indoor radon.

Some of the 18 epidemiologic studies of indoor radon noted above have been completed, and the results are mixed. Some show no association between levels of indoor radon and rates of cancer, and some show a trend in increasing rates with increasing exposure. All of the studies are hampered by their small size-a few hundred or fewer cases and controls—and all of them have limited power to detect increases in cancer that would be expected if the currently accepted method of extrapolating from the results of the miner studies is accurate. Combining the results of all studies in a meta-analysis will increase the statistical power of the analyses and may be able to inform scientists and policyrnakers about the level of risk posed by exposure to radon in homes.

Both DOE and EPA are considering meta-analyses that will begin when the ongoing studies have been completed and published. DOE has designated two university researchers as coordinators for the review, one in the United States for analysis of North American studies and one in England for analysis of European studies. The ongoing studies are expected to be completed in 1994; allowing 12 months for the analyses would mean that results from the meta-analysis should be available in 1995. (It may be more realistic, given how schedules slip, to expect the results of the meta-analysis in 1996.) Completion of the meta-analysis will not mark the end of the flow of new information about radon, however, and new information will be factored into other meta-analyses as it becomes available. For instance, two case-control studies, one in Iowa and one in Missouri, are expected to be quite informative but will not be completed before the end of 1997.

When the DOE or EPA meta-analysis is complete, the scientists involved will probably have satisfied themselves that the evidence supports one of three conclusions about the risks from indoor radon: 1) the studies of indoor radon and cancer justify no change in the estimates of the range of risks and the best estimate of risk based on the miner studies; 2) the studies justify changes in the estimates; or 3) the studies, for whatever reasons, do not provide sufficient information to decide between conclusions 1 and 2.

Reaching conclusion 1 or 3 would support EPA's continuing use of the current risk estimate, based on the miner data, in risk management decisions. Conclusion 2 would probably lead to consideration of a new risk estimate, and risk management decisions are certain to be influenced by such a change. Whatever conclusion is reached, Congress or a department or agency in the executive branch might consider an additional study to examine the question of how much lung cancer is associated with exposure to indoor radon.

Option B: Convene a planning group to consider a study to answer questions about risks from exposure to indoor radon.

Based on extrapolations from the studies of miners, EPA's best estimate is that residential exposure to radon is associated with about 14,000 deaths (with a range of between 7,000 and 30,000 deaths) from lung cancer annually. These estimates are sufficiently large that the risks, if they are realized, might be detectable in an epidemiologic study. One scientific justification for a large-scale study of the effects of exposure to indoor radon is that it offers the chance to test a risk assessment estimate-in this case, the estimate of risk from indoor radon that is based on the miner studies.

In 1981, OTA proposed a large-scale study of lung cancer to provide definitive answers about quantitative relationships between smoking patterns and lung cancer, as well as information about occupational and other exposures and lung cancer. To those still-valid justifications can be added the opportunity to learn about quantitative relationships between indoor radon and lung cancer.

Lung cancer is the most frequent cause of death from cancer in the United States. Congress could directly mandate that a committee be established to plan a large-scale study of lung cancer in the United States, or it could direct a department or agency of the executive branch, to establish such a committee. The committee could be housed in an executive branch organization, at the National Academy of Sciences, in a university or consortium of universities, or at OTA. Its functions would be to decide whether any study can provide a definitive answer to the question of how much risk is associated with indoor radon and, if it is possible, to design such a study. If an organization such as the Risk Assessment Research Agency (described in issue 2) or the Center of Research Policy (described in issue 1) were established, it would be appropriate to assign it the task of deciding whether a large-scale study of indoor radon should be undertaken.

A committee such as that just described offers several advantages. Its deliberations would be highly visible. It would call attention to the process of designing the study and invite the participation of everyone with a stake in its design; that inclusiveness would promote efforts to make the study as comprehensive as possible. If the study were comprehensive, it might provide substantial data not only about radon but also about smoking, occupational exposures, dietary habits, and perhaps other risk and protective factors. The committee could decide whether to collect and store lung tissue from subjects in the study to provide material for biochemical and molecular analysis, both with current techniques and with techniques yet to be developed.

Yet the chances of agreeing that such a study is possible and that it could provide definitive answers are probably rather small. Obtaining accurate measures of past exposure to radon is fundamental to the success of such a study, as is

obtaining accurate information about past or present smoking, exposure to environmental tobacco smoke, workplace exposures, and eating habits. The planners may well conclude that no study can obtain that information with sufficient accuracy to provide definitive answers. That decision would not be without value: the evaluation methods used by the committee would find further employment in the Government's consideration of requests for epidemiologic studies to investigate other environmental hazards.

If the planning committee decides that no feasible study could be designed to answer questions about indoor radon, Congress and the country might have to accept that radon reduction activities would continue to be based on risks estimated from the studies of miners. It is also possible that the costs of a study like the one described above or the time necessary to complete it would make the effortless than worthwhile, and Congress could decide not to fund it.

Finally, Congress could decide that the study was feasible and worthwhile and could allocate funding for its conduct. If that decision were made, policy makers would have to decide on a regulatory course for the time necessary to conduct the study. In particular, a decision would have to be made about whether to impose a moratorium on regulating radon until the study was finished.

Planning such a study could involve one or two staff members for perhaps 2 years and the cost of three meetings of the committee. It would also include evaluation and review of all documents and their publication. The total cost of the planning phase would be between $250,000 and $750,000.

Whatever the results of the epidemiologic effort, any result that does not support the current risk estimate is likely to cause few difficulties for scientists but substantial problems for regulatory agencies. Although scientists may have to modify their conclusions as new results are produced, the nature of their data-dependent work makes such revisions relatively commonplace. In contrast, EPA might have to adjust its regulations, which is a more difficult task. If the new studies show that the risk estimate on which the regulations are based is low, tighter regulations can be drafted in keeping with the new information. If the current risk estimate is found to be high, the regulations could be relaxed, but relaxing regulations has proved to be difficult in the past. Moreover, the expenses borne under the prior regulation would not be recoverable.

ISSUE 6: Can there be a consistent approach to reducing radon exposures?

The request that OTA examine questions relating to indoor radon was prompted by EPA's proposal to regulate the level of radon in water to 300 pCi/L under provisions of the Safe Drinking Water Act. According to EPA, that concentration in water will contribute 0.03 pCi/L radon to air because of the volatilization of radon from water. (The ratio of radon in water to radon in air that originates from the water source is about 10,000 to 1.) The request to OTA noted that the regulatory goal, 0.03 pCi/L, is lower than the concentration of radon in outdoor air, which varies between 0.1 and 0.5 pCi/L; in addition, it is more than a hundred times lower than EPA's ''action level" for indoor radon, which is currently 4 pCi/L. The request asked OTA to examine the inconsistency' between and among the levels and provide options for a more consistent approach to reducing risks from radon (see box l-A).

The apparent inconsistency arises because different laws apply to radon in different media. Under the SDWA, EPA sets goals for the maximum contaminant levels of toxic substances in water. For carcinogens, those goals are zero because of the policy position that exposure to any level of a carcinogen poses some risk. When zero is not attainable, EPA generally sets the maximum contaminant level (MCL) to allow the cancer risk from the substance in drinking water to range between 10^{-4} and 10^{-4}. Although EPA's

proposed MCL for radon in water, 300 pCi/L, was established because EPA concluded that the technology was available to achieve this standard, it is nevertheless associated with a risk of 2 X 10^{-4}, which is near the desired range.

The goal of the Indoor Radon Abatement Act (IRAA) is to reduce exposures to indoor radon to the same levels seen in outdoor air. Currently, EPA's action level of 4 pCi/L radon in air is greater than that goal, and it is based, at least in part, on practical considerations, As former EPA Assistant Administrator L.S. Wilcher noted:

> While the 4 pCi/L target risk for radon in indoor air represents a higher level of risk [than the risk associated with the proposed MCL for radon in water], it is the lowest risk level which the Agency considers to be technologically feasible for all homes.

The inconsistency takes on practical significance when the observer considers the contribution that radon in water makes to total exposure to radon. The proposed regulation of radon in water would reduce the concentration of radon in air that comes from water to 0.03 pCi/L and leave most of the exposure to indoor radon unaddressed. Indeed, EPA's Science Advisory Board said in 1992, ''Frankly, radon in drinking water is a very small contributor to radon risk except in rare cases, and the Committee suggests that the Agency focus its efforts on primary rather than secondary sources of risk. '

Formally, three approaches are available to address the inconsistency: 1) reduce exposure to radon from air that enters the house to the level of radon expected from the volatilization of radon from water under the EPA's proposed regulation; 2) relax the proposed regulation on exposures from waterborne radon so that exposures from water and air are reduced to some comparable level; or 3) work toward a politically acceptable compromise between reductions in waterborne and airborne radon.

The first approach is impossible. EPA's proposed regulation would reduce the concentration of radon in air that comes from water to 0.03 pCi/L. The 'background' concentration of radon in outdoor air is approximately 10 times higher than EPA's regulatory limit for radon in water. Therefore, the infiltration of outdoor air into a house produces a 10-fold higher concentration than EPA would allow from water. As is recognized by IRAA, it is impossible to reduce indoor concentrations below outdoor concentrations.

Under the second approach, the proposed regulation of waterborne radon could be put aside and new regulations brought forward so that the contribution from waterborne radon to inside radon is no greater than the contribution from outside air or no greater than some fraction of the contribution from outside air. This second approach is discussed in the options below. Its advantages include eliminating the inconsistency and reducing the costs of the water regulation; its primary disadvantage is that it would lessen the reduction in exposure to radon that would be achieved under SDWA regulation.

Acknowledging the tradeoff in the second approach leads to the third. Resolution of the inconsistency, should it be reached, would surely be a political act, perhaps involving Congress, EPA, other agencies, both Federal and non-Federal, and private sector organizations.

OTA offers the following three options that address the inconsistency identified in the request.

Option A: Accept the inconsistency and let the Environmental Protection Agency deal with exposures to radon under existing laws.

The inconsistency does not prevent actions to reduce exposure to radon. In responding to congressional inquiries, EPA points out that its approach to regulating radon parallels its approach to other waterborne carcinogens. In addition, the agency actively encourages citizens to test houses and other buildings for radon gas and to take action if the levels of radon in air are greater than 4 pCi/L. Should Congress do nothing

further about regulating radon, EPA will probably continue along this course.

Under its responsibilities for the SDWA, EPA estimates that about 41,000 water suppliers now produce and distribute water that would exceed the proposed regulatory standard. EPA specifies aeration as the best available technology to reduce concentrations of radon in those systems to the proposed regulatory limit, and it has estimated the benefits and costs of that course of action.

As a result of the so-called Chafee-Lautenberg Amendment (Section 591 of the Housing and Urban Development, Veterans Administration, and Independent Agencies Appropriations Bill of 1992), EPA completed a multimedia risk assessment for radon in July 1993. The same amendment imposed a moratorium, which expired on October 1, 1993, on EPA's proposed regulation. [Congress has extended the moratorium to October 1, 1994.] The amendment was prompted by the inconsistency of approaches to reducing exposure to radon and the costs of the proposed regulation. As Senator Chaffee said during consideration of the amendment:

> The dispute here is about the relative risk of radon in drinking water. And since the Federal Government does not require that any steps be taken to correct the principal source of the risk, namely the gas that comes from the soil, the drinking water suppliers, quite rightfully, wonder why they should be required to clean up drinking water at a great expense.

The results from the congressionally mandated 1993 multimedia risk assessment were very nearly the same as those that EPA presented in its proposed regulation in 1991. According to EPA, the regulation will save about 80 lives annually. Some organizations, such as the Natural Resources Defense Council (NRDC) and Friends of the Earth (FOE) have stated that an MCL of 300 pCi/L is too high and that it (and the attendant risk) can be reduced further. Some water suppliers, pointing to the costs of the measure, also object to the proposed MCL. In its draft regulation, EPA estimated that each averted cancer death would cost about $2.3 million. On one side of the argument, some water utilities estimate costs of between $65 million to **$89** million for each averted cancer death and between $443 million and $592 million for each averted cancer death in nonsmokers. Arguing on the other side, NRDC and FOE assert that a lower MCL would require regulation of more water suppliers with further reductions in radon exposures and in cancer risks at little additional cost.

The costs of regulating radon in water can be compared with the costs of childhood immunizations, a public health measure that has greatly increased in cost in recent years and produced calls for reducing the profits of pharmaceutical companies. The costs of childhood immunizations have increased from between $7 and $23 in 1982 to between $129 and $244 in 1992. The annual cost of regulating radon in water—estimated by EPA to be about $50 per family served by average-sized water supply systems and $120 per family served by small systems-ranges between a fifth to a little less than half the one-time cost of immunization. The estimate by the Association of California's Water Agencies of $340 per family per year for the radon-in-water regulation exceeds the one-time cost of immunization.

The continuing annual family cost—between $50 and $340-of the radon-in-water regulation (which will affect about 1 percent of the total exposure to radon) can also be compared with EPA's estimate of the cost of actions to reduce the amount of radon entering homes directly from the soil. Direct entry of radon from soil contributes, on average, 99 percent of the radon in indoor air. The one-time cost of bringing indoor radon concentrations down to 4 pCi/L or lower ranges from $500 to $2,500 per house, with an average of $1,200 and average operating expenses of $68.

Whatever the actual costs would be, it is likely that NRDC and FOE are correct in stating that reducing concentrations to levels below the MCL is possible and could be realized if the regulation

were made final. Given the capital and operating costs of reaching the proposed MCL and the possibility that the MCL would be changed as technology improves, many water suppliers will probably design their systems to reduce concentrations to a level well below the currently proposed MCL. Moreover, NRDC and FOE cite experts who state that the only additional cost, after aeration systems are installed, of lowering radon concentrations in water is the cost of electricity. The review by EPA's Science Advisory Board of the agency's 1993 multimedia risk assessment suggested that EPA should consider using granulated activated charcoal as an alternative for radon removal in some water systems. The costs of that course of action have not been estimated.

The option discussed here, allowing EPA to continue along the course it has plotted, will not address the inconsistency in the legislation, but it could nevertheless be presented to the public as the chosen option. The inconsistency is built into the current system; it does not make the system unworkable.

Option B: Use the reauthorization of the Indoor Radon Abatement Act to direct EPA to integrate all routes of exposure in considering acctivities to reduce exposure to radon.

The multimedia risk assessment demonstrates again that only a small part of the risk posed by radon comes from waterborne radon. It does not offer guidance for what is to be done as a result of that demonstration.

If Congress decides that the multimedia risk assessment or other considerations suggest a new approach to reducing radon exposures, it can use the reauthorization of the IRAA as a vehicle. However, while Congress is working out the details of an integrated approach to reducing exposures to radon, it would probably have to advise EPA about regulating radon in water.

If Congress anticipates that an integrated approach to reducing exposure to radon would produce a different level for radon in water than the level proposed under the Safe Drinking Water Act, it could direct EPA to continue the moratorium on the proposed regulation. Or, as an alternative to having no regulation of radon in water while EPA works out an integrated program of exposure reduction under the IRAA, Congress could require EPA to set a standard for water, taking into consideration other radon exposures. For instance, radon in water could be regulated so that it contributes no more radon to indoor air than is present in outdoor air. (As an approximation, the Science Advisory Board suggests that the regulatory level for radon in water under this approach be set between 1,000 and 3,000 pCi/L rather than at 300 pCi/L as in the current proposal.) Such an approach would serve at least three purposes: it would reduce the greatest risks from radon in water; it would provide valuable experience to EPA, utilities, and engineering and consulting firms in designing mechanisms to reduce concentrations of radon in water; and it would allow for adjusting those levels after the integrated exposure reduction program is completed under the IRAA. Moreover, results from ongoing or future epidemiologic studies may alter EPA's risk estimates. The period allowed for EPA to develop an integrated radon exposure program under the IRAA would permit the incorporation of new scientific information.

A congressional decision to delay the proposed regulation of radon in water has drawbacks as well. It will allow more exposure than would be permitted if regulation proceeded under the SDWA. As a result, some of the exposures that would have been averted under the SDWA would remain. A decision to delay the regulation would also insinuate Congress into EPA's regulatory program and interfere with the functioning and autonomy of that agency.

Option C: Include radon in a comprehensive law for regulating indoor air.

Some indoor air pollutants, such as radon, arise from soil and water. Others come from utilities, as

when natural gas is used for cooking and heating; from cooking itself; from building materials such as asbestos; from formaldehyde in carpeting; from commercial chemicals; and from biological sources-animal dander, insect parts, molds, and mildews. Over the years, legislators have considered enacting an indoor air pollution law to address these complicated exposures. Such legislation, combined with Congress's directing EPA not to regulate radon in water under the SDWA, could resolve the inconsistency in current approaches and give EPA the authority to approach indoor radon in a unified, multimedia way. Treating the risks presented by indoor air in a concerted fashion would probably lead to greater reductions in overall exposures than would be achieved under current laws. In general, the solutions to indoor air problems caused by different substances are all likely to follow similar paths, such as improving ventilation and filtration, among others. A single piece of legislation might facilitate considering the risks as a whole rather than piecemeal.

Given the time it takes to enact legislation, implement new programs, and draft regulations, a few years might pass before radon in water is regulated under a new, comprehensive law. To deal with that possibility, Congress could direct EPA to formulate interim regulations, as in option B, to limit radon in water to levels that contribute no more to total exposure than does outdoor air.

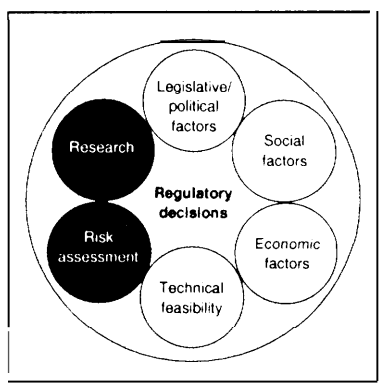
EPA administers 12 laws. That multitude of mandates and responsibilities reflects the twists and turns of increased concern about the environment over the years and Congress's intense interest in the agency's functioning. The suggestion of a new law directed at indoor pollutants does not mean that the number of laws would be increased by one. Rather, it could lead to subsuming the IRAA under the new law and keeping the number of laws constant.

An Introduction to Health Risk Assessment and Its Research Base

2

This chapter presents a brief introduction to the process of health risk assessment, the kinds of research and data that support it, and the controversies that have arisen in some areas of research and assessment. It is intended for the lay reader with little or no technical background. Because of its brevity, it cannot provide details about specific differences in the use of health risk assessment among the Federal agencies or a thorough review of the scientific literature. Readers interested in pursuing those topics are advised to look at recent, accessible reviews (Paustenbach, 1989a, 1989c; Rosenthal et al., 1992; Silbergeld, 1993; Zimmerman, 1990). The chapter does include a brief discussion of the costs of regulatory compliance and of treating environmentally related diseases.

Health risk assessment is most developed for estimating the risk to humans from exposure to carcinogens (box 2-A). Therefore, this chapter and, indeed, this report tend to focus on carcinogens, not because substances causing other risks to health are less important but because Federal agencies have more experience in assessing the risk of cancer. The report also emphasizes risk assessment associated with low levels of exposure to harmful substances in the environment, probably the area of greatest scientific controversy.



We estimate risks every day, every time we cross the street, every time we drive. Before making a left turn, we examine the hazard (the oncoming traffic), we consider the consequences of exposure to the hazard (dents, injuries, death), and we estimate the probability of occurrence (the likelihood of being hit). When we overestimate that probability, we hesitate and waste time. Usually, we assess the risks reasonably well, turn when the

Box 2-A—The Growth of Health Risk Assessment in the Federal Government

Although the connection between the environment and human health was recognized in ancient times, attempts to quantify that relationship are of more recent origins. Scientific papers published in the early 20th century described unusual diseases observed in workplaces, and by the 1930s, researchers were able to estimate quantitative relationships between occupational exposure to potentially hazardous substances and their effects on human health. One observer refers to the early use of these relationships to establish no-observed-effect levels (NOELs) for humans as "a primitive quantitative risk assessment methodology" (Friess, 1987). By the 1950s, research on safety factors (later known as uncertainty factors) was developing as well.

But using NOELs and uncertainty factors for quantifying the risks associated with carcinogens became increasingly problematic. Studies showed that even very low levels of ionizing radiation or certain chemicals seemed to cause corresponding low levels of disease, but thresholds could not be established. Researchers thus began to develop dose-response extrapolation models starting in the 1960s to estimate the effects on humans of low doses of carcinogens.

The Nuclear Regulatory Commission was probably the first government agency to use such models to estimate the risks to humans associated with ionizing radiation. The Food and Drug Administration (FDA), however, was the first Federal agency to employ those quantitative methods in a regulatory context. In 1973, FDA proposed using an extrapolation model to determine the level of sensitivity necessary for methods to detect residues in foods from drugs given to animals. Since then, the use of health risk assessment has spread to other agencies within the Department of Health and Human Services, such as the Centers for Disease Control and Prevention and the Agency for Toxic Substances and Disease Registry.

In the early 1970s, the Environmental Protection Agency (EPA) sought to suspend the registrations of pesticides that had been shown to be carcinogenic in animal tests. After being criticized for taking what some viewed as a zero-risk approach, EPA responded by developing comprehensive guidelines for assessing the risks associated with health effects other than cancer. Today, programs throughout EPA use health risk assessment.

The Occupational Safety and Health Administration (OSHA) proposed its generic cancer policy in 1977 and formally adopted it in 1980, despite intense criticism from the regulated community. But a 1980 U.S. Supreme Court decision on OSHA's benzene regulation forced the agency to make significant changes in its policy. Today, OSHA can use studies by the National Institute for Occupational Safety and Health to meet the Court's requirement of showing that an exposure poses a significant risk that would be reduced by imposing a regulation. The Consumer Product Safety Commission (CPSC) also turned to the use of health risk assessment in the 1970s, publishing its guidelines in 1978. Still other agencies, such as the Departments of Defense and Energy, use risk assessment to help protect workers and the public from the risks associated with their activities. These agencies, however, do not use risk assessment in a regulatory context.

Attempts to coordinate policy across the Federal agencies also began in the 1970s, particularly through the efforts of the Interagency Regulatory Liaison Group, formed in 1977 by agreement of the four main regulatory agencies: CPSC, EPA, FDA, and OSHA. The groups published a draft of a report on cancer policy in 1979. in the same year, the White House Office of Science and Technology Policy (OSTP) published another set of cancer guidelines. OSTP has continued its efforts to coordinate the use of health risk assessment across Federal agencies, publishing further cancer principles in 1985,

In short, health risk assessment is a relatively young method of analyzing data on toxic substances. As its use has grown since it was introduced into regulatory programs in the 1970s, it has been adapted to suit the needs of many agencies and programs. Since the late 1970s, efforts have been made that continue to this day to coordinate the use of health risk assessment across agencies.

SOURCES: S. Friess, "History of Risk Assessment," *Pharmacokinetics in Risk Assessment: Drinking Water and Health, vol. 8* (Washington, DC: National Academy Press, 1987); P.B. Hutt, "Use of Quantitative Risk Assessment in Regulatory Decisionmaking Under Federal Health and Safety Statutes," *Risk Quantitation and Regulatory Policy,* Banbury Report 19, D.G. Heel, R.A. Merrill, and F.P. Perera (eds.) (Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 1985) D.J. Paustenbach, "A Survey of Health Risk Assessment," *The Risk of Environmental and Human Health Hazard%,* DJ. Paustenbach (cd.) (New York: John Wiley & Sons, Inc., 1989); M.E. Rushefsky, Making *Cancer Policy* (Albany, NY: State University of New York Press, 1986).

probability of an accident is small, and make it safely through the intersection. Occasionally, however, we underestimate the probability of being hit and sometimes suffer the consequences.

Risk assessment uses similar thinking to determine the probability of harm or disasters—both natural ones, like fires and floods, and those resulting from engineering problems, like engine failure in aircraft, or from exposures to toxicants. This information is useful for those who work to prevent disasters-for example, the engineers who design safety features-and for those who insure potential disaster victims. It is also useful for governments, which seek to protect the health and safety of their citizens, and, ultimately, for citizens themselves, who participate in decisions about acceptable or tolerable and unacceptable or intolerable levels of risk.

Health risk assessment deals with the risks people face when they are exposed to harmful substances. It is generally used for agents whose health effects are hard to measure directly, such as low levels of exposure to chemicals and ionizing radiation. Time factors may also increase the difficulties involved in measurements. Diseases resulting from exposure to some harmful substances, like asbestos, may not develop for 20 or 30 years. And some substances, like lead, have no obvious acute effects at low levels but can cause subtle and significant effects after chronic low-level exposure.

In such situations, questions arise not only about the probability of occurrence but also about the relationships between the duration and intensity of the exposure to the hazard and the type and severity of the adverse health effect. Researchers have directed most of their efforts in developing health risk assessment toward answering the following questions: What health effects are associated with exposure to a particular substance? How large a dose—and at what frequency and over how long a period of time-does it take to cause those effects? How much of a substance are people likely to be exposed to? Given some level of exposure, how many people may be affected?

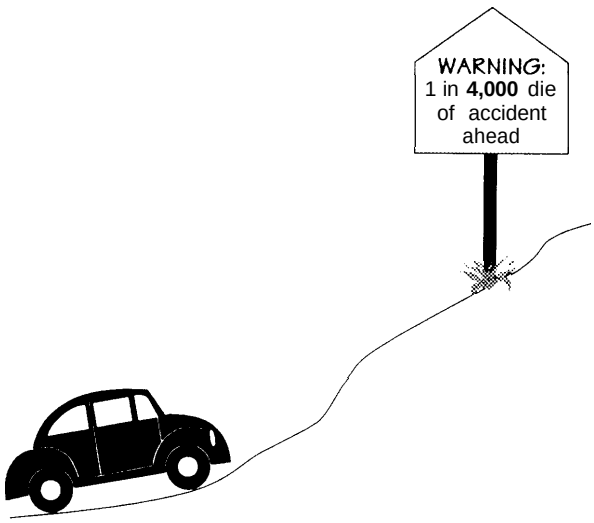
Table 2-l—Estimated Risk of Death From Various Human-Caused and Natural Accidents

Accident	Risk
Automobile	1 in 4,000
Drowning	1 in 30,000
Air travel	1 in 100,000
Lightning	1 in 2 million

SOURCE: C.D. Klassen, "Principles of Toxicology," *Casarett and Doull's Toxicology,* C.D. Klassen, M.O. Amdur, and J. Doull (eds.) (New York, NY: Macmillan, 1986).

Health risk assessment provides a systematic approach to evaluating and quantifying risk. As it pertains to the health effects of toxic substances, risk is the probability of injury, disease, or death for individuals or populations who undertake certain activities or are exposed to hazardous substances. It is sometimes expressed numerically (e.g., 1 excess cancer death in 1 million exposed people). A risk of 1 in 10,000 may be described as 10^{-4}, a risk of 1 in 1 million as 10^{-6}, and a risk of 1 in 100 million as 10^{-8}. Risks smaller than 10^{-6} are rarely regulated (Rosenthal et al., 1992; Travis et al., 1987). If quantification is not possible or necessary, risk may be expressed in qualitative terms (e.g., low, medium, or high risk).

Experts have quantified the risk of death from some familiar hazards (table 2-l). Traveling in an automobile, for example, involves a risk of accidental death of 1 in 4,000 (i.e., people on the road), which is relatively high. As might be expected, the risk of being killed by lightning is much lower (1 in 2 million). But the public's perception of risk does not always agree with the risk calculated by experts. Some people, for example, avoid air travel even though the risk associated with automobile travel is 25 times greater. In particular, people tend to overestimate the risk or number of deaths from rare, dramatic events and underestimate the risk from common, undramatic causes. Public perception of the annual rates of death from floods or tornadoes are



typically overestimated, whereas the risks from smoking and drinking alcoholic beverages are typically underestimated.

In everyday life, we evaluate the risks associated with various activities and make choices, considering such factors as benefits, costs, convenience, and past experience. As a society, we must make similar choices. Health risk assessment can help clarify those decisions by illuminating the kinds of hazards that result from exposure to a substance, by identifying those people who have been exposed, and by estimating the magnitude of the risk associated with different levels of exposure. But health risk assessments are only one of the factors on which such decisions are based. Decisionmakers may also need to consider the technical and economic feasibility of various control technologies, social values and political forces, the missions of their agencies, and their legal responsibilities.

The results of a health risk assessment are usually intended for use by "risk managers,' decisionmakers who determine what, if anything, should be done to reduce or eliminate a risk (Zimmerman, 1990). Health risk assessment is used not only by agencies of the Federal Government, the main focus of this report, but also by other organizations with an interest in the health effects of exposure to chemicals. Those groups may include State and local authorities, environmentalists, manufacturers, representatives of consumer organizations, and, increasingly, local citizens.

Health risk assessment is used for many different purposes as well. People may be exposed to many types of potentially harmful substances through the air they breathe, the water they drink, and the food they eat. They may be exposed in the workplace, outdoors, or at home. Those exposures may be regulated under a variety of Federal and State laws. Consequently, the details of the health risk assessment process may vary, depending on those circumstances.

RESEARCH DATA FOR HEALTH RISK ASSESSMENT

The primary source of data for assessing human health risks is epidemiologic, toxicological, structure-activity relationship, and exposure studies. Other research data on metabolism, pharmacokinetics, and mechanisms of toxicity are used to determine the relevance of those primary data for predicting adverse health effects in humans. The primary sources of data are described briefly below.

Epidemiologic Studies

Epidemiologic studies examine patterns of disease in human populations and the factors that influence those patterns. The greatest advantage of such studies is their direct relevance to human populations because they are based on the experiences of human subjects. Epidemiologic studies are especially informative when levels of exposure are well documented, the exposed population is well defined, and the adverse effect associated with the substance is known. Those conditions, however, are seldom met.

The essence of epidemiology is the observation of a natural experiment-the release of an agent into an environment, resulting in exposure of a population. Sometimes, however, relationships

between exposure and health effects may be obscured because of a lack of precise information about the amount and frequency of exposure or the presence of confounding factors, such as exposure to other substances. Factors such as genetic variability and population mobility are difficult to take into account. In addition, most epidemiologic studies are not sensitive enough to detect small increases in risk. Still when enough information is available and epidemiologic studies can be undertaken, they can provide valuable information about the relationships between exposure to hazardous substances and human health.

Epidemiologic studies may be descriptive, observational, or experimental (Lilienfeld and Lilienfeld, 1980). Descriptive epidemiologic studies provide clues to the causes of disease by examining the distribution and extent of disease in different groups of people defined by age, race, gender, or other parameters. In observational studies, scientists examine statistical associations between exposure to a hazard and disease in individuals or relatively small groups. In experimental epidemiology, scientists control the population groups in the study, determining in advance the groups to be exposed, often in occupational or clinical settings.

Toxicological Studies

Most often, the information needed to predict adverse health outcomes from exposure to potentially hazardous chemicals comes from testing substances in animals or through in vitro tests, that is, in cells or tissues isolated from animals and humans. Such toxicological studies allow scientists to test chemicals and control the amount and conditions of exposure and the genetic variability of the subjects, factors that cannot be controlled in most epidemiologic studies. Toxicological studies are the only means available to evaluate the risks of new chemicals.

Biologically, animals, even the rats and mice typically used in toxicity testing, resemble humans in many ways. A substantial body of evidence indicates that results from animal studies can be used to infer hazards to human health (Huff, 1993; Huff and Rail, 1992; NRC, 1991a). There are exceptions to this generalization, but each must be proved before setting aside the assumption that animal tests are predictive. The proof can be data on human toxicity that convincingly contradict a specific finding in animals, or mechanistic or physiological reasons that support the idea that the animal data are irrelevant to humans. Otherwise, the assumption is generally made that toxicity data from animals can be used to identify potential human hazards (NRC, 1991a; Perera and Boffetta, 1988; Silbergeld, 1993; U.S. EPA, 1986a). Much of toxicological research focuses on developing and employing various animal ‘‘models’ to predict adverse health effects in humans, understand mechanisms of toxicity, and verify that metabolic pathways and toxic effects are similar in test animals and humans.

Toxicological disciplines can be distinguished by the “endpoint” being studied, that is, the resulting disease or the organ affected by exposure to a toxic substance. Increasingly, researchers are studying subtle endpoints other than cancer, such as immunotoxicity (U.S. Congress, OTA, 1991a), lung toxicity (U.S. Congress, OTA, 1991b), neurotoxicity (U.S. Congress, OTA, 1991c), reproductive and developmental toxicity, and liver and kidney toxicity. Scientists are also devoting more attention to studying the effects of long-term (’ ‘chronic’ exposures, rather than the effects of large, short-term (’‘acute’ exposures.[1]

Toxicological studies, however, have limitations. Cost considerations limit most animal

[1] For excellent reviews and research papers on the various types of toxicological studies being conducted on health effects other than cancer, see volume 100 of *Environmental Health Perspectives* (1993), in particular, see Luster and Rosenthal (1993), Schwetz and Harris (1993), and Fowler (1993).

studies to a few hundred test animals, and in most instances, researchers use high levels of exposure to increase the likelihood of observing a statistically significant effect in a relatively small group of animals. It can also be very difficult to verify any quantitative extrapolation of the results of animal studies to human effects.

Structure-Activity Relationships

Structure-activity relationships refer to studies that compare the chemical structures of substances in order to make inferences about toxicity and identify candidates for further testing. The accuracy of prediction from this method of assessment has grown over time, but it is clear that there are no simple relationships between structure and toxicity (Friess et al., 1986; Klopman and Rosenkranz, 1991; Rosenkranz and Klopman, 1989).

Exposure Data or Models

Data for assessing human exposure come from measuring the presence of an agent in air, water, soil, or food. Frequently, such data are not available for a specific kind or level of exposure. In those situations, mathematically derived computer models are used to simulate the exposure conditions and predict the level of possible exposures.

Personal monitoring measures the actual concentrations of a hazardous substance to which people are exposed by using devices that individuals wear or by sampling the food, air, and water they eat, breathe, and drink. Biological monitoring measures the toxicant or its metabolize in biological samples such as blood or urine. Ambient monitoring measures hazardous substances in air, water, or soil at freed locations. That method is often used to provide some information about the exposure of large populations, such as people exposed to air pollution in a region.

THE HEALTH RISK ASSESSMENT PROCESS

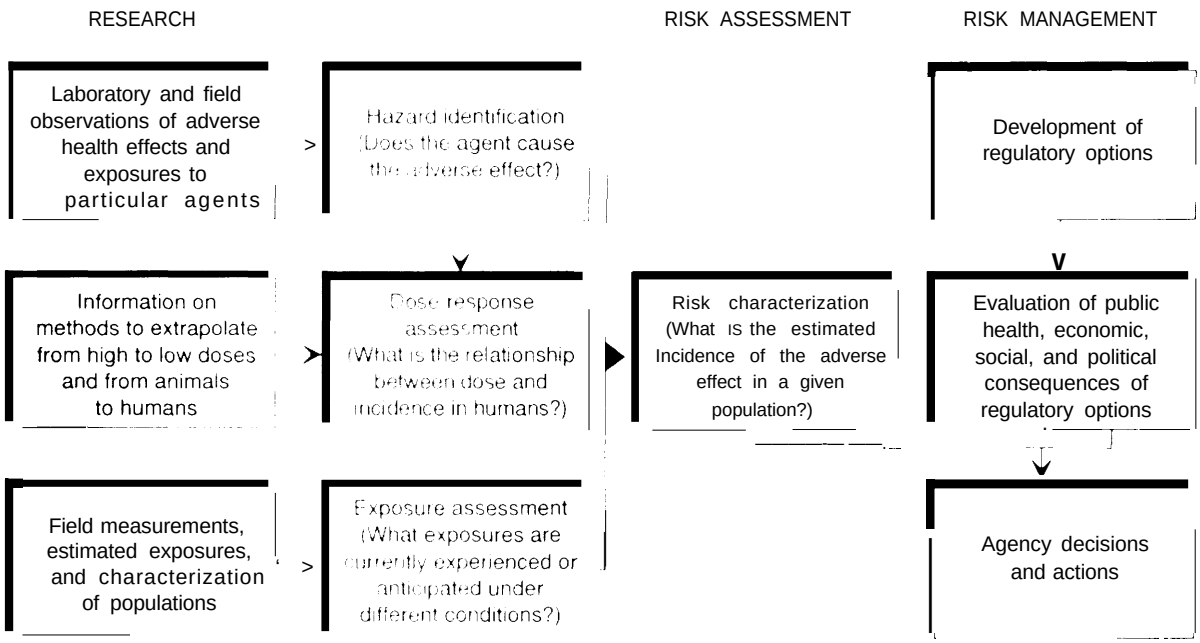
Health risk assessment uses tools derived from many scientific fields in a systematic way to organize and evaluate the available scientific information about a potentially harmful substance. The goal of health risk assessment is to identify the kinds of adverse health effects that may be associated with exposure to a harmful substance and to quantify the magnitude of the risk of experiencing those effects according to levels of exposure. As conducted by Federal agencies, health risk assessment consists of some or all of the following four steps: hazard identifi cation, dose-response evaluation, exposure assessment, and risk characterization (NRC, 1983; U.S. Congress, OTA, 1981; U.S. EPA, 1986a; U.S. OSTP, 1985). Originating in a 1983 National Research Council report, figure 2-1 is the most commonly used graphic representation of the risk assessment process.

Hazard Identification

Hazard identification evaluates the available data on the types of injury or disease that maybe associated with exposure to a substance and on the conditions of exposure under which the disease or injury maybe produced. For example, does a substance cause cancer or birth defects? Does it harm the nervous system or the immune system? Three types of scientific studies are used to identify adverse effects associated with exposure to chemicals: epidemiologic studies, toxicological studies, and structure-activity relationships (Cohrssen and Covello, 1989; Lave and Omenn, 1986; U.S. Congress, OTA, 1981; U.S. EPA, 1986a; U.S. OSTP, 1985).

Hazard identification involves judgments about the quality, relevance, and limitations of the available data. It typically includes an evaluation of all available toxicological data (much less frequently, an evaluation of all epidemiologic data) to identify those adverse effects that are best documented and those that are most relevant to

Figure 2-I—Relationship of Research, Risk Assessment, and Risk Management



SOURCE: National Research Council, *Risk Assessment* **In the** *Federal Government: Managing the Process* (Washington, DC: National Academy Press, 1983).

human health. Generally, the toxic effects causing the greatest concern are those that are the most severe, occur at the lowest levels, and persist after exposure ceases.

Dose-Response Assessment

In the second part of a health risk assessment, assessors determine the quantitative relationship between exposure to a substance usually expressed as a dose, and the incidence of disease. That relationship may be based on information from epidemiologic studies of exposed humans or tests on animals.

Only rarely, however, is information available on doses and responses in the range typical of human ''environmental'' exposure. More often, information derived from both epidemiologic and toxicity studies is based on far higher levels of exposure. Because for any given chemical and route of exposure, the severity and frequency of a biological response usually increase with the dose, it is necessary to estimate biological effects at the doses that people typically encounter, based on dose-response relationships. Currently, there are two main methods of using the high experimental doses to predict effects at the low doses of interest: one method for noncarcinogens and another for carcinogens. Such predictions of effects at low doses from the observed effects at high levels are termed extrapolations.

For noncarcinogens, biological effects are assumed to occur only when a certain level of exposure has been exceeded. That level is known as the threshold. Researchers usually derive an approximate threshold from identifying a‘ ‘no-observed-effect level’ (NOEL) or a “no-observed-adverse-effect level’ (NOAEL) in exposed people or experimental animals. The NOEL is that dose at or below which no biological effects of any type are detected; the NOAEL is that dose at or below which no harmful effects are detected. If scientists observe more than one effect in animal

tests, they generally use the effect occurring at the lowest dose in the most sensitive animal species and sex as the basis for estimating a NOEL or NOAEL. Safety factors or uncertainty factors (which are discussed further in the section on risk characterization) are used to account for uncertainties in the use of NOELs or NOAELs for determining g levels of acceptable exposure.

For carcinogens, researchers generally assume that there are no thresholds, that is, that carcinogens pose some risk at even the lowest levels of exposure. For those substances, extrapolations from high to low doses are done using mathematical models, and a number of those models fit data derived from toxicity tests fairly well; because such data are available only for high doses, the extrapolation models make quantitative predictions of risks at lower doses using different models, which can result in widely divergent predictions of risk. Because data are seldom available at those doses, those predictions can seldom be verified or falsified.

The most commonly used model among Federal agencies is the linearized, multistage model. It is based on the hypothesis that cancer develops in stages and that a carcinogen can have an effect at each stage (U.S. OSTP, 1985). Agencies use the model to estimate an upper limit to the increase in probability of cancer resulting from a given exposure, rather than a "most likely" or "best" estimate (U.S. EPA, 1986a).

When the dose-response relationship is based on animal data, yet another extrapolation is necessary. Researchers use species extrapolation factors, also called scaling factors, to account for differences between test animals and humans that may affect the response to exposure to harmful substances. Such factors can include considerations of lifespan, body size, genetic variability or population homogeneity, metabolic rate, and excretion patterns (Travis and White, 1988; U.S. OSTP, 1985).

Exposure Assessment

Exposure assessment determines or calculates the number and kinds of people exposed to a substance, the amount of the substance to which individuals or populations are exposed, and the distribution, sources, routes, frequency, and duration of exposures. Assessors then use this information to estimate the dose, that is, the amount of a substance that reaches the cells, tissues, or organs of people who have been exposed. In general, less information is available about actual human exposure than about other aspects of health risk assessment (Cohrssen and Covello, 1989; Paustenbach, 1989b). Paustenbach (1989b) states that "it is likely that the major improvements in risk assessment that will be achieved in the near future will be due to improvements in our ability to estimate the uptake the chemicals caused by specific exposure scenarios.

Exposure assessments vary widely because of the kinds of information that maybe available or that are possible to obtain. The most accurate information about exposure is based on monitoring, or actual measurement, of the amounts of a substance to which people are exposed (NRC, 1991 b).

Often, however, monitoring data are not available. As a result, assessors often estimate exposures to emissions from a distant source like a factory by using exposure models (NRC, 1991 b). Exposure models simulate the dispersion of substances in the environment. Many of the hundreds of published models are quite specific for classes of substances or for the types of environments the substances travel through, such as the atmosphere, ground or surface water, or the food chain. Other models are multimedia in nature and assess the combined impact of many routes of exposure.

Exposure assessments may also account for the movement and activities of people. Over the course of a day, people spend time in their homes, their cars, and their workplaces. Their activities, as well as their locations, can have an effect on

their exposure to different substances. Exercise or work, for example, affects the rate of breathing and increases the amount of airborne substances that people inhale. Assessors can combine information on activity patterns with information on environmental concentrations to estimate exposure (Lioy, 1990; NRC, 1991a).

Risk Characterization

This final step in a risk assessment summarizes and combines the main points in the hazard identification and the dose-response and exposure assessments to provide an integrated picture of the data. It describes the conclusions reached concerning the kinds of hazards associated with exposure, whether particular subpopulations are at special risk, the assumptions that were made in arriving at the conclusions, the strengths and weaknesses of the data, and the uncertainty surrounding the conclusions. Finally, it may provide a quantitative estimate of risk or a range of possible values.

Historically, risk characterization has received much less attention than the other components of risk assessment, but that state of neglect appears to be changing (Habicht, 1992). Gray (1993) discusses recent developments in this area.

Risk characterization for noncancer effects evaluate risks against an estimated threshold level of toxicity. The Environmental Protection Agency (EPA) calls the exposure level at which risk becomes a problem the reference dose (RfD), or the acceptable daily intake (ADI). However this level is identified, it is a ballpark value. If human exposure is consistently below the RfD, risk assessors assume that there is little or no health risk. If exposures exceed the RfD significantly, they assume that a risk exists.

To determine the RfD, assessors divide the NOEL or NOAEL (determined in the dose-response evaluation) by a series of uncertainty factors or safety factors, which attempt to account for areas of uncertainty or gaps in the data (Dourson and Stara, 1983), For example, if the NOEL or NOAEL is based on data from studies in animals, it may be divided by a factor of 10 to account for the possibility that humans may be more sensitive to the chemical than the test animals. Another uncertainty factor of 10 accounts for differences in susceptibility in human populations. Usually, a NOAEL for animal studies is divided by 100 (10X 10) to develop an RfD (or ADI). When assessors are faced with the problem of developing a long-term RfD but only short-term test data are available, they may divide the NOEL or NOAEL by yet another uncertainty factor. In addition, a factor is sometimes used to account for an incomplete database. The magnitude of the uncertainty factor may vary from chemical to chemical.

When a NOEL or NOAEL is not available, assessors may use the lowest-observed-effect level (LOEL) or the lowest-observed-adverse-effect level (LOAEL) in deriving an RfD. When the LOEL or LOAEL is used, it maybe divided by an additional uncertainty factor of 10.

A variation on the uncertainty factor approach is the margin of safety (MOS), which divides the NOEL or NOAEL by the current, desired, or most feasible level of human exposure. To judge the adequacy of the MOS, it may be compared with criteria of tolerable or acceptable safety margins, which vary according to the setting (e.g., environmental or occupational) (Tardiff and Rodricks, 1987). Risk assessors generally use this approach to make judgments about the safety of existing or proposed levels of exposure.

Risk characterization differs for carcinogens. Although the extrapolation model assessors actually use may involve a number of subtle factors, all models incorporate the idea that risk varies with exposure. Therefore, by knowing the relationship between dose and risk as well as exposure, as determined in the earlier steps of the risk assessment process, it is possible to estimate the number of people who may be expected to develop cancer as a result of exposure to a chemical. But those estimates should not be considered predictions of the future incidence of

disease. The many uncertainties in each part of the assessment, the difficulties of extrapolating from the results of scientific studies to predictions of human exposure at environmental levels, and the fact that the dose-response extrapolation models are used to generate an upper bound on risk preclude precise predictions. More appropriately, these figures should be considered estimates of risk with varying ranges of uncertainty.

As other areas of risk assessment mature, signs of interest in and dissatisfaction with the current process of risk characterization are becoming apparent. Most criticism is aimed at the generation of a single numerical risk estimate that does not provide information on how it was generated or the information used in that task. Recent reports and agency communications have called on risk assessors to ''convey what is known and what is not known about a particular risk in away that accurately reflects the current state of scientific knowledge and is useful to decision makers' (AIHC, 1989); they have also defined key aspects of good risk characterization (AIHC, 1989, 1991). Former EPA Deputy Administrator F. Henry Habicht released a memo that provided guidance for agency risk assessors and risk managers on risk characterization (Habicht, 1992). The Habicht memo emphasizes that risk managers must be made aware of the strengths and limitations of a risk assessment to allow them to make "informed evaluation and use of [it]."

Several common themes are present in the reports and in the Habicht memo. Specifically, they all stress that risk characterization must characterize more completely all uncertainties, assumptions, analytical alternatives, and the full range of plausible risk estimates.

ISSUES IN HEALTH RISK ASSESSMENT

Health risk assessment has several strengths: it provides a structure for collecting, organizing, and evaluating data; it gives agencies the capacity to base decisions on estimates of risk to people; and it provides information for ranking hazards, enabling agencies to focus their resources on the most significant risks to health (U.S. EPA, 1987, 1990b). This last point has become increasingly important because the ubiquity of carcinogens and other toxic substances in the environment make it impossible to prevent all human exposure (Ames and Gold, 1990; Loehr, 1991). Aspects of health risk assessment have prompted heated debate in recent years among scientists, regulators, the regulated community, and interested citizens. The issues being debated are more numerous than can possibly be introduced here. The National Research Council, in its groundbreaking 1983 report ***Risk Assessment in the Federal Government: Managing the Process,*** identified 50 points in the risk assessment process at which scientific uncertainty is encountered and inferential bridges are needed in order to continue (box 2-B). A consensus has developed on some of these issues since the council's report was published. For example, Federal agencies have proposed using a common scaling factor for interspecies extrapolation (U.S. EPA, 1992a). Most of the issues, however, are still being discussed a decade after they were frost listed.

The section that follows describes some of the issues that arise frequently in discussions of the use of health risk assessment by Federal agencies. Further research will clarify questions that stem from missing or ambiguous data or gaps in scientific theory. (For past examples, see ch. 5.) Other issues arise, however, not because of a lack of scientific consensus but because people hold different views about how much risk is acceptable and when it is appropriate to err on the side of caution. Further research may help to refine those policy debates, but it cannot and will not end them.

Conservative Assumptions

Agencies typically deal with the kinds of issues identified by the National Research Council by choosing a standard, or default, assumption and using it consistently. In the absence of data to the

contrary, agencies have tended to choose defaults that are said to be conservative; that is, they have erred on the side of caution.

During the Bush Administration, economists from the Office of Management and Budget (OMB) as well as others (Gori and Flamm, 1991, for instance) criticized Federal regulatory agencies for using default assumptions that were, in their opinion, overly cautious and unnecessarily expensive. OMB pointed to such common practices as the use of test data from the most sensitive animal species, the choice of an extrapolation model (the linearized, multistage model) that tended to yield the highest estimates of risk, and the use of exposure models that assumed that people lived close to hazardous waste sites or other sources of exposure continuously for 70 years (Belzer, 1991; U.S. OMB, 1990-1991). According to those arguments, risks are being overestimated, leading to burdensome, unnecessary regulatory costs and a disordering of agency priorities (Barnard, 1986, 1991; Belzer, 1991; Gori and Flamm, 1991; U.S. OMB, 1990-1991),

Regulatory agencies and many analysts defend those choices as being within their mission of protecting human health, and they point out why, despite the conservatism, risks may yet be underestimated (Finkel, 1989; Huff et al., 1991; Perera and Boffetta, 1988; Rail, 1991; Silbergeld, 1993). For example, test animals are not exposed at the beginning of their lives, during fetal development, when they are more susceptible to certain agents. In addition, agencies do not consider the cumulative effect of exposure to agents from all possible routes.

Animal Bioassays

Currently, tests in rats and mice are the main tool for assessing chemicals for carcinogenicity. In the absence of data from humans, information on animals is clearly the next best basis for decisionmaking. Its supporters defend the use of the rodent bioassay as science's most important method for identifying potential human carcinogens (Cogliano et al., 1991; Huff and Rail, 1992; Perera and Boffetta, 1988; Silbergeld, 1993). Huff (1993) examined the results from 2-year carcinogenesis experiments, in both sexes of at least two animal species, on 450 chemicals and concluded that ''carcinogenicity findings from experiments in laboratory animals are scientifically reasonable for identifying and predicting potential carcinogenic effects to humans. " Indeed, all known human carcinogens have been found to be carcinogenic in at least one other animal, although that fact does not necessarily mean that the converse is true, that is, that all animal carcinogens are carcinogenic in humans (U.S. OSTP, 1985).

Critics, however, have pointed out a number of problems with current testing methods. The traditional long-term carcinogen bioassay is quite expensive and time-consuming, so the number of animals it uses must be limited. To increase the likelihood of identifying carcinogens, researchers administer high doses of the test chemical. The highest dose used, the maximum tolerated dose (MTD), is that quantity of the substance that is just large enough to elicit signs of minimal toxicity without significantly altering the animal's lifespan as a result of effects other than carcinogenicity (NRC, 1993; U.S. OSTP, 1985). Lower doses, such as one-half the MTD, are also given. Unlike test animals, humans are rarely exposed to such high levels, aside from accidents and some workplace exposures, and never over their entire lifespan. Researchers assume, however, that if a chemical causes an increase in the incidence of cancer at a high dose, it will also cause cancer, albeit at lower frequencies at lower doses.

For agents like ionizing radiation and some chemicals, substantial scientific evidence supports that assumption (Huff et al., 1991). But others argue that at such high doses, many chemicals tested are carcinogenic (Ames and Gold, 1990), They suggest that this result may be due to secondary effects that do not occur at lower doses. They further suggest that doses at the MTD

Box 2-B-issues in Health Risk Assessment

HAZARD IDENTIFICATION

Epidemiologic Data

- What relative weights should be given to studies with differing results? For example, should positive results outweigh negative results if the studies that yield them are comparable? Should a study be weighted in accord with its statistical power?
- What relative weights should be given to results of different types of epidemiologic studies? For example, should the findings of a prospective study supersede those of a case-control study, or those of a case-control study those of an ecologic study?
- What statistical significance should be required for results to be considered positive?
- Does a study have special characteristics (such as the questionable appropriateness of the control group) that lead one to question the validity of its results?
- What is the significance of a positive findingin a study in which the route of exposure is different from that of a population at potential risk?
- Should evidence on different types of responses be weighted or combined (e.g., data on different tumor sites and data on benign versus malignant tumors)?

Animal-Bioassay Data

- What degree of confirmation of positive results should be necessary? Isa positive result from a single animal study sufficient or should positive results from two or more animal studies be required? Should negative results be disregarded or given less weight?
- Should a study be weighted according to its quality and statistical power?
- How should evidence of different metabolic pathways or vastlydifferent metabolic rates between animals and humans be factored into a risk assessment?
- How should the occurrence of rare tumors be treated? Should the appearance of rare tumors in a treated group be considered evidence of carcinogenicity even if the finding is not statistically significant?
- How should experimental-animal data be used when the exposure routes in experimental animals and humans are different?
- Should a dose-related increase in tumors be discounted when the tumors in question have high or extremely variable spontaneous rates?
- What statistical significance should be required for results to be considered positive?
- Does an experiment have special characteristics (e.g., the presence of carcinogenic contaminants in the test substance) that lead one to question the validity of its results?
- How should findings of tissue damage or other toxic effects be used in the interpretation of tumor data? Should evidence that tumors may have resulted from these effects be taken to mean that they would not be expected to occur at lower doses?
- Should benign and malignant lesions be counted equally?
- Into what categories should tumors be grouped for statistical purposes?
- Should only increases in the numbers of tumors be considered, or should a decrease in the latent period for tumor occurrence also be used as evidence of carcinogenicity?

Short-Term Test Data

- How much weight should be placed on the results of various short-term tests?
- What degree of confidence do short-term tests add to the results of animal bioassays in the evaluation of carcinogenic risks for humans?
- Should in vitro transformation tests be accorded more weight than bacterial mutagenicity tests in seeking evidence of a possible carcinogenic effect?

- What statistical significance should be required for results to be considered positive?
- How should different results of comparable tests be weighted? Should positive results be accorded greater weight than negative results?

Structural Similarity to Known Carcinogens

. What additional weight does structural similarity add to the results of animal bioassays in the evaluation of carcinogenic risks for humans?

General

- What is the overall weight of the evidence of carcinogenicity? (This determination must include a judgment of the ***quality of*** the data presented in the preceding sections.)

DOSE-RESPONSE ASSESSMENT'

Epidemiologic Data

- What dose-response models should be used to extrapolate from observed doses to relevant doses?
- Should dose-response relations be extrapolated according to best estimates or according to upper confidence limits?
- How should risk estimates be adjusted to account for a comparatively short followup period in an epidemiologic study?
- For what range of health effects should responses be tabulated? For example, should risk estimates be made only for specific types of cancer that are unequivocality related to exposure, or should they apply to all types of cancer?
- t-low should exposures to other caranogens, such as cigarette smoke, be taken into consideration?
- How should one deal with different temporal exposure patterns in the study population and in the population for which risk estimates are required? For example, should one assume that lifetime risk is only a function of total dose, irrespective of whether the dose was received in early childhood or in old age? Should recent doses be weighted less than earlier doses?
- How should physiologic characteristics be factored into the dose-response relation? For example, is there something about the study group that distinguishes its response from that of the general population?

Animal-Bioassay Data

- What mathematical models should be used to extrapolate from experimental doses to human exposures?
- Should dose-response relations be extrapolated according to best estimates or according to upper confidence limits? If the latter, what confidence limits should be used?
- What factor should be used for interspecies conversion of dose from animals to humans?
- How should information on comparative metabolic processes and rates in experimental animals and humans be used?
- If data are available on more than one nonhuman species or genetic strain, how should they be used? Should only data on the most sensitive species or strain be used to derive a dose-response function, or should the data be combined? If data on different species and strains are to be combined, how should this be accomplished?
- How should data on different types of tumors in a single study be combined? Should the assessment be based on the tumor type that was affected the most@ some sense) by the exposure? Should data on all tumor types that exhibit a statistically significant dose-related increase be used? If so, how? What interpretation should be given to statistically significant decreases in tumor incidence at specific Sites?

(continued *on next page)*

Box 2-B-issues in Health Risk Assessment-Continued

EXPOSURE ASSESSMENT

- How should one extrapolate exposure measurements from a small segment of a population to the entire population?
- How should one predict dispersion of air pollution into the atmosphere due to convection, wind currents, etc., or predict seepage rates of toxic chemicals into soils and groundwater?
- How should dieter habits and other variations in lifestyle, hobbies, and other human activity patterns be taken into account?
- Should point estimates or a distribution be used?
- How should differences in timing, duration, and age at first exposure be estimated?
- What is the proper unit of dose?
- How should one estimate the size and nature of the populations likely to be exposed?
- How should exposures of special risk groups, such as pregnant women and young children, be estimated?

Risk Characterization

- What are the statistical uncertainties in estimating the extent of health effects? How are these uncertainties to be computed and presented?
- What are the biologic uncertainties in estimating the extent of health effects? What is their origin? How will they be estimated? What effect do they have on quantitative estimates? How wil the uncertainties be described to agency decisionmakers?
- Which population groups should be the primary targets for protection, and which provide the most meaningful expression of the health risk?

[1] Current methods and approaches to exposure assessment appear to be medium- orroute-specific. In contrast with hazard identification and dose-response assessment, exposure assessment has very few components that could be applicable to all media.

SOURCE: National Research Council, *Risk Assessment in the Federal Government:* Managing the Process (Washington, DC: National Academy Press, 19S3).

may cause chronic cell killing and consequent increased cell division, which in turn causes increased rates of mutagenesis and carcinogenesis (Ames and Gold, 1990; Cohen and Ellwein, 1990, 1991a, 1992).

The use of the MTD was the focus of a recent report by the National Academy of Sciences. In an unusual occurrence for an academy committee, the participants failed to reach a consensus. Two-thirds of the 17-member panel favored continuing the use of the MTD, and one-third favored the use of more moderate doses (NRC, 1993; ***Science, 1993).*** Clearly, this issue remains unresolved.

Some carcinogenic mechanisms and pathways that occur in animals may not occur in humans. For example, unleaded gasoline, d-limonene, and 1,4-dichlorobenzene cause kidney tumors in male rats but not in mice or female rats. These substances appear to induce accumulation of a protein found only in adult male rats, which appears to be responsible for increased cell death and concomitant cell regeneration (U.S. EPA, 1991a). Because that protein does not occur in humans, substances that cause tumors in the kidneys of male rats through this mechanism may not be human carcinogens. Better understanding of the basic mechanisms of chemical carcinogenesis should help to resolve these and similar issues.

Models for Dose Extrapolation

Research has developed a number of different statistical "models for extrapolating from high to low doses, and all of them generally fit the data in the range of doses used in animal tests. (The White House Office of Science and Technology Policy offers a good description of various models; see U.S. OSTP, 1985.) However, the models can differ significantly in the low-dose region, the area of primary interest to risk assessment (Paustenbach, 1989a). In general, the one-hit model and the linearized, multistage model (LMS,) predict the highest risk (Munro and Krewski, 1981). EPA prefers the LMS model "in the absence of adequate information to the contrary' (U.S. EPA, 1986a).

All of the models now in use are based on the current scientific understanding of carcinogenesis induced by ionizing radiation or by one particular class of chemical carcinogens known as genotoxins, which interact with DNA. There is growing evidence, however, that these models may be inappropriate for other kinds of chemical carcinogens, some of which may even have thresholds. EPA has stated that it recognizes that the LMS model should not be used for certain chemicals; however, it prefers this model for chemicals whose mechanisms of action are unknown. Some observers have suggested that a better approach might be to report results using more than one model, citing the lack of evidence that the LMS model predicts the low-dose response better than other models (Paustenbach, 1989a).

Critics have charged that current models are ''overly simplistic. probabilistic representations of highly complex biological phenomena' (Sielken, 1987). They contend that the models do not take into account current knowledge of the mechanisms of carcinogenesis or the impact of other biological processes such as rates of cell turnover, repair processes, immune system responses, and physiological and pharmacokinetic models of the absorption, delivery, metabolism, and elimination of chemicals. Such critics suggest that methods be developed to permit consideration of more biological information in quantifying the dose-response relationship (Barnard, 1991; Cohen and Ellwein, 1991b; Sielken, 1987).

Weight of the Evidence

Scientific studies vary in their quality, but regulatory agencies tend to place heavy emphasis on any study suggesting that a chemical might be hazardous, regardless of the quality of the research. Increasingly, however, agencies are responding to criticisms of this practice by adopting a weight-of-the-evidence approach (U.S. EPA, 1986a, 1992b). That approach takes into consideration the quality and adequacy of the available data and the kinds and consistency of responses induced by a suspected toxic substance (U.S. EPA, 1986a; U.S. OSTP, 1985).

Evaluating Mixtures of Chemicals

People are exposed to multiple substances simultaneously, but with few exceptions, chemicals are studied and regulated individually. Little is known about the effects of most chemicals when encountered in mixtures. In fact, many components of common mixtures may be unknown. It is usually assumed, for the purposes of risk assessment, that each substance exerts its effect independently and that the effects are simply additive. Researchers have found examples, however, of substances whose toxic effects are not additive. For example, exposure to either tobacco smoke or radon is associated with an increased risk of lung cancer. Exposure to both poses an even greater risk than would be predicted by an additive model (see ch. 6). Such an effect is said to be synergistic. Although fewer cases are known, examples also exist of substances that show antagonistic effects; that is, when the substances are administered together, the toxic effects are less than the sum of the effects when each is administered individually. For example, administering dioxin before administering another carcin-

ogen reduces the rate of cancer. For most chemicals, however, such data are unavailable.

Chemical mixtures may be regulated as such (e.g., coke oven emissions or diesel exhaust) if data on the mixture itself are available. If they are not, assessments may be based on the data collected about a similar mixture or on some of the components of the mixture. EPA's guidelines for the health risk assessment of chemical mixtures (U.S. EPA, 1986b) recommend that assessors assume that effects are additive, that interactions decrease significantly with decreasing doses, and that they seldom play a role at the usual, low levels of human exposure.

Characterizing Uncertainties and Assumptions

Acceptance is growing for the need to move beyond simple numerical estimates of risk and to give risk managers a broader picture of the uncertainties associated with risk estimates (Habicht, 1992). When health risk assessments discuss uncertainties, they tend to take the form of lists of uncertain assumptions. It is unclear whether that practice improves the decisionmaking process. Some analysts have proposed a more complete picture of risk by replacing point estimates with uncertainty distributions that would show all the possible values of the risk and their associated probabilities of occurrence (Finkel, 1990).

Few in the risk assessment field would argue with the notion that the estimates provided by risk assessment are highly uncertain. In hazard identification, the exact relationship of animal tests to human risk and the predictive value of high-exposure occupational epidemiology to environmental exposures are quite unclear. There is generally no way to determine the most appropriate mathematical model for extrapolating from high to low doses in dose-response evaluation. And methods of exposure assessment, especially when exposure may be from many pathways, are rudimentary. All of these factors contribute to the great uncertainty present in estimates of risk (Rosenthal et al., 1992).

According to Gray (1993) and others (AIHC, 1989, 1991), making that uncertainty known to all of the users of a risk assessment is of paramount importance. As Habicht (1992) states, ' 'uncertainty should be acknowledged and expressed both qualitatively and quantitatively.' His memo directed EPA personnel to develop a statement of confidence in a given risk assessment and emphasized that identifying uncertainties is a key component of such a statement. In addition, Habicht emphasized that numerical risk estimates must not be allowed to stand alone, separated from the various assumptions and uncertainties on which they are based.

Current and future scientific research will help reduce the uncertainties in many aspects of risk assessment. Today, however, in the absence of definitive science, a number of default assumptions are made. For example, current practices in hazard identification assume that any animal carcinogen has the potential to be a human carcinogen even though exceptions to this rule are thought to exist; current dose-response evaluation assumes that the dose-response function for carcinogens has no threshold; and exposure assessments assume that maximally exposed individuals spend their entire 70-year lifetime at the point of maximum exposure. Some of the assumptions used in risk assessment are generally accepted, but others are matters of contention. Furthermore, a distinction can be made between science-based issues that can be answered experimentally and policy issues that are based on values and cannot be addressed by research.

WHY CONDUCT RISK ASSESSMENT RESEARCH?

Risk assessment—through its incorporation into dozens of Federal, State, and local laws and regulations—influences the expenditure of hundreds of billions of dollars in the domain of health and environmental protection. Accurate risk as-

sessment demands extensive knowledge that only research can generate. The approaches used in risk assessment depend on research findings. It is typically the lack of data and knowledge that limits the accuracy of, and confidence in, a given assessment.

Policymakers depend on health risk assessment and research in making regulatory decisions about which risks to tolerate and which to reduce or prevent. They also have to weigh the costs and benefits associated with those decisions. Overly cautious decisions to reduce the risks posed by contaminants in the environment, for example, may mean inappropriate expenditures of limited national resources for environmental cleanup operations. Complacent decisions to tolerate risks may result in increases in environmentally related illness.

The costs of complying with environmental regulations and the costs of environmentally related illnesses are discussed here as an illustration. The purpose of this discussion is not to argue the merits or costs and benefits of individual regulatory decisions but rather to capture the general magnitude of the public health, environmental, and economic interests at stake.

Hahn and Hird (1991) determined that the annual costs of environmental regulation alone in 1988 were between $55 and $135 billion, and the benefits were between $16 and $135 billion. These estimates do not include the costs and benefits of regulations covering the occupational workplace, consumer product, and food safety, Senator Daniel P. Moynihan's "Environmental Risk Reduction Act of 1993" (S. 110) states that the annual cost of protecting the Nation's environment is more than $115 billion. Moynihan said on introducing the bill that although ''this may not be too much money to spend on environmental protection, it is too much to spend unwisely. With so much riding on regulatory decisions, the Office of Technology Assessment (OTA) concludes that the time is ripe for attention to the foundation of those choices: research and its contribution to risk assessment.

The Costs of Compliance

What level, if any, of exposure to a chemical is ''safe' or tolerable? How clean must a waste site be to be considered cleaned up? Risk assessment cannot answer those questions because concepts of equity as well as laws and regulations play a role. It can, however, provide estimates of the harm that may result from inaction or from various actions. Those estimates can guide and inform regulators, influencing how billions of dollars may be spent on regulatory decisions to reduce cur-rent or prevent future exposure to potentially hazardous chemicals. That type of cost, which is incurred by complying with a law or regulation, is generally referred to as a compliance cost. The costs of handling, treating, and disposing of solid and hazardous wastes are examples of compliance costs.

In fiscal 1993, Congress appropriated more than $9 billion for environmental cleanup at Federal facilities of the Departments of Energy and Defense, an amount much larger than the $1.6 billion appropriated for cleaning abandoned hazardous waste sites under the Superfund legislation. (That effort is financed partly by a tax on the chemical industry and partly from general revenues.) As a direct result of such cleanup activities focused on military and nuclear waste, EPA has projected that Federal cleanup expenditures will increase by 140 percent over the 1987-2000 period (U.S. EPA, 1990a). In other words, the costs of compliance increasingly fall directly on the Federal Government.

The cost of complying with EPA regulations is not the only type of compliance cost, but it is the best documented. Compliance with Food and Drug Administration (FDA) regulations also consumes substantial resources, but a formal estimate is not available, The Pharmaceutical Manufacturers Association, however, states that its members spent $9.2 billion for research and development in 1991, some portion of which represented toxicity and safety testing to satisfy FDA regulatory requirements (PMA, 1991). Sim-

ilarly, compliance costs are incurred by complying with the rules and regulations promulgated by the Occupational Safety and Health Administration and the Consumer Product Safety Commission.

Costs of Environmentally Related Illnesses

Besides compliance costs, there are other risk-related costs. For example, what are the costs of existing environmentally related illnesses, and how would future costs be affected by regulatory decisions?[2]

The answers to those questions can only be estimated. Estimating the costs of some environmentally related illnesses is easier than assessing how regulatory decisions are likely to affect their costs. Regulatory decisions have a bearing on the costs of environmentally related illnesses, but the relationship is not as straightforward as that between regulation and the cost of compliance.

The costs of some environmentally related illnesses have been estimated to reach well into the billions of dollars, although no comprehensive estimates are available. The Institute of Medicine, for example, attempted to quantify such costs in 1981 in response to a congressional mandate (P.L. 95-623). The institute determined, however, that it was not possible at that time to document the costs of environmental pollution (the main focus of the study). Instead, it offered an extensive plan of study that would fulfill the goal envisioned by Congress (IOM, 1981).

Studies that attempt to assess the economic burden of illnesses generally rely on epidemiologic estimates of the number of people afflicted (i.e., the prevalence of disease), national surveys of health care expenditures, and studies that assign monetary values to disability and premature death. Because cost-of-illness studies are difficult to perform and depend heavily on the definitions of direct and indirect medical costs that researchers use, those who employ and interpret them must exercise caution. Direct costs usually include inpatient and outpatient expenditures; indirect costs may include costs related to loss of work, years of productive life lost, quality of life, and premature death.

One example of the costs associated with environmentally related illnesses comes from lead poisoning, a preventable environmental hazard that may affect the cognition, behavior, endocrinology, and growth of children in the United States (U.S. DHHS, 1991a). It is estimated that 250,000 children have lead levels greater than 25 micrograms per deciliter (ug/dl) of blood and require medical treatment and special education averaging about $4,600 per child (U.S. DHHS, 1991 b).

Although EPA has not performed a comprehensive study of the costs of lead exposure from all sources, it has analyzed the costs associated with exposure to some sources of lead. For drinking water, EPA's Regulatory Impact Analysis assigned a range of monetary values to the projected health benefits for children and adults of reducing exposure to lead from that source. The direct and indirect medical benefits (quantified as savings) that are expected to occur annually when States eventually meet EPA's new drinking water standards were estimated at between $2.8 and $4.3 billion (U.S. EPA, 1991 b). (The estimate is based on lead's adverse effects on adult male blood pressure and children's intelligence.)

It should be noted that overall mean blood lead levels declined by 37 percent during the 1976-80 period (Farfel, 1985), when lead in gasoline was reduced as a result of the passage of the Clean Air Act. In 1985, EPA estimated that its further phase-downs of the lead content of gasoline ordered in that year would produce health benefits for children and adults valued at approximately

[2]This question addresses the current economic burden of environmentally related illness. It might also be posed as, what are the savings or benefits of preventing environmentally related illnesses? It is a matter of convention regarding whether to cast the question in terms of costs or benefits, because economists typically define costs and benefits in opposition to one another.

$5 billion in 1992, based on 1983 dollars (U.S. EPA, 1985).

Analysts can also estimate the health costs that arise from other environmentally related diseases, which cannot be sufficiently discussed here. Relevant examples include respiratory problems from air pollution and environmental tobacco smoke, and occupational diseases such as mesothelioma from exposure to asbestos.

The Role of Research

Controversies or conservative assumptions in risk assessment stem from the lack of data or scientific knowledge about the risks being assessed. With so much at stake, it seems fitting to seize the opportunity of using scientific research to narrow the scope of uncertainty in health risk assessment.

In 1983, the National Research Council (NRC) concluded that improving the quality and comprehensiveness of the knowledge used in risk assessment is by far the most effective way to improve the process (NRC, 1983). The decade following publication of the NRC report saw impressive advances in the biological and biomedical sciences. Is an appropriate investment being made in research to harness those advances in developing a better knowledge base for health risk assessment?

In this report, OTA analyzes the resources devoted to such development. It also examines the nature, organization, and management of federally supported research on health risk assessment and whether this area of research is adequately supported. Subsequent chapters discuss how priorities are set for health risk assessment research and the relationship of this area of research to regulatory decisionmaking.

SUMMARY

Health risk assessment offers a systematic approach to evaluating data and formulating judgments about risk. It consists of some or all of the following four steps: hazard identification, dose-response analysis, exposure assessment, and risk characterization.

The primary source of data for assessing risks to human health is epidemiologic, toxicological, structure-activity relationship, and exposure studies. However, the data such studies provide are usually incomplete for evaluating the risk from the exposures being considered. Researchers therefore use various extrapolations (e.g., from high to low doses, animals to humans, and ingestion to inhalation) to predict the possible outcomes from the available data.

To perform those extrapolations, Federal agencies use assumptions or policy positions to bridge gaps in the data or knowledge. Because assumptions and policy positions contain value judgments and a large measure of scientific uncertainty, they are the main areas of controversy in risk assessment.

However uncertain the results of health risk assessment may be, they provide the scientific foundation for decisions about how to mitigate health risks (e.g., emission standards for incinerators). Those decisions, and the standards that are their frequent consequence, can lead to expenditures for compliance with regulations and medical expenses for exposure-related diseases that may run into billions of dollars.

With so much at stake and given the opportunity presented by advances in the biological and biomedical sciences, research is capable of narrowing the uncertainties in health risk assessment. This report reviews the Federal Government's research efforts to determine whether appropriate attention is being given to this field.

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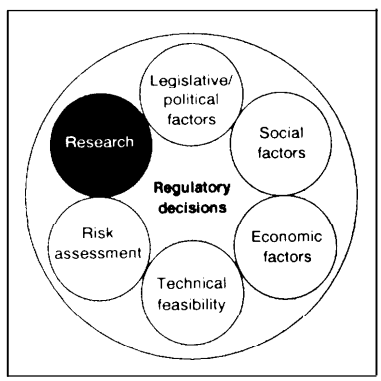
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Federal Research in Health Risk Assessment

3

This chapter describes the research that the Federal Government is now conducting to improve health risk assessments. It summarizes the results of the Office of Technology Assessment's (OTA) survey of such Federal research efforts and identifies their strengths, weaknesses, and trends.

To analyze the activities of the various agencies, OTA defined health risk assessment research as research to improve existing methods and develop new ones to reduce reliance on the assumptions and policy options that are currently necessary. We focus on research related to assessing adverse effects on the health of human populations, and exclude research to improve ecological risk assessments. The substances addressed in the research survey are chemical and physical agents present in environmental and occupational settings or as food additives or contaminants.



RESEARCH AT THE FEDERAL AGENCIES

OTA surveyed Federal programs that conduct research on the toxicity of environmental pollutants, occupational toxicants, and toxic contaminants in food. We collected information through written requests for data, which were followed up by interviews with agency representatives and visits to agency laboratories. Because of the controversies surrounding and the Federal experience with the methods for evaluating and estimating risks from exposure to carcinogens, we frequently use research to improve the assessment of carcinogens in order to illustrate the directions and needs of research on health risk assessment in general.

Environmental Protection Agency

The mission of the Environmental Protection Agency (EPA) is to protect the environment and the health of the public. In support of its regulatory functions, the agency conducts mission-oriented research, mostly within its Office of Research and Development (ORD), on a broad range of environmental contaminants. EPA conducts research in three general areas to support the agency's assessments of health risks: the health effects of environmental toxicants; the nature, patterns, pathways, and magnitudes of human exposures; and the relationships between exposure and toxicity.

A large research facility in Research Triangle Park, North Carolina, the Health Effects Research Laboratory (HERL), houses most of the agency's in-house research on the health effects of environmental pollutants. The research at HERL includes various approaches and emphases.

One area of interest is in developing and applying validated test methods for screening and characterizing the toxicity of new and existing chemicals.[1] A second area of study is the health effects of specific environmental agents in humans. A third area of activity focuses on developing methods to evaluate relationships between chemical structure and biological effects (structure-activity relationships). Last, research is being conducted to investigate the mechanisms of toxicity. HERL scientists also conduct research in comparative physiology and biochemistry as the foundation for improved methods to extrapolate from observations in animals to predictions of effects in humans.

Research to determine the nature of environmental pollutants and the extent to which humans are exposed to them is spread across a number of EPA laboratories. The goal of that research is to provide a foundation for answering questions about exposure assessment and risk management. For example, what are the magnitude, duration, and frequency of exposure to a particular pollutant for both the general population and for groups exposed to high levels of the pollutant? By what pathways are humans exposed, and which are the most important? What emission sources, activity patterns, lifestyles, or other factors are important determinants of human exposure? How many people are exposed within a given exposure scenario? Are people's actual or anticipated exposures expected to result in adverse health effects? The kinds of research activities conducted to answer those questions include developing cost-effective methods for collecting and analyzing samples; monitoring pollutants of interest in various media, materials, and biological samples and designing monitoring devices; integrating ingestion, dermal contact, and inhalation studies with other research to determine dose-response effects; and developing predictive models for estimating past, present, and future exposures.

EPA's research of the relationships between exposures to a substance and the effects of those exposures on health uses animal models to determine the effects of changing doses of a substance on response. In investigating exposure, researchers employ biochemical and physiological methods to estimate the dose received by selected organs or tissues of an organism. EPA is also working to corroborate and extend observations in animal models through clinical studies of humans exposed to air pollutants (box 3-A).

In recent years, more and more calls have come from a variety of sources for increased attention to health risk assessment research. In response, Congress in 1988 recommended that ORD establish an integrated, systematic program that would target research to improve risk assessments. Legislators earmarked $10 million for the effort but made no appropriation. ORD initially funded the Research to Improve Health Risk Assessment (RIHRA) program at $7 million by redirecting

[2] A total of $3 million was redirected to study ecological effects of environmental pollution.

Box 3-A-Agency-University Collaborations: Human Exposure Studies at EPA and UNC

The Human Studies Division (HSD) of the Environmental Protection Agency's Health Effects Research Laboratory has done much of its work under a cooperative agreement with the Pulmonary Medicine Division of the University of North Carolina Medical School at Chapel Hill (UNC), forming the Center for Environmental and Molecular Biology of the Lung (CEMBL). Physically locating HSD'S offices on the medical school campus has greatly facilitated this relationship.



The human clinical studies that HSD conducts require highly specialized facilities and expertise not readily available in EPA's own labs. By its UNC relationship, HSD gains access to a human inhalation chamber, a magnetic resonance imaging scanner, and an electron microscope. Furthermore, CEMBL currently has eight divisions that house more than 30 doctors and researchers on the medical school's faculty in various medical specialties. It also has joint programs for postdoctoral fellows and research assistants.

Given the facilities within CEMBL, humans can be exposed to air pollutants under controlled conditions in t he exposure chambers, and scientists can determine the resulting clinical health effects. Volunteers are exposed to concentrations of pollutants reflecting those generally found in the environment. Ozone is a prototypical pollutant for these exposure studies because it can be used with humans; it is a noncarcinogen, and its effects are reversible. The results obtained wit h ozone-exposed humans can be compared with the results of analogous studies using laboratory animals. The HSD-UNC collaboration therefore allows EPA scientists to address a major criticism of the risk assessment process: t he use of animal studies to predict effects on human health. The result has been a series of joint papers about the actual effects on humans of air pollutants such as ozone and sulfur dioxide.

SOURCE: U.S. Congress, Office of Technology Assessment, 1993.

funds from other programs.[2] The current level of funding for the program is $5.1 million (Vandenberg, 1993).

RIHRA both supports and coordinates research. Approximately half of its resources go to researchers outside EPA through its funding of collaborative ventures and grants. The program is meant to complement EPA's core research activities, which place more emphasis on the near-term needs of EPA's regulatory program offices. Now in its 4th year, RIHRA addresses research issues that cut across the various EPA regulatory pro-

[3] Because of the complex structure and relationship of the various agencies and centers, OTA includes the organizational chart for the U.S. Public Health Service in appendix B.

At this time, the program's success is difficult to assess. Some scientists interviewed by OTA criticized RIHRA for not doing enough methodological research to improve risk assessments but, instead, allowing funds to be used for ongoing activities in fulfillment of regulatory needs. Other observers argue, however, that the RIHRA program, in meeting its congressional mandate, has provided resources and support for methodological risk assessment research that the agency might not have conducted otherwise.

Because of EPA's diverse regulatory needs, until 1992 environmental program and media-specific research committees guided its health research agenda. (In 1993, EPA moved to a risk-based priority approach, as described below.) The committees consisted of ORD and program office staff who deliberated on and set priorities for research. Even today, funding for research is allocated on a program-specific basis all the way down to the labs. By maintaining the separation of research funds along program lines, this system constrains the ability of HERL's management, for example, to establish overall research priorities (Reiter, 1992) and also hinders their ability to anticipate new problems.

The agency is now reviewing its system of medium- and program-specific planning. The 1987 internal EPA report *Unfinished Business (U.S.* EPA, 1987) concluded that the greatest risks to the environment and the health of the public, as determined by senior agency officials, were not high on the agency's list of priorities. Instead, the report concluded that the agency's priorities reflected public perceptions of risk and legislative mandates. Subsequent reports by EPA's Science Advisory Board (U.S. EPA, 1990, 1992a) examined ways to use risk assessment and expert judgment in setting EPA's priorities. Those reports provided the cornerstone for EPA's shift to risk- and issues-based research planning to address ''environmental problems in the next decade and beyond" (Foley, 1993).

To set priorities for the agency in all areas including research, EPA is converting to "risk-based planning." Under this approach, the agency attempts to set priorities for action and research based on rankings of risks, as determined by senior agency officials and experts (U.S. EPA, 1992c). Officials in ORD are currently developing a strategic plan and a research planning document for each of 39 'research issues. ' Three of those issues contain most of the efforts to improve health risk assessment: no. 28, human exposure; no. 29, health effects research; and no. 30, health risk assessment. Both RIHRA and non-RIHRA projects are included in issue no. 30.

EPA has the largest formal health risk assessment program of any government agency. Even though each medium-specific program in EPA performs risk assessments, the Office of Health and Environmental Assessment (OHEA) in ORD is the focal point for such efforts. OHEA has three functions: it conducts risk assessments, coordinates agency and interagency activities in risk assessment, and conducts research to develop and improve methods of risk assessment. To promote consensus within the agency, EPA established the Risk Assessment Forum to address precedent-setting or controversial risk assessment issues, such as the association of chemically induced renal toxicity and neoplasia in the male rat (U.S. EPA, 1991).

Department of Health and Human Services

The Department of Health and Human Services (DHHS) includes protection from risks posed by environmental hazards in its widespread programs. Within the vast DHHS organization, the Public Health Service (PHS) is the organizational home of the National Institutes of Health (NIH), the Food and Drug Administration (FDA), the Centers for Disease Control and Prevention

(CDC), and the Agency for Toxic Substances and Disease Registry (among other agencies).[3]

Those PHS agencies conduct and support research on environmental, occupational, and food-borne health risks. For many of those activities, DHHS also serves as the focal point for interagency activities. Furthermore, Congress requires DHHS to publish annual reports concerning environmental health, including the *Annual Review of Carcinogens* (U.S. DHHS, 1991d) and a review of the toxicological research being conducted in DHHS, EPA, and the Department of Energy. DHHS has delegated those responsibilities to the director of the National Toxicology Program (U.S. DHHS, 1991a).

NATIONAL TOXICOLOGY PROGRAM

DHHS established the National Toxicology Program (NTP) in 1978 to coordinate activities related to the testing of potentially toxic chemicals. Specifically, it established the program to test selected chemicals for toxicity, develop and validate tests and protocols, set priorities for testing needs, and communicate results to government agencies, the scientific community, and the public. Administered by the director of the National Institute for Environmental Health Sciences (NIEHS), NTP coordinates toxicology-related programs within NIEHS, the National Institute for Occupational Safety and Health (NIOSH), and the FDA's National Center for Toxicological Research (NCTR).

Although NTP serves Federal health and regulatory agencies outside of DHHS as well as other groups and organizations concerned with public health, most of its resources come from NIEHS, which contributed $79 million of its $84 million budget in 1991. At the same time, NCTR contributed $0.06 million and NIOSH $4.5 million (U.S. DHHS, 1991c).

An executive committee made up of senior administrators of Federal health research and regulatory agencies oversees NTP activities. To ensure high-quality research, an independent board of scientific counselors, composed largely of nonfederal researchers, monitors the quality of the agency's technical research programs.

NTP selects chemicals for testing based on nominations from participating Federal agencies and other public and private organizations. It then contracts with outside organizations to perform the trots or arranges for testing onsite at the NIEHS campus (U.S. DHHS, 1991c). NTP interacts with the scientific community through plenary reports, interagency discussions of regulatory problems, workshops, and symposia; it uses information gathered in this way to identify and characterize relevant research issues and encourage research collaborations.

The number of chemicals tested annually by NTP has been declining because of the rising costs of conducting bioassays (U.S. DHHS, 1992). The impression of many that the bioassay program is the state of the art in this country and abroad is reinforced by the judgments of scientists and analysts that no other government or industry program is subject to equivalent levels of quality control and peer review (Huff et al., 1991; Ringen, 1992). Yet NTP program administrators are currently rethinking the program's primary functions. They are weighing the relative worth of toxicity testing against the value of basic science research in understanding the underlying biological responses to chemical and radiation exposures (Griesemer, 1992; Schwetz, 1992; Tennant 1992).

One of the forces driving this reconsideration has been the continuing public debate and controversy over NTP's testing role. A series of hearings by NTP's Scientific Advisory Council as well as public hearings were held during the fall of 1992 and the spring of 1993 to discuss the future of NTP. On one side of the argument are advocates such as Knute Ringen (1992) of the Center to Protect Workers' Rights, who argues that NTP's

[3] Because of the complex structure and relationship of the various agencies and centers, OTA includes the organizational chart for the U.S. Public Health Service in appendix B.

hazard identification efforts are unique and should remain an ''essential part of this Nation's prevention arsenal in public health." In contrast, some industry spokespersons argue that industry adequately addresses toxicity testing and that NTP should 'intensify efforts to understand basic mechanisms of action of toxicants' (Moolenaar, 1992). They contend that enough information exists to predict the toxicity of untested chemicals using structure-activity relationships.

In addition to the program's primary focus on toxicity testing, NTP administrators have identified three areas of priority for further improving hazard identification: developing new methods for chemical testing, selecting experimental animals and chemicals to refine and remodel experimental protocols to fill gaps in the data needed to address public health concerns, and reviewing and reorganizing the chemical selection process (Griesemer, 1992; Schwetz, 1992; Tennant, 1992).

NATIONAL INSTITUTES OF HEALTH

Most of the National Institutes of Health conduct and fund basic research in toxicology, some epidemiologic studies, and, occasionally, testing of toxicants (U.S. DHHS, 1991a). This section describes two of the institutes, NIEHS and the National Cancer Institute (NCI). Both are NTP agencies and active in research related to risk assessment. Before 1978, NCI conducted the carcinogenesis bioassay program, a function now performed by NTP. However, NCI remains active in NTP program development and review.

National Institute of Environmental Health

Sciences--NIEHS has the broadest responsibility among the Federal agencies for research to identify and characterize the adverse effects of environmental pollutants on human health. With the goal of informing activities in disease prevention, the agency focuses a considerable portion of its research resources on adding to fundamental knowledge of the mechanisms of chemical toxicity, including the mechanisms of environmental diseases and particularly cellular and molecular targets for carcinogenesis. It also works toward a greater understanding of biostatistics and techniques of quantitative risk assessment. Recently, the institute has been developing biomarkers of exposure, susceptibility, and effect and investigating noncancer disease endpoints.

Under its first director, NTEHS established a reputation for conducting state-of-the-art basic research on environmentally related diseases, especially cancer (Thigpen, 1993). That focus continues today as scientists at the institute investigate specific changes at the organ, cellular, and molecular level to understand the role environmental agents play in the development of cancer. Using recently developed tools of molecular and cancer biology, institute researchers are elucidating the roles of genetic factors, especially oncogenes and tumor suppressor genes, in carcinogenesis. In particular, this research attempts to understand the interaction of environmental agents with genetic determinants in the development of cancer (Barrett, 1993).

In addition to their expertise in the mechanisms of carcinogenicity, NIEHS scientists are expanding their research into health effects other than cancer. The institute has designed a program to determine the adverse effects on health of exposure to a variety of air pollutants (e.g., ozone, industrial emissions, and combustion byproducts) and the relationship of those exposures to the development and prevalence of respiratory diseases, such as asthma, emphysema, and other chronic lung disorders. NIEHS is also developing short-term tests of genetic toxicity-in particular, methods to assess the effects of environmental agents on human germ cells, which can be passed down to succeeding offsprings and play a role in heritable disorders.

Recently, the agency established a new set of research priorities, motivated in part by NIH-wide strategic planning (Healy, 1992), a new director, and a review of the environmental health sciences by the National Advisory Environmental Health Sciences Council (U.S. DHHS, 1991 b). The institute now has four areas of emphasis: basic

mechanisms of environmental disorders, environmental causes of diseases of public health import, clinical studies and clinical research, and an enhanced science base for public health policy decisions and health programs (Olden, 1992).

NIEHS provides support for internal and external investigator-initiated research on the biological mechanisms of response to environmental stresses. Formal processes within the agency determine whether NIEHS scientists or scientists in other institutions or agencies should conduct specific projects. A variety of advisory boards and committees determines the internal allocation of funds for institute programs, and project boards review the activities and performance of each program. Activities within the Division of Intramural Research are overseen by a board of scientific counselors, all of whom are nonfederal scientists. The board approves or disapproves of initial concepts, monitors ongoing research, and reviews research results. For specific environmental health topics, NIEHS also holds workshops and convenes symposia to gauge the scientific knowledge base and obtain information for setting research priorities.

NTEHS administrators are considering shifting some resources and programs into new research efforts that would promote more multidisciplinary activities. This internal reorganization will move the institute away from its present programmatic focus to one more oriented toward process as a way to foster multidisciplinary interactions, especially for research on health risk assessment (Lucier, 1993). NIEHS is also supporting collaborative research, not only within the institute but with other agencies and universities.

Until 1992, an in-house NIEHS program in biometry and risk assessment developed statistical methodologies for analyzing toxicological data and conducting risk assessments. In that year, NIEHS's new director created the Laboratory of Biochemical Risk Analysis to examine more cross-cutting issues in risk assessment. The lab serves as a focal point of risk assessment research for both basic molecular biologists at the institute and the toxicologists conducting the . toxicity testing at NTP (Lucier, 1993; Stone, 1993). In addition to risk assessment methodology, these investigators are also actively studying carcinogenic chemicals that do not directly interact with DNA but instead bind to receptors and seem to work by increasing growth rates of normal or abnormal cells. This research features centrally in risk assessment policies for so-called ''nongenotoxic chemicals, which include the animal carcinogen dioxin (Lucier et al., 1993).[4]

More recently, in May 1993, NIEHS's director established the Laboratory of Quantitative and Computational Biology (LQCB) (Portier, 1993). It will conduct independent and collaborative research on mathematical and statistical models based on biological mechanisms. The lab's programs are intended to increase understanding of the use and application of mathematical and computational models in the primary fields of research at NIEHS. Plans include developing novel computing hardware and software and applying them to problems in environmental health through computer modeling, artificial intelligence, and related advances in computer technology. In its strategic planning, LQCB scientists anticipate exploring the use of virtual reality technology in conducting risk assessments and making risk management decisions.

National Cancer Institute-NCI broadly sponsors research on cancer to fulfill its mission to reduce the incidence, morbidity, and mortality of cancer in humans (NCI, 1992). NCI's Division of Cancer Etiology conducts research related to assessing the risks of carcinogens. Its activities include studies of the mechanisms of carcinogenesis, cancer biology and causation, epidemiology and biostatistics, physical and chemical

[4] Dioxin is the commonly used term to refer to the chemical 2,3,7,8-tetrachlorobenzene-p-dioxin, which is a prototype for a variety of structurally related organohalogens. See discussion on dioxin in chapter 5.

carcinogenesis, biological carcinogenesis, and nutrition as a modulating factor.

Current toxicological research at NCI investigates the biological fate of chemical carcinogens and the mechanisms by which they exert their carcinogenic effects. Those studies include basic biological research, development and validation of short-term in vitro assays, development of methods to use tissues from humans and nonhuman primates, and research on the interaction of chemical carcinogens with the primary defense against foreign chemicals, the cytochrome P450 enzyme system.

Epidemiologic studies conducted by the Division of Cancer Etiology in NCI contribute to many aspects of risk assessment. In fact, NCI conducts more epidemiologic research than all other agencies of the Federal Government combined (Adamson, 1992). Some of the epidemiology research is aimed at identifying risk factors and geographic ''hot spots" for cancer, that is, locations in which the number of cancer cases is statistically greater than the national average. Those results are then linked with the priority-setting process at NCI, NIEHS, and other agencies. NCI, NIEHS, and EPA scientists, for example, are collaborating on a large prospective epidemiologic study of farmers (box 3-B).

NCI establishes its research priorities for extramural and intramural research programs on the basis of the incidence of and mortality from specific types of cancers. But the institute also exploits opportunities for pursuing recent scientific developments, such as studies linking cancers to chromosomal abnormalities or the presence of oncogenes (Adamson, 1992). It determines priorities for its research programs through a budget review process that includes site visits to its research sites, which occur every 3 to 4 years for each project (NCI, 1992). The site visit procedure is a formalized process, with specific requirements for the reviewers to report back to NCI management. Their reports provide material for discussion at the twice-yearly retreats of directors and associate directors at which priorities are set. NCI also funds extramural research to stimulate investigations of particularly understudied areas and holds workshops to foster interest in a topic and gather information on its significance.

FOOD AND DRUG ADMINISTRATION

Organizationally, FDA consists of six centers, three of which conduct health research aimed at improving risk estimates or the risk assessment process: the Center for Food Safety and Applied Nutrition, the National Center for Toxicological Research, and the Center for Devices and Radiological Health. The other three FDA centers-the Center for Veterinary Medicine, Center for Drugs and Biologics, and Center for Drug Evaluation and Research--do not directly conduct related research.

Center for Food Safety and Applied Nutrition—The Office of Toxicological Sciences (OTS) is the focus of risk assessment activity within the Center for Food Safety and Applied Nutrition. It conducts long-term animal studies on substances with potentially carcinogenic and other health effects. The research is chemical-specific and restricted to analyzing methods, dose-response outcomes, and the relevance of mechanisms of action of potentially toxic food additives and contaminants (Scheuplein, 1992).

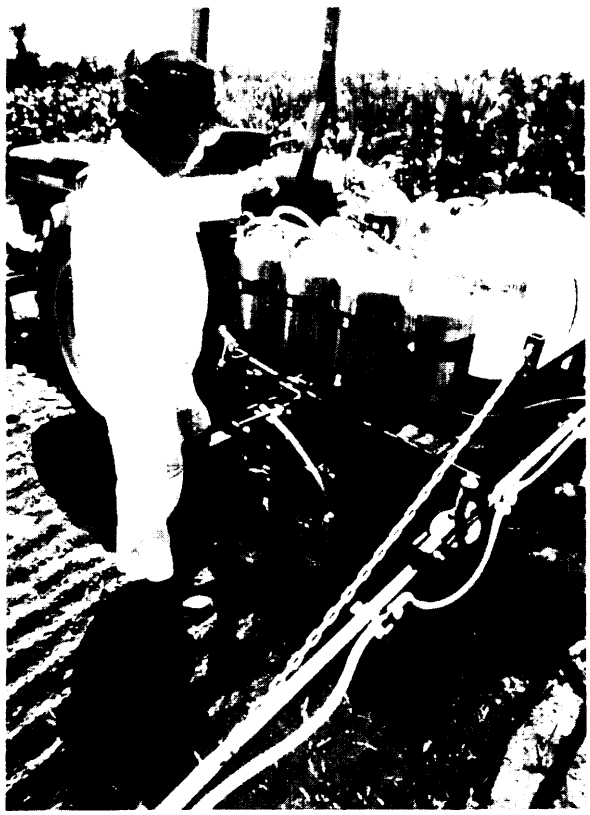
OTS is split into a research component and a regulatory review group, both of which report to the office manager.[5] The office sets priorities informally, and there is no external review of research plans or activities. Upper management establishes priorities for research, which are based on regulatory needs, and subsequently communicated to research scientists.

National Center for Toxicological Research —NCTR was begun in 1971 under the joint sponsorship of EPA and FDA, but EPA withdrew

[5] OTS underwent restructuring in fiscal year 1992, and its new structure was unavailable to OTA at the time this report was prepared.

Box 3-B-Government Interagency Collaboration: Farmworkers Cancer Study

One of the long-standing issues in cancer epidemiology has been the possible role of pesticides as a risk factor among agricultural workers. Although various studies have reported links between pesticides and lymphomas, methodological weaknesses have often hindered interpretation of the results. Gauging exposures accurately and ensuring an unbiased study cohort have been difficult with the small, retrospective studies that have been conducted. In turn, assessing the risks posed by pesticides has been problematic with such highly variable data.


ENVIRONMENTAL PROTECTION AGENCY

The Environmental Protection Agency, National Cancer Institute, and National Institute of Environmental Health Sciences have launched a joint epidemiologic study of farmers and their families. Known as the Agricultural Health Study, this investigation will assess factors that may account for reported excesses of certain cancers found among farmers, including leukemia, multiple myeloma, non-Hodgkin's lymphoma, and cancers of the brain, prostate, stomach, skin, and lips. The study will establish a large cohort of 75,000 people that can be followed prospectively for 10 years or more. The cohort will be composed of men and women who are either farm owners or operators or commercial pesticide applicators and their spouses and dependents.

The study will attempt to achieve many goals. Its objectives include the following: identifying and quantifying cancer risks among men and women associated with specific agricultural practices; evaluating cancer risks among women and children that may arise from indirect (i.e., nonoccupational) exposure to agricultural chemicals (e.g., ambient air drifts, handling contaminated clothing, residues on rugs and children's toys, residues in drinking water and food); and identifying and quantifying cancer risks associated with diet, cooking practices, and the chemicals resulting from the cooking process. The study is also designed to investigate biomarkers of exposure and disease.

The three agencies plan to develop an integrated strategy for predicting exposures. Their general approach will be to measure agricultural exposure (both occupational and nonoccupational) by periodic interviews, environmental and biological monitoring, and biomarker techniques. The research will also evaluate the relationship between agricultural and dietary exposures and biomarkers of exposure, biological effects, and genetic susceptibility factors relevant to mechanisms of carcinogenesis.

The project will be the largest, most complex study of cancer and other health effects ever undertaken among workers in agriculture and their dependents, and its organizers expect it to yield definitive information regarding the association of cancer risk with diet and occupational exposures In the farming industry. The project will also provide a resource population, among agricultural populations, for research on health outcomes other than cancer including neurotoxicity, reproductive hazards, and agricultural safety hazards.

SOURCE: Office of Technology Assessment, 1993, based on National Cancer Institute, Board of Scientific Counselors Meeting, March 1992.

its support in 1980. Today, the agency, which is located in Jefferson, Arkansas, pursues a research agenda that responds to the needs of FDA. The major objectives of its seven programs are to conduct basic research aimed at understanding the mechanisms of chemical interactions and develop better methods to assess toxicity. Collectively, its studies seek to define risks to human health from exposure to toxicants in foods, animal and human drugs, cosmetics, medical devices, and biologics. A further goal is to improve the agency's ability to predict the risks posed to humans by toxic agents.

Four programs at NCTR conduct basic research aimed at improving risk assessment (U.S. DHHS, NCTR, 1992). Three of them investigate the mechanisms by which environmental agents can cause adverse health effects, and the fourth examines the effects of nutrition on toxicity. The Developmental Toxicology Program attempts to understand how compounds produce developmental effects such as mental retardation and other birth defects. Similarly, the Neurotoxicology Program uses a multidisciplinary approach to integrate information from all avenues of neurotoxicity, in order to understand how chemicals may produce brain-related and nervous system toxicity. The Secondary Mechanisms of Toxicology Program investigates the role of normal biochemical processes in the bioactivation of compounds-that is, how enzymes found in normal individuals may transform relatively nontoxic compounds into toxic chemical intermediates.

Unlike the other programs conducting basic research, the Nutritional Modulators of Risk and Toxicity Program examines the effects of a normal diet on the biological responses of animals to toxic substances. In conjunction with the National Institute on Aging and FDA's Center for Food Safety and Applied Nutrition, the program is in year 6 of a 10-year project to examine the effects of calorie-restricted diets on responses to toxic chemicals. The program also conducts toxicity studies of food contaminants, which occur in a portion of the products FDA regulates.

Focusing on methodological studies, the Quantitative Risk Assessment and Extrapolation Program conducts studies that focus on improving the statistical procedures for analyzing data that identify adverse effects on health. In addition, the program examines the assumptions used to extrapolate experimental results to different situations, such as extrapolating the results from animal models to humans or from high doses in test conditions to the low levels found in the environment (U.S. DHHS, NCTR, 1992). Adding to earlier studies on low-dose extrapolation for carcinogens (Gaylor and Kodell, 1980), NCTR's recent work includes developing procedures to examine the risks of mixtures of carcinogens (Kodell, 1993), developmental and reproductive effects (Kodell et al., 1991), and neurotoxic effects (Gaylor, 1993).

The agency has recently created two new programs. The major goal of the Biochemical and Molecular Markers of Cancer Program is to develop and validate biomarkers of exposure, susceptibility, and effect. The Transgenics Program exploits current biochemical and molecular biological methods to incorporate human DNA into human or rodent cells or whole-rodent systems to provide scientists with a tool for studying how chemicals interact with human DNA.

NCTR's current structure and emphasis results from several efforts to link its research activities more closely to the regulatory activities of FDA. In 1985, DHHS's Committee to Coordinate Environmental and Related Programs, which oversees the department's environmental health activities, prepared a report on risk assessment and risk management that included a section on research needs (U.S. DHHS, 1985).[6] Based on the committee's recommendations, NCTR decided to direct more of its research funds toward risk

6 In 1990, the Assistant Secretary for Health formed a task force to evaluate the implementation and relevance of the report (Houk, 1992).

assessment (Houk, 1992). Thus, by 1990, NCTR was allocating nearly 70 percent of its research funds to reducing key uncertainties in risk assessment (Anson, 1993). Its research will continue to be investigator-initiated but at the same time will focus more on the regulatory needs of FDA.

Center for Devices and Radiological Health --CDRH develops and implements national programs to regulate medical devices and radiological health risks, The center's Office of Science and Technology provides the scientific foundation for an array of CDRH functions and leads CDRH activities in risk assessment. Its research mission includes laboratory and field research related to the effects on human health of ionizing and non-ionizing radiation and of medical devices, such as breast implants (Scheineson, 1992).

CENTERS FOR DISEASE CONTROL AND PREVENTION

The National Center for Environmental Health (NCEH) and the National Institute for Occupational Safety and Health are the primary participants in risk assessment research at the Centers for Disease Control and Prevention (CDC). NCEH, formerly the National Center for Environmental Health and Injury Control, conducts investigations, epidemiologic studies, and surveillance programs on environmental hazards as causes of human diseases. It emphasizes epidemiologic studies and exposure surveys in its investigations. Its research to improve risk assessments is a small subset of its programs, but it includes such public health concerns as lead and dioxin (Houk, 1992).

National Institute for Occupational Safety and Health—The National Institute for Occupational Safety and Health, which administratively resides in CDC, conducts research aimed at protecting the health and safety of U.S. workers. NIOSH coordinates its research program of lab investigations, field surveys, and epidemiologic studies so that appropriate standards and control measures can be recommended to the appropriate regulatory offices, the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), within the Department of Labor (U.S. DHHS, CDC, 1992).

NIOSH's research programs are divided among its several divisions. For example, the Division of Biomedical and Behavioral Science investigates the neurobehavioral and neurophysiological effects of exposure to chemical and physical agents in the workplace. The division's toxicology program develops assays for biomarkers of exposure, effects, and host susceptibility and seeks to understand the dose-response effects and mechanisms of action of toxic agents.

The Division of Respiratory Disease Studies conducts epidemiologic studies at mines, mills, and other industrial, construction, and agricultural workplaces to assess the risk of respiratory disease from exposures in the workplace. It also performs clinical studies to clarify the mechanisms of human responses. The division collects data on occupational exposure and also develops animal models for toxicological studies and for identifying early markers of respiratory disease.

The Division of Surveillance, Hazard Evaluations, and Field Studies monitors the Nation's work force and workplaces to assess the magnitude and extent of job-related illnesses, exposures, and hazardous agents. Fulfilling its legislative mandate, this unit conducts evaluations of worksite health hazards at the request of unions, employers, or employees; it also performs industry-wide epidemiologic and industrial hygiene surveys. For example, the division is currently managing and conducting analytic epidemiologic studies of workers at DOE facilities.[7]

Most of the research at NIOSH involves toxicological and epidemiologic studies to iden-

[7] This responsibility was transferred from DOE to NIOSH through a memorandum of understanding between the agencies in December 1990.

tify occupational hazards. The agendas of the regulatory agencies, OSHA and MSHA, largely drive research priorities at the institute.

In addition to research, NIOSH conducts risk assessments. These risk assessments are presented in the NIOSH criteria documents on specific occupational hazards. Scientists in the newly formed Risk Assessment Program conduct risk assessments for the institute, and they also conduct methodological research as part of the assessments. They are currently expanding risk assessments to topics of public health concern, in addition to responding to OSHA-MSHA regulatory rulemaking (Stayner, 1992).

Quite apart from the scientific and risk assessment capacities of NIOSH, its relationship with OSHA has been and remains problematic. Several authors have discussed the stresses and strains of the relationship under different directors and Presidential priorities (Bingham, 1992; Hardin, 1992; Robinson et al., 1991).

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY

The Comprehensive Environment Response, Compensation, and Liability Act of 1980 (more often called 'Superfund' established the Agency for Toxic Substances and Disease Registry (ATSDR). The agency's mission is to conduct applied research on the health effects resulting from exposure to hazardous substances at hazardous waste sites. Most of the research efforts under way at ATSDR relate to exposure assessment (Johnson, 1992b; Johnson and Jones, 1992), especially at EPA-designated Superfund sites (Johnson, 1992a), and ATSDR is instituting several programs devoted to assessing exposures at hazardous waste sites. The agency is also planning a Center for Exposure Characterization, which will develop interdisciplinary research programs for characterizing complex exposure scenarios. In collaboration with EPA and NTP, ATSDR is developing a program of applied research that will assess the risks posed by particular hazardous substances at hazardous waste sites and develop a list of the needed data for each substance.[8]

Department of Energy

DOE's health research focuses on the study of effects of exposure to radiation and chemicals associated with the production of energy. Under this broad mandate, DOE supports many areas of research on risk assessment, and its historical emphasis has been on epidemiology and experimental toxicology. Currently, as DOE moves from the production of weapons to disarmament, those two areas of research are being transformed in different ways: epidemiologic research is growing, but research in experimental toxicology (i.e., DOE's "health effects" research) is contracting as the department's emphasis shifts to more basic research, especially research for the Human Genome Project. In addition, Congress designated DOE as the lead agency to coordinate the Federal research efforts that are investigating the health effects of prolonged exposure to power-line electromagnetic fields.

The budget for DOE's health effects research, which includes agent-specific toxicity studies of radiation and toxic chemicals, mostly in vitro, is currently about $30 million, much reduced since the 1980s. In contrast, DOE's budget for epidemiologic research has doubled in the past 2 years and now stands at about $60 million. Compared with NCI, DOE's epidemiologic studies are more narrowly focused, and the agency supports researchers conducting studies at DOE facilities and at other national and international energy production sites (Ripple, 1992). About a third of DOE's budget for epidemiologic research is funneled to CDC, which manages DOE's studies of worker mortality through NIOSH, overseeing grants and contracts to researchers at universities and DOE facilities (U.S. Congress, OTA, 1993).

[8] The Superfund Amendments and Reauthorization Act of 1986 directs ATSDR to conduct this activity,

The DOE laboratory system comprises more than 30 laboratories. Most of those are federally owned ''national laboratories, ' which are operated for DOE by universities, university consortia, or industrial contractors. Nine of the largest are multiprogram national laboratories with multidisciplinary capabilities and extensive research facilities. OTA identified specific kinds of health risk assessment research at the following national laboratory facilities: Argonne, Illinois; Brookhaven, New York; Lawrence Livermore, California; Oak Ridge, Tennessee; Pacific Northwest Laboratory, Washington; the Inhalation Toxicology Research Institute, New Mexico; and the Laboratory of Biomedical and Environmental Science, California. Health effects research at the national laboratories includes research at Brookhaven to measure the ability of human cells to repair DNA in response to DNA damage from exposure to ionizing radiation and organic solvents. DOE funds research at Lawrence Livermore Laboratory for research in epidemiology and health effects. The Pacific Northwest Laboratory is located at the Hanford, Washington DOE facility and has some research that can be directly linked to the cleanup efforts at the Hanford facility.

Two DOE offices, the Office of Health and Environmental Research and the Office of Epidemiology and Health Surveillance, account for the bulk of research in health risk assessment through grants and contracts to university-based researchers and researchers at the DOE national laboratories. Although the distribution of funds among those two types of recipients varies from year to year, estimates are that about 50 percent of DOE's health effects research and 25 percent of its epidemiologic research are carried out at the national laboratories (Beall, 1992; Goldsmith, 1992)$_0$

The Office of Health and Environmental Research manages about a third of all health risk assessment research at DOE. This office does not conduct research per se. Rather, it reviews, oversees, and funds research applications; provides for external peer review; and sets research priorities in conjunction with DOE-supported researchers in universities and the DOE national laboratories.

The Office of Epidemiology and Health Surveillance is in the midst of expansion, reorganization, and renewal following a commitment by DOE to strengthen its health and safety research. The vast majority of the research funded by this office is devoted to human studies, but it also funds some animal research. The health surveillance program targets DOE workers—including those engaged in cleanup activities-and communities living near cleanup sites. A new effort is focusing on the potential effects on health of new energy technologies.

Until the late 1980s, historical commitments to Japan, the Marshall Islands, and the U.S. military dictated multimillion-dollar expenditures for long-term epidemiologic studies. The scale of those commitments appears to have left little discretion in establishing priorities. Many of those long-term projects are continuing, but because the budget for epidemiologic research has increased, research managers now have an opportunity to advance other priorities. Indeed, DOE has instituted myriad changes in its priority-setting process, in part as a result of criticism that the epidemiology program had not developed clear goals (U.S. DOE, 1990).

DOE is also preparing a milestone planning document, a research agenda that carefully sets specific research priorities for the agency's epidemiologic research over the next several years. The Office of Epidemiology and Health Surveillance drafted the agenda in consultation with the National Academy of Sciences, and the document is now undergoing review. DOE plans to use the agenda, which should be available to the public in late 1993, as the blueprint for research project grants that the office would like to fund.

Department of Defense

The mission of the Department of Defense (DOD) is to protect national security and ensure

military preparedness, and its priorities for research related to risk assessment are set within that context. In the area of toxicology, priority-setting takes into account forces external to the military that drive research priorities, such as scientific advances, regulatory requirements, and public concerns, and the ongoing impetus to increase cross-service coordination and cooperation, as initiated by Project Reliance and the Base Relocation and Closure Commission (U.S. DOD, 1993). Research efforts that receive priority are those to develop improved methodologies for describing, quantifying, and understanding toxicity (particularly the endpoints of special concern to the military), and expanding the ability to predict toxicity from existing data or from limited data sets.

A primary consideration for toxicity testing at DOD is preventing adverse health effects from exposure to defense-related chemicals in the workplace. Although the research needs of the three services differ, similarities in their occupational settings result in many overlapping research projects, which provide opportunities to share resources and information. As part of the move toward consolidating service activities and avoiding needless duplication of projects, the Army is relocating its toxicology program to Wright-Patterson Air Force Base in Ohio, which already hosts the "collocated" toxicology programs of the Navy and Air Force.[9] The Army's decision has fostered further efforts toward joint planning with the goal of developing a Tri-Services Center for Toxicology and Risk Assessment at Wright-Patterson.[10] One cross-service research project, for example, is looking at alternative methods of evaluating toxicity by using simpler animal models. A particularly promising test model is the medaka, a fish that can be exposed to a variety of service-related substances (Ostermann, 1992).

Consumer Product Safety Commission

The Consumer Product Safety Commission (CPSC) is an independent commission of three members appointed by the President. CPSC both performs and funds research on chemicals of regulatory interest (i.e., chemicals in consumer products to which the public may be exposed). CPSC staff perform exposure studies that relate the results of exposure testing to potential human risk; they supplement those data in most cases with information from research on marketing and product use to gain a more complete picture of consumer exposure.

The three presidentially appointed members of the Commission decide which projects CPSC will undertake. They also approve an operating plan for each fiscal year and conduct a mid-year review to determine program progress and adequacy of funding (Cohn, 1992). In some cases, Congress specifies topics on which resources are to be spent. CPSC staff usually recommend projects to the commissioners, who then set priorities. Statutory mandates require that the commissioners hold public hearings on priorities and announce the hearing in advance in the ***Federal Register.***

Department of Agriculture

The Agricultural Marketing Service (AMS) of the U.S. Department of Agriculture (USDA) began the pesticide residue testing program in May 1991 as part of USDA's Pesticide Data Program (PDP). This program collects actual concentration levels of pesticide residues in fresh fruit and vegetables reaching the consumer. AMS developed PDP's policy and operations procedures and residue testing priorities in close cooperation with EPA and FDA. These data are used by EPA for pesticide risk assessment and serve as a database for national residue levels so that the government can respond more effectively

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9 The Navy and Air Force have collocated their toxicology programs at Wright-Patterson for 15 years (U.S. DOD, 1993).

10 A tri-services program has existed intermittently over the course of the past 5 years, but unstable funding has kept it from remaining viable. Now, however, military administrators are showing renewed interest in the program (Macys, 1993).

to food safety issues. The residue monitoring program is being implemented in stages, based on the data needs expressed by EPA. The data will be collected in California, Florida, Michigan, New York, Texas, and Washington.

Nuclear Regulatory Commission

Activities related to risk assessment at the Nuclear Regulatory Commission (NRC) cover a wide range of research, especially that on the health risks from exposure to radiation. Scientists in NRC's Division of Energy and Materials are studying the potential adverse effects of electromagnetic fields on health, as well as the effects of radiation. Work is also under way examining the feasibility of reducing the uncertainties in estimating risks from protracted exposure to low doses of ionizing radiation. NRC has also funded research on placental transfer and other factors affecting the dose of radiation to the developing embryo.

TRENDS AND GAPS

Over the course of this study, OTA observed several major trends in the array of Federal research activities that support health risk assessment. To begin with, agencies are expanding the scope of their activities, previously focused on cancer, to include other adverse health effects. EPA's RIHRA program, for example, now devotes only 10 to 20 percent of its resources to cancer-related research (Vandenberg, 1992). NIEHS is also reorganizing and broadening its research program to investigate mechanisms of noncancer toxicity (Olden, 1992).

Many scientists interviewed by OTA expressed the belief that research on health effects other than cancer has the potential to influence regulatory policy significantly. One reason that such research may have a substantial impact on policy is that noncarcinogenic mechanisms do not give rise to the often acrimonious policy debates associated with issues related to carcinogenesis, such as thresholds for carcinogens (see ch. 2). Those debates have precluded any indication of flexibility in the policy positions of many agencies. The scientists interviewed also believe, however, that the current science base is not sufficient for adequate risk assessments of noncarcinogenic endpoints.

Along with expanding the focus of their studies, many agency research programs have also been undergoing some form of organizational restructuring. In most of those cases, the restructuring reflects a greater emphasis on social relevance: EPA is shifting to risk-based planning, with the intention of directing agency resources to areas posing the greatest health risks (Reilly, 1991; U.S. EPA, 1992a); NIEHS is expanding its role in improving the science base for human risk assessment (Olden, 1993; Stone, 1993); and the research activities of NCTR scientists are being more closely aligned with the regulatory needs of FDA (Norris 1993; U.S. DHHS, FDA, 1991). All of those restructuring efforts constitute a departure from the traditional notion of allowing scientists to "follow their noses' and focus on investigator-initiated areas of interest (Carnegie Commission, 1992; Stone, 1993; U.S. Congress, House Committee on Science, Space, and Technology 1992). OTA was unable, however, to evaluate the effectiveness of those efforts because they had not yet been fully implemented.

As agencies link their research activities more closely to the needs of society, their research becomes, by necessity, increasingly multidisciplinary. No one field of academic training or research covers all of the data needed for a sufficiently comprehensive risk assessment; the relevant fields range from basic biomedical research to computer models for simulating experimental conditions. The increasing complexities of the science involved and the need to incorporate more science into regulatory rulemaking have made it clear that multidisciplinary research is required to provide the requisite scientific underpinning for future risk assessments. Dwindling agency resources have also catalyzed these interactions as the necessity for cooperation is

becoming apparent. Setting aside turf battles, Federal agencies are beginning piecemeal approaches to promoting these multiagency, multidisciplinary interactions.

Yet overall, few incentives exist for long-term multiagency, multidisciplinary research on health risks, and very few resources are allocated to that work. Scientists from all of the environmental health disciplines, including toxicology, epidemiology, biostatistics, and clinical studies, make contributions to health risk assessments and are the mainstay of agency research efforts to improve the risk assessment process (Paustenbach, 1989). Nonetheless, those fields remain **disparate,** and collaborative studies are still the exception rather than the rule. Without more and better incentives to collaborate, disciplinary myopia may continue and grow more pronounced and entrenched. Compartmentalization by agency or discipline can only hinder the progress of risk assessment research and prevent the infusion of newly developed technologies and knowledge arising from the rapid advances now occurring in the biomedical sciences.

Collaborative research is particularly needed to evaluate and validate new methods and models with experimental data. Despite the importance to risk assessment research of systematic efforts in this area, OTA found little indication of such work, especially in the important field of corroborating experimental results from animal studies with studies in humans. A few examples were observed: EPA employs exposure chambers to study the clinical effects of air pollutants and uses the results to examine the predictive success of test animal models (U.S. Congress, OTA, 1991b; U.S. EPA, 1992b) (see box 3-A), and NTP and NOSH collaboratively evaluate and compare human and animal responses in the areas of reproductive toxicology and immunotoxicology (Schwetz, 1992). Researchers from NIEHS initiated a study of carcinogenicity prediction methods by comparing the results of predictions based on chemical structure and short-term tests against the results of rodent bioassays for 44 chemicals tested by NTP (Hileman, 1993). Beyond those few programs and studies, however, little research appears to be under way to bridge the gap between data gathering and basic research by examining or validating whether testing or extrapolation models can be applied to specific chemicals. In fact, at least one analyst contends that the government's public health programs have been hamstrung by their lack of ability, funding, or motivation to conduct such "bridging" studies, which would validate risk assessment methodology (Mirer, 1992).

With additional resources, Federal agencies could conduct bridging studies on existing data sets that are presently underused (if used at all) for analysis and methods development. Such data are available from several sources. The Federal Government has collected toxicity information in response to mandates for registering or approving drugs and chemicals (U.S. Congress, OTA, 1991c). FDA requires manufacturers to submit clinical studies on pharmaceuticals but makes little or no effort to use those data for analysis, such as in pharmacokinetic studies or for validating the results of animal assays (Gaylor, 1993). Similarly, EPA has performed little analysis of the manufacturer-supplied information on pesticides that it collects (Kozumbo, 1993), nor has NTP fully analyzed the entire set of data from the rodent bioassays it conducts (Huff, 1993b).

Although some advances are being made in those areas (see, for example, Quest et al., 1993; Huff, 1993a; and Ashby and Tennant, 1993), in general the agencies provide few incentives or funding opportunities. Of course, in some cases, formidable obstacles prevent agencies from using these data, which are often from tests of proprietary chemicals and drugs, and whose release could hamper industrial competitiveness. Nevertheless, this information constitutes a repository of valuable research data that could improve risk assessments. Both the animal and human data in conjunction with an improved understanding of the mechanisms of environmentally induced diseases could be used to evaluate and validate

existing models as well as develop new ones. But, such research requires better collaboration between and among agencies and research disciplines.

SUMMARY

Federally supported risk assessment research is spread out across at least 12 different Federal agencies, institutes, and centers. That dispersion has both positive and negative consequences. On the one hand, agencies can monitor their own research efforts without having to overcome bureaucratic hurdles, and they can target their research to the areas they consider of highest priority. On the other hand, work is fragmented and diffuse. Fragmentation generally impedes the dissemination of information (Klein, 1990; U.S. Congress, OTA, 1991a), and hampers progress toward a stated objective—in this case, better risk assessments. In addition, this diffusion works against developing multiagency programs that could produce solutions to common risk assessment problems.

The past decade has witnessed nearly revolutionary developments in the biological sciences. Researchers are poised to incorporate those advances into the field of environmental health, especially into improving health risk assessments (Olden, 1993; U.S. DHHS, 1991 b).

Yet despite the potential for advances, the present Federal risk assessment research and development infrastructure remains a source of controversy. Many scientists interviewed by OTA claim that this research system is ''broke. ' Resources, they argue, are squandered on a system that is incapable of setting priorities. Consequently, the perception exists that the areas of research of highest priority-those most likely to improve risk assessment approaches—are not being funded or studied, at the expense of lower-priority or even irrelevant research. The nature of the ''right' research, however, remains an area of active debate. How agencies determine their research priorities is an important element of that controversy.

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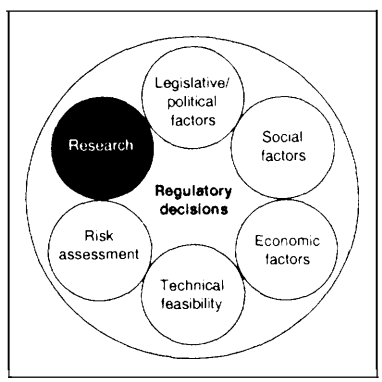
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Setting Priorities for Risk Assessment Research

4

Congressional mandates for risk reduction, the public's desire for health and safety, and court rulings requiring justification of health-based regulatory actions have increased pressure to provide ever greater scientific underpinnings for health risk assessments. Judged by the rate of change in risk assessment methodology and the controversies that surround risk assessment, Federal agencies lack the necessary resources to meet that demand and can only support a portion of the research that could or would be useful to them. This chapter examines how Federal agencies determine their priorities for health risk assessment research, that is, the type or types of research an agency will support and conduct. For this analysis, the Office of Technology Assessment (OTA) categorized such research as methodological, basic, or chemical-specific data development.

Priority-setting is influenced by factors that operate at the national, agency, or programmatic levels. The impact of national goals on individual projects or, conversely, the effect of individual projects on national goals, is difficult to gauge, but generally one can expect that effects at one level will reverberate to another. For example, the acquired immunodeficiency syndrome (AIDS), became a national concern, and more resources were directed toward understanding the disease, which resulted in greater participation by scientists from different disciplines in the research, The influx of talent and resources affected the nature of the approaches used to combat the disease and also contributed to research in other fields (U.S. Congress, OTA, 1990).1



[1] See Joseph (1992) for a discussion of the role of politics in setting the scientific and public health priorities for AIDS research and treatment.

CATEGORIZING HEALTH RISK ASSESSMENT RESEARCH

The types of research that Federal agencies conduct to improve health risk assessments can be categorized using several different approaches. One approach is the traditional division between basic and applied scientific research (Merton, 1973). That approach would distinguish research focused on, expanding knowledge about human diseases and their relationships to environmental factors from research more directly linked to regulatory agendas.

Basic or pure science involves studies "ordered around the expansion of knowledge and competence without any regard for practical application' (Barnes and Edge, 1982). For health risk assessment, this kind of research usually occurs within well-defined disciplinary boundaries-for instance, genetics, molecular biology, chemistry—and involves testing explanatory hypotheses (e.g., about the normal and abnormal functions of organ systems or mechanisms of carcinogenesis) with a variety of experimental methods.

Applied science, in contrast, focuses on increasing and improving "the stock of existing practically useful techniques, processes, and artifacts" (Barnes and Edge, 1982). It involves developing information that may be useful for resolving outstanding practical questions (Lindblom and Cohen, 1979). For health risk assessment, those questions are usually determined by the management problems that regulatory agencies confront (e.g., should human exposure to air pollution be reduced?), and they require interdisciplinary efforts to characterize the pros and cons of taking action. Applied research in health risk assessment can involve experimentation that also contributes to basic scientific understanding, but its predominant motivation is to provide a basis for regulatory decisionmaking.

There are two broad subcategories of applied research in health risk assessment: 1) substance-specific investigations, e.g., conducting toxicity tests or monitoring exposures; and 2) methodological research that can improve either qualitative or quantitative risk assessment techniques, e.g., developing new testing methods or new low-dose extrapolation models.

Although these categories of risk assessment research are useful for characterizing the activities of Federal agencies, they are not absolute because the boundaries between basic and applied research are frequently blurred. Neurotoxicity testing, for example, can contribute to a basic understanding of neurobiology even as it produces results that are useful for identifying neurotoxic agents for regulatory purposes. Similarly, basic scientific findings, such as the discovery of oncogenes, have important implications for applied research on chemically induced cancers.

Both sociologists of science and regulatory policy analysts have developed their own approaches to categorizing risk assessment research. If one focuses on why research is undertaken and on the standards used to evaluate its results, it is possible to distinguish between ***normal*** (Rushefsky, 1986) and ***mandated*** (Salter, 1987), or ***regulatory*** (Jasanoff, 1990), science.

In ***normal*** science, researchers conduct investigations as part of a basic research program (Lakatos, 1978), and results are evaluated on the basis of their reproducibility and the contribution they make to resolving outstanding scientific questions. The standards of proof for accepting findings are quite rigorous because scientists are reluctant to mistakenly assert that relationships exist—for example, between a chemical exposure and human cancer—when such relationships might in fact be due to chance (Cranor, 1993).

In contrast, ***mandated*** science is conducted in response to statutory mandates-instructions to regulatory agencies to identify potential health hazards and control exposures to them to prevent human illness. The results of research conducted within that kind of institutional environment are evaluated against a broader set of criteria than is typical of normal science and frequently involve standards of proof that can conflict with the standards of basic research science (Clark and

Majone, 1985; Jasanoff, 1989). Findings that indicate potential risks to human health, for example, will be judged not only on the basis of the standards of normal science but also on the basis of regulatory standards. If a regulatory agency concludes that a risk is present and if opportunities are at hand to prevent a public health problem, regulatory action may be taken on the basis of less-than-conclusive scientific evidence.

Science used in policymaking can be broken down further into three basic types of activities: knowledge production, knowledge synthesis, and prediction (Jasanoff, 1990). Knowledge production takes in research that is conducted to fill gaps in the information base relevant to regulation; an example would be toxicity testing. Knowledge synthesis involves collecting, evaluating, and characterizing the available scientific information about potential environmental problems and often results in comprehensive risk assessment reports. The most contentious aspect of regulatory science involves predicting the health risks posed by exposure to different toxic agents. Prediction usually depends on a variety of models and assumptions that bridge the gaps between current scientific understanding of relationships between exposure to toxic agents and health outcomes and a projection of what relationships might exist under different conditions.

Because all of these activities are oriented toward resolution of questions on policymaking, a characteristic feature of mandated science is the extensive involvement of nonscientific institutions, such as Congress, the courts, and the media, in the process of producing and certifying knowledge. In that political environment, normal science's approach to reducing uncertainty (conducting further research) is frequently unsatisfactory, because decisions to wait are often interpreted as decisions not to act to protect public health.

Although the distinction between normal and mandated science cannot easily be used to class@ the research activities of Federal agencies, it nevertheless illuminates a number of current policy debates about the appropriate focus of scientific research conducted by regulatory bodies. The results of agency research programs are sometimes evaluated by using criteria from basic science; that practice may lead critics to conclude that the products of agency research are deficient and that increased attention to basic research is necessary to produce "credible' science (U.S. EPA, 1992). An example is the controversy over testing priorities at the National Toxicology Program (NTP). From a normal science perspective, rodent bioassays should be conducted as part of a research program to discover basic mechanisms of toxicity and to define the relevance of positive results in animal tests for assessing the risks to humans. But from the perspective of mandated science, bioassays are part of a large-scale screening effort to identiy potential chemical hazards in the environment. Increased attention to studying mechanisms for determining human relevance means that fewer chemicals are screened and that exposure to avoidable causes of human disease is potentially greater.

Another approach to categorizing risk assessment research is by examining the potential for new scientific investigations to increase the knowledge base and decrease policy conflicts. A simple model developed by policy analysts categorizes the results of research along two dimensions: the extent to which they contribute to scientific knowledge and the extent to which they increase or decrease policy conflict (Graham et al., 1988). This perspective on the contributions of health risk assessment research is clearly helpful for establishing priorities and formulating a national research agenda. Investments in research that contribute to the knowledge base and reduce policy conflict are clearly optimal. But because of the way science works, results may uncover new conflicts that require additional experimentation well beyond what can be accomplished with available techniques. Case studies of U.S. regulatory policy regarding carcinogens have concluded that more research, leading to

more knowledge, does not necessarily result in less policy conflict. Extensive investigations of the mechanisms by which formaldehyde causes cancer in rodents, for example, have raised more questions about the possibility of low-dose risks to humans than they have answered. The result is an increase rather than a reduction in policy conflict (Graham et al., 1988).

These analytical perspectives on the different rationales for conducting basic and applied research on risk assessment and on the varied effects that research can have on the knowledge base and the policy process are essential for a balanced assessment of current efforts by Federal agencies. Scientific optimists, for example, might look at the tremendous advances being made in molecular biology, and conclude that support for that research is more worthwhile than support for less scientifically interesting programs of toxicity screening. But the results of basic science research may not be immediately applicable for regulatory decisions. There is clearly a need for applied research to provide data for preliminary determinations about possible hazards before acquiring a complete understanding of the hazard. Similarly, there is a need to develop risk assessment methodologies that address the inevitable gaps in scientific understanding in order to characterize potentially significant risks to health. However, to the extent that uncertainties are ever reduced, the reduction is more likely to come from an integration of basic and applied research.

To narrow its range of inquiry, OTA restricts risk assessment research to two types of activities:

1. Generalizable research to improve methods for assessing the risks of adverse health effects from food contaminants and environmental and workplace exposures, and
2. Research to improve estimates of risks from exposure to specific agents.

Because of the controversies surrounding the methods for evaluating and estimating risks from exposure to agents suspected of causing cancer, this report frequently uses research to improve the assessment of risk from potential carcinogens to illustrate the directions and needs of research on health risk assessment in general.

Given that framework, OTA divided health risk assessment research into three key areas (table 4-l). Two of the areas encompass more general research, and the third encompasses chemical-specific research. Methodological research, the first area, is specifically aimed at improving the approaches and methods used for assessing risks. The second, basic research, contributes to an understanding of how environmental agents perturb normal biological functioning. The third category involves research that expands the database about specific chemicals for use in risk assessments. The results of all three types of research are crucial; inadequate development in any one area could impede progress toward the overarching objective of making risk assessment more credible and its results more widely accepted. For instance, the models developed in methodological research depend on the results of basic research and chemical-specific data development.

OTA used these classifications as a better representation of research activities than the process of risk assessment outlined by the National Research Council (NRC) in 1983 (NRC, 1983). As discussed more fully in chapter 2, NRC's sequential four-step process begins with hazard identification, progresses to dose-response and exposure assessments, and ends in risk characterization. The NRC "paradigm' laid out and formalized the risk assessment process and made it transparent for decisionmakers and the public alike, but it does not delineate the different kinds of research that underpins each step (Paustenbach, 1989; Rosenthal et al., 1992). OTA's analysis focuses on three distinct objectives of health risk research: improving health risk assessment methodologies, understanding how environmental agents produce their adverse effects, and filling chemical-specific data gaps.

Table 4-l-Categories of Health Risk Research

Methods Development
Method and model development—Developing tests and structure-activity analysis for identifying toxicants; developing models for predicting human exposures; developing methods for extrapolating effects, dose, and dose-response from laboratory study results to humans. Activities for method and model development include: . Toxic effects identification and extrapolation . Exposure extrapolations * Dose-response extrapolations . Uncertainty analysis
Met hods evaluation and validation—The iterative process for validating new methods by comparisons to methods of known and established veracity. When validated, methods can be applied to risk assessments.
Basic Research
Toxicity mechanisms—Research to determine the nature, sequence, and combinations of events that result from exposure of test animals or humans to toxicants. This includes the study of the concentration of the toxicant or its metabolize that reaches the site of action, the rates and nature of the reactions with target organs or tissue that are causally linked to disease or the development of toxic effects, and an understanding of how the toxic effect comes about.
Biological and biomedical-Research on the structure and function of molecules, cells, organs, physiological systems, and organisms. The resulting knowledge of comparative genetics, biochemistry, and physiology can be used to guide studies on toxicity mechanisms or reduce uncertainty in effects, dose, and dose-response extrapolations.
Chemical and physical sciences—Research on physical and chemical properties that govern absorption, distribution, fate, transport, and transformation in the environment and in biological systems.
Chemical-Specific Data Development
Toxic effects—Research designed to identify the toxic effects of agents and the nature of dose-response relationships under defined conditions of exposure. Activities include: . Human studies • Whole-animal studies • Mammalian tissue, organ, and cellular studies . Microorganism and other studies
Human exposure data--Measuring toxicant levels indifferent media or commodities and biological materials to test predictive models and to validate measurement methods.

SOURCE: Office of Technology Assessment, 1993.

Research to Improve Health Risk Assessment Methods

OTA sees the goal of research on health risk methodology as development of better methods for extrapolating results: from animal models to humans, from high to low exposures, and from emission data to predictions of population or individual exposure. It also encompasses efforts to estimate uncertainty and develop new methods for toxicity testing. An important and often overlooked part of methods research is evaluating and validating the methods with experimental data.

Many scientists argue that methodological research holds the most immediate promise for substantive improvement of risk assessments. To begin with, generic methodology research, in contrast to chemical-specific studies, can have considerable impact on assessing the risks from exposure to many different chemicals and radiation. Moreover, when the methods are directed at the most uncertain aspects of risk assessments (extrapolations from high to low doses and from animal models to human populations and predicting the risk of chemicals for which few or no toxicity data exist), they can reduce the range of uncertainties in current risk assessment approaches. Because of a number of characteristics, methodological research falls in between basic and chemica.l-specific research, making it a bridge between basic and applied efforts. In other respects,

however, this research is sufficiently unique that its practitioners refer to it as ‘‘risk science. ’

Basic Research To Support Risk Assessment

For the purposes of this report, basic research is separated into two types: basic health risk research and basic sciences research. Basic health risk research investigates the mechanisms of disease associated with exposure to toxic agents. These studies examine the fate and transport of chemicals and physical agents, the avenues of exposure, and interactions with living systems and biological tissues, all of which feed into health risk assessment research. The focus of basic health risk research on the application of results to risk assessment problems and opportunities sets it apart from the basic sciences.

Basic sciences research encompasses the basic biological and biomedical, chemical and physical sciences. Although some research in the basic sciences contributes to risk assessment research, basic sciences research is a very broad endeavor, and it is not included in OTA’s analysis of relevant research. These studies examine the structure and function of molecules, cells, organs, and physiological systems and their relationship to the functioning organism, as well as the properties of chemicals and physical agents.

Of the three types of health risk assessment research, findings from basic research usually require the most time to be incorporated into decisionmaking. The research has also been generally characterized as having the lowest probability of success. Nevertheless, it can serve as the foundation for developing new methods in generating or applying primary data for health risk assessment and affect risk assessment in a far-reaching way, as it does other applications of science. Recently, techniques and findings from basic research have been rapidly incorporated into health risk research. Within the past several years, for example, many molecular biological principles and techniques have proliferated throughout the field of toxicology (Olden, 1993).

Chemical-Specific Data Development

Chemical-specific data development identifies the toxic effects of agents and characterizes dose-response relationships under defined conditions of exposure. Efforts to identify toxicants probably constitute the broadest and most diverse type of data development. Usually, they involve testing agents in laboratory animals, sometimes complemented by results from epidemiologic studies. This type of research also includes collecting data on exposure of humans to environmental agents. Some scientists dismiss the idea that collecting or gathering data using “routine” tests or monitoring methods is research. In contrast, the majority of scientists who advised OTA in the study and who reviewed drafts of this report voiced the opinion that such activities are properly classified as research. In OTA’s evaluation of research funding, only two Federal agencies reported collection of exposure data as a research activity, but many included toxicity testing in research activities. The programs that carry out toxicity tests do more than provide the basic information for risk assessments, they also do research that leads to better tests and basic research on mechanisms of disease causation.

A look at the number of existing chemicals and the new compounds that appear each year explains the need for further toxicity testing and data development. Since 1965, more than 12 million chemicals have been entered into the Chemical Abstract Service’s registry file (although the actual number of chemicals to which individuals might be exposed is considerably smaller). The reporting provisions of the Toxic Substance Control Act require an inventory of the chemicals currently being manufactured in this country; that list contains more than 61,000 chemicals (Lao, 1993). More than 3,000 chemicals are registered as pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act, a listing that consists

of *880* active pesticidal ingredients and 2,200 inert ingredients (Colledge, 1993). The number of food additives is 3,151 (Hudson, 1993).

After reconciling for overlaps, OTA estimates that 62,512 chemicals are present in commerce in the United States. A recent gathering of environmental experts estimated that ''good' data on the health effects from exposure are available for only 10 percent of chemicals existing worldwide, with nearly 1,500 being developed each year (Environmental Health Letter, 1993).

FEDERAL RESOURCES FOR HEALTH RISK ASSESSMENT RESEARCH

The Federal Government's support for research on health risk assessment extends from basic studies in the biological and biomedical sciences to methods for extrapolating observations from one setting to another. That breadth was evident during OTA's attempts to evaluate the resources devoted to improving health risk assessment. Under the broadest definition of research that affects health risk assessment, a significant portion of the Federal Government's obligations in health research and development (R&D) generally can be considered as contributing to the effort.

OTA used the research objectives and the categories of risk assessment research discussed above, which parallel the categories used by the executive branch,[2] as the framework for the analysis of agency research resources. This analysis used three main sources of information: the 1992 data book of the National Institutes of Health (see app. C); the annual National Toxicology Program (NTP) review of the research related to toxicology (U.S. DHHS, in press), which includes basic toxicology research, epidemiologic and methodologic research being performed by the Department of Health and Human Services (DHHS) agencies (see app. D), Department of Energy (DOE) and Environmental Protection Agency (EPA); and OTA's requests to the various agencies for data on resources. OTA also contacted organizations such as the National Science Foundation and the American Association for the Advancement of Science, which have recently completed reports on Federal environmental research. The best of these sources, for the purposes of this report, proved to be the NTP review .

OTA's call for information from the various Federal agencies resulted in estimates of resources that were highly dependent on how the responder defined health risk assessment research. For example, with a broad definition of research related to health risk assessment, about 33 percent of the 1993 budget of the National Cancer Institute (NCI) or about $600 million, would be related to this activity (Lee, 1993). But using data from NTP's review of current research (U.S. DHHS, in press) as representative of their research on health risk assessment, the NCI support would be estimated at $80 million, or about 4 percent of the 1993 NCI budget. Consequently, OTA concluded that it had not obtained wholly reliable estimates of resources; nonetheless, OTA discerned some general trends and directions.

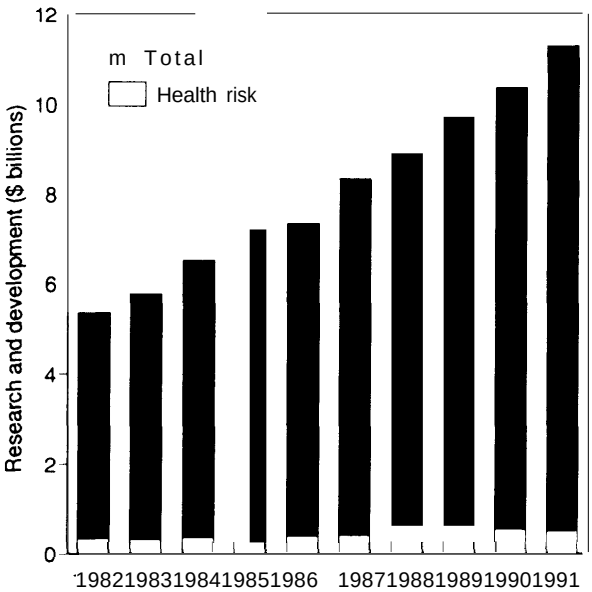
using Summary data issued between 1982 and 1991 from the NTP review of research related to toxicology as a surrogate for health risk R&D,[4] OTA determined that total support of health risk assessment research increased from $336 to $520 million, a 55 percent increase before adjusting for inflation. During the same period, Federal obligations for health R&D, as reported in the National

2 The NTP Annual Reviews of Research Related to Toxicology compiles data on agency programs in the Categories of Basic Toxicology Research, Toxicology Testing, and Toxicology Methods Development (U.S. DHHS, in press).

3 The NTP review includes human epidemiology studies as toxicology testing,

4 OTA's survey in 1993 indicates health risk research is also carried out by the Department of Defense, Department of Agriculture, the Consumer Product Safety Commission and Nuclear Regulatory Commission. NTP data did not cover resources for those agencies. However, their contributions are small relative to the agencies covered in the review.

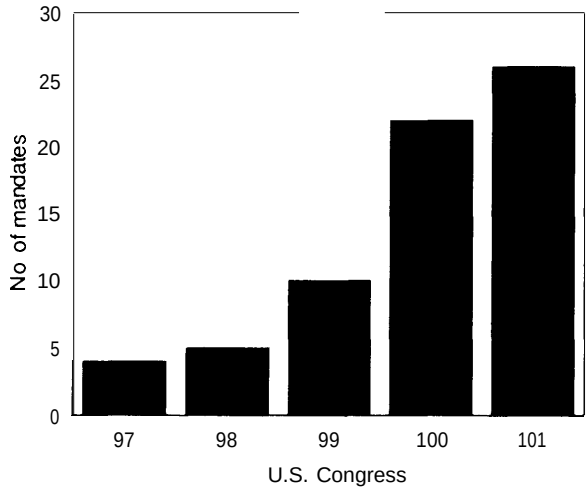
Figure 4-l—Funding **for Federal Health Research and Development, Fiscal Years 1982-91**



[a] Total.
[b] Health risk.

SOURCE: **Office of Technology Assessment, based on National Institute of Health Data Book, 1992; and Review of Current DHHS, DOE and EPA Research Related to Toxicology, Fiscal Years 1982 through 1991, National Toxicology Program, U.S. Department of Health and Human Services.**

Figure 4-2—Environmental **Legislative Mandates**



SOURCE: Office of Technology Assessment,1993.

Institutes of Health data book, increased from $5.0 to $10.7 billion, a 123 percent increase before inflation (figure 4-l).

With the above data, OTA estimated health risk R&D's share of total Federal health R&D dropped from 6.8 percent in 1982 to 4.9 percent in 1991. Moreover, this relative decline in health risk R&D took place during a period of expanding Federal legislation and responsibilities to protect human health from environmental pollutants. During that period, the number of environmental legislative mandates increased with each successive Congress-horn 4 in the 97th Congress (1981 and 1982) to 26 in the 101st Congress (1989 and 1990) (figure 4-2).

The NTP data describe the fuding support for research related to chemical toxicology in methods development, basic toxicology, and testing (data development) (figure 4-3). These data represent the research priorities for the three types of health risk research. Of the $524.8 million spent for the total research effort in fiscal year 1992, methodological research received 15.6 percent, basic research 58.3 percent, and testing 26.1 percent.

In addition the NTP data also illuminated trends in how the various agencies separately apportioned support and resources for those types of research (figure 4-4). In general, over the 1980-92 period, research agencies such as the National Institute of Environmental Health Sciences (NIEHS) and the National Cancer Institute increased the percentage of basic toxicological research that they conducted. In contrast, regulatory agencies such as EPA and the Food and Drug Administration (FDA) devoted a larger proportion of their health R&D to methods research than did the research institutes.

In this figure, the personnel numbers, in full-time equivalents (FIEs), devoted to this research reflect the size of the intramural program. In general, the regulatory agencies have sizable intramural programs compared to their R&D budgets, while the research agencies support relatively larger extramural programs. The number of FTEs at EPA, for example, is nearly

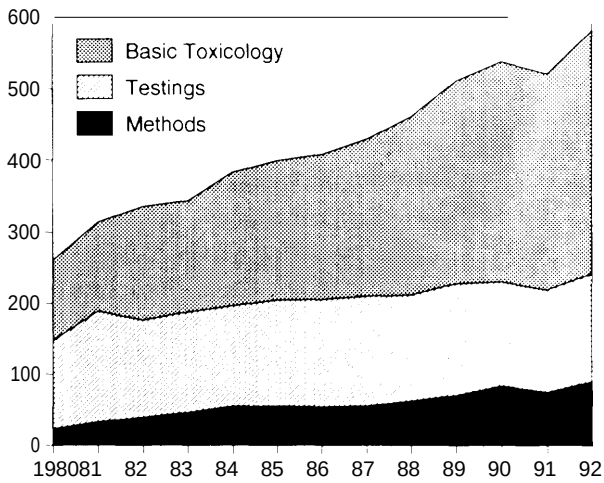
equivalent to NIEHS, but EPA's R&D budget is only about one-third the size.

Taken together, the budget and personnel figures provide a picture of the Federal health risk R&D effort and the priorities of the agencies. To begin with, these data show that NIEHS devotes the most resources, in both dollars and FTEs, to health risk research. Furthermore, the agencies with substantial extramural programs, NIEHS and NCI, to a large extent support basic research. The intramural program at NCI is predominantly basic in nature, whereas it is more evenly distributed at NIEHS among the three types of research. As the graphs in figure 4-4 demonstrate, NCI transferred its carcinogen testing program to NIEHS in 1982. The remaining four programs in this figure operate mostly intramural research programs. As the agencies reported in the NTP Review, EPA and NIOSH programs conduct mostly methodological research, while, at the FDA, the National Center for Toxicological Research's (NCTR) research is mostly basic and the Center for Food Safety and Applied Nutrition's (CFSAN) is more evenly distributed.

Based on fiscal year 1993 estimates in the OTA survey of research (table 4-2A), less than 11 percent ($65 million) of the total R&D budget of $600 **million** for environmental and occupational health and food safety is devoted to research on methods. It is possible only to estimate roughly the total amount that was actually spent on methods research during the period, because of the difficulties in categorizing the research. Nevertheless, the small size of the risk research analysis programs at the NCTR and NIEHS, and the reported part-time participation of researchers at the regulatory agencies, support a conclusion that methodological research is underfunded.

To get a broader accounting of the FY 1992 research resources, OTA incorporated data from the Departments of Defense and Agriculture with the NTP review data (table 4-2B). In table 4-2B, OTA estimates that the agencies devote nearly 16 percent ($91.6 million) of the total $589.5 million spent in FY 1992 to methods research. The

Figure 4-3-Federal Research Related to Chemical Toxicology (In **millions of dollars)**



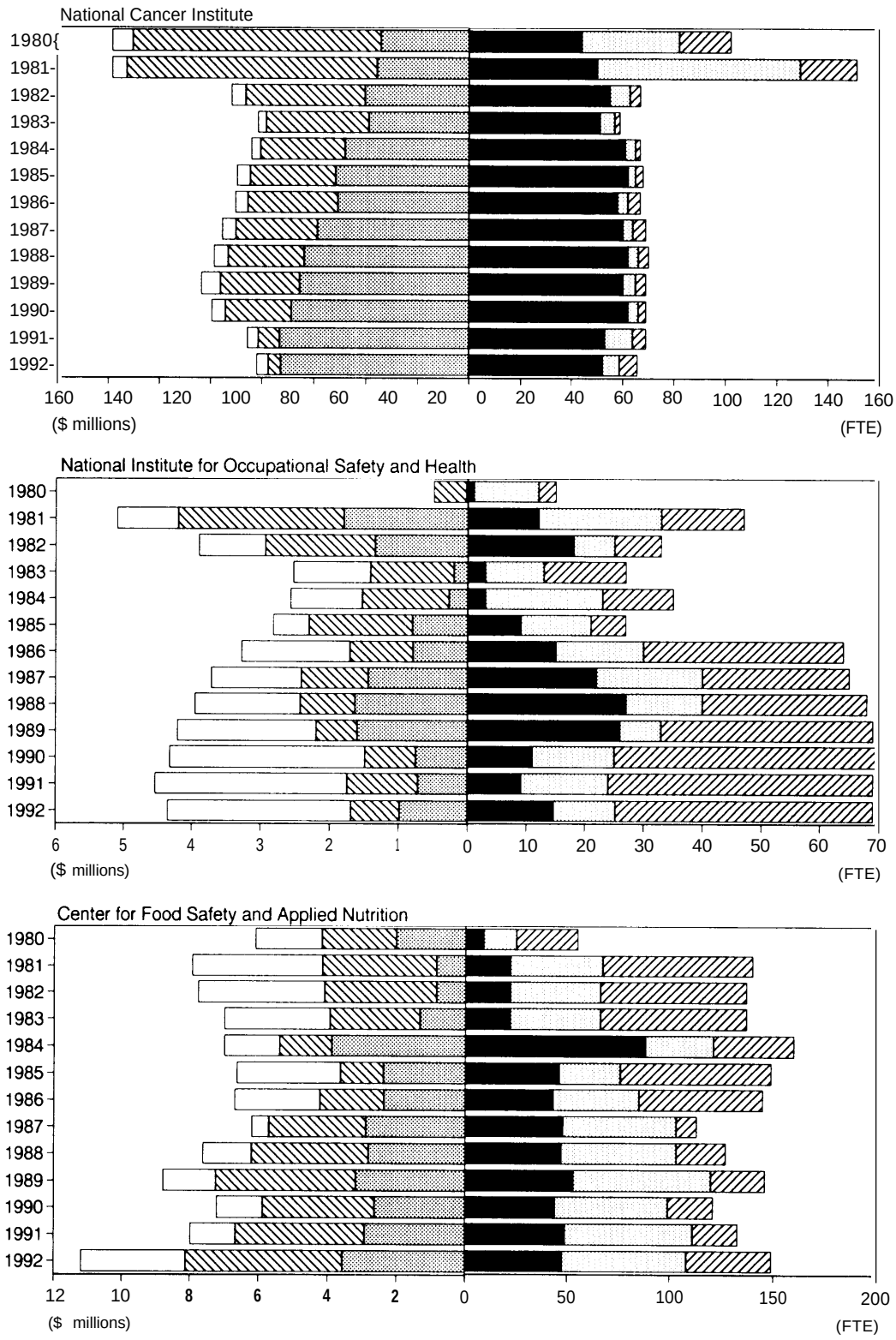
SOURCE: Office of Technology Assessment, 1993, based on data from Review of Current DHHS, DOE and EPA Research Related to Toxicology, Fiscal Years 1980 through 1992, National Toxicology Program, U.S. Department of Health and Human Services.

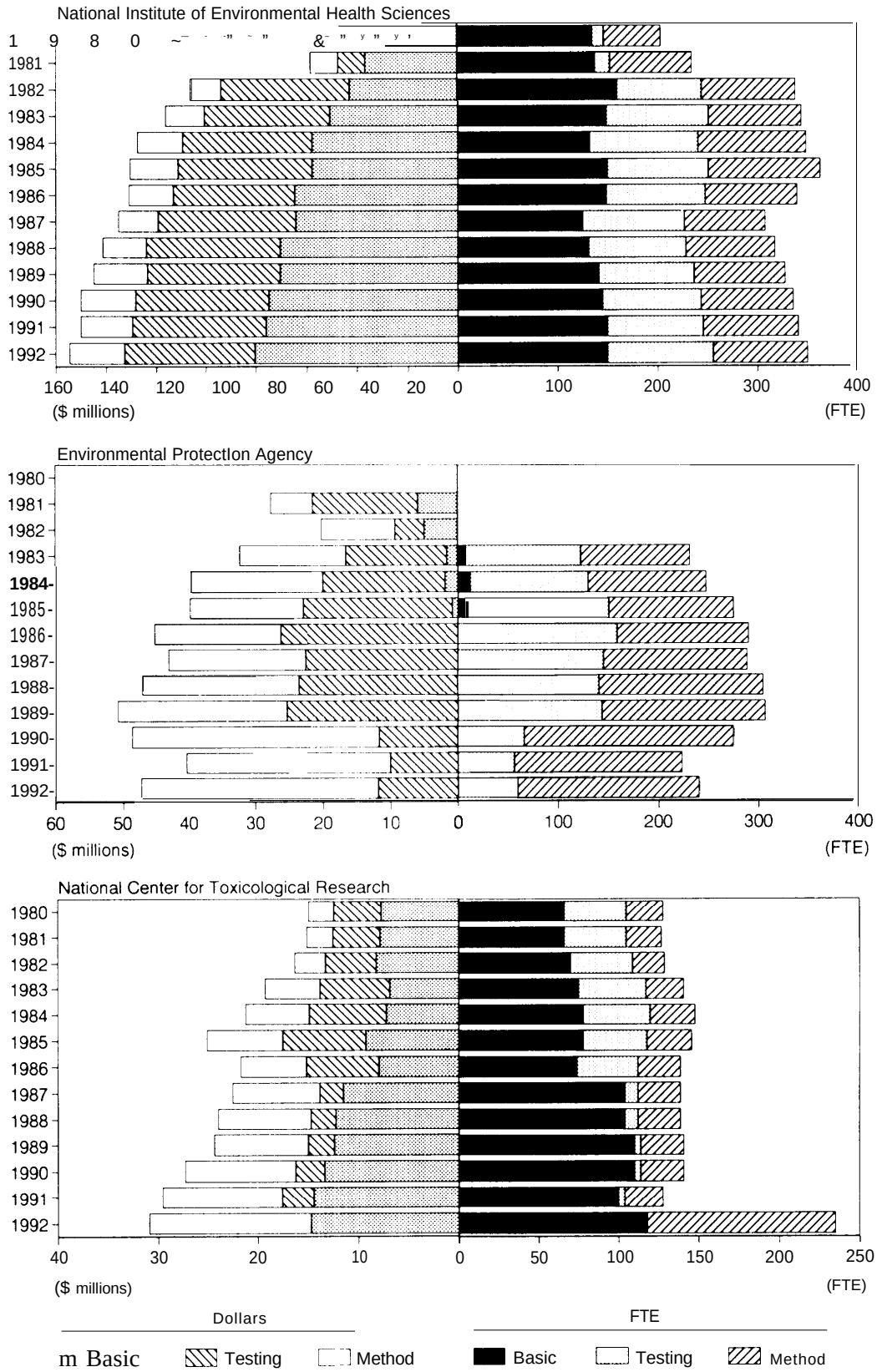
discrepancy between the 1992 and 1993 figures may result from different reporting methods: OTA based the FY 1993 estimates on the results of its agency survey, whereas the 1992 estimates are based on the results of the 1992 NTP review DHHS, DOE, and EPA research (U.S. DHHS, in press). The differences between the two tables illustrate the difficulties in obtaining accurate resource figures.

A consistently understudied area is human exposure measurement. Historically, exposure-related research efforts have concentrated on identifying the presence or determining the fate and transport of pollutants in various media. OTA's survey did not cover the entire range of Federal efforts allocated to human exposure measurements. However, EPA devoted about $6.7 million to such efforts in 1993, and the U.S. Department of Agriculture (USDA) allocated about $11 million for analyzing pesticide residues on produce.

As would be expected for activities as broad as risk assessment research, some fields of inquiry have received more funds, some fewer. However,

Figure 4-4-Federal Research Related to Chemical Toxicology, 1980-92
(In millions of dollars and full-time equivalents)





SOURCE: Office of Technology Assessment, 1993, based on data from Review of Current DHHS, DOE and EPA Research Related to Toxicology, Fiscal Years 1982 through 1991, National Toxicology Program, U.SDepartment of Health and Human Services.

Table 4-2A—Health Risk Research and Development Estimates, 1993
(In millions of dollars)

Agency	Health risk research*		Agency total: health or biomedical research**
	Total	Methods	
National institute of Environmental Health Sciences	129.0	14.0	251.2
Department of Energy	10.0'	3.0[a]	90.0'
Department of Defense	19.6	2.5[b]	300.0'
U.S. Department of Agriculture	11.5d	0.5[d]	11.5*
Agency for Toxic Substances and Disease Registry	16.9	0.0	16.9[nd]
Environmental Protection Agency	32.0	21.30	49.0[f]
Food and Drug Administration (other than NCTR)	13.oa	3.5[a]	13.0[nd]
National Center for Toxicological Research	33.6	7.6	38.92*
National institute for Occupational Safety and Health	49.0	6.1	49.0"
National Cancer institute	82.0[a]	4.4a	1,981.4
Other NIH	140.0[a]	2.2[a]	6,929.9
Alcohol, Drug Abuse, and Mental Health Administration	64.0[a]	O.O[a]	1,164.1
Total	600.6	65.1	10,894.5

a Estimate based on agency's 1992 funding for research on toxicology, as reported in the National Toxicology Program Review of current DHHS, DOE, and EPA Research Related to Toxicology, Fiscal Year, 1992.
b Calculated as 13 percent of agency R&D for health.
c Steinberg. 1993. *Journal of NIH Research* 5:35. Data on biomedical research, which excludes $210 million for breast cancer research.
d Data supplied by the U.S. Department of Agriculture, budgeted under expenses and not research and development.
e Research to reprove Health Risk Assessment program estimated to be $5 million; $21.3 million is sum of funding for human exposure, health effects, and risk assessment methods.
f Figure represents Health Effects Research Laboratory total budget: EPA-wide data are not available.
nd No data (research related to toxicology was used).
● Based on data from the OTA survey of agency resources.
● *U.S. Congress, CRS, 1993. Research and development funding: fiscal year 1993; issue brief (IB2062).

SOURCE: Office of Technology Assessment, 1993.

environmental health research funding has neither kept up with the increase in health research nor increases in environmental mandates that depend on that research for decisionmaking. Methodological research, in particular, seems inadequately supported, despite the most immediate promise that OTA sees for this research to improve risk assessment.

NATIONAL RESEARCH PRIORITIES

A complex interplay among social, economic, and scientific factors influences national research priorities. Depending on the political and social milieu of the Nation, Government research to protect the health of the public from environmental agents fluctuates between being more applied or more basic in nature. In response to the environmental and social activism of the 1960s and 1970s, policymakers called for the Government to play a larger role in applying the advances of research and development to achieving societal goals, including environmental protection and improved public health (Smith, 1990). In contrast, the Reagan Administration during the 1980s channeled research resources toward national security and basic science (Smith, 1990), Judging from the early budget figures, science policy in the Clinton Administration will return to emphasizing applied research and development (Long, 1993).

Mission-oriented research, a type of applied research, is directed toward identifiable ends related to meeting an agency's responsibilities. After World War II, mission-oriented research became established in agencies, and basic research tended to be located in universities (Smith, 1990; U.S. Congress, OTA, 1991). The role of the Federal Government in support of research grew as regulatory decisions became increasingly technical and complex, and more science-based expertise was needed for agency decisionmaking.

Table 4-2 B-Research Related to Toxicology, 1992
(In millions of dollars)

Agencv	Chemical Toxicology*		Agency total: health or biomedical research**
	Total	Methods	
National Institute of Environmental Health Sciences	154.6	22.0	251.6
Department of Energy	9.8	2.7	*90.09*
Department of Defense	15.0[b]	2.&	300.0[d]
U.S. Department of Agriculture	11 .8[e]	O.5[c]	11 .8[f]
Agency for Toxic Substances and Disease Registry	17.5	0.0	17.5~
Environmental Protection **Agency**	47.3	35.4	47.3[nd]
Food and Drug Administration (other than NCTR)	12.5	3.5	12.5[nd]
National Center for Toxicological Research	30.9	16.2	30.@
National Institute for Occupational Safety and Health	4.4	2.7	4.4[nd]
National Cancer Institute	82.0	4.4	1,947.6
Other NIH	139.7	2.2	6,729.8
Alcohol, Drug Abuse, and Mental Health Administration	64.0	0.0	1,131.4
Total	589.5	91.6	10,574,8

a Estimate is based on personal communication.
b The Army portion is estimated using 1993 data from Department of Defense.
c Calculated as 13 percent of agency research and development for health, based on earlier allocations.
d Steinberg. 1993. *Journal of NIH Research* 5:35. Data on biomedical research, which excludes $25 million for breast cancer research.
e Data supplied by U.S. Department of Agriculture, budgeted under expenses and not research and development.
f N. data available. Health risk R&D used. USDA FY 1991 health R&Dis$115 million, from NIH databook.
nd No data (research related to toxicology was used).
● Review of current DHHS, DOE, and EPA Research Related to Toxicology, Fiscal Year 1992, National Toxicology Program, U.S. Department of Health and Human Services.
● *U.S. Congress, CRS, 1993. Research and development funding: fiscal year 1993; issue brief (IB2062).

SOURCE: Office of Technology Assessment, 1993.

Under congressional direction, agencies pursued research to support a ‘‘scientific base for public policy, ” with EPA emerging as ‘‘the epitome of the new expert agency” (Jasanoff, 1990).

Many of the researchers surveyed by OTA claim that Federal funding, divided between applied and basic research, allows risk assessment research “to slip through the cracks.” Consequently, most research efforts to improve risk assessment have inadequate support. No study section at the National Institutes of Health, for example, reviews proposals for health risk assessment research. At a more general level, few funding opportunities exist for multidisciplinary collaborations among basic and applied scientists, despite the acknowledged need for such endeavors to make risk assessment research more effective (U.S. DHHS, 1991c).

Below the surface of the debate over the balance between basic and applied research lie questions about the objective and nature of the research on risk assessment that the Government should be supporting and conducting. The environmental movement of the 1960s, for example, stimulated intense Federal efforts to identify pollutants that can affect human health and the environment. As a result, NTP was established to set national priorities for toxicity testing (U.S. DHHS, 1991a), and both supporters and critics of the program consider it the Nation’s premier testing program (Moolenaar, 1992; Ringen, 1992).

If tests of a commercially important substance reveal that hazards exist, manufacturers or users who want to retain the commercial uses for the substance may perform additional research to clarify the nature of the hazard and support quantitative risk assessment. In efforts to shift research priorities, some scientists and industry spokespersons have called for the Government to conduct more research on the mechanisms of toxicity (Abelson, 1993; Gori, 1992; Moolenaa, 1992). Such a controversy currently surrounds the

proposed directing of NTP research away from toxicity testing and rodent bioassays and toward studies on such mechanisms (U.S. DHHS, 1992). As the debate is framed, toxicity tests, on the one hand, can identify potential hazards to public health, which can trigger intervention strategies designed to prevent exposures to the agent. On the other hand, mechanistic studies can determine the applicability of the results of toxicity tests to predict human risks from exposure.

The debate suggests that these types of research —toxicity testing and mechanistic research— have necessarily mutually exclusive objectives, that resources can be used for either type of research but not both. In fact, the NTP Board of Scientific Counselors concluded that these research activities can be integrated to complement each other (U.S. DHHS, NTP, 1992). The results of toxicity studies often illuminate fruitful avenues of mechanistic research. Similarly, data from mechanistic studies can illuminate the implications for human health risk of the results from toxicity testing. In addition, mechanistic research provides a foundation for identifying untested chemicals and chemical classes for toxicity testing.

The debate over the role of Government research does not end at NTP. Related discussions are heard concerning the research priorities of NTEHS, NCTR, and EPA.

Setting National Priorities

In the past, the United States has embarked on national multiagency efforts in public health. Some were strikingly successful; others were not. As part of a worldwide campaign, this country aggressively attacked the childhood scourges smallpox and polio, culminating in the complete eradication of smallpox and the virtual eradication of polio. The U.S. ‘‘wars’ on cancer in the 1970s (Epstein, 1979) and AIDS in the 1980s (Joseph, 1992), however, produced less tangible results, but those consequences may be more a reflection of the complexities of those diseases than of the Federal effort. Generally, the scientific process is difficult to reconcile with a war mentality. Science proceeds in discreet, incremental, and often publicly imperceptible steps confounded by missteps and mistaken paths (Kuhn, 1962). Moreover, the most brilliant technological breakthroughs often are not planned; recombinant DNA techniques revolutionized cancer biology, but they were not anticipated in the detailed planning that went into the war on cancer. Still, although cancer and AIDS are problems that currently lack solutions, indisputable progress has been made in both cases. Indeed, the recent advances in the molecular biology of cancer, for example, offer promise and optimism unimagined in the “war years” (Barrett, 1993).

Arguably, the President has the most influence in setting national priorities for research at the agencies. With a variety of administrative tools, such as executive orders (Olson, 1984), the President can emphasize or reemphasize certain areas of scientific research. The increased research on cancer in the 1970s, for example, stemmed from presidential efforts (Epstein, 1979; Rushefsky, 1986).

Related to presidential influence, the degree of centralized authority at the national level has implications for implementing a national research effort. A centralized program, often a multiagency activity coordinated through a central authority such as the Executive Office of the President, provides focus and direction, but the agencies lose a portion of their authority. A decentralized effort, in contrast, gives the agencies more autonomy but the objectives can be less defined, the effort more fragmented, and the goals of the agencies given more importance than goals of the effort.

In centralizing research efforts, the President has at his command several administrative processes to set national priorities. The Federal Coordinating Council on Science, Engineering, and Technology (FCCSET), which the Bush Administration greatly strengthened, serves as the Federal Government’s focal point for setting

priorities within the executive branch. Overseen by the White House Office of Science and Technology Policy, FCCSET policymakers and scientists from various research agencies operate in specialized subcommittees and working groups, directed at specific problems. Under D. Allan Bromley, President Bush's science adviser, FCCSET conducted ''crosscuts, ' in which an interagency committee inventors Federal activities and establishes objectives and priorities for coordinating basic and applied research in high-impact areas, Some examples include research on global change, high-performance computing and communications, mathematics and science education, advanced materials and processing, and biotechnology (Bromley, 1992).

FCCSET in 1991 and 1992 had some focus on health risk assessment research: its Subcommittee on Risk Assessment of the Committee on Life Sciences began an effort to identify future health risk assessment research needs. Although this activity was not aimed at coordinating research projects, the activities of the subcommittee were a first step in creating an inventory of ongoing research, which could be useful in future coordinating efforts. A research inventory would have allowed FCCSET members to identify redundant research, areas of little or no activity, and research efforts that could be usefully integrated across agencies. However, this project apparently has been put quietly to rest with the transition to the Clinton Administration. OTA carried out a similar survey as part of this assessment (see ch. 3).

According to the National Performance Review, the Clinton Administration is planning to eliminate FCCSET. In its place, the White House will coordinate agency research programs through a new National Science and Technology Council. This new council combines FCCSET with the National Materials Council and the National Space Council, but it will remain within the Office of Science and Technology Policy (Hanson et al., 1993).

The Office of Management and Budget (OMB) also influences executive branch decisions concerning science priorities. Through its review function, OMB can delay research and regulatory activity (Olson, 1984). For example, OMB currently reviews proposed Federal research involving human subjects. In many cases, the resulting delay effectively diminished or even halted research in certain areas, such as in the use of questionnaires in epidemiologic research (Lilienfeld, 1993).

The legislative branch also sets and influences national research priorities. Congressional members and committees charged with responsibility for broad areas, such as environmental protection or public health, may influence the direction of research in those areas through legislation, appropriations, or reports. Similarly, congressional research agencies such as the General Accounting Office or OTA can affect national priorities through their analyses of related issues. For example, congressional representatives (Brown, 1993) and congressional reports (e.g., U.S. Congress, OTA, 1991; U.S. Congress, House Committee on Science, Space, and Technology, 1992) recently suggested changes in U.S. research policy that would link research more tangibly to national goals.

When a particular topic is designated a national research priority, it is accorded leadership at the highest echelons of government, strategic initiatives that span many Federal agencies, and resources that are commensurate with the magnitude of the problem. Health risk assessment research possesses none of those hallmarks. Moreover, OTA did not find a systematic, national multiagency process for setting research priorities for improving health risk assessments. Apparently, the FCCSET subcommittee on risk assessment research needs will not release the results of its survey of Federal research efforts. As a result, that effort has had little impact, if any, on the direction of research. Some observers and participants remain sanguine about the FCCSET process, but the predictions that the research needs study will end without a product are strong counter arguments, The proposed

National Science and Technology Council is designed to have more "teeth" than FCCSET (Hansen et al., 1993).

In examining agency research, OTA found that Federal research on health risk assessment, as a whole, is largely decentralized. Agencies have different priorities because they have different legislative mandates and missions. Within agencies and departments, risk assessment research programs conduct research in support of their parent organizations. This behavior parallels that seen for environmental research and development (Schaefer, 1991; Carnegie Commission, 1992) and for the Federal research and development effort in general (U.S. Congress, OTA, 1991). Leadership from the White House or Congress could improve health risk assessment research by bringing cohesion and focus to research goals.

As pointed out in chapter 2, more than 50 assumptions have been identified that are used in risk assessments. Use of those untested assumptions underlines the promise of research to illuminate some of the areas of current ignorance. A coordinated effort, for example, could determine the extent to which research can reduce the dependence on assumptions. More than a decade has passed since the NRC report, and research efforts have expanded on some of these, but priority-setting to increase the impact of research does not exist. Assumptions that can be replaced by research need to be distinguished from assumptions that cannot be replaced by research.

AGENCY PRIORITIES

An agency's risk assessment research depends on priorities in its mission, its enabling legislation (table 4-3), and court decisions. In line with their missions, the agencies that conduct research related to risk assessment can be separated into those with responsibilities for risk management (regulatory agencies) and those without such responsibilities (research agencies). Risk management, as described in chapter 5, integrates and synthesizes myriad information (such as economic, political, and technological factors) along with risk assessments, to set, implement, and enforce regulatory standards (NRC, 1983).

Research at the regulatory agencies, especially at EPA, the Occupational Safety and Health Administration (OSHA), Consumer Product Safety Commission (CPSC), and FDA, is mostly driven by regulatory needs, as mandated by congress. Regulatory agencies need chemical-specific data to set standards and establish priorities for rulemaking (Rosenthal et al., 1992). EPA's authority to conduct environmental health research derives mainly from the major Federal laws protecting public health and the environment. The research programs of its Health Effects Research Laboratory (HERL) are mandated in at least six major pieces of legislation, and funding is appropriated on a medium-specific basis.[5] By requiring EPA to protect public health, the statutes give the agency discretionary authority to conduct research on health effects.[6]

Although the Occupational Safety and Health Administration (OSHA) is not required under the Occupational Safety and Health Act (OSH Act) to conduct risk assessments, a U.S. Supreme Court decision on workplace exposure to benzene requires OSHA to determine whether risks are "significant" before imposing regulation.[7] Risk

[5] The research programs are mandated under one of the following: Clean Air Act; Safe Drinking Water Act; Federal Insecticide, Fungicide, and Rodenticide Act; Toxic Substances Control Act; Comprehensive Environmental Response, Compensating and Liability Act; or Resource Conservation and Recovery Act (U.S. Congress, CRS, 1993).

[6] The Environmental Research and Development Demonstration Act (ERDDA) of 1976 brought EPA's research programs under a single mandate, but authorization for it ended in 1981 (U.S. Congress, CRS, 1993). Recently, the Subcommittee on Technology, Environment, and Aviation of the House Science, Space, and Technology Committee has been developing the Environmental Research, Development and Demonstration Act of 1993 (H.R. 1994).

[7] OSHA does not perform risk assessment research (Martonik, 1992). The National Institute for Occupational Safety and Health, the research arm of OSHA, conducts studies on workplace agents that affect worker safety and health (Mintz, 1984).

assessment is the method OSHA uses in making that determination (Mintz, 1984).[8] The OSHAct stipulates that the National Institute for Occupational Safety and Health (NIOSH) would conduct heath effects research for OSHA rulemaking (P.L. 91-596).

Among the Federal agencies, DHHS has the broadest set of research responsibilities for investigating possible health risks. Within DHHS, are the research agencies of the Public Health Service—specifically, NIEHS, NCI, NCTR, NIOSH, and the Agency for Toxic Substances and Disease Registry (ATSDR) (see app. B). The charters of these agencies mandate a research mission.

The Departments of Defense (DOD) and Energy (DOE) are neither regulatory agencies nor public health research agencies. However, they perform and support research on health risks as part of their risk management responsibilities (Macys, 1993; U.S. DOE, 1991).

To gain insight into agency research priorities, OTA examined the funding and FTEs as a percentage of the total contribution to research in toxicology by NIEHS, NCI, NCTR, EPA, and CFSAN, as reported in the NTP review.[9] This additional analysis attempts to get a snapshot of the trends in resource allocation to the three areas of toxicological research-methodological, basic, and chemical-specific data development, by the agencies most active in this research. As shown in figure 4-5A, the agency resources are presented as percentages of the total for the years 1982, 1986, and 1991. For these agencies in those years, funding for basic research increased from 41 to 53 percent, toxicology testing declined from 45 to 24 percent, and methodologic research increased from 14 to 22 percent. Figure 4-5B provides a snapshot for the intramural researchers at the agencies and the nature of their research. In 1991, 39 percent of the full-time equivalents (FTEs) were conducting basic research, 24 percent in testing, and 34 percent in methods research. The relative proportions of FTEs to funding in dollars suggests that most basic toxicological research is supported by extramural grants, whereas most methodological research is conducted in intramural research.

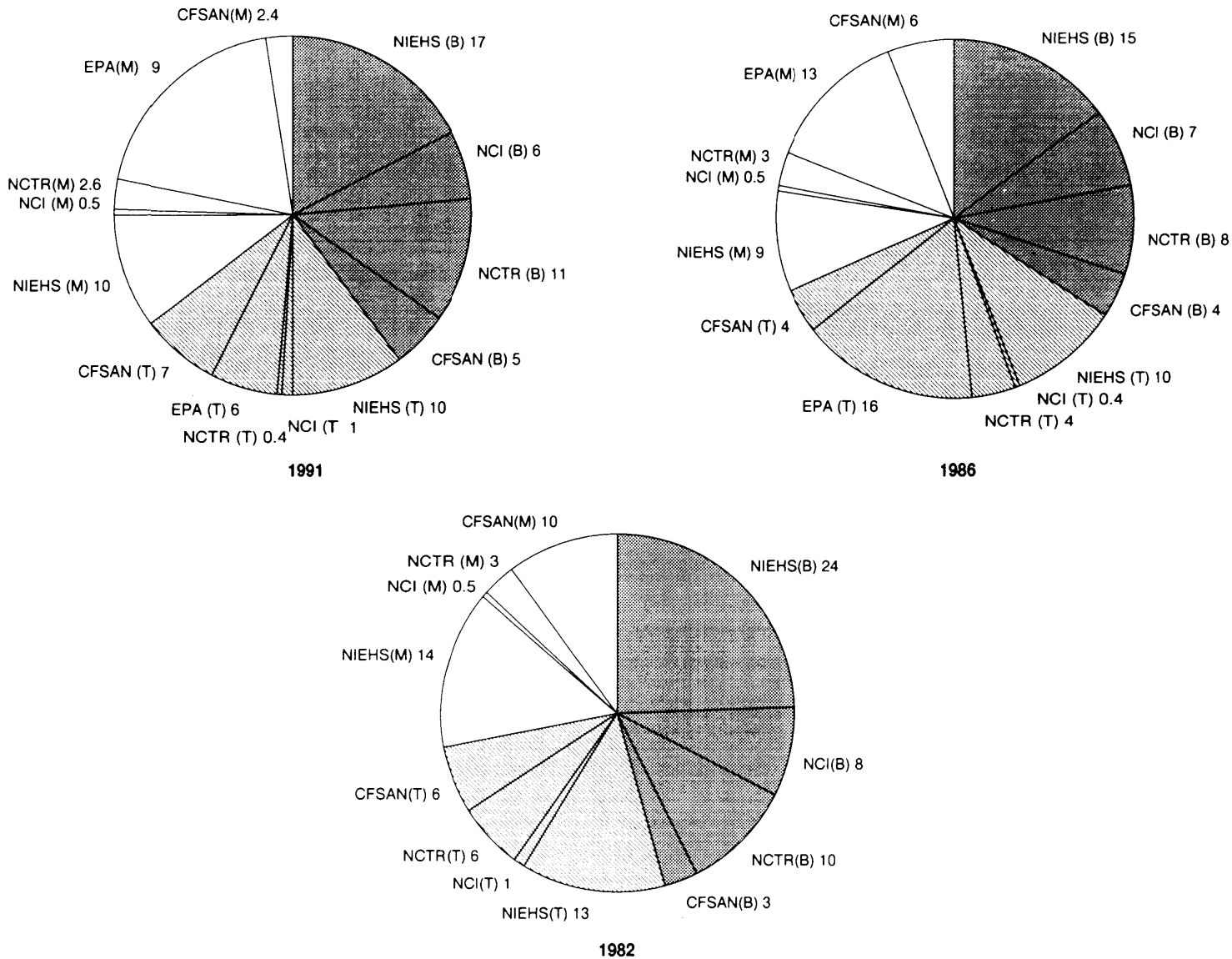
OTA estimates that in 1993 the agencies will spend nearly $600 million on health risk research, but that only $65 million of that total will be spent on methodological research. Even considering that these estimates are based on agency definitions of research, methodological research receives disproportionately less than the other areas of research. In times of restricted resources and in the wake of congressional imperatives, the agencies tend to maintain their existing core programs. Thus, regulatory agencies focus on chemical-specific data development, and research agencies perform basic research. Methodological research remains marginalized in the process.

A variety of reasons can be forwarded to explain the relative neglect of methods research. Incorporating the results of research into policy requires overcoming substantial bureaucratic hurdles and usually necessitates some sort of scientific consensus on an issue. (Chapter 5 discusses the difficulties in changing agency policy.) Furthermore, agencies-especially regulatory agencies, which are bureaucratic by nature and slow in responding to changes—must gain the acceptance of the scientific community before they adopt new methodologies (Jasanoff, 1990; Rosenthal et al., 1992). That sort of support is crucial to providing credibility to new policies. Moreover, methodological research requires validation with experimental data, an activity to which agencies allocate few resources. These obstacles to the use

[8] The 1981 U.S. Supreme Court decision on OSHA's workplace standard for benzene states that rulemaking must protect workers from ' 'significant' risk. Significance under the Occupational Safety and Health Act has since been interpreted by OSHA to be one adverse effect, such as cancer, in 1,000 workers (Mintz, 1984; Rodericks et al., 1987).

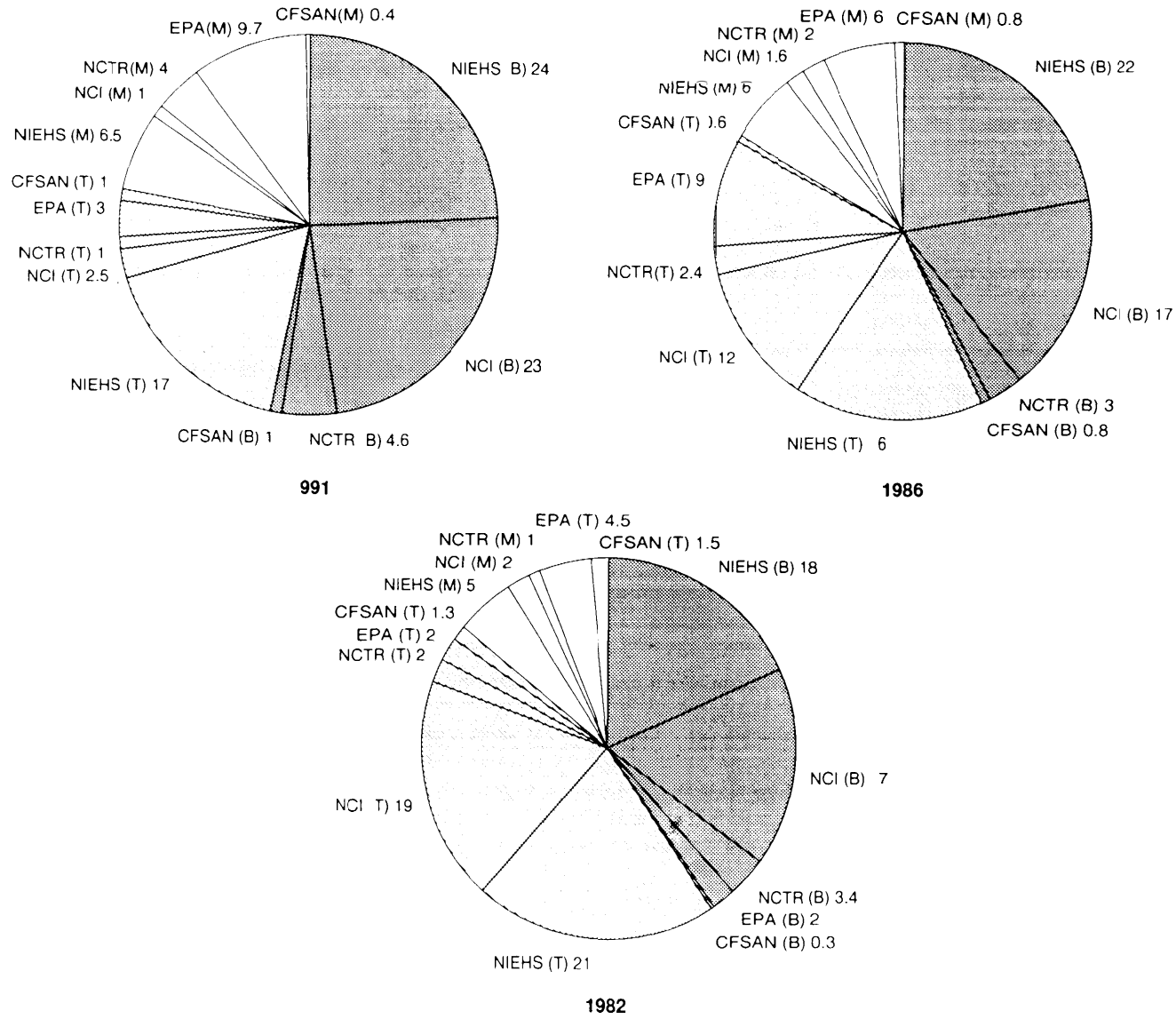
[9] OTA did not include the resources of NIOSH in this analysis because their support reported to NTP are resources committed to the NTP program and is not representative of the total NIOSH contribution to this research.

Figure 4-5A—Agency Shares of Health Risk Research by Research Area, 1982, 1986, and 1991 (Funding in Dollars)



SOURCE: Office of Technology Assessment, 1993, based on data from Review of Current DHHS, DOE, and EPA Research Related to Toxicology, Fiscal Years 1982, 1986, and 1991. National Toxicology Program, U.S. Department of Health and Human Services.

Figure 4-5B—Agency Shares of Health Risk Research by Research Area, 1982, 1986, and 1991 (Personnel in Full-Time Equivalent)



SOURCE: Office of Technology Assessment, 1993, based on data from Review of Current DHHS, DOE, and EPA Research Related to Toxicology, Fiscal Years 1982, 1986, and 199' National Toxicology Program, U.S. Department of Health and Human Services.

Table 4-&Key Features of Federal Laws Regulating Toxic Substances

Statute	Regulatory authority (regulatory agency)	Toxic substance or effect of concern
Part I--Licensing Laws		
Federal Food, Drug, and Cosmetic Act	Control levels of added substances (FDA)	"Any poisonous or deleterious substance which may render it injurious to health"
	Control levels of natural components of food (FDA)	"Poisonous or deleterious . . . does not ordinarily render it injurious to health"
	Control levels of environmental contaminants (FDA)	"Poisonous or deleterious . . . does not ordinarily render it injurious to healh"
	Set (EPA) and enforce (FDA, USDA) tolerances for pesticide residues on food and feed crops	"Poisonous or deleterious. . . not general recognized as safe for use . . . to the extent necessary to protect the public healh"
	Regulate introduction of new drugs and biologics (FDA)	"Substantial evidence at safe and effective:" no "imminent hazard to public health"
	Report on adverse reactions to drugs (FDA)	"Any adverse experience . . . includes any side effect, injury, toxicity, or sensitivity reaction"
	Label cosmetics (FDA)	"Poisonous or deleterious . . . may render it injurious"
Federal Insecticide, Fungicide, and Rodenticide Act	Register pesticides (EPA)	Will not generally cause any unreasonable risk to man or the environment"
Toxic Substances Control Act	Require testing of existing chemicals where data are inadequate to assess risk (sec. 4); prohibit introduction into commerce of chemicals that will present an unreasonable risk (sec. 5); restrict or prevent production, use, or disposal of existing chemicals that present unreasonable risk (sec. 6) (EPA)	Unreasonable risk of injury to human health or the environment. . . includ[ing] carcinogenesis, mutagenesis, teratogenesis, behavioral disorders, cumulative or synergistic effects, and any other effect . . ."
Part I~tandard-setting Laws		
Clean Air Act	Conduct research on air pollution (EPA)	"Adverse effects on health, including, but not limited to, behavioral, physiological, toxicological, and biochemical effects"
	Set air quality standards; regulate emissions of hazardous air pollutants; set standards for vehicle emissions, fuels, and fuel additives (EPA)	"Endanger public health"

Federal Water Pollution Control Act; Clean Water Act	Set effluent standards for water; establish water quality criteria (EPA)	"Identifiable effects on health and welfare"
Safe Drinking Water Act	Set MCLs and MCLGs for public drinking water supplies (EPA)	"May have an adverse effect on the health of persons"
Consumer Product Safety Act	Promulgate consumer product safety standards (CPSC)	"An unreasonable risk of injury"
Federal Hazardous Substances Act	Ban hazardous substances for household use (CPSC)	"Toxic . . . may cause substantial personal injury or substantial illness"
Federal Mine Safety and Health Act	Set standards for airborne contaminants in mines (MSHA)	"Protection of life and prevention of injuries. . . material impairment of health or functional capacity"
Occupational Safety and Health Act	Set standards for airborne contaminants in the workplace (OSHA)	"Material impairment of health or functional capacity"
Part 111-Control-Oriented Laws		
Comprehensive Environmental Response, Compensation, and Liability Act; Superfund Amendments and Reauthorization Act	Fund cleanup of hazardous waste sites; designate reportable quantities for environmental release; report on community preparedness and release; prepare toxicity profiles on contaminants (EPA)	"Substantial danger to the public health or welfare"
Controlled Substances Act	Control drugs that have potential for abuse (USDJ, FDA)	"Substantial and detrimental effect"
Lead-Based Paint Poisoning Prevention Act	Determine, if possible, a safe level of lead in paint (CPSC)	Poisoning of children by lead-based paint
Marine Protection, Research, and Sanctuaries Act	Regulate ocean dumping (EPA)	"Adversely affect human heath, welfare or amenities"
Poison Prevention Packaging Act	Promulgate standards for packaging substances that could produce effects of concern (CPSC)	"Serious personal injury or serious illness"
Resource Conservation and Recovery Act	Regulate the handling of hazardous wastes; list hazardous wastes on basis of constituents (EPA)	"Protect human health . . . serious irreversible or incapacitating reversible illness . . . substantial present or potential hazard"

NOTES: FDA - Food and Drug Administration; EPA. Environmental Protection Agency; USDA. U.S. Department of Agriculture; USDJ. U.S. Department of Justice; CPSC. Consumer Product Safety Commission; MSHA - Mine Safety and Health Administration; OSHA - Occupational Safety and Health Administration; MCL - maximum contaminant level; MCLG - maximum contaminant level goal.

SOURCE: Office of Technology Assessment, 1993.

of the results raises important questions about the usefulness of methodological research and its likely impact on policy.

Bureaucratic reluctance to accept new methods provides an especially strong disincentive for researchers. Why do the work if it is likely to be ignored. Individual promotions and advancement in the scientific community are predicated on research output and visibility. As a result, researchers either conduct chemical-specific research, which responds directly to agency needs, or basic research, which is held in higher esteem in the scientific community and is likely to be published in more prestigious scientific journals. Taken all together, there are few incentives for a researcher to conduct methodological research: the agencies consider it a secondary priority and allocate fewer resources to it, and the results of the work face substantial hurdles before being incorporated into agency practice or being accepted by the scientific community.

In addition to the mission of an agency and its enabling legislation, each agency has its own "culture' as well, which is a powerful determinant of future research directions (Yosie, 1987; Zimmerman, 1990). The collective knowledge of agency personnel often governs the ''way things are done, " reflecting the style of the agency's management (U.S. Congress, OTA, 1991; Wilson, 1989). Moreover, the composition and professional interests of an agency's work force can influence research priorities. NIEHS affords an example of the role agency culture can play in establishing the direction of research. Because scientists at that institute consider themselves basic scientists, some of them have a certain disdain for the more applied research needed for regulatory decisionmaking (Stone, 1993). Consequently, those scientists rebelled in 1992 during the agency's reorganizing and reordering of its priorities, which required it to conduct more applied research; the tension from that confrontation resulted in some scientists leaving NIEHS. Over the long term, the effects of NIEHS's new structure and direction remain to be seen.

PROGRAMMATIC PRIORITIES AND PROGRAM MANAGEMENT

An agency usually divides its research into programs or divisions of researchers who share a common discipline or objectives. For risk assessment research, the disciplinary distinctions are often found in the disciplines of the environmental health sciences—for example, EPA's HERL has programs in, among other areas, neurotoxicology, immunotoxicology, genetic toxicology, and reproductive and developmental toxicology. Rarely, do Federal programs cut across disciplines; the exceptions include EPA's Research to Improve Health Risk Assessment program and NTEHS's Laboratory of Biochemical Risk Analysis.

Setting priorities at the program level is generally a more developed-that is, both a more systematic and more formal-process than at the agency or national levels. Generally, one of two distinct types of management methods is used to determine program priorities for individual research projects (U.S. Congress, OTA, 1991). One style, termed 'bottom-up, " allows research ideas and priorities to originate with individual researchers, who communicate those ideas to their superiors or to grant managers. As ideas rise through intermediate levels of management to the upper tier of program decisionmakers, the better and more important proposals are selected. In contrast, "top-down" management has the most senior decisionmakers in an agency deciding the priorities for research. Those directives are transmitted down the organizational ladder in consultation with managers, eventually reaching researchers.

OTA observed both styles of management in its survey of risk assessment research, as well as a mixture of styles, which is consistent with federally funded science in general (U.S. Congress, OTA, 1991). At DOD, managers at all levels exert a great deal of influence in selecting and funding projects. But research agencies such as NIEHS and NCI employ mostly bottom-up management,

with individual researchers initiating projects and influencing the directions of research. The styles of EPA and DOE are a mixture of the two: priority-setting is responsive to the choices of top management but also provides an opportunity for initiative by individual investigators. The management style of an agency mirrors its research needs and whether it has risk management responsibilities, Agencies that use the results of research for decisionmaking require data for their short-term regulatory needs and rely on top-down approaches to engender those data. In contrast, agencies seeking to expand the scientific knowledge base support investigator-initiated projects.

ADMINISTRATIVE TOOLS FOR PRIORITY-SETTING

Changes in leadership often alters an agency's objectives and organization. New directors took over the reins of NIEHS in 1991, and EPA and National Institutes of Health (NIH) in 1993, and FDA is completing its search for a new director of NCTR. Those new leaders are restructuring or will restructure their agencies along the lines laid down by the larger Government organization to which they are responsible. A past example of such leadership is the former director of the NIH, who initiated strategic planning for the institutes (Healy, 1992). All of the institutes within NIH, including NIEHS, were developing strategic plans for future priorities, but the future of this initiative is now very much in doubt. What is clear is that initiatives launched and policies set by a new director of NIH will influence NIEHS'S future.

Restructuring occurs under new directors and under established directors when conditions, needs, or wants dictate. At the agency level, NIEHS's new director has restructured programs following consultation with advisory panels (Olden, 1992). A new FDA commissioner restructured the Center for Food Safety and Nutrition and gave NCTR the mandate to integrate its research activity more closely with FDA's regulatory needs.

Yet even though agency directors can influence, shape, and promote research priorities, they must solicit scientific, technical, and stakeholder opinions to satisfy procedural rules and maintain credibility, not only within the agency but also the scientific community and other agencies in the Federal Government. Agencies have a variety of common administrative tools for establishing the directions their research will take.

Use of Advisory Committees

To change directions or to set new policy, agency directors often employ outside experts to evaluate research programs and recommend policy shifts (Smith, 1992; Zimmerman, 1990). Internally, the agencies also receive advice from institutional committees established as science advisers. Expert committees, which can be set on a continuing or ad hoc basis, provide scientific credibility for administrative decisions (Jasanoff, 1990; Smith, 1992). Carrying out the recommendations of these external and internal advisory panels remains more problematic.

EPA uses a variety of established and ad hoc advisory committees to assist it in setting priorities for research. The role of EPA's Science Advisory Board has expanded from that of an independent technical reviewer of EPA documents to include advising on science policy (Jasanoff, 1990; Yosie, 1991; Smith, 1992). When it was formed in the early 1970s, the board was meant to function as an external review body located in the Office of Research and Development. In 1976, however, it was relocated (and organizationally ''elevated") to the Office of the Administrator (Yosie, 1991).[10]

EPA committees have released documents recently that have proved influential in agency actions. Among the 10 committees of the Science Advisory Board (SAB), the Research Strategies

10 The 1978 Environmental Research and Development, Demonstration Act codified the board's mission and mandated that the Science Advisory Board report directly to the administrator (42 U.S.C. 4365 (a)(c)(e)).

Advisory Committee examines scientific issues and problems that cut across the agency's many offices and sets research priorities (Barnes, 1992). In 1988 and 1990, the Committee released two influential documents, both of which concluded that EPA should set priorities for its research and regulatory programs based on magnitudes of risk (U.S. EPA, SAB, 1988, 1990). (On a much more defined level, the EPA SAB provides advice about such discrete problems as indoor and waterborne radon; see chapter 6.) In addition to SAB, EPA forms expert panels for specific purposes, such as the ad hoc 'blue-ribbon' panel of outside experts that is evaluating EPA's science base. The panel's report concluded that the agency's science programs should be given greater visibility and access to agency administrators (U.S. EPA, 1992).

NIEHS also employs outside experts in environmental health on its Boards of Scientific Counselors to evaluate priorities and research directions. Three such boards and several subboards retrospectively reviews the science of the institute and other agency matters (Olden, 1992; Griesemer, 1992; Schwetz, 1992; Tennant, 1992). For example, the institute based its recent restructuring on extensive meetings with those permanent and ad hoc advisory councils and boards. In an attempt to be responsive to the public as well as the scientific community, NIEHS administrators are also holding meetings with public organizations across the country and are pursuing discussions with congressional representatives (Olden, 1993).

To understand the relative importance of a particular field of study, NIEHS convenes various consensus conferences and workshops. The 1991 House Appropriations Bill directed the advisory council for NIEHS to identify those environmental problems threatening public health over the coming decade. In response to the congressional mandate, the council formed the Fourth Task Force for Research Planning in the Environmental Health Sciences (U.S. DHHS, 1991c). The task force identified and characterized the areas of particular challenge and promise in the environmental health sciences and influenced the ''big-picture" directions of the agency (Olden, 1992; U.S. DHHS, 1991c).

Outside experts are important to the workings of other agencies as well. In addition to the regular meetings of NCI's directors and associate directors, the agency uses the recommendations of the National Cancer Advisory Board to help set priorities. (The board's membership includes representatives from EPA, NIEHS, NCI, OSHA, and other agencies.) Moreover, an external advisory board triggered the reorganization at NCTR. The Edwards Commission report on FDA provided the background for reconciling investigator-initiated research at NCTR with the regulatory needs of FDA (U.S. DHHS, 1991 b). The agency redesigned its Science Policy Committee in 1992 to address the scientific issues arising from its new priorities (Anson, 1993).

Funding Mechanisms

Agencies have a number of mechanisms by which to fund research projects. Resources can be allocated through intramural or extramural grants, cooperative agreements, contracts, and in-house work (Jasanoff, 1990; U.S. Congress, OTA, 1991).

Grants and contracts are largely used to fund extramural research done at locations other than Federal facilities. Agencies often use a two-tiered process in determining which grant applications will be funded. They select applications for funding based on the scientific and technical 'merits' of the work, as determined by peer review.[11] The product of a peer review of grant proposals is a priority score, by which that proposal can be ranked with others. By design, peer review is supposed to be a self-regulatory

[11] Peer review is a process by which scientists involved in an area of research judge the scientific merit, technical competence, and significance of proposals by their professional peers. In general, peer-review is conducted by better known and more successful scientists.

process for scientists that obviates the need for external controls (Jasanoff, 1990). Although peer review possesses a variety of positive attributes that undoubtedly contributes to this country's scientific and technological successes, nonetheless, the process has several faults, such as inconsistency and the inability to guarantee quality in science (Jasanoff, 1990; US Congress, OTA, 1991).

Determination of mission relevance is the second tier of review. It can justify shifting resources to particular areas of research that may not earn the highest marks in peer review. Such alterations are unusual, even rare, in basic research. They do occur, however. NIEHS, for example, may redirect funds to projects that receive less favorable priority scores if the areas of research need further development or appear particularly promising (Olden, 1992). ultimately, grant-sponsoring agencies are accountable to Congress; thus, both scientific and political factors are incorporated into decisions on grants.

Agencies also use contracts to support work of a specific, technical nature. Contract proposals do not undergo the type of peer review used for grants applications. Even though many contract proposals go through a competitive bid and selection process, the process can lend itself to abuse. For example, EPA has been criticized for its extensive use and mismanagement of the contracts process (U.S. Congress, GAO, 1992).

Extramural funding by an agency—for example, to individual university investigators—represents an effort to provide national leadership in a field of study. Extramural grants are used to support university research and as seed money to develop fields of research. In reality, some fields of research are almost completely dependent on Federal support. Generally, basic research, which can have long-term payoffs, is seen as especially deserving of Federal support. Many investigators interviewed by OTA commented that extramural funding for risk assessment research is inadequate because the research is considered too applied to be supported by basic research funds and too basic for applied research funds. Extramural funding for risk assessment research also tends to be unstable, which may result in researchers being forced to leave the field and new researchers being dissuaded from entering because of the limited resources. The largest extramural programs in health risk assessment research are at NIEHS and NCI; to a smaller extent, EPA's Research to Improve Health Risk Assessment program (RIHRA) funds university researchers (Adamson, 1992; Olden, 1992; Vandenberg, 1992).

The process for funding internal projects differs because the objectives of intramural research often differ from the objectives of extramural programs. An agency will support internal projects provided it has the expertise and the resources. Usually, internal projects are more closely tied to the agency's mission and are more limited in their scope.

A variety of funding mechanisms allow agencies to collaborate with other institutions and organizations on projects, sharing resources and avoiding any duplication of efforts. These mechanisms include memoranda of understanding between and among agencies and cooperative agreements to foster collaborations between the government and universities or private institutions. NIEHS, for example, has a memorandum of understanding with NIOSH for collaborative research in epidemiology and risk assessment of occupational hazards.

Targeting Risk Assessment Research

Agencies use targeted research to direct resources to areas of highest priority. In broad terms, targeted research is designed to solve a specific problem or meet an objective set in advance by an agency or by congressional imperative. In the context of this report, research can be targeted to areas likely to have the greatest impact on policy and decisionmaking. Targeted research is a tool that can be used to link research to the decisionmaking process.

Targeted research on health risks is especially appropriate for regulatory agencies that use risk assessment to develop standards, guidelines, and regulations. It is also appropriate for agencies like DOD and DOE that have research capability as well as an operational investment in the outcome of research-in the form of cleanup programs designed to reduce risk.

Targeted research is especially useful for filling gaps in the data required for specific risk assessments and, more generically, for developing new methods of performing risk assessment. It should not be confused with "mandated" or ''manager-directed research, in which the scope and methods of a research project are dictated in advance by the managers of an agency. Such projects are less likely to undergo peer review and be awarded competitively.

Frequently people think of targeted research as synonymous with applied research, but targeted research can be either basic or applied, as long as its goal is to meet an agency's established objective. The Human Genome Project of the NIH/DOE is an example of targeted research that is basic in orientation. As defined by OTA in this report, targeted research is linked to a specific goal; thus, terms such as "directed," "identified," or "prioritized" research are also appropriate. Any of those terms expands the concept of targeted research beyond the narrow connotation of applied research.

The most familiar method for Federal agencies to target research is Requests for Proposals issued to the scientific community to solicit research intended to address a specific problem. Scientists inside or outside the agency prepare competitive applications detailing how they would study the problem. After a process involving peer review and ranking of the proposals, funds are awarded to scientists whose applications appear most likely or best suited to yield an answer.

Only a few examples of targeted risk assessment research exist. (See ch. 7 for a discussion of the features of successful research programs.) A small-scale model of targeted research is found in EPA's RIHRA program (box 4-A). Another example of a targeted research program is emerging at FDA's NCTR, where research proposals are now reviewed not only on the basis of scientific merit but also on the basis of relevance to the needs of the regulatory centers of FDA. (Previously, proposals were funded solely on the basis of scientific merit.) To ensure that regulatory relevance plays a role in proposal review, members of the reviewing committees are drawn from each center in FDA with regulatory responsibility (Norris, 1993).

DOE represents a case in which a targeted research program in health risk assessment would be useful to meet the challenge of environmental cleanup. DOE's Office of Environmental Restoration and Waste Management is responsible for over $5 billion in cleanup programs at DOE facilities in 1993. With the exception of the epidemiology program (under the Office of Epidemiology and Surveillance), DOE's experimental toxicology effort is moving toward answering basic research questions related to molecular biology and the mechanisms of toxicity. Some point out that this shift toward basic research will improve the quality of DOE's research and ultimately pay off in the applied arena. But others contend that valuable opportunities are being lost because research is not being targeted to the problems raised by the most costly cleanup effort ever undertaken by the Federal Government.[12]

FINDINGS AND CONCLUSIONS

To evaluate Federal research to improve health risk assessment, OTA used three distinct categories to classify health risk assessment research: 1) research to improve health risk assessment methodologies; 2) basic science and basic health risk research to understand how environmental agents produce their adverse effects and basic biological,

[12] For the first time in history, the cleanup costs for nuclear weapons facilities will exceed the cost of producing nuclear weapons.

Box 4-A–The Research To Improve Health Risk Assessment Program at EPA

The objective of EPA's Research to Improve Health Risk Assessments (RIHRA) program is to identify and conduct systematic, targeted research to improve the scientific basis and methods used in health risk assessment In 1988, Congress mandated EPA to develop an integrated research program to reduce uncertainties in the risk assessment process. RIHRA is the agency's response to the environmental health risks aspects of the mandate.

RIHRA serves to complement other EPA research programs and address risk assessment issues facing the agency that cut across the regulatory programs. The program includes investigators from the Environmental Protection Agency's Health Effects Research **Laboratory** in its Office of Health Research; Office of Health and Environmental Assessment; and the Office of Modeling, Monitoring Systems, and Quality Assurance.

Projects are selected using defined criteria and awarded competitively. RIHRA's four major project areas include: 1) integrated exposure assessment; 2) physiologically based pharmackinetic models; 3) biologically based dose-response models; and 4) analyses of uncertainty in risk assessment. Resources other than RIHRA funding are also used to support those areas of research at the agency.

EPA integrated RIHRA into its new research planning scheme, which is based on specific issues needing research support This new issue-based planning places RIHRA under the Health Risk Assessment Methods issue. The major emphasis of this issue is scientific studies in the laboratory to support the development of predictive models for assessing health risks but also includes some chemical-specific assessments (eg., dioxin). It is intended to complement the development of biological assays and chemical-specific data that is emphasized in other issues. Related research issues for RIHRA include the Health Effects issue, which emphasizes complementary development of data on the **way agents** produce adverse effects, and the Human Exposure issue, which provides information on the route, magnitude, frequency, and duration of exposures to environmental pollutants.

SOURCE: U.S. Environmental Protection Agency, Office of Research and Development, "Strategic Issue Plans" (April 1993).

physical, and chemical sciences; and 3) research to fill chemical-specific data gaps. OTA believes that progress must be made in all three areas to substantially improve the process of risk assessment and reduce the uncertainty of estimates of risk.

Taken as a whole, Federal research to improve risk assessment **at** the national level appears neither well integrated nor well planned. In particular, given the promise that methodological research offers, the resources allotted to it appear disproportionately small: in FY 1993, methodological research received approximately 11 percent of the estimated $600 million spent on health risk assessment research. As a result, methodological research is a secondary priority for both research and regulatory agencies. In times of restricted resources and in the wake of congressional imperatives, the agencies tend to maintain their core programs and not enter into new programs. Often, methodological research becomes marginalized as a consequence.

Yet expanding methodological research is not simply a matter of redirecting funds at the expense of either basic research or research on data collection. Instead, methodological research should be considered complementary to the other types of research that agencies are conducting and should be integrated into a complete research program. The results of basic research on biological processes and mechanisms of toxicity provide the biological framework for many of the methods and models being developed. Dose-response and pharmacokinetic models, for example, are based on information about physiology and metabolism obtained from basic research. Similarly, risk assessments benefit from research on data collection; a complete risk assessment requires data on toxicity, dose-response relationships, and exposures. Further-

more, methodological research, especially extrapolation models, and basic research are closely linked with chemical-specific data.

Charting a course for improving risk assessment research requires that Federal agencies work at several organizational levels. OTA examined the priority-setting process for such research at three different levels: national, agency, and program. Each level employs different processes and methods. Setting priorities at the program level involved the most formalized and systematic processes; the national level involved the least. In addition, several factors influence the choice of one type of research over another.

Despite the national implications of decisions based on risk assessment, Federal research to improve risk assessment is largely decentralized and uncoordinated. There is no central coordinating Federal presence. Most Federal research is done in support of the agencies and departments that sponsor the research, as is the case for environmental research and development in general (Carnegie Commission, 1992; Schaefer, 1991). OTA observed few multiagency efforts. An example is the FCCSET process, but participants and nonparticipants alike displayed little optimism about possible outcomes from it.

The absence of an identified central leader in risk assessment research contributes to the pessimistic viewpoint and to the current level of funding and disciplinary and agency fragmentation in the effort to improve health risk assessments. A nationally recognized leader could provide leadership and assurances about political support for research, promote multiagency collaborations, and provide incentives for overcoming bureaucratic hurdles and turf battles. A national leader in the White House in a position equivalent to the "Drug Czar" or "AIDS Czar, " could bring national visibility and unify and coordinate research activities across agencies, in addition to articulating the needs of the field to Congress and the President. Furthermore, this central figure could instill a sense of common purpose among researchers and program managers.

At the agency level, priorities are based on the different constituents, legislative mandates, and missions of the organizations. They are also influenced by historical factors and the composition of the work force, which gives rise to an agency culture that is important in determining how the organization establishes its directions and priorities. Often, political and public pressure dictate priorities to a greater extent than does a formal process within the agency (U.S. EPA, SAB, 1988).

The priorities for risk assessment research vary with the mission and function of the agency: specifically, whether the agency's responsibilities include risk management. The health regulatory agencies, DOD, and DOE conduct mostly chemical-specific data development, whereas the research agencies, by and large, conduct basic research.

Setting priorities at the program level is generally a more developed process-both more systematic and more formal-than it is at the agency or national levels. Generally, two distinct types of management methods are used to determine programmatic priorities for individual research projects (U.S. Congress, OTA, 1991). One style, termed ''bottom-up," allows research ideas and priorities to originate with the individual researchers, who communicate those ideas to their superiors or to grant managers. In contrast, ''top-down' management assigns priority-setting to the most senior decisionmakers in an agency. OTA observed both styles of management in its survey of risk assessment research, as well as a mixture of styles, which is consistent with federally funded science in general (U.S. Congress, OTA, 1991).

Risk assessment research has not kept abreast of the needs of our modem society. It is estimated that 1,500 new chemicals are introduced worldwide each year, which joins the more than 62,000 chemicals OTA estimates is already in use in the U.S. Studies suggest that only a fraction are

adequately, if at all, tested for toxicity. New insights from research can produce better tools to decide which chemicals require more investigation and which do not; which require regulation and which do not. Without better tools, governmental agencies and private companies will never catch upon the backlog of untested chemicals and unanswered questions, and the public will never have the assurance that sufficient research is being brought to bear on the risks that concern it.

CHAPTER 4 REFERENCES

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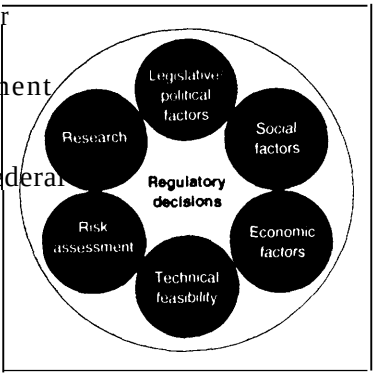
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Research and Decisionmaking 5

Science and policymaking are uneasy partners. In an address at the press conference to release the 1983 National Research Council report on risk assessment in the Federal Government, the former administrator of the U.S. Environmental Protection Agency (EPA), William D. Ruckelshaus, said "The main reason for the uneasiness lies, I think, in the conflict between the way science really works and the public's thirst for certitude that is written into EPA's laws. Science, as you all know, thrives on uncertainty" (Ruckelshaus, 1983).

Yet despite that uneasy relationship, the primary criterion for health risk assessment research is that it be useful for decisionmaking. With that observation in mind, the Office of Technology Assessment (OTA) examines three interrelated questions in this chapter:

1. How has research influenced Federal risk assessment guidelines and risk assessment practices?
2. What impact has research had on decisionmaking?
3. How can research be designed to make risk assessment more useful in decisionmaking?



To answer those questions, we review the evolution of Federal risk assessment guidelines and risk assessment practices and the comments and criticisms made regarding them. The analysis focuses on Federal activities in this area in part because the record of Federal regulatory decisionmaking is more accessible than the record of decisionmaking in the private sector.

Research findings from epidemiology and toxicology provide the primary database for health risk assessment. But those data

are seldom extensive enough for answering many of the questions that arise in regulatory decision-making. Weinberg (1972) characterized such issues as "transience questions"--questions that "can be asked of science and yet . . . cannot be answered by science. " Agencies frequently confront them, and because science cannot answer them, agencies adopt so-called science policy assumptions in order to make decisions. The assumptions can be divided into two general types: those that are used to bridge gaps in scientific knowledge and those that compensate for a lack of agent-specific data (NRC, 1983).

IMPACT OF RESEARCH ON RISK ASSESSMENT GUIDELINES AND DECISIONMAKING

EPA is the main player in developing and revising risk assessment guidelines. Although the Consumer Product Safety Commission (CPSC), the Food and Drug Administration (FDA), and the Occupational Safety and Health Administration have also published health risk assessment guidelines in the ***Federal Register, only*** EPA has completed scientific reviews of some of its guidelines and formally modified them in response to new scientific information. This chapter considers three of EPA's guidelines. The agency first adopted guidelines for assessing the risks of ***carcinogens*** in **1976;** it formally modified those guidelines in 1986 and is now revising them further. It adopted its first guidelines for ***developmental toxicants*** and for ***estimating exposures*** in **1986,** modifying the developmental toxicants guidelines in 1991 and the exposure guidelines a year later. Also discussed in this chapter is the International Agency for Research on Cancer's most recent revisions of its procedures for evaluating the risks to humans posed by carcinogens.

Reviewing the EPA risk assessment guidelines and their revisions makes it clear that the agency has changed relatively few of its science policy assumptions in response to new scientific information. The impact of research on the guidelines is more evident in EPA's increased attention to identifying all of the relevant scientific questions that the guidelines should address. Often, new questions reveal new uncertainties that have to be bridged with assumptions.

Guidelines for Risk Assessments of Carcinogens

Reflecting society's concern about cancers and the Federal Government's regulatory focus on them, extensive scientific research has been and is being conducted to identify the causes of cancers and the mechanisms of carcinogenesis. To date, that research has had only a modest effect on efforts to revise the EPA's carcinogen risk assessment guidelines. It has, however, had a substantial impact on chemical-specific risk assessments and consequently on regulatory actions. In addition, it is currently generating considerable debate as EPA considers new revisions to its 1986 cancer policy (U.S. EPA, 1988b, 1992a). In general, research has had greater impact in displacing assumptions that EPA adopted to bridge inadequacies in the data than in changing assumptions to compensate for theoretical uncertainties.

EPA's 1976 interim guidelines for carcinogen risk assessment (U.S. EPA, 1976) discussed the assumptions underlying the agency's regulatory approach, but they provided no explicit list of agency science policy positions. In contrast, EPA's 1986 guidelines on carcinogen assessment (U.S. EPA, 1986a) detailed several major science policy positions that guide the agency's interpretation of incomplete or uncertain data (see box 5-A).

Among the most controversial agency policy positions is the use of the results of animal tests to predict human effects. The 1981 OTA report ***Assessment of Technologies for Determining Cancer Risks from the Environment*** (pp. 124-

127) discussed a number of objections to the use of animal bioassay data:[1]

1. The doses given to test animals are too high, and the results do not predict carcinogenic effects in humans.
2. Routes of exposure in test animals are not the same as routes of exposure in humans.
3. Some life processes of test animals (e.g., physiology and metabolism) are so different from those of humans that the test results may not be relevant for predicting human cancer risks.
4. Some test animals and animal organs are so sensitive to certain chemicals which induce tumors that the test results do not predict cancer risk in humans.
5. Benign tumors in test animals do not predict human cancer risk.

Twelve years later, such objections are still being raised—most often, of course, when tests indicate that a commercially important chemical causes cancer in animals and the chemical's manufacturer, distributors, and users face regulation. As long as the bioassay remains the basic source of information for evaluating carcinogenic risks to humans, those objections will be raised.

The sensitivity of test animals and test organs is an issue because certain chemicals cause tumors only in the liver of male B6C3F1 mice (and not in other mouse organs), female mice, or in rats. EPA's 1986 guidelines describe the problems posed by agents that cause cancer only in certain organs in a single species. In discussing the evaluation of animal test results for assessing human risk, EPA has stated that it accords more weight to conclusions based on results showing that a chemical causes cancer in more than one species. The agency classifies the evidence for carcinogenicity in a descending scale that runs from "sufficient," through "limited," "inadequate," and ''no data, ' to ''no evidence. ' EPA defines "sufficient" as follows:

> Sufficient evidence of carcinogenicity, which indicates that there is an increased incidence of malignant tumors or combined malignant and benign tumors [footnote]: (a) in multiple species or strains. . . (U.S. EPA, 1987b, pp. 1-11).

But EPA's statement does not mean that it always accords less weight to results that are obtained in only one species. In fact, the two footnotes in the definition of sufficient' dismiss two arguments that scientists have not been able to resolve. The first footnote states:

> An increased incidence of neoplasms that occur with high spontaneous background incidence (e.g., mouse liver tumors and rat pituitary tumors in certain strains) generally constitutes ''sufficient' evidence of carcinogenicity, but may be changed to "limited" when warranted by the specific information available on the agent (U.S. EPA, 1987b, pp. 1-11).

The footnote not only gives the agency the flexibility to judge sufficiency of evidence in the absence of positive results from two species, but it also allows agency staff to ignore the great uncertainty that many scientists attach to any conclusion based on a chemical's causing only mouse liver tumors. As EPA's guidelines note:

> For a number of reasons, there are widely diverging scientific views about the validity of mouse liver tumors as an indication of potential carcinogenicity in humans when such tumors occur in strains with high spontaneous background incidence and when they constitute the only tumor response to that agent. These Guidelines take the position that when the other conditions for a classification of "sufficient' evidence in animal studies are met . . . the data should be considered as 'sufficient' evidence of

[1] Bioassay is a term used for long-term (e.g., 2 years for rodents) experimental studies for cancer induction. Rodent bioassays generally employ both sexes of rats (Fischer 344/N) and mice (B6C3F1 hybrid), using two or three exposure levels plus untreated controls in groups of 50 animals for 2 years.

Box 5-A–Major Science Policy Positions for EPA Cancer Guidelines

- Benign tumors should generally be combined vvith malignant tumorsfor risk estimates unless the benign tumors are not considered to have the potential to progress to the associated malignancies of the same histogenic origin.
- Agents that are positive in long-term animal experiments and also show evidence of promoting cocarcinogenic activity in specialized tests should be considered as complete carcinogens unless there is evidence to the contrary because it is, at present, difficult to determine whether an agent is only a promoting or cocarcinogenic agent.
- These guidelines take the position that when the only tumor response is in the mouse liver and when other conditions for a classification of "sufficient" evidence in animal studies are met (e.g., replicate studies, malignancy; see section IV), the data should be considered as "sufficient" evidence of carcinogenicity.
- Because it is possible that human sensitivity is as high as the most sensitive responding animal species, **in the** absence of evidence to the contrary, the biologically acceptable data set from long-term animal studies showing the greatest sensitivity should generally be given the greatest emphasis in estimating human carcinogenic risk
- Where two or more significantly elevated tumor sites or types are observed in the same study, extrapolation may be conducted on selected sites or types. To obtain a total estimate of carcinogenic risk animals with one or more tumor sites or types showing significantly elevated tumor incidence should be pooled and used for extrapolation. The pooled estimates will generally be usedin preference to risk estimates based on single sites or types.
- In the absence of adequate information to the contrary, the linearized multistage procedure will be employed for estimating human carcinogenic risks.
- In the absence of comparative toxicological, physiological, metabolic, and pharmacokinetic data for a given suspect carcinogen, the Agency takes the position that the extrapolation on the basis of surface area is considered to be appropriate because certain pharmacological effects commonly scale according to surface area.
- Unless there is evidence to the contrary in a particular case, the cumulative dose received over a lifetime, expressed as average daily exposure prorated over a lifetime, is commended as an appropriate measure of exposure to a carcinogen. That is, the assumption is made that a high dose of a carcinogen received over a short period of time is equivalent to a corresponding low dose spread over a lifetime.
- In characterizing the risk due to concurrent exposure to several carcinogens, the risks are combined on the basis of additivity unless there is specific information to the contrary.

The basic source of information for most risk assessments is the carcinogenesis bioassay, which is **a test** of the suspect carcinogen's capacity to cause tumors in laboratory animals, generally rats and mice. Because of reliance on the bioassay, much of the cancer risk assessment guidelines are devoted to the execution **and** interpretation of the bioassay.

SOURCE: US. Environmental Protection Agency, "Guidelines for Carcinogen Risk Assessment," *Federal Register* 51(1986):33992-34003.

carcinogenicity. It is understood that this classification could be changed on a case-by-case basis to ''limited," if warranted, when factors such as the following are observed: an increased incidence of tumors only in the highest dose group and/or only at the end of the study (U.S. EPA, 1987b, pp. 1-5).

EPA's science policy thus considers results that show that a chemical causes tumors only in mouse livers as sufficient evidence of carcinogenicity. The agency's discussion of this policy admits that not all scientists agree with that decision, but it does not address the arguments of those who disagree. Instead, the guidelines discuss the replication of test results and consistent

test design. But no matter how many times tests are replicated or how well they are done, those that generate false signals can do no more than that.

Many observers believe that EPA persists in treating mouse liver tumors as sufficient evidence because the agency has regulated several chemicals on the basis of such findings. For example, the agency banned the organochlorine pesticide DDT ostensibly on the basis of potential liver carcinogenicity (Dunlap, 1988). To back away from the sufficient classification might open up some of EPA's past actions to renewed scrutiny and criticism.

The second footnote in the paragraph about sufficient evidence deals with benign tumors:

> Benign and malignant tumors will be combined (to arrive at a count of total turners) unless the benign tumors are not considered to have the potential to progress to the associated malignancies of the same histogenic origin (U.S. EPA, 1987b, pp. 1-11).

The language of the footnote indicates that EPA will consider other evidence in deciding how to count benign tumors. But it stops short of saying what kind of evidence would be considered, much less what kind would be considered convincing. As a practical matter, it is probably impossible to demonstrate that a "potential to progress to the associated malignancies" does not exist.

The guidelines about sensitive organs and sensitive test animals retain the features that caused objections more than a decade ago. Those features, like most parts of the guidelines, are designed to protect health, especially in circumstances of few or no data. That position is not likely to change. Nevertheless, EPA has altered some of its science policy assumptions to accommodate new information.

Extrapolating from the results of tests in animals to predictions of risk to humans is at the heart of most risk assessments, and recent years have seen three examples of altered approaches to it. The first is a change from a general ''default' extrapolation method to a particular ''default' factor derived from specific data and applicable to all chemicals. The second example describes the process used to develop specific data for a chemical to replace a default approach. The last example notes a few incidence in which specific information about a chemical altered risk assessment decisions,

SCALING FACTOR FOR CROSS-SPECIES EXTRAPOLATIONS

In extrapolating test results, allowances must be made for the differences in size, shape, life-span, physiology, and biochemistry between test animals and humans. When toxicologists and risk assessors lack specific information for making those adjustments, they have traditionally used one or the other of two standardized ''scaling factors. ' One scaling factor is body weight; thus, a dose of 1 milligram per kilogram body weight in a rat is treated as equivalent to 1 milligram per kilogram body weight in a human, The other factor is body surface area. Surface area is difficult to measure, but it can be approximated by raising body weight to the 2/3 power. Although that approximation is used, it has been challenged as likely to be in error (Slone, 1993).

Regardless of the certainty of either factor being appropriate, FDA uses the body weight scale, and EPA uses the surface area scale, with the result that EPA predicts higher risks than FDA. Given the same data about toxicity, EPA would predict a risk 14 times higher than the risk FDA would predict when the tests are done in mice and a risk 6 times higher when the tests are done in rats (U.S. Congress, OTA, 1981).

Recently, EPA proposed, for itself and on behalf of FDA and CPSC, changing its choice of scaling factor. The proposal was made in response to three events: an analysis of all available interspecies scaling data (Travis and White 1988), a reassessment of the rationale

underlying the use of the surface area factor (Travis et al., 1990), and a political effort to harmonize the approaches of different Federal regulatory agencies. The new scaling factor that EPA has proposed lies between the body weight and surface area scaling factors. It will result in risk estimates about midway between the estimates that would be produced by the two older methods.

USING METABOLIC AND PHARMACOKINETIC DATA FOR CROSS-SPECIES EXTRAPOLATION

Researchers have long believed that studies in pharmacokinetics and metabolism provide important information for understanding the mechanisms by which agents evoke toxicity (see Slone, 1993). Pharmacokinetic studies examine the rates of absorption, distribution, metabolism, and excretion of a compound. They also examine the time-dependent features of those processes, as they link to the compound's toxicological effects. Metabolic studies examine the coordinated reactions and pathways that transform the compound into reactive or inactive intermediates that can be toxic entities. Information from pharmacokinetic and metabolic studies provides a basis for determining the internal dose and the validity of various extrapolations from the level of exposure to the expected response.

The case of methylene chloride is an example of the use of pharmacokinetic and metabolic data, by government and industry scientists to improve animal-to-human extrapolation. Three factors seem to have influenced the collaboration. First, influential members of the scientific community were interested in using pharmacokinetic information to obtain better estimates of the doses of methylene chloride necessary to produce turners in test animals and doses that may affect humans. Second, staff from various agencies wanted to work with industry and each other to evaluate metabolic data and determine how such information could be used in risk assessment. Third, the EPA Science Advisory Board encouraged a thorough review of the data obtained using pharmacokinetic methods (Preuss, 1992).

The story begins in the early 1980s, when the U.S. Air Force supported a research project at the Wright-Patterson Air Force Base Inhalation Toxicology Laboratory to develop methods to better assess the risks associated with human exposure to organic solvents. The Air Force-supported scientists first developed a generic, physiologically based pharmacokinetic (PBPK) model to assess exposure of humans to organic solvents through inhalation. Following a 1986 review of EPA's risk assessment of methylene chloride, members of the advisory board concluded that the PBPK model was a valid alternative to other approaches for estimating the dose of methylene chloride that can cause human toxicity based on animal study results. As a result of that encouragement, scientists from EPA, CPSC, FDA, Dow chemicals, ICI (a U.K. fro), and the European Council of chemical Manufacturers Federation began to hold periodic meetings to discuss their research needs and share information. The meetings identified gaps in the database for methylene chloride, produced a commitment to initiate further studies, and provided a forum to share and discuss protocols and experimental results.

The effort to understand the mechanisms by which methylene chloride induces cancer stimulated research in PBPK modeling and enthusiasm for improved interspecies extrapolations. For methylene chloride specifically, both EPA (1987c) and the California Department of Health and Human Services (1988) have concluded that additional data are necessary to clarify metabolic differences between rodents and humans. The agencies expect some of these data to come from ongoing Navy-supported research at Wright-Patterson (Gearhart, 1992). Additional information will be generated by a research program at the National Institute of Environmental Health Sciences to better characterize the tumorigenic response in mice exposed to methylene chloride.

The ongoing research on methylene chloride is an example of collaborative research that has led

to additional studies. To date, these investigations have not resolved to EPA's satisfaction the question of how potent a carcinogen methylene chloride is in humans. They have, however, pointed to additional projects that may clarify questions of human risk. More generally, the methylene chloride experience underlines the difficulties of animal-to-human extrapolation and should caution risk assessors against too-ready an acceptance of generalized approaches (e.g., scaling factors) in those extrapolations.

RESEARCH AND CHANGES OF PRESUMPTIONS

The fundamental premise of toxicology is that animals and humans respond similarly to chemicals. Some see accruing evidence for that premise (Huff, 1993), For others, substantial problems are surfacing in extrapolating results from animal models to human populations (Ames and Gold, 1990a,b; Cohen and Ellwein, 1991, 1992). In carcinogenic risk assessments, regulators and scientists have established criteria for evaluating the effects of chemicals in animals to help in deciding whether the chemicals present carcinogenic hazards to humans (IARC, 1992a; U.S. OSTP, 1985). Once a substance has been classified as a potential human carcinogen, U.S. regulatory agencies consider it appropriate to use linear, no-threshold extrapolation models to estimate the magnitude of human risk (see ch. 2). Arguing against these general procedures is the increasing recognition that biological mechanisms, physiology, and biochemistry or differences in routes of exposure may affect the agent's interactions with the target tissue. Those effects could alter the toxicological consequences in humans compared with those observed in animals.

Demonstrating the validity of generalized extrapolation procedures requires information about mechanisms of toxicity in sufficient detail such that no important gaps remain. That's seldom the case. Instead, limited mechanistic data become the focus of controversies about interpretation. One such debate arises in assessing the risk of cancer in humans from exposure to agents that are not DNA-reactive but that test positive for carcinogenicity in animals. The mechanisms by which the diverse array of nonmutagenic, carcinogenic chemicals induce cancer are little understood. As a result, new generic approaches to interpret those tests and project their results to human risk estimates are not likely to be available soon.[2] Nevertheless, specific studies of some chemicals have led to deviations from the general presumption of risks to humans and the application of the linear, no-threshold model.

Some substances induce cancer through indirect mechanisms that operate at high doses in test animals but are unlikely to operate at lower doses. Or they may operate through mechanisms that do not exist in humans. An example of the former mechanism, which renders linear, no-threshold extrapolation inappropriate, is ethylene thiourea. That chemical disrupts hormone levels in the rodent thyroid gland only at high doses (U.S. EPA, 1988c). An example of a situation in which positive findings in animals are not applicable to humans is the induction of kidney tumors in male rats through the interaction of d-limonene and a protein present in male rats but not in humans (U.S. EPA, 1991a). Some chemicals that cause bladder cancers in test animals (e.g., melamine, aliette, and saccharin) are considered unlikely or impossible human carcinogens because exposures in humans are unlikely to reach the extremely high levels required to cause urinary calculi, which are the proximal cause of those cancers induced at very high doses (see Huff, 1992, for a review). These examples demonstrate the importance of chemical-specific mechanistic data and the growing importance of understanding mechanisms of toxicity for more realistic extrapolations from animals to humans.

2 In contrast t. U.S. regulatory agencies, which use no-threshold models for all carcinogens, regulatory agencies in some other countries assume a safe level of exposure exists in estimating risks from nongenotoxic carcinogens (see appendix A).

Guidelines for Developmental Toxicity

EPA first formulated science policy assumptions for developmental toxicity in 1986 (U.S. EPA, 1986c) and made few changes when the guidelines were revised in 1991. Yet in response to criticism from its Science Advisory Board, EPA did modify one assumption. The agency agreed to use results from a species most relevant to humans for estimating potentially toxic effects on human development whenever data were available, rather than automatically selecting results from the most sensitive responding species.

The most significant change, however, was the agency's decision to merge the hazard identification and dose-response phases of the risk assessment process to "reflect hazard within the context of dose, route, duration and timing of exposure' (U.S. EPA, 1991 b). The 1991 guidelines also abandoned a proposed weight-of-the-evidence scheme that would have classified substances as having "definitive," "adequate," or "inadequate' evidence of toxicity during human development (U.S. EPA, 1989b). The approach that EPA adopted takes into account extensive scientific research that suggests that manifestations of developmental toxicity depend strongly on species and exposure. EPA's new approach thus addresses scientific concerns about dependence of developmental toxicity on the contexts of test animal and duration and timing of exposures. But it also clearly expands the extent of scientific analysis required by the agency even to identify a substance as a potential developmental toxicant.

There are both scientific and policy arguments for replacing EPA's current approach to noncancer risk assessment (the no-observed-adverse-effects level divided by uncertainty factors; see ch. 2) (Pease et al., 1991). Most of the alternatives, however, demand significantly more data and analysis. Looking beyond the relatively simple modeling of the benchmark-dose approach, EPA is supporting research to develop ''models that are more biologically based to provide more accurate estimates of low-dose risk to humans" (U.S. EPA, 1991 b).

Guidelines for Exposure Assessment

The changes in EPA's guidelines for assessing exposures to toxic chemicals exemplify expanding scientific examination in the risk assessment process. EPA's initial 1986 guidelines (U.S. EPA, 1986b) were relatively brief (8 pages), "laying out a set of questions to be considered in carrying out an exposure assessment in order to help avoid inadvertent mistakes of omission. ' In contrast, the 1992 revisions present a detailed discussion (45 pages) of the scientific foundation of exposure assessment and state that extensive data acquisition and analysis are necessary to produce good assessments (U.S. EPA, 1992b).

Probably the most important change in agency guidelines has been the development of methods for displacing ''worst-case' assumptions about exposure with more reasonable estimates of "high-end" exposures. "The concept of high-end exposure is fundamentally different from terms such as worst case, in that the estimate is by definition intended to fall on the actual exposure distribution" (U.S. EPA 1992b). This change has the advantage of basing risk estimates and potential regulation not on the maximum possible exposure but on the exposures that are likely to be occurring to some members of the actual population. However, this approach requires considerably more data and analysis to characterize those exposures.

In contrast to other guidelines, the exposure assessment guidelines require relatively few assumptions. Both EPA's 1986 and 1992 exposure assessment guidelines contain the same fundamental science policy assumption: in the absence of measurement data, exposure assessment may be based on mathematical models.

The Limited Impact of Research

Given the length and breadth of EPA's guidelines, the agency has made few changes in the

assumptions and procedures included in those directives. Three interacting factors account for the limited impact of new scientific research on EPA's science policy assumptions.

First, the nature of the assumption is a factor. An assumption that bridges a specific, well-defined information gap that can be resolved experimentally is more likely to be displaced when the needed information is generated. In contrast, an assumption bridging broad areas of scientific uncertainty, especially gaps in scientific knowledge, and understanding is less likely to be replaced.

Second, the relative importance of the assumption to the paradigm underlying the predominant regulatory approach is a major factor in whether new research changes science policy. The no-threshold assumption for carcinogens (no amount of exposure, however small, is not without an effect) is central to EPA's cancer risk assessment guidelines (U.S. EPA, 1986a). In comparison, the assumption of surface area as the appropriate default scaling factor among species is more peripheral. Displacing the no-threshold assumption for carcinogens has proved difficult, not only because important aspects of the question cannot be resolved experimentally but also because displacement requires developing an alternative model of carcinogenesis that can command a scientific consensus. Because it lacked such a consensus, EPA failed in the early 1980s to modify the agency's cancer policy by separating carcinogens into two classes based on their mechanism of action, which would have allowed threshold-based risk assessment for nonmutagenic carcinogens (Rushefsky, 1986).

The third and final factor influencing the agency's response to new scientific research involves the policy reverberations associated with changing specific default assumptions. The policy consequences of changing some agency default positions are slight: shifting interspecies scaling factors reduces EPA's risk estimates slightly and raises FDA's slightly, but it also encourages interagency consistency and does not conflict with public expectations. In the area of extrapolating from high to low doses, however, existing agency guidelines have been significantly influenced by a policy commitment to err on the side of public safety in order to fulfill statutory mandates. Changing the default assumption of low-dose linearity can dramatically reduce estimates of risk, as well as conflict with public beliefs that no carcinogenic exposure is safe. To a large extent, the predominant role policy considerations played in their adoption explains the resistance to changing EPA's default assumptions for establishing the relevance of animal cancer to humans and estimating low-dose risks.

New scientific findings that are promoted because they result in less "conservative" estimates of risk are likely to be strongly contested because they may be perceived as undermining the government's or a particular agency's commitment to protect public health in the face of uncertainty. Rushefsky (1986) referred to these inferential choices as being either ''risk averse' or "risk tolerant, ' depending on the choice of assumption made (see table 5-l). In general, public health agencies are risk averse and more protective of public health to compensate for the inherent uncertainties in the process. Whenever changing a traditional assumption causes substantial policy reverberations, the change confronts very high hurdles indeed.

Which interest group introduces new scientific information into the regulatory arena and how that information is used in the political process may affect the fate of those findings in the risk assessment process. Often, research sponsored by industry is perceived as less-than-objective science and as a self-interested effort to undercut regulation. Federal agencies are not immune to such suspicions. When the Office of Management and Budget selectively used scientific information to attack regulatory risk assessment during the Reagan and Bush Administrations, it may have stigmatized pharmacokinetic and mechanism-based modeling as procedures that weaken regu-

Table 5-l—Patterns of Inferential Choices in Developing Cancer Policy

	Position	
Controversy	Risk-averse	Risk-tolerant
Evidence	Bioassays sufficient	Epidemiology only
Bioassays	Indicate human carcinogenicity	May not be accurate
Positive/negative	Positive more important	Negative may indicate species sensitivity y
Conflicting studies	Positive more important	All evidence should be weighed
Benign/malignant	Benign sufficient	Only malignant significant
Dose levels	High dose provides qualitative evidence	At least three levels should be used; iow doses show reversibility; high doses may overwhelm defense mechanisms
Mathematical models	Linear	No-observed-effects level for epigenetic carcinogens
Thresholds	Insuffident evidence	May exist for promoters and epigenetic carcinogens
initiators/promoters	Cannot demonstrate distinction	Distinction important
Genotoxic/epigenetic	Cannot demonstrate distinction	Distinction important

SOURCE: M.E.Rushefsky, *Making Cancer Policy* (Albany, NY: State University of New York Press 1986), p. 41.

lation rather than improve risk assessment (Pease, 1992).

IARC Procedures for Classifying Carcinogens

The International Agency for Research on Cancer (IARC), a World Health Organization, publishes monographs on the evaluation of carcinogenic risks to humans. The monographs are used widely as source material for assessing risks from exposure to carcinogens. Currently, IARC classifies chemical agents into one of four groups (see box 5-B).

IARC convenes working groups from time to time to evaluate the need for procedural changes in its methods for evaluating carcinogenic risks. (See appendix A for a description of IARC and its policies.) In 1983, a working group concluded that classifying carcinogens according to their mechanism of action could be neither exhaustive nor definitive. Nine years later, in 1991, another working group noted that mechanistic data have always been used in determiningg human carcinogenic risks. It then considered whether the procedures that were currently in use might be revised (IARC, 1992b).

The group concluded that it was impossible to formulate definitive guidelines for all of the possible situations in which mechanistic data may influence the evaluation of carcinogens. Nevertheless, it identified two circumstances in which alternative criteria could be considered for deciding to which category a chemical belongs.

Mechanistic data, according to the working group, can be considered in deciding whether an agent belongs in group 1 or group 3. For group 1, the category ‘‘may be extended to include agents, mixtures, or exposure circumstances for which evidence of carcinogenicity in humans is less than sufficient but there is sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent acts on a relevant mechanism of carcinogenesis." The working group agreed that group 3 “maybe extended to include agents for which there is sufficient evidence of carcinogenicity in animals and strong evidence that the mechanism of carcinogenicity in animals does not operate in humans.

Box 5-B—IARC's System of Classifying Carcinogenic Risks to Humans

The International Agency for Research on Cancer (IARC) classifies carcinogenic risks into four groups:

Group l—The agent (mixture) is carcinogenic to humans. The exposure circumstance entails exposures that are carcinogenic to humans.

This category is used when there is sufficient evidence of carcinogenicity in humans. Exceptionally, an agent (mixture) may be placed in this category when evidence in humans is less than sufficient but there is sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent (mixture) acts through a relevant mechanism of carcinogenicity.

Group 2—This category includes agents, mixtures, and exposure circumstances for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost sufficient, as wel as those for which, at the other extreme, there are no human data but there is evidence of carcinogenicity in experimental animals. Agents, mixtures, and exposure circumstances are assigned to either group 2A (probably caranogenic to humans) or group 2B (possibly carcinogenic to humans) on the basis of epidemiologic and experimental evidence of carcinogenicity and other relevant data.

Group 2A-The agent (mixture) is probably carcinogenic to humans. The exposure circumstance entails exposures that are probably carcinogenic to humans.

This category is used when there is limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals. in some cases, an agent (mixture) may be classified in this category when there is inadequate evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent, mixture, or exposure circumstance maybe classified in this category solely on the basis of limited evidence of carcinogenicity in humans.

Group 2B-The agent (mixture) is possibly carcinogenic to humans. The exposure circumstance entails exposures that are possibly carcinogenic to humans.

This category is used for agents, mixtures, and exposure circumstances for which there is limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals. it may also be used when there is inadequate evidence of carcinogenicity in humans but there is sufficient evidence of carcinogeniaty in experimental animals. in some instances, an agent, mixture, or exposure circumstance for which there is inadequate evidence of carcinogenicity in humans but limited evidence in experimental animals together with supporting evidence from other relevant data may be placed in this group.

Group 3--The agent (mixture or exposure circumstance) is not classifiable as to its carcinogenicity to humans.

This category is used most commonly for agents, mixtures, and exposure **circumstances** for which the evidence for carcinogenicity is inadequate in humans and inadequate or limited in experimental animals.

Exceptionally, agents (mixtures) for which the evidence of carcinogenicity is inadequate in humans but sufficient in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Agents, mixtures, and exposure circumstances that do not fall into any other group are also placed in this category.

Group 4-The agent (mixture) is probably not carcinogenic to humans.

This category is used for agents or mixtures for which there is evidence suggesting lack of carcinogenicity in humans and in experimental animals. in some instances, agents or mixtures for which there is inadequate evidence of carcinogenicity in humans but evidence suggesting lack of carcinogenicity in experimental animals, consistently and strongly supported by a broad range of other relevant data may be classified in this group.

SOURCE: International Agency for Research on Gamer, *Monograph*, vol. 55 (Lyon, France, 1992), pp. 34-35.

THE INTERDEPENDENCY OF RESEARCH AND DECISIONMAKING

As is evident from the above discussion of the effects of research on EPA's guidelines for risk assessments and assessment practices and the procedures used by IARC, the speed with which science influences assessment procedures and science policy assumptions is very slow indeed. Besides the factors noted above, other barriers exist to incorporating the results of research into agency actions.

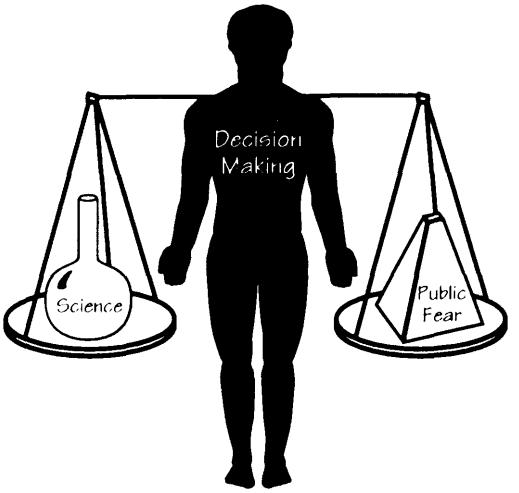
In its 1989 report on improving risk communication, the National Research Council included a guidance paper by B. Fischoff in which he described the interrelationship of science and policy:

> Science is a product of society; as such, it reflects the values of its creators. Conversely, society is partly a product of science. And understanding these inter-dependencies is essential to, on the one hand, discerning the objective content versus inherently subjective science and, on the other hand, directing science to serve socially desired ends. An understanding of these relationships is also necessary to appropriately interpret the conflicts between lay and expert opinions that constitute the visible core of many risk controversies (NRC, 1989),

OTA has chosen two examples of environmental decisionmaking that illuminate this interdependency. Each shows that research is driven by public concern about risk and incomplete risk data for decisionmaking. The dioxin case also demonstrates that researchers and analysts can produce decisionmaking tools in the absence of desired information.

Power-line Electromagnetic Fields and Cancer

Recent public apprehension about the health risks of exposure to power-line electromagnetic fields (EMFs) has been driven by widespread dissemination of the outcomes of epidemiologic studies, even though the evidence was, and still is, considered inconclusive by many scientists. In response to the situation, EPA prepared a draft report in 1990 evaluating the potential carcinogenicity of EMF exposures. But EPA's Science Advisory Board and the White House Committee on Interagency Radiation Research and Policy Coordination were critical of parts of the report (an outcome that may have resulted in part from inadequate analysis and imprecision in the writing of that report). The White House Committee requested a review of the literature on EMF and cancer by the Oak Ridge Associated Universities, which assembled an expert panel.



The panel reported that the epidemiologic findings about EMF and cancer were inconclusive, inconsistent, and without a plausible mechanism (ORAU, 1992; Young, 1993). It also concluded that, given the ever-decreasing resources for basic health and science research, further research investigation of this topic should not receive high priority. Subsequent to the Oak Ridge report, new epidemiologic data appeared (Feychting and Ahlbom, 1992; Floderus et al., 1992), which the interested parties interpreted to support their original positions. The net effects were polarization of the affected groups and heightened public concern.

Earlier, public concern about EMFs had spurred political, legal, and market reactions. In 1989, a background paper prepared for an OTA study proposed prudent avoidance as a policy option if it could be achieved without significant cost or inconvenience (U.S. Congress, OTA, 1989). But such a scenario was and still is unlikely, given that prudent avoidance often involves reconfiguring, rerouting, or burying transmission lines.

The conflict between the public's apprehension about the potential risk posed by EMFs and society's need for reliable, inexpensive electricity elicited political action. After a number of congressional hearings and legislative deliberations, the 102d Congress passed legislation that provided funds for research and dissemination of information to the public (P.L. 102-486, H.R. 776, Oct. 24, 1992). The Department of Energy (DOE) was designated as the lead agency to coordinate the Federal research effort. About $60 million was authorized over 5 years, including $5 million for information dissemination (CRS, 1993).

Interestingly, in the 1960s and 1970s, the U.S. Navy was a major source of finding for studies of the biological effects of extra-low-frequency (76 Hz) because of EMFs associated with submarine communication systems. The research found no significant biological impacts, and the available data were judged inconclusive and controversial (NRC, 1977). Since the 1970s, DOE has been the primary source of support for research on the health effects of exposure to power-line EMFs. The Electric Power Research Institute, an industry-supported, private nonprofit organization, has also been active in the field since the mid- 1970s. Studies of the health effects of EMFs are continuing, but many observers expect that legislative initiatives will be considered in the near future to regulate or otherwise limit exposures. Court cases in which nearby residents are claiming damages to their health and losses in property values are another force driving decisions about power lines,

Dioxins

The polychlorinated dibenzo-p-dioxins ("di-Oxins," or PCDDs) and polychlorinated dibenzofurans ("furans," or PCDFs) make up a family of 210 structurally related chemical compounds. Many researchers believe that these substances that often coexist as contaminants in various materials produce similar effects on health. The chemical most often called dioxin, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), is the most thoroughly studied and most toxic of this group of chemicals. Formerly, it was inadvertently produced during the manufacture of 2,4,5-trichlorophenol, which was a precursor in the production of some important disinfectants and herbicides, including one of the herbicides in Agent Orange, It is also formed as a byproduct of combustion and chlorine bleaching of paper and pulp.

Concerns about dioxins and furans are rooted in toxicity studies that found TCDD the most potent rodent carcinogen ever studied. Nevertheless, despite more than a decade of epidemiologic studies, there is still no convincing proof that dioxin causes cancer in humans (Bailar, 1991; Gough, 1992/1993). Yet carcinogenicity is not the only concern: TCDD causes adverse effects to every organ system in at least one test animal species (Gough, 1986). Is humankind more like the most sensitive or the least sensitive species tested-or is it somewhere in between? The dioxin problem has prompted intense research *to* support decisionmaking about TCDD as well as about dioxins and furans in general. That research has enhanced scientists' ability to detect and measure dioxins and furans in environmental and biological materials and has expanded the body of knowledge about dioxin's effects and its mechanism of action. Nevertheless, an understanding of the sensitivity of humans to dioxin remains elusive.

The size of the dioxin research effort can be measured by the number of research papers it has produced. The frost dioxin symposium, held in

Rome in 1980, saw 50 papers presented. The 12th symposium, held in Research Triangle Park in 1992, included 10 times that number. Both government and industry have contributed to the more than 20,000 dioxin-related papers and presentations in circulation, and that number continues to increase linearly (Gallo, 1993).

The expansion of dioxin research is due in part to a belief by both scientists and decisionmakers that intense research efforts could resolve the problems that dioxin raises. Because dioxin is a contaminant and has no commercial value, no one has a vested interest in keeping it in the market, and much attention is being given to ways to control its release and to mitigate TCDD already in the environment. But arguments continue to arise about how much such mitigation is worth and who should pay for it.

In 1985, EPA prepared a health assessment document on PCDDs (U.S. EPA, 1985). Because IARC (1987) and EPA (1985) considered the evidence for carcinogenicity in humans inadequate, EPA based its risk estimate on the Dow Chemical Company's study of dioxin and cancer in rats (Kociba et al., 1978). In 1988, pathologists reevaluated the Dow pathology data using revised criteria from the National Toxicology Program for classifying liver tumors. In response to the reevaluation, EPA prepared a draft report that proposed revising the "potency" estimate for TCDD (U.S. EPA, 1988a). The report also proposed methods to derive average risk estimates with models using different mechanistic underpinnings. EPA's Science Advisory Board rejected the methodology, however, and the document remains in draft form while research continues.

Prompted by publication of a new epidemiologic study of cancer mortality in workers exposed to TCDD (Fingerhut et al., 1991) and the conclusions about dioxin toxicity mechanisms from the 1990 Banbury Conference (Banbury, 1991), EPA announced that in 1991 it was reassessing dioxins. The agency held workshops in September of 1992 to review its draft reports and continues to work on the report, with release expected soon. To involve the public and invite its participation, EPA has held public meetings as part of its assessment process.

Studies of TCDD have produced almost all of the current knowledge of dioxins and furans, but most human exposures are to mixtures of dioxins and furans, about which very little is known. The need to address the risks posed by other dioxins and furans has stimulated development of an interim procedure, the toxicity equivalency factor (TEF) procedure. This interim method is being used to estimate risks from exposure to mixtures of PCDDs and PCDFs in the absence of specific information about their specific toxicities. The TEF method is a science-based response to a regulatory need—to estimate the toxicity of dozens of chemicals that have not been tested. In many respects, it represents the response of scientists to the demands of regulators.

The TEF approach is a numerical procedure based on scientific data and scientific judgment. It was first considered for use in the late 1970s and early 1980s when data began to reveal the relative toxicity of some of the different dioxins and furans. In 1986, EPA's Risk Assessment Forum requested that the Science Advisory Board convene a panel of experts to review the TEF methodology and its scientific support. The board's panel of scientists accepted the procedure with some reservations. First, the panel emphasized that the procedure should be considered an interim method. Second, it noted that the procedure lacked scientific validity and therefore needed validation. Third, it accepted the report with the understanding that EPA would fulfill its commitment to periodically review and update the procedure. The frost report on dioxin and furan toxicity equivalency factors was published by the Risk Assessment Forum in 1987 (U.S. EPA, 1987a); it was updated by the forum and republished in 1989 (U.S. EPA, 1989a).

Because of the universality of the dioxin problem, the North Atlantic Treaty Organization (NATO) adopted a TEF procedure for use in

Europe. The NATO committee that adopted a TEF scheme expressed some of the same reservations that the EPA Science Advisory Board noted. It said that the procedure should be considered an interim one and recommended that a ''vigorous program of research be conducted to address areas of uncertainty, to test, refine, or replace the TEFs" (U.S. EPA, 1989a).

Research Into Feedback From Decisionmakers to Researchers

At its most basic level, the relationship between research and decisionmaking can be seen as a feedback loop: one-half of the loop is the impact of research on decisionmaking, and the other half is the impact of decisionmaking on the research that needs to be done. Taken together, the relationship provides a panoply of options, not only for possible decisions but for research priorities as well.

The first half of the loop, which has already been discussed, allows the results of risk assessment (and by extension, risk assessment research) to provide the range of options to be considered in decisions about how to manage particular risks. The past decade witnessed the increasing use of risk assessment in decisionmaking, whether for standard-setting or as a tool for screening and priority-setting (Rosenthal et al., 1992). As described earlier in this chapter, the impact of research on risk assessment may be felt slowly and can be difficult to measure. Nevertheless, changes in agency guidelines for risk assessment and in case-specific regulatory decisions have been observed.

Few inquiries have been made about the other half of the feedback loop, in which policy decisions influence priorities for research. Based on meager evidence, some analysts argue that the poor record of applying analytical thinking to developing research priorities will change as research resources dwindle. In that case, studies will be planned, ranked, and ultimately funded in the light of the decisions on which they will have an impact (Finkel, 1993). Agencies, in turn, will give high priority to the research that is most likely to reduce compliance costs, minimize controversies, and reduce the health toll that hazardous agents may pose. In such circumstances, the value of information to the decisionmaker, not just the increase of knowledge, should influence what research will be given high priority.

The few researchers who are examining feedback from decisionmakers to researchers expect to obtain some insight into this portion of the feedback loop. The notion that information has a measurable value allows decisionmakers to use a quantitative process to evaluate both the need for additional information and the nature of that information.

An additional line of research is the exploration of the relative value and costs of various types of studies for decisionmaking. Lave and Omenn (1986), for example, developed a framework for decision analysis that examines the cost-effectiveness of short-term tests as predictors of carcinogenicity. Their framework estimates both the direct cost of testing and the total social costs of correctly classifying true-positive and true-negative carcinogenic chemicals; it also calculates the costs of misclassifying chemicals. Similar work has been done on the value of animal bioassays and the information they provide (Lave et al., 1988; Taylor et al., 1993). Based on this modeling, decisionmakers can decide on the relative worth of different testing schemes.

THE LIMITS OF SCIENCE IN SOCIAL DECISIONS

Whatever is expected of risk assessment in any given set of circumstances, it is only one of the elements in the formulating regulatory actions. Legislative mandates, social values, technical feasibility, economic factors, and the achievements or shortcomings of the research that feeds into risk assessment may assume a more prominent role than expert projections of risk (figure

5-1). The case study about regulating radon in drinking water in the next chapter illustrates some of the interplay between science and decisionmaking. Scientific research can provide a more solid foundation for the decisionmaker in choosing among alternatives to manage risk, but by itself it will not necessarily influence decisions so as to control the most significant risks. Moreover, the capacity of science to inform decisions even on many technical risk-related issues is limited.

The limits of science manifest themselves at a variety of levels. Uncertainty in measurements and observations constrains science at the most fundamental level, and the scientific underpinnings of risk assessment are more subject to that limitation than are experimental sciences. At a higher level of complexity, the interpretation of data and observations to predict outcomes introduces additional uncertainties. And risk management actions can themselves produce uncertainty.

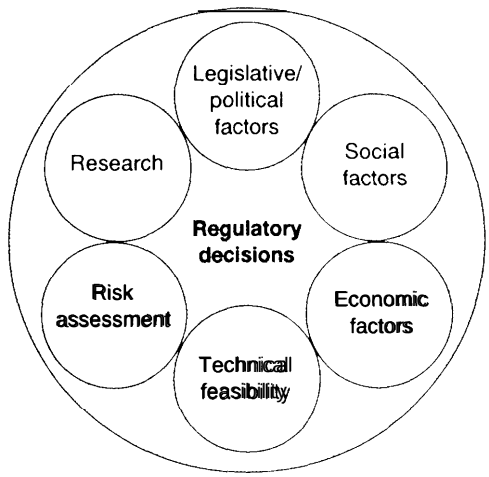
Measurements and Observations

Information for assessing risks to human health comes from epidemiologic observations, animal toxicity testing, various laboratory studies, and measures and estimates of human exposures. As detailed in this report, guidelines are available for the use of this information, but all measurements and estimates are subject to the limits of the methods used and uncertainties. There are technical bounds to the experimental methodologies and equipment as well as limitations that prevail in interpreting and analyzing data.

Epidemiologic Data for Assessing Risks

The availability of epidemiologic data eliminates the problem of extrapolating from animal data to humans, but epidemiologic data can suffer from a number of substantial limitations. Some are methodological in nature and may be overcome with new techniques. For instance, many investigators attempt to couple epidemiologic studies with cellular-molecular techniques so that the results will provide information about the mechanism of carcinogenesis.

Figure 5-l-Research as an Element in Regulatory Decisionmaking



SOURCE: U.S. Congress, Office of Technology Assessment, 1993.

The lack of exposure measurements can limit the usefulness of results from epidemiologic investigations because it forces researchers to rely on estimates and can lead to errors. For example, scientists who are studying health effects in the "Ranch Hands," the men who sprayed dioxin-contaminated Agent Orange in Vietnam, used records of job assignments and recall by the men to estimate exposure to the chemical. When techniques became available for measuring exposure directly, researchers found flaws in the classification of exposures on the basis of job category, a standard practice in many epidemiologic studies (Air Force Health Study, 1991a). In a related study, Needham (1991) reported few, if any, correlations between activities around dioxin-contaminated soils and measured exposure levels.

More generally, "confounders" complicate the design and interpretation of epidemiologic studies. As an example, Air Force scientists reported that diabetes is more common in Ranch Hand veterans with higher dioxin levels (Air Force Health Study, 1991 b). But a connection between that disease and dioxin exposures was

confounded by the finding that more obese veterans, who are more likely to have diabetes, also tend to have higher dioxin levels. The connection between obesity and dioxin levels is largely explained by differing rates of dioxin elimination from Ranch Hand veterans: dioxin persists longer in more obese men (Wolfe et al., 1993). Therefore, although the details remain to be sorted out, the connection between obesity and dioxin metabolism confounds the interpretation that can be put on the observation that diabetes is more common in men with higher levels of dioxin.

More common confounders are exposure to multiple agents in the environment, the effects of different lifestyles-including eating, drinking, and smoking habits—and genetic differences. All of these factors complicate extrapolating from study data to estimations of risk to the general population.

Results From Animal Toxicity Testing

Most often, information about the toxicity of substances comes from tests in animals, and all tests are compromises. To compensate for the small number of animals (usually rodents) that can be tested, rodents are exposed to higher concentrations of the agent than the levels that humans are expected to experience. There maybe differences in response to high and low doses or to particular routes and patterns of exposure, and between species.

Some of these limitations can be overcome by appropriate pharmacokinetic studies and analysis, which relates exposure to time-dependent distribution of the chemical in the body, and by pharmacodynamic analysis, which examines internal doses and effects at the organ, tissue, cellular, and molecular levels and relates them to the development of toxic effects. Almost always, however, comparative metabolic and pharmacokinetic data are incomplete; frequently, they are simply unavailable. Even when data are available, sites of toxic action can vary among species, further complicating interpretation and prediction. Unless the target organ is known, physiologically based pharmacokinetic modeling is of limited value.

A further complication is that a chemical frequently causes several effects in test animals. In evaluating animal studies, toxicologists must decide whether the response caused by the agent is well within the range of normal physiological adjustments (homeostatic response) or an abnormality that constitutes a toxic response. In many instances, homeostatic and toxic responses represent different parts of the same continuum. Put more simply, the question is, when does a response represent an adverse effect on health?

In carcinogenesis, a process that involves many etiologic factors, more than one mechanism may be operative in each of the steps or stages, which are often called initiation, promotion, and progression. Sometimes, information on the mechanism of carcinogenic action of a chemical or product are developed years after it is found to be carcinogenic in rodent studies. Sorting through the possible mechanisms can involve a broad range of issues and fields-for example, direct interactions with DNA, disturbance of hormonal balances, changes in cell organelles, organ-specific cytotoxicity, immunomodulation, perturbation of DNA methylation, peroxisome proliferation, and inhibition of intercellular communication. In some (perhaps many or most) cases, the explanation may be found in combinations of those mechanisms. When the information about a substance is incomplete, interpretations that draw connections between animal data and estimates of human cancer can produce great disagreement among scientists. As far as scientific understanding of the mechanisms of carcinogenicity has come, it remains far short of certainty.

Information on Exposure

After a chemical is released into the environment, it maybe transported or transformed, it may persist, enter, and be concentrated in the food

chain, or it may be degraded or deposited where humans cannot come in contact with it. It can reach humans through the air they breathe, the food they eat, or the water they drink, or by contact with their skin. There are many ways to predict, **estimate,** and measure the exposures of humans to environmental agents, but it is a complex, uncertain undertaking.

Typically, researchers measure levels of pollutants at the sources of their discharge into the environment and then use models to predict the concentrations reaching humans. Personal monitoring devices produce more realistic measurements of human exposure. Even so, age, physical activity, nutritional conditions, and other factors related to lifestyle can affect the body's uptake of the pollutant, leading to uncertainty about the dose that any one individual receives.

The most direct measure of human exposure is through biological monitoring of body fluids or tissues. But these techniques are expensive and not without risk if they require biological samples. Generally, **estimates** of exposure are generated by reconstruction of behavior and surveys of recall as in early parts of the Ranch Hand study mentioned above.

Social and Political Factors in Decisionmaking

As research identifies the potential adverse health effects of toxicants to which humans may be exposed, the public conveys its concerns to Congress, and Congress considers and often passes laws to address those concerns. This reactive mode may limit the capacity of agencies, such as EPA, to structure long-term solutions **that are** both efficient and effective. In 1991, then EPA Administrator William K. Reilly stated:

> For 20 years we have established goals on a pollutant-by-pollutant and medium-by-medium basis without adequately considering broader environmental quality objectives. We have seldom if ever been directed by law to seek out the best opportunities **to** reduce environmental risks, in toto, or to employ the most efficient, cost-effective procedures.

Regulatory decisions are often made with inadequate data and in response to statutory mandates. This limits the capacity of science to support regulatory decisions. Furthermore, scientific input is but one element in the formulation of regulatory decisions. As in all kinds of human activity, change is difficult, and various factors—risk perception, economic impact, social values, lack of **trust** between the public and industry, and less than complete confidence in government—play a role in decisionmaking. In such **a** context, new facts from science may have little impact.

Some analysts and scientists (e.g., Abelson, 1993; Gori, 1992; Moolenaar, 1992) maintain that more scientific information is needed to support environmental rulemaking by the agencies. Openly critical, they contend that advances in the biological and biomedical sciences make their way too slowly into regulatory decisionmaking and that those decisions remain mired in the science of the past two decades. Jasanoff (1990) characterizes the contention that better decisionmaking will result from more and better scientific information as the ''technocratic viewpoint. '

Not everyone shares that view. First, it is difficult to prove that better (or "more," as some detractors say) science has improved decisionmaking. Since the risks that most regulations address are below the limits of detection by epidemiology, it is impossible to know if one approach or the other produced better results in protecting health. Understandably, few examples of improved decisionmaking exist, and the social and political implications of decisionmaking may mask any effect science has on the process (Jasanoff, 1990).

A more basic point is that risk assessment is contentious because scientific data are seldom definitive and consensus on some issues appears unlikely. A recent National Research Council report on risk assessment included rare majority and minority recommendations; the issue with no

agreement was whether toxic effects observed at the maximum tolerated dose are predictive of human risk. This topic has been debated for decades (NRC, 1993).

Moreover, research findings can complicate risk assessment (Huff, 1993). Research takes time, and more research can be used to serve the political objective of delaying regulatory action (O'Brien, 1993; Olson, 1984; Silbergeld, 1993). Finally, risk assessment may be the last point at which science is considered because of the power of policy mandates that place more weight on the side of safety (Graham, 1991).

Tradeoffs, Teamwork, Trust, and Leadership

An optimistic view is that the field of health risk assessment is still young. With the advances being made in the biological and biomedical sciences, the field of toxicology will evolve to provide better data; combinations of epidemiologic and laboratory-based investigations will produce more revealing information; and measurements of exposure to environmental chemicals will sharpen risk assessments.

Nevertheless, it is unrealistic to expect research to resolve all uncertainty and eliminate all differences in interpreting data. Solving the problems in environmental risk assessment goes beyond more and better science: it requires building trust among government, industry, and citizens. It also requires leadership in setting realistic goals and arranging collaborations of researchers from various disciplines and sectors of society.

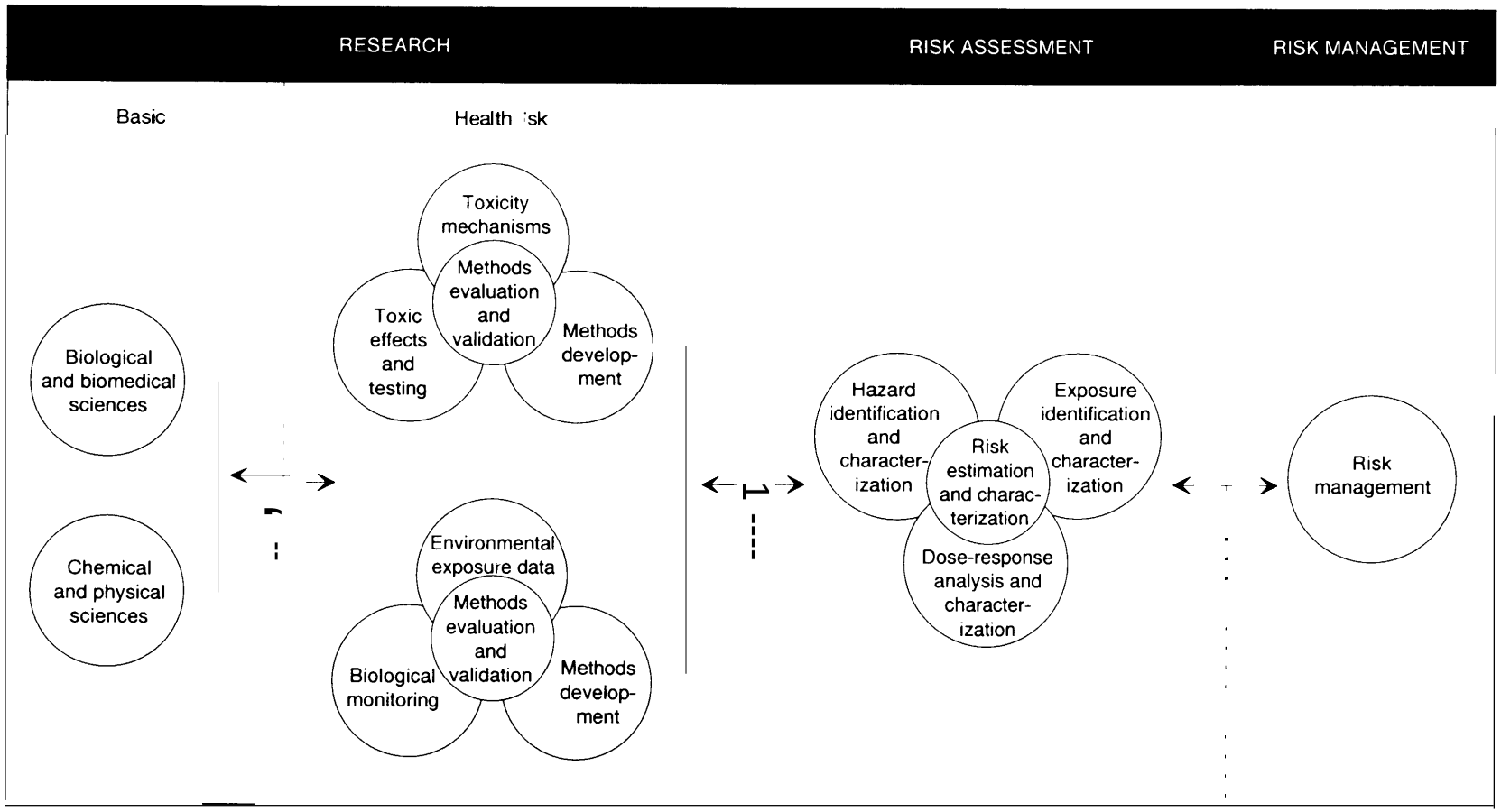
In 1983, the National Research Council Committee on the Institutional Means for Assessment of Risks to Public Health called for separating risk assessment and risk management (NRC, 1983). This recommendation was taken up by the agencies, which separated the functions of scientists and decisionmakers to prevent 'subtle value judgments" from influencing empirical analyses before they reached the regulators. Now, a decade later, some scientists argue that opportunities are being lost in an inefficient system whereby those making decisions are unaware of the process generating the information on which their decisions are based. One of the principal deficiencies of that system, according to Finkel (1990), is that decisionmakers remain insulated from the inherent uncertainty in the process.

Still, the division between risk management and risk assessment has never been complete. All kinds of policy judgments reach back into the risk assessment process. For example, the decision to accord greater weight to public health than to industrial output greatly influences the default position that estimates cancer risk using a no-threshold model. However rigid or flexible the boundary between risk assessment and management, it is clear that the relationships between the two are under discussion and perhaps in flux. Moreover, as Congress expresses interest in risk assessment, its discussions and mandates will influence both the process itself and risk assessment research.

LINKING HEALTH RISK RESEARCH TO DECISIONMAKING

The relationship between research and decisionmaking is complex. OTA developed figure 5-2 to describe the relationships among the various research activities in health risk assessment and decisionmaking. Previously, the National Research Council (NRC, 1983) depicted a unidirectional flow of information from research to decisionmaking, which emphasized the compartmentalization of the process for providing public transparency (see figure 2-1). Yet information sharing throughout the process is important to increase the efficiency of research for decisionmaking. Thus, figure 5-2 highlights the bidirectional flow of information as well as the integration and synthesis of information from the various disciplines and types of research. The evaluation and validation of methods can serve as the focal point for integrating all the areas of health risk

Figure 5-2—Linking Research on Health Risks to Decisionmaking



SOURCE: U.S. Congress Office of Technology Assessment, 1993.

research, given that a new model or method must be examined and compared with methods of known and established veracity. Figure 5-2 also indicates OTA's stress on the interdependency of research activities, the risk assessment process, and policymaking.

The link between health effects research and the basic biological, chemical, and physical sciences has often been neglected in discussions about health risk assessment research. Now, however, bridges are being constructed between basic and health risk research in response to calls from Congress (Brown, 1993; U.S. Congress, House Committee, 1992) and the private sector (Carnegie Commission, 1992) for linking science to social needs. Although some basic scientists may respond grudgingly at first, later they may actually find it rewarding to modify and redirect their research to serve health risk assessment. Much as research on AIDS or cancer links social needs and unexplored avenues of research, improving risk assessment can similarly endow toxicological research with an objective that transcends the purely scientific.

Health risk assessments, to be valid, require the participation of scientists from many disciplines. Those from the toxicological and biomedical sciences are best qualified to critique the validity of the scientific underpinnings of assessments. But when data are lacking, assumptions and policy positions with embedded value judgments are used, arguably, as tools to complete the assessment, their selection may benefit from involving practitioners of disciplines other than the biological, chemical, or physical sciences. Jasanoff (1993) argues for "bridging the two cultures of risk analysis' '—the ''hard, ' or quantitative, sciences and the ''soft, ' or nonquantitative, disciplines, such as the behavioral and political sciences.

Although OTA did not address whether risk assessment itself should be formally considered a scientific endeavor, making risk assessment an active field of research may well be what is needed to facilitate the application to health risk assessments of the new biological understanding of diseases and toxicological mechanisms. From that perspective, OTA sees risk assessment as involving the analysis and synthesis of all that is known about the risk at hand, such as a specific chemical or class of chemicals. For example, risk assessments use findings from epidemiologic studies or results from animal toxicity tests to generate hypotheses about risks to human health. A substantial amount of reasoning and judgment is required in determining whether the composite data on toxic effects, exposure, and dose-response characteristics as a whole make the risk hypothesis tenable.

In contrast to the approach described here, risk assessments are all too frequently performed by merely stacking up the positive findings that imply that risk exists, without careful attention to conflicting results and alternative interpretations. A more iterative process of questioning can reveal the strengths and weaknesses of the case for the existence of risk and identify the need for further research at each step. In that way, gaps in the data can be recognized and research conducted in response. Not every alternative interpretation need be considered or presented every time. Risk characterization and communication can serve as a focus for the iterative process of risk assessment and abridge between risk assessors and decisionmakers.

Risk characterization summarizes and interprets the information available about a given risk for risk managers and the public. There is general agreement that methods of risk characterization are poorly developed and that efforts to improve them have been neglected (Gray, 1993). Research to improve risk characterization is directed toward developing methods to describe more completely the uncertainties and assumptions and to express the full range to plausible estimates of risk.

For example, one of the methods frequently proposed for distinguishing among alternative estimates of risk is the distributional approach, which is an outgrowth of uncertainty analysis in

the decision sciences (Morgan and Henrion, 1990). It uses explicit expert judgment to analyze and quantify the plausibility of alternative interpretations of available data (Otway and von Winterfeldt, 1992). This method can capture the range of scientific evidence and opinion on key biological uncertainties. Proponents of describing ranges of risk believe that it avoids the focus on a single numerical estimate of risk and requires risk managers to confront qualitative uncertainties, such as the likelihood that a compound is or is not a carcinogenic hazard to humans (Gray, 1993).

The purpose of risk characterization is to help risk managers and others understand the results of complex risk assessments. For a risk manager, good risk characterization will aid decisionmaking. But for that to occur, a risk manager must understand the basis for risk estimates including the scientific, analytical, and policy choices that underlie the assessment. Improving risk characterization will also help legislators, journalists, and the public understand the nature and magnitude of the day-to-day risks citizens in this country face.

Two Federal programs support research on risk communication and decisionmaking. EPA's Office of Policy, Planning, and Evaluation conducts and supports research in risk communication. In addition, the agency holds workshops and offers training in risk communication and decisionmaking. The National Science Foundation funds research on decisionmaking through the Decision, Risk, and Management Science (DRMS) program in the Division of Social and Economic Sciences. For the past decade, DRMS has operated a competitive grants program that supports research to develop new methods in the field of decision theory and methods to optimize the technical handling of risk probability. The program funds research on social factors that influences risk assessment, and it seeks to distinguish between technical and social definitions of risk (Cantor, 1993).

SUMMARY

Research has had only a modest effect on efforts to revise the science policy assumptions adopted in EPA's risk assessment guidelines. It has, however, had a substantial impact on chemical-specific risk assessment and consequently on regulatory actions, and it is currently generating considerable debate as EPA considers revisions to its 1986 cancer risk assessment guidelines.

Three interacting factors account for the limited impact of new scientific research on the science policy assumption adopted in EPA's risk assessment guidelines. The nature of the assumptions, the importance of the assumption to the paradigm underlying the regulatory approach, and the policy reverberations associated with changing specific default positions all jointly limit any expedient change of the agency's science policy assumptions based on new knowledge.

Health risk research and decisionrnaking are interdependent. As research identifies potential adverse effects on health, the public conveys its concern to Congress, and Congress considers and passes laws to address those concerns. This reactive mode limits the capacity of agencies to structure long-term solutions including appropriate research.

Although the sciences can provide solid foundations for choices about reducing health risks, their contribution is limited because measurements and interpretations of data are inherently uncertain. In addition, science is only one of the elements in regulatory decisions. Legislative mandates, social values, technical feasibility, and economic factors may assume more prominent roles, depending on the specific issue. Solving the problems in health risk assessment goes beyond more and better science, it requires building trust among government, industry, and citizens. It also requires leadership in setting realistic goals and encouraging collaboration in research.

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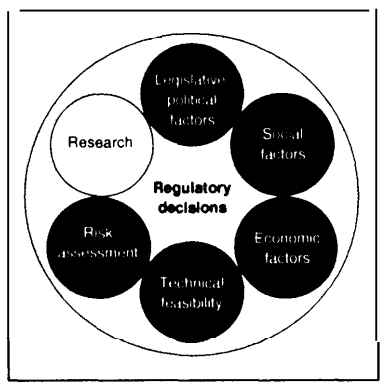
Indoor Radon: A Case Study in Decisionmaking

6

When radon gas, which originates in the Earth's crust, is emitted into the open air, it is rapidly diluted to the low 'background' or 'outside' levels that are found everywhere and are inevitable. When it is emitted into a home, school, or other building, dilution is slower, and the concentrations of radon inside structures are usually higher than the concentrations outside. These higher levels raise health concerns because studies have shown higher levels of radon are associated with higher rates of lung cancer in uranium miners and other workers exposed.

Responding to those concerns, Congress and the Environmental Protection Agency (EPA) have considered methods to reduce the risks posed by indoor radon. Most indoor radon enters buildings directly from the soil, and efforts to reduce those exposures include EPA programs to inform homeowners about the radon risks and how to reduce radon inflow into buildings. The private sector has also acted to reduce radon in homes by imposing requirements for measuring and, if deemed necessary, reducing indoor radon as a condition in real estate contracts.

EPA cannot, of course, regulate radon from soil because radon from that source enters homes directly without passage through any entity that can be regulated. Some radon, however, enters buildings through the water supply, and the agency can regulate radon in water just as it regulates other contaminants under the Safe Drinking Water Act (SDWA) (P.L. 93-523 and 99-339).



Some Members of Congress, including the Chairman of the House Committee on Science, Space, and Technology, asked the 0ffice of Technology Assessment (OTA) to examine an ' 'inconsistency' in EPA's approach to radon. The request, which

arrived after this study of health risk assessment research had begun, resulted in an analysis of issues related to radon, which is included in this report.

This chapter reviews and comments on the bases for assessing the risks posed by indoor radon and radon in water and discusses ongoing and possible future research projects. It also discusses the policy issues surrounding the congressionally identified "inconsistency' that arises because of differences between the goal of the Indoor Radon Abatement Act (IRAA) (P.L. 100-551), EPA's proposed level for the regulation of radon in drinking water under the SDWA, and the level of indoor radon at which EPA urges homeowners to take voluntary action to reduce radon infiltration (box 6-A). The inconsistency is quantitative: The IRAA sets the target for indoor air concentrations of radon as equal to concentrations in outdoor air. The proposed regulation under the SDWA sets a stricter level, imposing regulations on water suppliers so that emissions of radon from water to air would be reduced to about one-tenth of the level of radon in outdoor air. The voluntary action level EPA urges for homeowners-about eight-times higher than the level of radon in out-door air-is higher than either the IRAA goal or the SDWA regulatory limit. In response to the congressional request, this chapter also includes a rationale for "policy options for developing a consistent approach to reducing the risk from radon. '

HOW LARGE IS THE WATERBORNE RADON PROBLEM?

EPA (U.S. EPA, 1993b) estimates that about 19 million people are served by water systems that exceed its proposed regulatory limit for radon in water of 300 picoCuries per liter (pCi/L).[1] To reduce current concentrations that exceed that hit, the agency has selected aeration as the Best Available Technology (BAT). A number of aeration methods are available, which, according to EPA, will eliminate up to 99.9 percent of the radon as well as some fraction of other volatile, toxic contaminants from water (U.S. EPA, 1991). The volatility of radon, which makes aeration EPA's treatment of choice, results in waterborne radon being a problem primarily in water supplies that depend on groundwater because radon in surface water volatilizes into the outdoor air before it enters buildings.

Some background information is necessary to put the proposed regulation of radon in water into perspective. The proposed regulation depends upon the interpretation of epidemiologic studies, congressional actions in response to the projected regulation, some risk assessment models developed by EPA, and a series of reviews by EPA's Science Advisory Board (SAB).

RADON, MINING, AND INDOOR EXPOSURES

Radon is a decay product of radium, which itself is a decay product of the uranium found ubiquitously in the Earth's crust. Radon also undergoes radioactive decay, and it is the products of radon decay (called radioactive "progeny' or "daughters") that are associated with lung cancer. Radium and radon, of course, are especially abundant in radioactive deposits, and the Federal Government's demand for uranium to make atomic bombs during and after World War II resulted in a rush to mine such deposits. As a consequence, miners were exposed to high levels of radon. Beginning in the 1950s, results from

[1] A pico (p) Curie (Ci) is a measure of radioactivity. "Pico" means one-trillionth, so a pico Curie (pCi) is one-trillionth of a curie. One Curie is equal to 3.7×10^{10} radioactive disintegrations per second and a pCi is then 3.7×10^{-2} per second or 2.2 disintegrations per minute. The measure 4 pCi/L means that the radioactivity in one liter (L) of air (or water) produces 4 X 2.2 disintegrations per minute = 8.8 disintegrations per minute. Although pCi/L is the unit of measure most often used in the United States to express concentrations of radioactivity, in other countries, "Bq/rn^3" is more commonly used. A becquerel (Bq) is equal to 37 pCi, and one cubic meter (m^3) is equal to one L. Therefore, 1 pCi/L is equal to 37 Bq/m^3. (Usually, when conversions between the two units of measure are made and no calculator is available, the conversion factor is 40; that is, 1 pCi/L is about equal to 40 Bq/m^3.) Various detectors are available to measure radioactive disintegrations.

Box 6-A--Reducing Exposures to Radon: A Goal, an Action Level, and a Regulatory Standard

Nazaroff and Teichman (1990)[1] calculate that **current** exposures to radon are associated with about 15,700 lung cancer deaths annually. They estimate that 97 percent of those deaths will occur in smokers, and 3 percent will occur in nonsmokers. Indoor concentrations of radon are higher than those outdoors, and the Federal Government is directing several efforts at reducing indoor exposures. At present, there is a goal for reducing indoor radon concentrations, an action level to guide voluntary reductions, and a proposed regulation to reduce concentrations of radon in water.

A **Goal:** The Indoor Radon Abatement Act sets the goal of reducing indoor radon concentrations to the concentrations found outdoors-0.4 pCi/L. Currently, the average indoor concentration is about 1.5 pCi/L, with about 6 percent of all houses having concentrations greater than 4 pCi/L. The Environmental Protection Agency states that it is difficult to reduce indoor levels below 2 pCi/L (apparently for houses that have levels greater than 4 pCi/L).

An Action Level: EPA recommends that indoor radon concentrations be reduced to 4 pCi/L or below, a level considered technologically feasible for all houses. Reducing all indoor radon concentrations that are now greater than 4 to 2.7 pCi/L is expected to eliminate about 3,500 deaths (a reduction of about 17 percent). (The level of 2.7 pCi/L is the mean between the national average of about 1.5 pCi/L and the action level of 4 pCi/L.)

A Regulatory Standard: Under provisions of the Safe Drinking Water Act, EPA proposes regulating radon in drinking water so t hat t he concentration of radon in air that results from the volatilization of radon from drinking water is no more than 0.03 pCi/L. According to EPA, reducing all higher concentrations of radon in water to this level would eliminate 80 radon-associated lung cancer deaths annually (a reduction of about one-hatf of 1 percent).

[1] W.W. Nazaroff and K. Teichman, "Indoor Radon," *Environmental Science and Technology* 24(1990):774-782.

SOURCE: Office of Technology Assessment, 1993.

studies by the Atomic Energy Commission showed that lung cancer was more common in U.S. uranium miners than in other men, and studies of miners elsewhere—in Czechoslovakia, Sweden, and Canada—reported similar results (Brill, 1990).

Results from studies of miners identify radon as a hazard to human health, and assessing the risk that radon poses to human health is free from the problem of animal-to-human extrapolation that besets most health risk assessments. Those results identify radon as a hazard, but they leave risk assessors and decisionmakers with the problem of extrapolating from the effects seen at ''high exposure levels' in the miners to estimates of expected effects at the, generally, ''low exposure levels" found in houses, Such high-to-low extrapolations are a common issue with substances that are identified as a hazard to human health as a result of studying human populations. Usually, researchers accumulate the human data from studies of people exposed to high concentrations of chemicals or radiation in the workplace or in medical practice. Then those data must be used to extrapolate to the risks at lower ''environmental' exposures (U.S. Congress, OTA, 198 1; U.S. DHHS, National Toxicology Program, 1991).

In the late 1970s, Congress recognized some risks posed by nonoccupational exposures to radon and passed the Uranium Mill Tailings Radiation Control Act of 1978 (P.L. 95-604). That act directed EPA to set limits on radon emissions from inactive uranium processing sites and to establish acceptable levels for indoor radon in buildings associated with those sites.

That narrow focus on occupational or residual exposures that remained from closed-down mining and refining operations disappeared in 1984.

As the story is commonly told, it ended when Stanley Watras, an engineer at the Limerick Nuclear Power Plant in eastern Pennsylvania, passed through a radiation detector at the plant. He triggered the detector's alarm every day for almost 2 weeks in a row, which was surprising given that his co-workers seldom triggered the alarm. Mr. Watras guessed that his radioactive contamination might be coming from a source other than his work, and as an experiment one morning, he went directly to the detector before he went to his job. The alarm sounded. A subsequent inspection showed that Mr. Watras was bringing in radon from his house on his clothing and his person. Measurements in his house showed radon levels that resulted in a radiation dose well above those permitted in industrial settings (Taylor, 1990). What is less commonly reported is that Mr. Watras' house was directly over the tunnel of a uranium mine and that the house next door had only background levels of radon, about one-thousandth of those detected in his house (Moeller, 1989).

Although some scientists had identified indoor radon as a hazard by the late 1970s (Nero, 1990), Mr. Watras's saga began the process that widely publicized radon in homes as a health risk. Within 2 years, EPA (1986) published *A Citizen's Guide to Radon,* which" attributed between 5,000 and 20,000 lung cancer deaths annually to exposure to radon. A year later, when the agency (U.S. EPA, 1987) cataloged sources of environmental cancer risks, the numerical estimate for cancer mortality from indoor radon (between 5,000 and 20,000 annual deaths) was about the same as the estimate for mortality from skin cancer (10,000) caused by exposure to sunlight. Both of those estimates were much higher than risks of cancer associated with other sources (table 6-l). In the 1992 revision of *A Citizen's Guide to Radon,* EPA and the Department of Health and Human Services (DHHS) estimated that radon causes about 14,000 cancer deaths annually (U.S. EPA and DHHS, 1992). Although EPA's estimates have varied across the years, they have consistently associated several thousand cancer deaths with exposures to radon.

Table 6-1—Major Environmental Cancer Risks and Cancer Risks From Water

Source of risk	Estimated annual cancer mortality
Indoor radon	*5,000-20,000'*
Sunlight	10,000
All airborne cancer risks (excluding radon and environmental tobacco smoke)	2,267-3,294
Pesticides	3,075-6,150
Radiation in drinking water	37-730[b]
All chemicals in drinking water	215-430

a Other EPA estimates vary upwards from this range.
b Other EPA estimates vary within this range.

SOURCE: M. Gough. 1989. "Estimating Cancer Mortality." *Environmental Science and Technology* 23:925-930, *based* on U.S. Environmental Protection Agency. 1987. *Unfinished Business.*

Smokers are much more likely than nonsmokers to develop lung cancer as a result of radon exposure. Nazaroff and Teichman (1990) estimate that only 3 percent of the projected mortality from radon-associated lung cancer will occur in nonsmokers; EPA (1992a) estimates that 70 percent of deaths from radon-related lung cancer will occur in smokers, 24 percent in former smokers, and 6 percent in nonsmokers. In the 1992 *Citizen's Guide (U.S.* EPA and DHHS, 1992), EPA and DHHS point out that, for smokers, the most important step to reduce risks from radon is to quit smoking.

Currently, EPA recommends that homeowners take action to reduce indoor radon concentrations to 4 pCi/L, a level that can be reached in almost every home. The agency also states that levels in many homes can be reduced even more, to about 2 pCi/L (U.S. EPA and DHHS, 1992). This goal of 2 pCi/L is a little higher than the average indoor concentration in the United States (1.25 pCi/L), and it is from about 3 to 6 times higher than the outdoor average concentration of 0.3 to 0.5 pCi/L. Remediation methods recommended by EPA include increasing ventilation below slabs and sealing basements and foundations to reduce entry of radon.

Interest in the health effects of indoor radon has prompted more than a dozen epidemiologic studies comparing the rates of lung cancer in people who live in homes with higher levels of radon with those of people who live in homes with lower levels. Interpreting results from the various studies and attempting to reconcile conflicting results require that some attention be given to how the studies were designed and executed.

EPIDEMIOLOGIC STUDIES OF RADON-RELATED LUNG CANCER

Epidemiology is the study of the distributions of diseases in populations and the conditions that contribute to the appearance or progression of diseases. The most basic epidemiologic information is provided in a case report, which describes the occurrence of a disease (usually rare and therefore attracting attention) or a cluster of cases of a disease. Such reports identify populations for further investigation or study, but they provide no analysis of the putative links between exposure and disease, For example, a report of a rare form of muscle disease in a worker in a chemical plant would alert health professionals to a possible link between that disease and exposures to some toxic agent in the plant. But the disease could have occurred completely by chance, and further investigation would be necessary to examine the worker's exposures to specific chemicals and other studies would be needed to see whether other exposed workers suffered from the same disease or some precursor to it.

Beyond case reports, most epidemiologic research can be classified as one of three kinds: ecological studies, case-control studies, and cohort studies. Researchers have used all three types to investigate relationships between radon exposure and lung cancer. In general, ecological and case-control studies have been used to examine questions about indoor radon and case-control, and cohort studies have been employed for investigations in occupational populations.

In ecological studies, scientists compare rates of lung cancer in populations in geographical areas that have different average levels of exposure to radon. Case-control studies involve locating cases (persons who have lung cancer or the records of people who have died from lung cancer) and comparing the exposures of the cases to the exposures of controls (people who do not have lung cancer). In a cohort[2] study, scientists compare the rates of lung cancer in a group of people, such as miners, who share types, times, and intensities of radon exposure that differ from those of other groups. In ecologic and cohort studies of a disease as common as lung cancer, many cases of the disease will be expected in all the studied populations. Finding that the rate of the disease is higher in a population exposed to higher levels of radon is taken as evidence of a connection between exposure and disease after ruling out other factors that might account for the difference. For instance, if smoking was more common in the group with higher rates of lung cancer, a careful analysis would be necessary to ascertain the separate and combined effects of smoking and radon.

Ecological studies provide no direct comparisons between the exposures of individuals and their diseases. Such studies are relatively easy to do in areas in which records of disease incidence or deaths are available and in which there have been enough measurements of indoor radon that scientists can estimate average levels of exposure for the area. When completed, however, ecological studies provide no information about whether the persons who developed the disease had exposures near the average level or well above or below it.

Case-control studies are useful for studies of both indoor radon and exposures in the workplace, and they can provide information

[2] As an epidemiologic term, a' 'cohort' is a group of people who share certain characteristics (the word cohort originally identified one-tenth of a Roman legion).

about individual exposures and frequency of disease. One stumbling block for such studies is the difficulty of determining all past exposures to radon. For instance, many people move several times during their lifetimes, and a complete inventory of their exposures to indoor radon would require measurements in each of their homes. A further complication in interpreting such studies is how to make allowances for ''competing risks' that contribute to the risks of developing lung cancer. The most important is smoking; the second most important is probably environmental tobacco smoke (Brownson et al., 1992).

Most of the available quantitative information about the risks posed by radon comes from cohort studies of uranium miners that compare the rates of lung cancer among the miners with rates among other workers. Because of the latent period of 20 or more years between exposure to radon and the appearance of lung cancer, scientists who study rates of lung cancer among miners are most interested in their levels of exposure over two decades ago and more. That need for a long-term view complicates interpretation of the studies because accurate measurements are seldom available for past exposures.

Ecological Studies

The absence of direct ties between the exposure of an individual and his or her health status complicates interpreting the results of ecological studies. Using average (or group) information to estimate exposures results in the "ecological fallacy,' which links together specific health consequences among individuals and estimates or measures of average exposures. Only careful (and perhaps impossible) analysis would clarify whether the group measure was appropriate to describe the exposure of a person with a disease.

Although it may seem reasonable to conclude that people with an illness in a group exposed to a higher average level of radon were exposed to more radon than people exposed (on average) to lower levels of radon, there is no way to be certain of that. No single ecological study nor the complete set of such studies taken together will resolve the question of whether nonoccupational exposure to radon increases the rate of lung cancer.

Samet (1989) reviewed 11 ecological studies:

> In spite of crude exposure measures, most of these studies showed associations between exposure to radon decay products and the incidence of or mortality from lung cancer. Two studies of counties in the Reading Prong [the area of Pennsylvania in which Mr. Watras lived] are of particular interest because of the high number of homes in this region with high radon concentrations.

Of particular interest in discussions of radon in water and health risks are two studies reviewed by Samet (1989) that analyzed rates of lung cancer in relation to levels of radioactivity in water supplies. One of the two studies found an increase in rates of lung cancer in both men and women as a function of estimated greater exposures to radon; the other found an increase in men but not in women. The latter result would be an unexpected one if radon in household water made a significant contribution to the risk of lung cancer.

Overall, Samet (1989) concluded that 5 of the 11 studies were consistent with a correlation between exposure of higher levels of radon exposure and lung cancer, and one (one of the "water' studies) found an increase in men but not in women. Four of the 11 found no statistically significant increase in rates of lung cancer; one study reported an inverse correlation between exposures to radon and rates of lung cancer. That ''negative study and others done by the same scientist and his colleagues have received a great deal of attention, perhaps because the associations run counter to conventional ideas about radon and risk (Hanson, 1989).

Cohen (Cohen, 1990, 1992) investigated associations between rates of lung cancer and levels of radon using tens of thousands of measurements in

living areas and basements in houses in the 48 contiguous States of the United States. On the one hand, Cohen accepts that the ecological fallacy means that such studies cannot shed light on the question whether radon causes lung cancer because there is no way of knowing the levels of exposure of the people who develop lung cancer. On the *other* hand, he argues that the ecological fallacy does not prevent such studies from answering the question of whether a linear, no-threshold relationship exists between exposure to radon and lung cancer (see the discussion in ch. 2). According to Cohen, if that relationship is correct, cancer rates should vary directly with average countywide exposures. Cohen found that rates went down as exposures increased.

Immediately, objections were raised to Cohen's finding. For instance, how does smoking vary from county to county? Cohen's response was to compare cigarette sales in different States, factor that information into his analysis, and demonstrate that the negative correlation between levels of radon and lung cancer persists. What kind of correlation would be expected between current rates of lung cancer and current household exposures? Given the latent period between exposure and manifestation of disease, the exposures of interest occurred many years ago. Cohen has adjusted his analysis to consider that fact and has accumulated measurements of radon levels in far more houses than any other investigator. Nevertheless, other investigators have reported no replications of Cohen's results.

Taken together, the ecological studies present a confusing picture. Each additional study, whether it shows a positive association, no association, or a negative association, can be added to the tally, but no one study by itself nor all the ecological studies taken altogether will convince everyone about whether low-level radon is associated with lung cancer. Moreover, calculating reliable, quantitative estimates of risk from such studies is impossible.

Case-Control Studies

Case-control studies provide more definitive information about exposure than do ecological studies. In case-control studies of indoor radon, scientists (Blot et al., 1990; Schoenberg et al., 1990; Svensson, Pershagen and Klominek, 1989) often focus on women because fewer women smoke compared with men, and women typically spend more time at home.

Like the ecological studies, the case-control studies have yielded contradictory results. For instance, both Schoenberg et al. (1990) and Svensson et al. (1989) reported elevated levels of lung cancer among women who lived in houses with higher levels of radon. As the authors of those papers pointed out, the numbers of women included in the studies, especially the numbers of women exposed to higher levels of radon, were quite small. Only 24 of 433 women with lung cancer in the Schoenberg et al. (1990) study had lived in homes with concentrations of radon greater than 2 pCi/L. The small number of cases makes it difficult to interpret those studies, and many results showing excesses of cancer in the more highly exposed women were not statistically significant; that is, the excesses that were detected might have arisen by chance. Furthermore, no consistent relationship was found between smoking habits and lung cancer in the Schoenberg et al. (1990) and Svensson et al. (1989) studies, which introduces some uncertainty in interpretation because smoking and rates of lung cancer rates usually vary directly with each other.

Blot et al. (1990) studied women in a province of China and found that 'No association between radon and lung cancer was observed regardless of cigarette-smoking status, except for a nonsignificant trend among heavy smokers. ' Those authors go on to interpret their results as indicating that "projections (of cancer risk) from surveys of miners exposed to high radon levels may have overestimated the overall risks of lung cancer associated with levels typically seen in this

Chinese City. ” Letourneau et al. (1993) reported comparable results from a case-control study of 750 people with lung cancer in Winnipeg, Canada. They found that ‘‘no increase in the relative risk of any of the histologic types of lung cancer observed among cases was detected in relation to cumulative exposure to radon. ’

Lubin et al. (1993) prepared an analysis and comparison of the Blot, Schoenberg, and Svensson studies and concluded that any link between exposure to radon and risk of lung cancer is only weakly demonstrated in the studies, if it is present at all. Nevertheless, the fact that no increase was detected does not necessarily mean that none was there. It might have been present but undetectable because of the (small) size of the study.

Similarly, Ruosteenoja (1991) found “no significant correlation between the average radon exposure and incidence of male lung cancer. Yet, as the author pointed out, her study had little chance to detect the level of risk predicted from the miner studies. As in other studies, the small number of cases made it possible that any effect of radon that was present went undetected against the number of lung cancer cases expected regardless of the presence or absence of radon.

So far, case-control studies leave open the two possibilities that either the risk of developing lung cancer from exposures to indoor radon are zero (or at least below the limit of detection) or that it is compatible with the level of risk estimated from the miner studies. Additional case-control studies of sufficient size and ‘‘power’ might provide the information needed to determine whether risks projected from the miner studies are realized in people exposed to lower levels.

One alternative to a single large study is to carry out a meta-analysis of the already completed and soon to be completed studies and to combine those results to produce a more definitive answer. Meta-analysis is not a panacea, but it is a developing subdiscipline with applications to epidemiology (Dickersin and Berlin, 1992) and risk analysis (Society for Risk Analysis, 1993) as well as in health and behavioral sciences in general (Olkin, 1992). The Department of Energy has begun preparations for conducting a meta-analysis of case-control studies to begin in about 2 years when some ongoing studies will have been completed.

Researchers expect important findings from two ongoing studies in the United States that involve Midwesterners who tend to live in one house for long periods and who live in either Missouri or Iowa, States with relatively high radon concentrations. Of 524 homes examined in Missouri, 33(8 percent) had radon concentrations of 4 pCi/L or greater, and 8 (2 percent) had concentrations more than 8 pCi/L. Results already reported from that study verified predictions by Lubin et al. (1990) that people who move frequently have lower exposures than people who remain in a single home. Given the relative rarity of ‘hot homes, ’ a person who moves from such a home is more likely than not to move to a house with lower levels. Alavanja et al. (1992) report that 11 percent of Missouri women who lived in a single house for 30 years had been exposed to concentrations greater than 4 pCi/L for that time; 6 percent of women who lived in two houses had exposures that high; and none of the women who lived in three or more houses had such exposures. Investigators expect to complete their analysis of the relationships between levels of radon and cancer incidence in the 600 nonsmoking women with lung cancer in the study by mid-1993 and to publish them by the end of the year.

A research team at the University of Iowa is conducting the second Midwestern study. The investigators are studying women who smoke, to shed light on interactions between smoking and radon in cancer causation; studies of women who do not smoke are expected to identify any direct relationships between radon and lung cancer (Lynch, 1993). Equal in size to the Missouri study, the Iowa study includes a total of 600 cases of lung cancer and 1,400 controls. From the results of the EPA survey of radon in homes, it appears that about 70 percent of Iowa homes have radon concentrations greater than 4 pCi/L, and

those higher radon 1evels favor detecting associations between exposures and lung cancer-if they exist. The principal investigator of the study expects results to be published in late 1997.

Cohort Studies

Since the 1950s, scientists have studied the health of miners (in particular, uranium miners, who were frost seen to be at risk) and determined that exposure to radon increases the incidence of lung cancers. Samet (Samet, 1989) reviewed 20 studies of underground uranium miners and concluded that the data show consistent relationships between exposure to radon and elevated rates of lung cancer.

Exposure levels of the miners are expressed in working-level months (WLM), which are an approximation of the radiation exposure experienced by a uranium miner in 1 month's work. Miners in the various epidemiologic studies of radon had histories consistent with cumulative occupational exposures that ranged from 1 to 10,000 WLM. The current occupational limit for exposure to radon is 4 WLM annually (NRC, 1988), and a miner exposed at the current limit for 40 years would accumulate 160 WLM from his workplace. In comparison, the 70 years lifetime cumulative exposure of residents of homes with average concentrations of indoor radon is about 20 WLM (Samet, 1989).

As might be expected, cancer is far more frequent in the miners exposed to hundreds or thousands of WLM than in those exposed to lower levels. However, Bodansky (1990), in a review of those data, stated " . . . miner studies do seem to suggest a statistically significant positive effect, for cumulative exposures as low as 20 to 50 WLM. When the cumulative exposure is low, however, either due to low radon levels or short duration of employment, the data is vulnerable to confounding factors. ' Despite the suggested effect at exposures below 100 WLM, correlations between rates of lung cancer and higher levels of exposure dominate the risk assessment.

A question is raised whether the relationships seen between cancer and radon at hundreds of WLM, which are experienced in a few years, accurately predict cancer risks at levels of 10 or 20 WLM accumulated over a lifetime. Some scientists in EPA's Office of Science, Planning and Regulatory Support (Ulsamer, 1993) describe the problem this way: "The potential effects of differences in dose rates between miners (who are exposed for an average of 7 years to 20+ WLM/yr) and home residents (who are exposed for an average of 72 years to 0.22 WLM/yr from soil radon and 0.01 WLM/yr from water radon) . . . needs to be discussed." In this respect, indoor radon is a prime example of a problem in high-to-low-dose extrapolation.

Other Cancers

Henshaw and his colleagues (Henshaw et al., 1990; 1992) reported associations between levels of radon and the incidence of some cancers other than lung cancer in several countries. Those investigators relied upon ecological studies, making their results subject to the ecological fallacy, which reduces their value for decisionmaking. Although some scientists have treated the associations as possibly indicating a role for radon in other cancers (Pete, 1990), Doll (1992) points out that rates for none of the cancers that Henshaw et al. (1990) associate with radon exposure were elevated among miners, and a recently published study of 4,000 Czech miners found no association between radon exposure and leukemia (Anon, 1993a). Moreover, Miller et al. (1993) directly examined the possibility of an association between residential exposure to radon and the occurrence of a form of leukemia that had been suggested by Henshaw et al. (1990). They found no evidence for the association. Currently, there is little support for an association between exposures to radon and other cancers.

POLICY

EPA divides its regulatory programs along media lines-air, water, industrial wastes, and so forth. It has approached the issue of indoor radon as a media problem; thus, it has different policies toward radon entering buildings in air and water. The agency has not proposed regulating radon that is emitted directly from the soil, but it has proposed regulation of water suppliers as a method to reduce exposures to radon. Some scientists, Members of Congress, and other policymakers have recognized that indoor radon is only a single part of the larger issue of indoor air pollution, which presents assessment, remediation, and regulatory difficulties different from those associated with pollutants in outside air.

Air

In 1986, EPA estimated that 7 million U.S. homes had concentrations of radon above 4 pCi/L, the level at which the agency would recommend remedial action. Subsequently, as a result of its National Residential Radon Survey (EPA, 1992b) which involved measurements of radon in houses around the country, the agency reduced that estimate. Based on that survey, EPA now estimates that between 60,000 and 100,000 homes have concentrations of radon of 4 pCi/L or more and that the average home has a concentration of around 1.25 pCi/L.

The fact that EPA does not regulate airborne radon does not mean that those exposures have gone unaddressed. EPA distributed *A **Citizen's Guide to Radon in 1988*** and a revised document in 1992 as part of an information program to alert citizens about the risks from indoor radon. Some experts have questioned whether the guides provide the appropriate information. In particular, Nero (1992) and others have criticized EPA for urging that all houses be tested because they see that policy as distracting attention from homes in the areas with the highest concentrations of radon. The critics have also faulted EPA for not focusing on persuading residents to mitigate concentrations of radon in houses with levels of 20 pCi/L or higher. Those levels are higher than the exposures currently allowed for miners and other workers exposed to radon. According to those critics, EPA has dissipated the force of its message by calling for remediation in any house with levels greater than 4 pCi/L. Some experts have also objected to EPA's telling citizens to act on the basis of short tests of 2 to 7 days rather than testing for a year to obtain more accurate results.

Table 6-2-Comparison of Short-Term In-Basement Measurements of Radon in Air and Estimated Annual Exposures in Living Areas

If short-term result is:	Then estimated annual radon level is:
1 pCi/L	0.3 pCi/L
2	0.7
3	1.0
4	1.3
5	1.7
6	2.0
7	2.3
8	2.7
9	3.0
10	3.3
11	3.7
12	4.0

NOTE: pCi/L = pico Curies per liter.

SOURCE: Office of Technology Assessment, based on U.S. Environmental Protection Agency, *Reporting on Radon* (1989), personal communication from M. Reimer, U.S. Geological Survey.

The data in table 6-2 demonstrate the importance of appropriate testing techniques. Several years ago, EPA recommended that testing for radon be done with radiation detectors placed in the basements of homes and that the homes be kept closed up during the measurement period. As a result, the measurements were taken in the area of the house with the highest level of radon, regardless of whether anyone spent any time in that area, and under conditions that reduced dilution of indoor radon by outside air entering through open doors and windows. As shown in the table, measurements under those conditions were three times higher than the year-round

Table 6-3-Current Estimates of Radon-Associated Lung Cancer Deaths and Reductions Expected From Reducing Indoor Exposures

Source	Smokers	Former smokers	Non-smokers	Total
Estimated number of annual radon-associated cancer deaths				
Nazaroff and Teichman	15,200'		**500**	**15,700**
Environmental Protection Agency	9,600	3,200	800	13,700

Estimated number of annual averted deaths at reduced exposures					
	Exposures reduced to	Smokers	**Former** smokers	Non-smokers	Total
Nazaroff and Teichman	2.7 pCi/L	2,300		**200**	**2,500**
Environmental Protection Agency	4.0	1,500	**500**	**100**	**2,200**
Environmental Protection Agency	3.0	1,800	600	**200**	**2,600**
Environmental Protection Agency	2.0	2,300	**700**	**200**	**3,100**
Office of Technology Assessment	1.3[b]				**5,000'**

NOTE: pCi/L = pico Curies per liter.
a Nazaroff and Teichman combine current and former smokers in their calculations.
b Average indoor concentration of radon in the United States.
c Interpolated from figure 6-1.

SOURCES: W.W. Nazaroff and K. Teichman, "indoor Radon," *Environmental Science and Technology* 24(1990):774-782; U.S. Environmental Protection Agency, *Technical Support Document for the 1992 Citizen's Guide to Radon,* EPA 400-R-92-011 (Office of Technology Assessment, 1993).

average measurement of radiation in the living quarters of the house with ordinary ventilation and household traffic. EPA now recommends that measurements be made in the lowest living quarters of the house rather than in the basement.

Despite disagreements about the content of EPA's information materials, some people have clearly heard the message that indoor radon is a risk that can be addressed. Indeed, in some States and counties, radon inspections, like inspections for termites, are now part of real estate transactions. As a rule, inspecting for radon is not required by law or regulation but is part of the agreement between buyer and seller. For example, in Montgomery County, Maryland, most sales contracts require a 2-day sampling for radon. If the concentration is 4 pCi/L or higher, the buyer may require the seller to take remedial action to reduce the level.

Both Nazaroff and Teichman (1990) and EPA (1992a) have calculated the number of deaths from lung cancer that might be avoided by reducing exposures to indoor radon. Nazaroff and Teichman (table 6-3) estimate that reducing concentrations of radon to 2.7 pCi/L in all homes that currently have concentrations above 4 pCi/L would prevent 200 deaths per year from lung cancer among nonsmokers and 2,300 deaths per year among smokers (leaving about 12,000 radon-associated lung cancer deaths).

EPA's (1992a) estimates are quite similar. EPA currently recommends that all homeowners take action to reduce any exposure in excess of 4 pCi/L, and that level *is* often called the ''action level.' Reductions of all current exposures above the action level to 4 pCi/L are calculated to reduce the lung cancer death rate by 2,200, with 100 deaths being prevented in nonsmokers (table 6-3). The expected reductions in death rates increase with further reductions in exposures to radon: reducing all indoor exposures now above 3 pCi/L to 3 pCi/L would prevent about 2,400 deaths annually in smokers and former smokers and 200 deaths among nonsmokers; reducing exposures to 2 pCi/L, which EPA (1992a) considers near the practical limit for mitigation efforts, is calculated

to lower the annual death rate from lung cancer by about 3,100, leaving about 10,500 such deaths associated with radon (figure 6-l).

As is apparent from figure 6-1, the bulk of cancers associated with radon exposure occurs in the population exposed to low levels, below 2 pCi/L. The primary reason for that is that many more people are exposed to those levels than to higher levels. Given EPA's conclusion that it is impossible to reduce levels below 2 pCi/L in some houses, the practical lower limit on the number of deaths associated with radon maybe as high as 10,500. This estimate is based, of course, on extrapolations from the miners studies, and refinement of those extrapolations might reduce or increase the estimate of the number of cancers associated with radon.

Interpolating from the data on figure 6-1, OTA estimates that reducing all indoor exposures now above 1.25 pCi/L to that level, which is the U.S. average, would avert about 5,800 radon-associated lung cancer deaths annually (table 6-3). That would leave 7,900, a little over half, of radon-associated lung cancer deaths unabated.

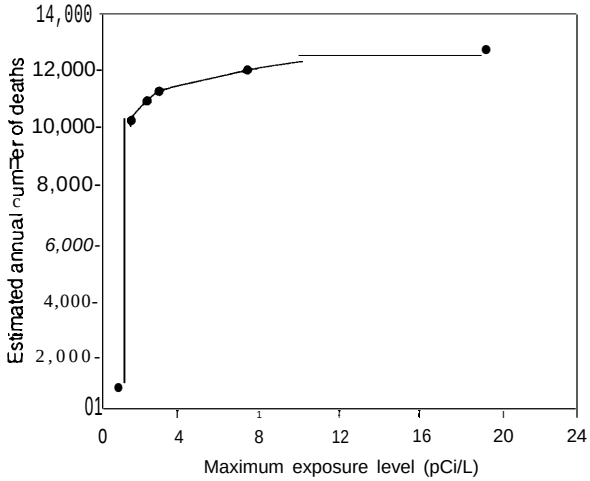
Because radon is present in all air, both inside and outside, it is impossible to have zero radon exposures. Thus, some risk of death from radon-associated lung cancer is always present if it is assumed that there is no threshold for radon-associated lung cancer deaths, and as is shown on figure 6-1, exposures to radon in outside air are associated with about 500 lung cancer deaths annually.

The National Research Council's (NRC, 1983) distinction between risk assessment and risk management calls for deliberations at two levels:

1. Is there a risk?
2. If there is one, what methods are most suited for its control?

For radon in homes, EPA's ***Technical Support Document for the 1992 Citizen's Guide to Radon*** (EPA, 1992a) provides the agency's reasoning behind choosing 4 pCi/L as the level at which homeowners should obtain more information about exposure and remediate to bring levels below that concentration. But, because EPA does not regulate radon in air, the Federal Government did not have to provide an administrative forum to debate whether the projected benefits of reaching 4 pCi/L of radon justified the associated costs. Figure 6-2 summarizes EPA's cost-effectiveness analysis for reducing concentrations of indoor radon to various levels. Reducing exposures to 8 pCi/L is expected to save lives at a cost of less than $0.5 million per life; the cost per life saved just about doubles (to a little less than $1.0 million) at 4 pCi/L and increases further at lower action levels.

Figure 6-1—Estimates of Deaths From Lung Cancer at Different Levels of Radon Exposure



SOURCE: Office of Technology Assessment, 1993.

Water

The Safe Drinking Water Act Amendments of 1986 require EPA to develop regulations for toxic chemicals in water. The agency has decided to regulate radon like any other waterborne carcinogen; it also considers radon to pose, quantitatively, the greatest risk of cancer from water (table 6-l). That regulatory process can be considered in two time periods. Before the summer of 1992, EPA was developing the regulation under its

usual procedures, but at that time Congress intervened in the process. Congress mandated EPA to make a reassessment of its estimates of risks and costs in relation to radon in water. In its action, Congress reflected some opinions expressed by EPA's Science Advisory Board.

THE SCIENCE ADVISORY BOARD'S COMMENTS

EPA's Science Advisory Board weighed into the radon in water issue in 1992. It w-rote a letter to the EPA Administrator:

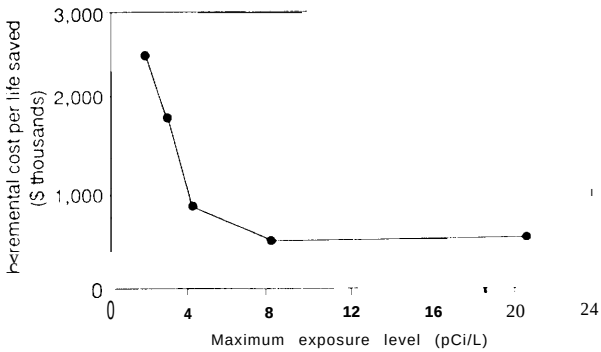
> ... to convey its concern about the inconsistent approach within the Agency regarding reducing risks from radon exposures in homes. . . .
>
> The purpose of this letter is two-fold: (a) to address the fragmented and inconsistent approach regarding reduction of radon risk, and (b) to provide our closing comments on the revised drinking water criteria documents that support the proposed regulations (Loehr et al., 1992).

The letter points out the proposed regulation would reduce the concentration of radon in water so that the amount that volatilizes from water to air would be more than 100 times smaller than EPA's action level (a voluntary guideline) of 4 pCi/L for indoor air. It also notes that that concentration is well within normal variations in levels of radon in homes, and about 10 times smaller than the average concentration of radon in outdoor air.

The SAB concluded that "Frankly, radon in drinking water is a very small contributor to radon risk except in rare cases and the Committee suggests that the Agency focus its efforts on primary rather than secondary sources of risk" (Loehr et al., 1992). The board also acknowledged that it understood that the SDWA required the regulation of radon in water. But it returned to a theme developed in its 1990 report *Reducing Risk* (U.S. EPA, SAB, 1990) and urged EPA to base its plans on "ongoing assessments of remaining environmental risks, the explicit comparison of those risks, and the analysis of opportunities available for reducing risks, rather than on past efforts at risk reduction or existing programmatic considerations. It went on to urge EPA to conduct a multimedia risk assessment of the options for regulating radon in drinking water and to include risks engendered by the treatment process and the disposal of any wastes produced from it. The board recommended that EPA develop and present better treatments of uncertainty in the water criteria documents.

Several of the SAB's recommendations, including the multimedia risk assessment, became part of the 1992 congressional mandate.

Figure 6-2—Cost-Effectiveness of Different Action **Levels for Reducing Indoor Radon Exposures**



SOURCE: Office of Technology Assessment, 1993.

PUBLIC LAW 102-389 AND THE MULTIMEDIA RADON RISK ASSESSMENT

Section 591 of the Housing and Urban Development, Veterans Administration, and Independent Agencies Appropriations Bill of 1992 put a hold on EPA's proposed regulation of radon in water. That section, commonly called the Chaffee-Lautenberg Amendment after its senatorial sponsors, directed EPA to complete a study July 6, 1993, that considers "the risks from various pathways of radon exposure-air and water, inhalation and ingestion. " The study was also to examine the costs of controlling various pathways, detailing the costs to households and communities (including small communities), and any risks posed by disposing of materials used to

remove radon from water. The study was to be reviewed by EPA's Science Advisory Board, and the board was to submit its recommendations to the EPA Administrator, who would then report to Congress. After completing the analyses and reviews, EPA was to issue regulations for radon in water by October 1, 1993.

Congress adopted the Chaffee-Lautenberg Amendment after the Senate narrowly defeated the broader Domenici Amendment that would have placed an outright moratorium on EPA's capacity to promulgate drinking water standards. According to Senator Chaffee's discussion of the amendment:

> The dispute here is about the relative risk of radon in drinking water. And since the Federal Government does not require that any steps be taken to correct the principal source of the risk, namely the gas that comes from the soil, the drinking water suppliers, quite rightfully, wonder why they should be required to clean up drinking water at a great expense. In other words, yes, some radon comes up with the drinking water, but more of it comes from infiltration through basement walls, et cetera.
>
> So there is much to be said for the line of reasoning for those who object to the testing of it in water. Thus our amendment delays promulgation of the radon standard until the end of 1993. During the interim, the EPA is asked to provide better data on the relative risk of radon from various sources, from water, from cellars, and so forth. So we can revisit that next year in 1993, because this postponement goes to the end of 1993 (Chaffee, 1992).

Given the time the amendment allotted for the risk assessment, EPA could do Little more than review the existing literature about radon risks and address specifically some uncertainties in its risk assessment. Although the conclusions from the reassessment were very close to those in EPA's (1991) water criteria document for radon in water, the multimedia risk assessment (or reassessment) did not answer all the questions raised by the SAB and by the amendment.

PROPOSED REGULATION

The SDWA imposes a goal of zero for concentrations of carcinogens in water. That goal is unattainable for radon (extensive aeration of radon-bearing water would discharge the radon into the air but there would always be radon at least at the concentration found in outside air). EPA bases its proposed regulation on its determination that the lowest ''practical quantification level" for radon in water is 150 pCi/L, and it set the regulatory maximum-contaminant level at that value in its proposed rule in 1991 (U.S. EPA, 1991). The half-life of radon is 4 days; that is, half of the radon decays in 4 days. Because EPA allows up to 4 days for transporting the water to the testing lab, the agency decided that a measurement of 300 pCi/L was the lowest feasible level for its regulation. Differences in procedures for measuring radon in air and water account for the fact that airborne measurements of 2 pCi/L of air are routinely obtained while EPA contends that measurements below 150 pCi/L in water are not practical.

There is general agreement that 10,000 pCi/L of radon in groundwater results in 1 pCi/L of radon in air from volatilization (U.S. EPA, 1991). Therefore, the 300-pCi/L limit on radon in water, if imposed, would mean that no more than 0.03 pCi/L of radon in indoor air would result from the waterborne radon. That concentration is 10 percent or less of the radon in outdoor air, and it would contribute about 5 percent to total indoor exposures. Supplying a house with water that contains 1,000 pCi/L of radon does not increase the airborne radon content by 1 pCi/L because when no water is running, there is little transfer of radon from water to air. EPA has carefully examined such things as how much radon is released into the air from water during showering, laundering, and flushing the toilet in order to estimate the contribution of radon from water to indoor air.

The Natural Resources Defense Council (NRDC) and the Friends of the Earth (FOE) dispute EPA's claim that 150 pCi/L in water is the lowest

practical quantification level (Olson et al., 1991). They point to published studies that show that changes in sampling and methods of analysis for radioactivity can lower the detection level to 25 pCi/L, which makes it possible to set a standard 12 times more stringent than the one EPA proposed. EPA's own analysis of amounts of radon in water casts doubt on 150 pCi/L being the minimal detection level because it reports on the number of water systems that exceed 100 pCi/L and presents some information about those between 50 and 100 pCi/L (U.S. EPA, 1991).

NRDC and FOE also point out that EPA calculates that the cancer risk at the proposed regulatory limit of 300 pCi/L is 2×10^{-4}. Not only is that risk level twice as high as the 10^{-4} level that is EPA's usual upper limit on acceptable risk; it is also much higher than the risks from other waterborne carcinogens, which are often in the range of 10^{-6}.

Arguing from the viewpoint that concentrations of radon in water below 300 pCi/L can be measured, NRDC and FOE also claim that imposing regulations on water supplies with concentrations below 300 pCi/L would greatly reduce exposures and risks at little additional cost. In particular, they calculate that such a regulation could avert twice as many cancers for an increase in cost of between 28 and 40 percent.

Water suppliers also disagree with EPA's proposed standard. They question whether the risk assessment is accurate and whether the proposed standard will save 80 deaths annually as EPA calculates; they also draw attention to the estimate that about 90 percent of the risk of lung cancer risk is confined to smokers. Like NRDC and FOE, but for very different reasons and by reaching very different conclusions, water suppliers draw attention to the fact that the proposed standard is based on a measurement level. Improvements in the capacity to measure radon in water (which NRDC and FOE contend are already here) could be translated into a constantly shifting, and constantly decreasing, standard. That kind of situation would leave the water suppliers facing an uncertain future of tighter standards and higher costs.

RISK

In 1991, EPA (1991) estimated that current concentrations of radon in water were associated with about 200 deaths annually from cancer, and the agency estimated that lowering all water supplies that were then higher than 300 pCi/L to 300 pCi/L would avert about 80 cancer deaths. At that time, EPA associated 80 percent of the risk from waterborne radon with radon that volatilized from water and was inhaled. Because of a National Research Council (1991) study that said certain adjustments were necessary to allow for differences between radon exposures in mines and in homes, EPA, in its reassessment, reduced its estimate of the number of cancer deaths associated with volatilized radon. At the same time, it increased its estimate of the number of deaths from cancer expected to result from ingested radon. When EPA (1993) added together the number of deaths from cancer that it associates with inhalation and ingestion of radon from water, the total came to about 160 annually, a number not different from the approximately 200 deaths from cancer that it previously associated with inhaled radon from water.[3]

EPA predicts ingested radon will cause cancer of the stomach and other digestive system organs. However, unlike other estimates of radon risk, the risk from ingested radon is not based on direct evidence of adverse effects in miners or other

[3] EPA calculates precise point estimates for risks along with a range of possible risks, For example, its estimate for annual deaths from ingested radon is 46, with a range of 11 to 212. Such precision is unwarranted because of uncertainties in measurement and models, and OTA prefers to present EPA results in less precise terms, such as 'about 50.' More importantly, the calculated range is not the same as the uncertainty that surrounds the estimate. As the Science Advisory Board noted (Loehr and McClellan, 1993), the uncertainty of the risk from ingested radon is so great that there may be zero risk.

populations. Indeed, there is no evidence for increases of those cancers in miners. Moreover, according to the Agency for Toxic Substances and Disease Registry (1992), there is no evidence for an association between groundwater radon and gastrointestinal cancers or leukemias. EPA bases its estimates of risk for ingested radon on modeling of the distribution of xenon gas in the human body and on the observed increase of stomach and other digestive system cancers in survivors of atomic bomb blasts. The modeling, which is the basis for estimating doses of internal radiation from ingested radon, is taken from a paper that has not been peer-reviewed. And, although both radon and atomic bombs release radiation, they release different kinds of radiation—alpha particles are released from radon, and gamma rays and neutrons from atomic bombs. Moreover, the two sources deliver radiation quite differently: ingested radon is a long-term internal exposure, and atomic bombs produced an external, one-time exposure. Those differences point to the problems involved in estimating the risk from ingested radon.

The upward revision of the number of deaths expected from ingested radon elicited several negative comments. In particular, Harley and Robbins (1993) estimated that the exposure of the stomach to radiation from ingested radon is about 100 times less than did EPA. EPA scientists defended their process (Chiu, Puskin, and Barry, 1993), but Crawford-Brown (1993), the author of the paper on which EPA depends for its estimate of radiation exposure to the stomach, agrees with Harley and Robbins that the estimate of exposure may be too high.

More fundamentally, Crawford-Brown (1993) objects to EPA's assuming that the mathematical equation it used to extrapolate risk is correct: "I believe the USEPA is both philosophically and scientifically far from the mark in suggesting that uncertainties in extrapolation equations are to be characterized . . . (as if) . . . there is no uncertainty in these equations . . . ." This comment questions the risk assessment based on miner data that EPA has used to estimate the cancer risks from radon in water. Some scientists within EPA have made parallel comments about the uncertainties in the dose-response equation that is used in EPA's risk assessment (Ulsamer, 1993).

Scientists at Brookhaven National Laboratory (BNL) responded to a request from EPA's Office of Research and Development that the Department of Energy (DOE) review EPA's risk assessment of radon in water. The resulting review was sent from DOE to EPA accompanied by a letter (Pelletier, 1993) that summarized the DOE position: "BNL concludes that the draft report contains significant flaws which seriously detract from its usefulness." The review itself is quite critical of EPA's risk analysis (Morris, Rowe, and Baxter, 1993). The BNL scientists agree with Crawford-Brown (1993) that EPA may have overestimated exposures from ingested radon by a factor of 100, and they point to a number of computational errors that they found in the EPA report. The EPA scientists who developed the risk assessment profoundly disagreed with the DOE review (Chiu, Puskin, and Barry, 1993) and responded to its summary comments.

In its review of the reassessment, EPA's Science Advisory Board was quite critical of the methods used to estimate cancer rates from ingested radon. It characterized the methods as more indirect than those used to estimate risks from airborne radon and concluded: "In the absence of direct evidence, it is not possible to exclude the possibility of zero risk from ingested radon" (Loehr and McClellan, 1993). As it did in 1992, the SAB drew attention to the small risk associated with radon in water as compared to the overall risks from radon. The SAB also, as in 1992, made comparisons between the number of deaths that might be associated with waterborne radon (about 160) and the 2,500 deaths that are expected to occur annually from radioactive potassium that occurs in the human body and the 500 or so expected from outdoor radon.

COSTS

The three parties-EPA, NRDC, and FOE, and the water suppliers-also disagree about expected costs. In 1991, EPA estimated that the costs to reduce radon to 300 pCi/L in all 25,907 water supplies that exceeded that level would be $1.6 billion in capital costs and $0.18 billion in annualized costs (U.S. EPA, 1991). The cost of averting a case of radon-associated cancer was estimated at $2.3 million. In February 1993, EPA increased those estimates. Currently, its best estimate is that 41,000 water supplies exceed 300 pCi/L and that the best estimates for capital and annualized costs are $1.8 billion and $0.26 billion, respectively (U.S. EPA, 1993a).

NRDC and FOE accept EPA's cost estimates for reducing concentrations to 300 pCi/L and use the agency's estimates to project the additional cost of reducing radon in water to lower levels (Olson et al., 1991). EPA's proposed regulation would reduce current levels by 80 percent. NRDC and FOE contend that reducing levels to 1 percent of current levels, which might double the expected health benefits, would cost only an additional 28 to 40 percent, and in fact, the greater reductions might be achieved at even smaller cost increments. (Experts who work for water suppliers have said that they would expect costs to fall as more efficient aeration systems are developed to remove radon from water.)

The SAB (U.S. EPA, SAB 1993) did not endorse EPA's proposal for wholesale adoption of aeration to reduce radon concentrations in water. EPA had considered and rejected granulated activated charcoal (GAC) as a control measure, in part because of the problems raised by disposing of the radioactive charcoal after its use. The SAB urged the agency to look again at GAC because of its potential to hold down costs as compared to the costs of aeration in some applications. The Board made no projections of the costs. The board also urged EPA to revisit its estimates of costs for water supplies of different sizes and to consult with the water suppliers to obtain more information. Whether aeration or GAC is used to remove radon, either technique allows the introduction of microbes into water supplies, and SAB (U.S. EPA, SAB 1993) cautions that "costs of disinfection, especially in small systems, needs to be reviewed thoroughly.

The Association of California Water Agencies commissioned an engineering study of the costs of bringing public water suppliers in California into compliance with the 300-pCi/L standard (Fensterheim, 1992). According to the association, the capital costs to bring 9,420 California wells into compliance would be $3.73 billion; the annualized costs would be $0.7 billion. According to one projection from the associations results, total national capital costs are expected of between $12 and $20 billion; those expenditures are expected to reduce total radon exposures by about 1 percent (Abelson, 1993).

The SAB (U.S. EPA, SAB 1993) compares EPA's estimate of $3.2 million to avert a death from lung cancer from waterborne radon to the EPA estimate that remediation to reduce airborne radon to 4 pCi/L will avert a death for about $700,000. The Association of California Water Agencies calculates much higher costs; it estimates that the cost to avert a death from radon-associated lung cancer would range between $65 and $87 million in California. The cost to avert a death from lung cancer in a nonsmoker in that State would be between $433 and $592 million. (The much higher cost for averting the deaths of nonsmokers results from the fact that lung cancer is so much rarer among them.)

Part of the reason for the California Association's much higher cost estimate is its survey that shows many more water supplies exceed the proposed 300-pCi/L regulatory limit than is estimated by EPA. The SAB (Loehr and McClellan, 1993) also points to uncertainty in the estimates of how many water supplies would be subject to regulation (''may seriously underestimate the number of community water systems impacted . . . ") and states that "this uncertainty

in exposure estimates ultimately impacts the costs of mitigation.

EPA has estimated that the average annual cost for radon reduction for houses served by the smallest water utilities would be $120; most houses are served by larger systems and would pay about $50 per year (Wilcher, 1991). Based on Association of California Water Agencies estimates, former Senator William E. Dannemeyer wrote to EPA that every household that has to pay for radon reduction would pay an extra $340 per year (Dannemeyer, 1991). The town of Hastings, Nebraska, has a population of 23,000 and water that exceeds EPA's proposed limit for radon in water. According to an analysis that the town conducted, a water treatment plant to remove the radon would cost $65 million and be the single largest drain on the town's treasury (Schneider, 1993).

NRDC and FOE do not accept that small water suppliers will bear sizable new costs as a result of setting a standard of 300 pCi/L or lower for radon in water (Olson et al., 1991). They argue that smaller suppliers could tie into larger suppliers to gain economies of scale or look for water that contains less radioactivity. Moreover, Olson et al. (1991) cite experts who state that technologies are available that are much less costly than those EPA considered in its 1991 cost estimates. In EPA's 1993 recalculation of estimated costs, total capital costs increased by 20 percent and annual costs increased by 44 percent, whereas the number of water suppliers increased by 60 percent, indicating that EPA had found some savings in costs per supplier.

The costs of the proposed regulation on radon in water regulation can also be compared with the costs of a public health measure that has become more expensive in recent years and that has produced public outcries for reducing the profits of pharmaceutical companies. The cost of childhood immunizations has increased from between $7 and $23 in 1982 to between $129 and $244 in 1992 (Orenstein, 1993). Even so, the annual cost of the radon-in-water regulation-estimated by EPA to be about $50 per family served by averaged-sized systems and $120 per family served by small systems-ranges from between a fifth to a little less than half the one-time cost of immunization. The estimate of the Association of California's Water Agencies of $340 per family per year for the radon-in-water regulation exceeds the one-time cost of immunization.

The continuing, annual estimated family cost of the regulation, which will affect about 1 percent of all exposures to radon, of between $50 and $340 can also be compared with EPA's estimate of the one-time cost of bringing indoor radon concentrations down to 4 pCi/L or lower. EPA (1992a) estimates for the one-time cost for remediation of a house ranges from $500 to $2,500 with an average of $1,200 and average operating expenses of $68.

SCIENCE ADVISORY BOARD COMMENTS, JULY 1993

The Science Advisory Board review gave EPA high marks for its general approach to the multimedia risk assessment, but it focused on areas such as estimates of the population exposed to concentrations of radon greater than 300 pCi/L in water, calculated risks from ingested radon, and capital cost estimates in which it thought the agency could make efforts to refine its approaches and calculations. A letter from the chair of the SAB Executive Committee and the chair of the SAB Chafee-Lautenberg Study Review Committee (Loehr and McClellan, 1993) returned to the Board's 1992 position that EPA should apply relative risk approaches in its consideration of risks from radon. The relative risk approach ''caLls for giving the highest priority to mitigating the largest sources of risks first, especially when the cost-effectiveness of risk reduction of such sources is high. '

As part of that approach, Loehr and McClellan (1993) encourage EPA to continue its efforts "to encourage voluntary actions to reduce indoor air radon in view of the cost effectiveness of this approach for reducing risks. " About radon in

water, they conclude that the proposed regulatory limit of 300 pCi/L is "the most costly in terms of costs per cancer death avoided. " They suggest that EPA also consider setting limits for radon in water at either 1,000 or 3,000 pCi/L. Even the higher numbers would result in water contributing no more radon to indoor air than is present in outdoor air.

Nero (1993) has also suggested alternatives to the 300-pCi/L limit on radon in water. Like the SAB, he suggests setting the water limit so that radon from water would make no more of a contribution to indoor air than does the radon in outside air, which would be in the range of 1,000 to 3,000 pCi/L in water. An EPA official also reported to a newspaper that agency staff were forwarding at least three options for a radon-in-water rule to the EPA Administrator: 300, 1,000, and 2,000 pCi/L (Anon, 1993 b).

Should a limit of 1,000 to 3,000 pCi/L in water be set, EPA could continue to accumulate information about the levels of radon in water, the number of water supplies with various concentrations, and the risks from ingestion of radon. The additional information would reduce the uncertainties in the estimates of risks, costs, and cost per life saved, and pave the way for alterations in the regulation if needed.

"Inconsistency" in EPA's Approach to Radon

The letter that requested this OTA examination of indoor radon cited the SAB 1992 concerns about inconsistencies in EPA's approach to reducing risks from radon. It contrasted the goals of the IRAA both with EPA's action level for indoor radon and with its proposed level for regulating radon in water under the SDWA: The IRAA goal is to bring indoor radon level down to those commonly found outdoors (0.1 to 0.5 pCi/L), whereas EPA urges that remediation be undertaken to reduce concentrations of radon in homes to 4 pCi/L or lower. In contrast, EPA's proposed regulation would set 300 pCi/L of radon in drinking water as the highest permitted level, limiting radon in indoor air to 0.03 pCi/L from this source (given the assumption that 10,000 pCi/L of radon in water produces 1 pCi/L of radon in air because of volitalization). Clearly, the goal, the action level, and the proposed regulation set different exposures as acceptable (box 6-A).

These inconsistencies are no surprise given the way that the goal, the action level, and the regulation were derived. Congress, in the IRAA, acknowledged that the outdoor level of radon in air is unavoidable and that concentrations cannot be reduced below that level. At the same time, reducing concentrations to that level would be as health protective as possible.

EPA, in setting the 4-pCi/L action level, accepts a risk of cancer from radon that is far higher than the 1 X 10^{-6} (one excess cancer per million people) exposed for a lifetime that the agency routinely uses as a goal in regulating exposures to toxic chemicals. *The Citizen's Guide to Radon* (U.S. EPA and U.S. DHHS, 1992) provides some examples of comparative risk; for instance, the risk that a nonsmoker bears from constant exposure to radon at 4 pCi/L is roughly the same as that person's risk of drowning.

The proposed radon-in-water standard under the SDWA is risk- and measurement-based. The level of 300 pCi/L of radon in water, set at what EPA had determined is the practical limit on quantification, was projected to reduce risks to about 2 X IN. In its preamble to the proposed rule, EPA raised the question of the significance of waterborne radon to the total radon issue: ''In evaluating the various alternatives for proposing a radon MCL [maximum contaminant level; the regulatory standard], EPA considered the critical policy questions of whether radon in water should be regulated like other drinking water contaminants, or whether it should be regulated more in accord with its importance compared to overall radon exposure. EPA decided to regulate radon as other waterborne contaminants, and the SAB (Loehr et al., 1992) criticized that action because

of the small contribution that waterborne radon makes to overall exposure to radon.

Congress's mandating of the multimedia risk assessment produced some refinements in EPA's risk and cost assessment, but whether it will make a difference in regulation remains to be seen. The risk estimate hardly changed at all, and, according to EPA% assessment, radon in water remains associated with a risk greater than 10^{-4}, which is the usual upper limit on the risk that EPA finds tolerable.

Indoor Air

Risks to health from contaminants in indoor air-lead paint, asbestos in buildings, environmental tobacco smoke (ETS), and other substances—have spotlighted the indoor environment as a source of hazards. In the 102d Congress, Representative Joseph Kennedy and Senator George Mitchell introduced the Indoor Air Quality Act of 1991 in the House and Senate, respectively (H.R. 1066 and S. 455). Had either bill passed, it would have authorized research, development, and demonstration projects concerned with improving air quality; the House bill would have imposed some regulations. Both Kennedy and Mitchell have introduced bills in the 103d Congress that focus on research and development.

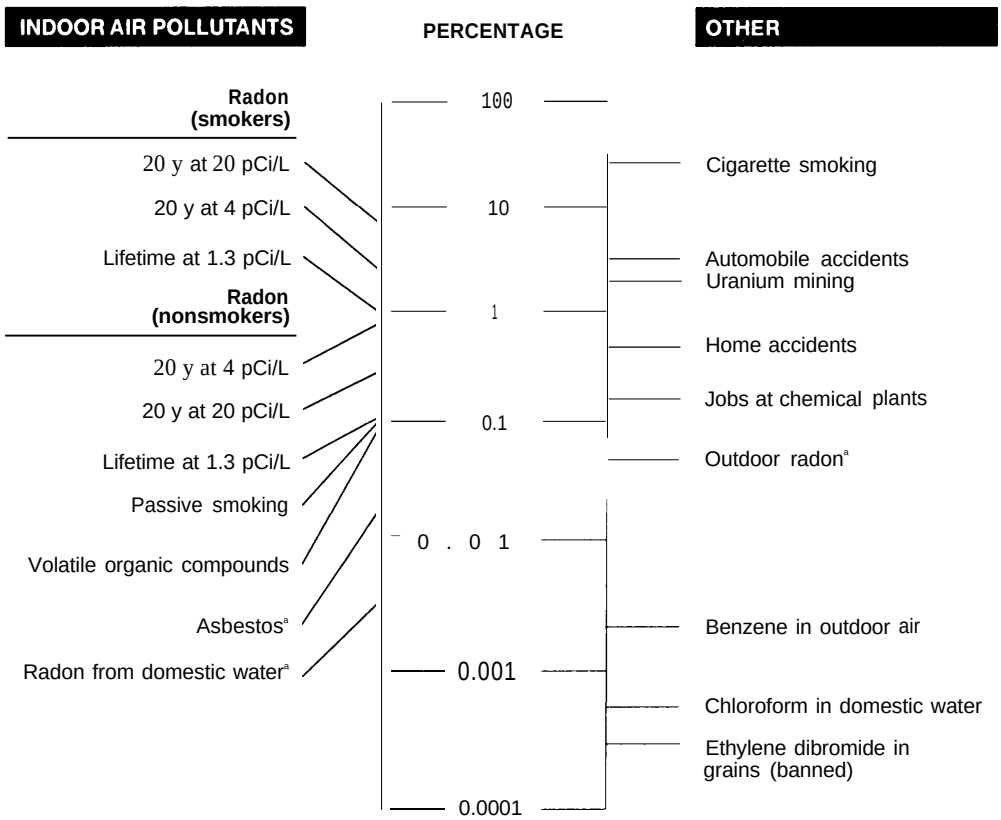
The contents of the bills demonstrate the complexity of the issues arising in legislation regarding the quality of indoor air. In addition to the agents mentioned above, indoor air can contain hazardous chemicals that are carried home in clothes and on the skin from the workplace; any number of volatile organic compounds from common household chemicals such as paints and soaps; and allergens that arise from pets, insects, molds, and mildews. The bills addressed indoor air quality in homes, which are probably the setting that is most often considered when thinking about indoor air, but they also treated air in educational facilities and commercial and Federal buildings. Clearly, legislation dealing with indoor air would apply to many substances and various kinds of buildings.

A decade ago, Spengler and Sexton (1983) discussed the special problems of indoor air pollution; more recently, Nero (1992) has argued that indoor air problems merit approaches different from other environmental issues. As shown on figure 6-3, risks from substances in indoor air fall over a wide range, with the radon-related risk of death for smokers as high as 8 percent and the risk from waterborne radon about 0.006 percent (more than 1,000 times lower). [Because of computational differences, figure 6-3 shows that the risk of death from waterborne radon is less that 0.01 percent, which is less than the approximately 0.02 percent (2 X l@) risk that EPA associates with waterborne radon.] The highest risk shown on the figure is for smoking, which increases the risk of premature death by about 25 percent. Accidents and certain occupations are associated with levels of risk around the level associated with radon.

EPA has concluded that the risks associated with indoor radon are greater than any other that it contends with (with the exception of risks of cancer posed by sunlight). The agency thus argues that indoor radon and waterborne radon require immediate attention. Nero (1993) counters that the risks from indoor radon are not put in the proper context when compared with outdoor risks. Instead, he maintains that indoor radon should be considered in the context of indoor risks that are typically higher than outdoor risks.

Considering the risks posed by indoor radon in the context of indoor risks would create monumental obstacles to setting the SDWA's limit of 10^{-4}(0.01 percent) on cancer risks as a consistent goal for risk reduction. As shown in figure 6-3, many indoor risks are far above the proposed regulatory limit for radon in water. It is very unlikely that the risks from radon in indoor air can be lowered from the nearly 1 percent associated with the average concentration in U.S. homes of 1.3 pCi/L or that the risk of fatal home accidents can be lowered from about 0.8 to 0.01 percent.

Figure 6-3-Estimated Lifetime Risk of Premature Death From Various Sources



SOURCE: Office of Technology Assessment, 1993.

Treating the risks presented by indoor air in a concerted fashion, which might result from legislation on indoor air quality, would probably lead to greater reductions in overall exposures than would be achieved under current laws. For instance, improved ventilation could be designed to reduce the concentrations of environmental tobacco smoke, volatile organic compounds, radon and other substances in the air, with an expected decrease in risks. In general, the solutions to indoor air problems are likely to follow similar paths-that is improving ventilation and filtration, considering the volatility of substances introduced into the indoor environment, and so forth. A single piece of legislation might facilitate considering the risks together rather than piecemeal.

The SAB (Loehr and McClellan, 1993) recognized 'that the large number of laws under which EPA operates makes it difficult to implement a relative risk reduction strategy across the Agency. . . . The SAB strongly encourages the Agency and the Congress to work together to consider changes in existing statues that would permit implementation of relative risk reduction strategies in a more efficient and effective manner.

THE FUTURE

"Enforcement' of the 4 pCi/L level for radon in indoor air is being accomplished through nonregulatory means, and given the possible liability concerns that might result if a house were sold with a higher level, realtors, attorneys,

buyers, and sellers probably will not alter their practices even if research findings show that risks at that level are smaller than is now believed. On the other hand, an increase in the estimate of risk would probably be quickly reflected in real estate transactions because of reasons of liability.

EPA's proposed regulation of radon has been delayed beyond October 1, 1993. The Agency is, reportedly, still deciding on its response to the Science Advisory Board's comments on its multimedia risk assessment. It is expected that work on the proposed regulation will follow that response. The regulation may be delayed for 1 year by Congress, if an amendment passed by the Senate is also approved by the House. Whenever EPA writes the regulation, the Science Advisory Board has offered alternatives to its proposed limit of 300 pCi/L radon in water. It is possible that the agency could set a higher limit that would, in effect, apply only to water systems that contribute a significant fraction of overall radon exposures. Setting a limit higher than 300 pCi/L would be expected to engender lawsuits from citizens and organizations concerned about risks from waterborne radon.

In contrast, if NRDC's and FOE's petition to set a stricter standard were successful, it would require that EPA reduce concentrations of waterborne radon, tightening the standard. Alternatively, Congress could relieve EPA of the responsibility for regulating radon in water, or shift it from the SDWA to the IRAA, or enact a new law on indoor air. Any shift might result in a standard different from 300 pCi/L.

No regulatory agenda requires a new study about the level of risk presented by indoor radon. The current risk assessment, based on the miner studies, is sufficient for regulatory action and indeed, being based on studies of humans, is more certain than animal-based risk assessments that form the basis for many regulations. Nevertheless, a convincing study of the risks associated with indoor radon would provide a great deal of information as well as a technical foundation for future policy decisions. A study that answered the question of whether the risks predicted from the miners studies were accurate would do more than inform the radon debate. It would also provide the first test of the accuracy of any extrapolated estimate of an environmental risk. Moreover, because it would provide more certain information about risks from radon in air at low levels, it would reduce the uncertainty of the risk assessment for radon in water because the major part of that risk is associated with inhalation.

Such a study would make a real contribution to scientific understanding and, depending on what it reveals, could have different effects on debates about regulatory levels. If the study revealed that the current levels were about right, it would confirm the appropriateness of the methods used to generate current risk estimates. If the study showed that current risk estimates were too low, EPA could tighten up the regulations. If, however, the results of the study indicated that the risks were lower than are now estimated, EPA might be confronted with the problem of backing off on some of its regulations and guidelines.

Doll (1992) is confident that studies now being performed will produce valid data about relationships between indoor radon and cancer within the next few years. In anticipation of the completion of those studies, both EPA and DOE are planning to carry out meta-analyses of the findings from those studies. Yet, despite Doll's optimism, there is no guarantee that the ongoing studies will produce a clear-cut answer about cancer risks from indoor radon. In that case, the government could assemble a group of experts to decide whether it is possible to design such a study, and design it, if it is feasible. A study of that kind would probably have to be larger than any done to date, and it would have to be carried out in areas (such as Missouri and Iowa) in which radon exposures are higher than average. To have scientific and political credibility, the study would have to be planned in an open process with explicit discussions of what results would be expected under different planning assumptions.

Furthermore, the planning would have to determine the study's chances of resolving the issue. If the chances were low, policymakers could decide not to go ahead with the study. Still another nonconvincing, nonconclusive study would not justify the expenditure of resources necessary for its completion.

At quite a different level of research, studies of molecular mechanisms of radon-caused carcinogenesis and of movements of radon in buildings (for examples, see DOE, 1993) and of carcinogenesis in general (see chs. 3 and 4) may provide more information about risks from radon. Scientists can design epidemiologic studies and decide, in advance of doing them, whether the studies have sufficient power to answer questions important for policymaking and how long the studies will take---certainly they will take years. But, advances in molecular studies, which may provide better estimates of exposure, pre-disease conditions, or mechanisms of action, cannot be put on a timetable. They may come in months, or they may take years.

The specific questions raised by radon maybe answered by congressional or EPA decisions that impose new regulations or that leave the current approaches intact. New epidemiologic results may inform those decisions by revealing more certain evidence of the level of risk posed by radon at environmental levels. And it is possible that research into mechanisms of carcinogenesis may shed some light on such risks. More generally, radon is a case that illustrates the difficulties posed by an environmental risk of uncertain size that reaches human beings through different media.

As of mid-October 1993, Senator Baucus had introduced a bill that would direct EPA to regulate radon in water by a method different from that now being considered. In addition, Senator Chaffee was considering introduction of legislation as was Representative Slattery. This legislative action indicates that policy on radon in water may well be set by legislative modifications to the SDWA.

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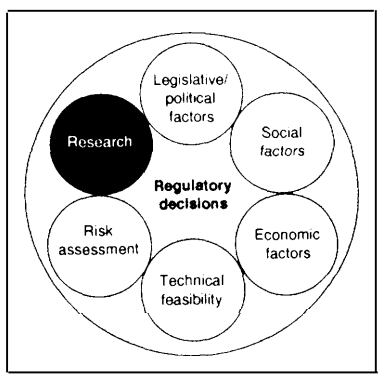
Structuring the Future of Health Risk Assessment Research

7

Research provides the foundation for risk assessment and risk management. It can lead to new ways of performing risk assessment, new approaches to regulating risks, and new avenues for preventing, treating, or remediating risks that have already been identified. Simply put, research offers innovation in approaches and decisions about whether and how to control exposures to hazards.

Research in health risk assessment plays such a diverse and important role that its vitality should concern policy-makers. Yet this Office of Technology Assessment (OTA) study finds that health risk assessment research is itself "at risk" because Federal agencies have not demonstrated the characteristics of high quality research:

- Given what is at stake--both in health and dollars-for decisions based on health risk assessment, health risk assessment research is not at an appropriate level of priority. Approximately $600 million is available for health risk assessment research in 1993.
- Too little research is targeted toward areas expected to have the greatest impact on policy decisions and regulatory actions. For example, only an estimated $65 million in 1993 is devoted to research on risk assessment methodology.
- Health risk assessment research is fragmented within and across Federal agencies, resulting in inefficient and ineffective use of resources.
- Opportunities to link government, university, and industry are being lost.



If policymakers want to create a better climate to advance health risk assessment research, how would they structure the research environment, what scientific areas would they nurture, and what types of research linkages would they pursue to achieve their goals?

This chapter describes the characteristics of high-quality research programs and discusses the benefits of fostering appropriate research linkages among the Federal Government, universities, and industry. This chapter ends by illuminating promising scientific areas to advance health risk assessment, with a special emphasis on research in risk assessment methodology.

STRUCTURING A HIGH-QUALITY RESEARCH PROGRAM

OTA, along with many in the scientific community, associates scientific excellence with high-quality research programs that share certain characteristics: leadership, defined objectives, investigator initiation of research, competitive awards and peer review, criteria for evaluating success, collaboration and coordination, training opportunities, and advisory input. Each of the characteristics is described below in the context of health risk assessment research, regardless of whether the Federal Government supports or conducts the research.

Leadership

Leaders-at all levels of management—guide a research program by instilling a sense of collective purpose, ensuring the coherence of the program, linking it to policy, encouraging collaboration and cooperation, conferring stature, ensuring communication of research findings, and attracting resources. Whether a research program is carried out within an agency or outside it, the leader of the program must be given the responsibility and authority to make decisions and set priorities. He or she must also be held accountable when a program is evaluated. One attribute of leadership in research is recognizing that innovation is most likely to occur when investigators are free to explore.

Defined Objectives

Clear, well-defined goals are critical to all research endeavors. The goals of basic research are guided by the pursuit of fundamental knowledge, whereas applied research is linked to problem solving-in support of agency objectives or societal goals. Yet despite the difference in orientation, clarity of purpose should underlie both.

Health risk assessment by its very nature requires input from abroad portfolio of basic and applied research-although in practice the distinction between the two is usually ambiguous (U.S. Congress, OTA, 1991). Whatever the balance, it is generally agreed that research goals should also incorporate flexibility in order to take advantage of the unexpected-the hallmark of scientific research.

Investigator Initiation

Investigator-initiated research comes from the ideas of scientists who then seek funding and institutional support for carrying out their work. It is often contrasted with research in which the objective and the methods are dictated in advance by managers, often at agencies with mandated social missions.

Investigator-initiated research need not be limited to basic research. In practice, another type, “targeted research,” either basic or applied, is designed to solve a specific problem or meet an objective set in advance by an agency. Such programs can capitalize on investigator-initiation of research to solve the problems that are targeted. That situation often occurs when an agency sets research objectives, solicits proposals to meet those objectives, and competitively awards funds through a grant or contract to the most creative approach. An objection can and is raised, however, when targeted research is seen as constrain-

ing the investigator and taking resources away from basic research.

Competitive Awards and Peer Review

Allocating funds to projects of scientific excellence is best accomplished through competition and peer review—the ranking of prospective projects by scientific experts external to the funding agency. Peer reviewers are asked to evaluate the technical merit of a proposal, the competence of the investigator, and the proposal's potential scientific impact. Competition and peer review have gained general support as principles for funding research.

Criteria and Plans for Evaluating Success

How do we know whether a research program has successfully met its objectives? There is no uniform or perfect way to judge the effectiveness and excellence of a program, but there are common indicators. For example, were important discoveries made? Were the scientific publications that resulted cited by scientists in subsequent publications (IOM, 1988)? In the case of health risk assessment research, were the results useful for risk assessment and decisionmaking?

Ideally, researchers and program administrators would agree in advance on the criteria for evaluating a program's success, and those criteria would be tailored to the nature of research inquiries. Once the criteria for success are decided upon, a plan can be devised to determine how effectively the criteria were met. The National Institutes of Health, for example, has a formal means of retrospective review for each of its intramural laboratories that employs outside periodic evaluations by panels of experts called boards of scientific counselors,

Coordination and Collaboration Within and Across Disciplines and Organizations

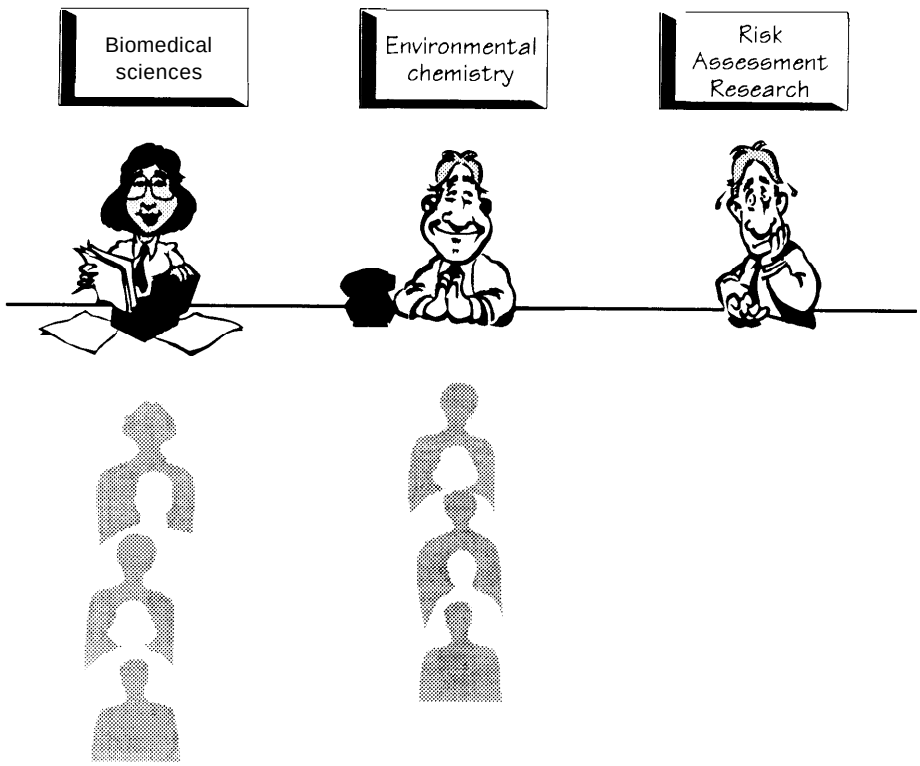
Health risk assessment research encompasses a broad spectrum of scientific disciplines, Coordination within and across those disciplines is so critical that without it, communication may be impaired, important gaps in the research may remain, unnecessary duplication may occur, and research progress may be stymied. Linkage to regulatory decisions is also a distinctive feature of health risk assessment research and a compelling reason for coordination among researchers and policymakers. A high-quality research program can be structured to encourage coordination within and across agencies formally through leadership, and the creation of committees, and through a variety of informal methods.

Coordination can be achieved through formalized research collaborations. Given the need for multidisciplinary research, collaborations have the advantages of sharing resources and bringing together individuals with appropriate expertise. Some factors are considered essential to a successful collaborative effort: the goals must be clear and understood by all participants; each participating unit must see the potential gains of the effort as greater than its costs; the leaders of the collaborative effort must act as honest brokers; and ongoing relationships between individuals must be supported (Needleman et al., 1984). Collaborations between the public and private sectors are discussed later in this chapter.

Training Opportunities

Training opportunities must be available to educate researchers. They are also critical for overcoming a national shortage of professional environmental health scientists and engineers with advanced, yet practical, knowledge of how to develop scientific data for improved health risk assessments and to solve environmental problems (U.S. DHHS, 1991a; U.S. EPA, 1990). Those fields of environmental health science considered to have the most pressing needs for researchers include environmental epidemiology, the study of human exposures to toxicants, and clinical environmental medicine (U.S. DHHS, 1991 b).

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Advisory Input

Advisory input, either through chartered, independent committees or informal means, provides guidance to an agency in establishing a research program, setting its priorities, and ensuring that the program remains scientifically productive, credible, and responsive to societal goals. Advice can be sought from the public and from outside experts on scientific topics, management, or policy.

PROSPECTS FOR RESEARCH

Breakthroughs and rapid developments in the biological sciences-especially in molecular biology and genetics-coupled with improved microelectronics and high-speed computers provide scientists with new research opportunities in environmental health and toxicology that were previously unavailable and virtually unimaginable.

The knowledge developed using new techniques has already had a significant impact in stimulating new thinking about the role of toxic substances in the development of diseases. A more in-depth mechanistic understanding of toxicity can replace some traditional assumptions used in inferring and estimating risk. In addition, this new mechanistic understanding now calls into question certain accepted practices in health risk assessments that can now be examined for their validity using new techniques.

Methodological Research

Toxicological and biomedical research in the past decade has produced a large volume of information. But areas still in need of improvement or development are methods for identifying toxicants, exposed individuals, and populations; models for inferring the effects and estimating the magnitude of risk of toxic substances on human health from the results of animal studies; and techniques for estimating risks and predicting health effects with few data. Some observers expect the most immediate impact to come from evaluations of existing data to determine the credibility of current methods and to guide the development of alternative approaches. This evaluation can also identify specific short-term and long-term research to improve health risk assessment.

NEW METHODS FOR TOXICITY STUDIES

With nearly 1,500 new chemicals introduced worldwide into commerce each year *(Environmental Health Letter, 1993),* improved methods to determine which chemicals pose hazards to human health will remain an important and integral component of health risk assessment research. Improvements are expected in new cost-effective tests for identifying toxic agents and in methods to evaluate relationships between the structure of a chemical and its biological activity.

Model toxicity systems were developed in the past decade using transgenic animals, cells and tissues (both animal and human), and biomolecules. Such systems need to be integrated, evaluated, and validated as new testing methods. These new methods can then be used for acquiring toxicity information based on mechanisms of action.

Using research tools and methods borrowed from molecular biology, animals can be genetically constructed to study the role of toxicants in the development of specific diseases. For example, by inserting genes that predispose the animal to certain types of cancers, such transgenic animals can be developed to study the actions of specific carcinogens.

These improvements will not be restricted to studies of the carcinogenicity of chemicals. Currently, new testing methods are being developed for identifyinagents with toxic effects on human development and on the human immune, respiratory, reproductive, and neural systems.

Improving structure-activity relationship methods enhances scientists abilities to predict toxicological activities of untested chemicals. This effort requires the collaboration between chemists, biologists, and, increasingly, computer scientists. With new computational techniques such as artificial intelligence systems, virtual reality, and improved mechanistic understanding of toxicity, this area of research promises to deliver more than it has in the past.

BIOCHEMICAL AND MOLECULAR EPIDEMIOLOGY

The greatest obstacle to designing efficient, sensitive epidemiologic studies is the limited ability of epidemiologists to characterize individual exposures to toxicants or environmental hazards of concern (Shore et al., 1992). Using biochemical and molecular techniques in epidemiological studies can overcome this difficulty (box 7-A). Biomarkers (e.g., DNA adducts, which are complexes of environmental chemicals and DNA) can provide direct evidence and quantitative measures of exposure to environmental agents. However, they require researchers to obtain biological samples from study subjects.

A variety of factors, including genetics, diet, age, and lifestyle, makes some individuals more susceptible to the effects of toxic agents. Such factors may be shared by members of groups and place the group at increased risk. Biomarkers can be developed for some of those characteristics to identify individuals or subpopulations at higher risk. Such biomarkers of susceptibility can be used in preventing exposures to the most sensitive populations.

Box 7-A–A New Branch of Health Risk Research: Molecular Epidemiology and Biomarkers

In the past decade, research in molecular biology has advanced our understanding of the genetic and environmental factors in disease processes. These advances provide a common ground for the molecular biologist, toxicologist, and epidemiologist to join forces in studying environmentally induced diseases. Molecular epidemiology-the exploitation of molecular laboratory techniques in analytical epidemiologic studies-has the promise of overcoming a number of methodological difficulties confronting epidemiology.

This field of research can be described as the multidisciplinary efforts integrating molecular biology, laboratory models, biochemistry, and epidemiology in the study of diseases. Molecular epidemiology holds potential benefits for the design and conduct of epidemiologic research by identifying etiologic factors for disease, determining the internal dose of those factors and the relationship between the dose and the response, and understanding the mechanism of disease processes.

In addition to understanding disease etiology, molecular epidemiology promises to develop new tools and open up new strategies for preventing disease. The results of this research can provide early markers of disease and identify susceptible high-risk groups for intervention through treatment Furthermore, it can be used to validate new animal and laboratory studies for testing toxicants.

An important component of molecular epidemiology is the biological marker, or biomarker. Biomarkers are measurable indicators of events or changes in cellular, molecular, or biochemical systems, such as human tissues, cells, fluids, or organs.

Biological markers can be divided into three general types: markers of exposure or dose, markers of health effects or response, and markers of susceptibility. The first type, biomarkers of exposure or dose, can be measures of original contaminants in the body and thus provide clear-cut evidence of a specific environmental exposure; an example is lead in the bloodstream. Markers of exposure can be a transformed original contaminant; an example is cotinine, a metabolite of nicotine, in a person's blood as a marker of exposure to tobacco. The next type, biomarkers of effect or response, are those indicators that represent changes between exposure and the clinical manifestation of disease. One example is reduced plasma acetytcholinesterase levels fallowing exposure to organophosphate insecticides. Finally, biomarkers of susceptibility are indicators of inherited or acquired factors that affect an individual's response to exposure to an etiologic factor. An example is a mutant adenomatous polyosis coli gene in people with familial adenomatous polyosis as a predisposing factor for colon cancer.

Biomarkers can be used to improve epidemiologic studies in Providing quantitative dose and response data for risk assessments. Typically estimates of exposure are the weakest aspect of epidemiologic studies, which makes many epidemiologic associations of exposure and disease uncertain. Biomarkers of exposure or dose can be used to replace job history or recall of activities as ways to estimate exposures. Some markers can be used for exposure and response, and provide data for dose-effect analysis. Biomarkers of effect can be used to quantify the response to a toxic agent. These applications of biomarkers can increase the accuracy of exposure assessment, which enhances the power of an epidemiologic study by providing firmer evidence linking exposure with disease.

At present, the use of biomarkers remains limited. Most of them are still being developed and need testing or validating, pointing to important areas of future research.

SOURCES: B. Hulka, T. Wilcosky, and J. Griffith. 1090. *Biological Markers in Epidemiology,* Oxford University Press, New York; National Research Council. 1991. Human *Exposure Assessment for Airborne Pollutants: Advances and Opportunities,* National Academy Press, Washington DC; P. Schulte and F. Perera. 199S. *Molecular Epidemiology: Principles and Practices,* Academic Press, San Diego.

HUMAN EXPOSURE METHODS

Many people in the risk assessment community whom OTA interviewed contend that research on human exposure is currently underdeveloped and inadequately supported, despite its significant short- and long-term implications for both policy and public health. A report by the National Research Council (NRC, 1991) recommended measuring contaminant concentrations in air, water, and soil, to characterize the exposures of individuals and populations. The council sees the measuring of human exposures as advancing prevention efforts and thereby mitigating the health effects of exposure to hazardous substances. Carrying out the council's recommendation will require scientists to improve personal monitoring, identify and measure biological markers of exposures, and develop and validate mathematical models for estimating exposures among individuals and populations.

Currently, most exposure estimates depend on models that have not been validated. To understand the relationship between the emission of pollutants from a source and human exposures, researchers are developing models of the transport and transformation of chemicals released into the environment and on human exposure pathways. Data are critically needed to test and eventually validate these exposure models.

MECHANISTICALLY BASED EFFECTS AND DOSE-RESPONSE EXTRAPOLATIONS

The advances in understanding the biology of, for example, cancer will influence testing and data collection, as well as the methods used for constructing dose-response models for estimating risks from exposure to carcinogens. The roles of oncogenes and tumor suppressor genes (box 7-B) that have been uncovered during the past decade have changed the way environmental health scientists approach their studies of environmental carcinogens. Research results affirm that cancer develops through a multistep process that can involve the accretion of multiple genetic alterations (Aaronson, 1992; Barrett, 1993; Weinberg, 1992). Understanding how carcinogens affect the critical steps of cancer development will improve knowledge of environmentally mediated carcinogenesis and methods for assessing carcinogenic risks.

Many scientists argue that advancing the field of mechanistically based dose-response modeling will substantially reduce uncertainty in risk assessments of potential carcinogens. The objectives of these models are to base risk estimates on understanding how the agent produces its carcinogenic effects. To promote such modeling, researchers are integrating knowledge from testing, epidemiologic, exposure, mechanistic, and pharmacokinetic studies in an iterative fashion for some compounds, including tetrachlorodibenzodioxin (TCDD) (Vanden Heuvel and Lucier, 1993).

Physiologically based pharmacokinetic (PBPK) models estimate both the concentration of a toxicant, or an active metabolize of it, at the target site and the time it spends there. As the next step in the process, biologically based dose-response (BBDR) models use pharmacodynamic information to examine the relationship between the concentration and persistence of a toxicant at the target site and the observed adverse effects on health. Computer models can incorporate both PBPK and BBDR data, to offer a closer representation of the human body. Such improved models should reduce the reliance of risk assessors on the assumptions that have been used in risk assessments. Furthermore, computer simulations can describe not only the action of chemicals throughout the body but also identify gaps in the information base, suggesting areas of additional research.

Biological and biomedical research is building our knowledge of the normal life processes. This understanding is demonstrating the complexities of the various levels of control at the cellular, tissue, and organismal functions. Yet, little is known about the effects of exposures to toxic agents at different stages of the life cycle. Research suggests that exposures at different times can cause different effects on health. The

Box 7-B-The Biology of Oncogenes and Tumor Suppressor Genes

During the normal development of an organism, a chemical "conversation" occurs among the developing cells that directs their specialization and maturation into tissues. This chemical "conversation" is mediated by a variety of biological molecules, some of which are the products of genes.

Genes and gene products are potential targets for radiation and chemical damage. Damaged genes or gene products can disrupt the ability of cells to carry out their business or change the information being communicated to other cells. Altered information sent to cells can cause some of them to become "confused" and proliferate uncontrollably, which can result in cancer. Before cancerous growth begins, however, several specific genetic changes may have to accumulate within a cell and cause normal cell functioning to break down.

At present, scientists have identified at least two families of interacting genes--proto-oncogenes and tumor suppressor genes-that are linked to cancer in humans and other animals. Under normal circumstances, both of these kinds of genes are necessary for the proper growth and development of an organism. Working in balance to maintain cell growth and differentiation, the two families of genes have been termed the "yin and yang of cancer biology."

Proto-Oncogenes and Oncogenes

Proto-oncogenes, as their name implies, are genetic precursors of oncogenes, or cancer-causing genes. Found in all healthy cells, proto-oncogenes are involved in regulating ceil growth, or cell division and differentiation. Proto-oncogenes produce growth factors that play a role in normal cellular growth.

Oncogenes arise when critical parts of proto-oncogenes undergo structural changes brought about by, among other things, exposure of cells to radiation or chemicals. These altered genes may maintain the role of the original proto-oncogenes in directing ceil proliferation but ignore the influence of information coming from outside the cell. Consequently, cells divide regardless of the content of the chemical conversation.

Tumor-Suppressor Genes

Recent findings suggest however, that creating oncogenes alone is insufficient to induce malignancy in most cells. Tumor suppressor genes must also be dissuaded from functioning normally.

Tumor suppressor genes, also known as anti-oncogenes, act to restrain cell division, providing a balancing force against the growth-promoting proto-oncogenes in normal cells. They also seem to be successful in overriding the uncontrolled-growth instructions that oncogenes put out. For a cell to become malignant, therefore, one or more proto-oncogenes are converted to an oncogene, and one or more tumor suppressor genes are removed or becomes inactivated. The same types of exposures that create oncogenes can remove or inactivate tumor suppressor genes—namely, exposure to DNA-damaging chemicals or radiation.

A useful analogy of the relationship of proto-oncogenes, oncogenes, and tumor suppressor genes is to imagine the cell as a car. The normal proto-oncogene is like a car's accelerator pedal. Once changed into an oncogene, one could imagine the car's accelerator welded to the floor. Tumor suppressor genes might be viewed as the car's brakes, holding back the effects of the oncogenes. When agents damage the tumor suppressor genes, it is similar to the car's brakes being removed, sending the cell careening down the path toward cancer.

SOURCES: S. Aaronson. 19S1. Growth factors and cancer. *Science* 254:1 14S; J. Barrett. 199S. Mechanisms of multistep carcinogenesis and carcinogen risk assessment. *Environmental Health Perspectives* 100S-20; E. Solomon, J. Borrow, and A Goddard. 1991. Chromosome aberrations and cancer. *Science* 254:1153; N. Touchette. 1S92. Dying cells reveal new role for cancer genes. *Journal of NIH Research* 4:48; H. Varmus. 19S7. Oncogenes and transcriptional control. *Science* 238:1337-1339; R. Weinberg. 1991. Tumor suppressor genes. *Science* 254:1141; S. Young. 1992. Dangerous dance of the dividing cell. *New Scientist* 92:6.

endocrine system, for example, is integrally related to the growth and functioning of nearly all cells. Depending on its stage of development, chemical perturbation of the endocrine system may lead to different adverse effects (e.g., reproductive effects or cancer). As with many new discoveries in risk-related research, opportunities exist for multidisciplinary collaboration— linking

biomathematicians, molecular biologists, toxicologists, and epidemiologists-to develop new models of biological processes and to understand how chemicals disturb those systems.

Basic Biomedical Research

The results of ongoing basic biological research have long-term implications for future health risk assessment research. Applying the knowledge gained from studies in basic biology to basic toxicological research may happen quickly, but usually it requires a considerable amount of time and resources. Scientists and decisionmakers interviewed by OTA stressed the importance of the relationship between conducting basic research and improving risk assessment methodology. Of arguably the greatest long-term signtificance for the environmental health sciences is the study of the interaction between genetic susceptibility and environmental factors. Molecular techniques give scientists the capacity to tease out specific genetic damage associated with environmentally related diseases and to monitor damage to DNA following exposure to environmental toxic agents. Such studies can identify those genes that are susceptible to damage by toxicants, as well as groups of people who are particularly sensitive to the adverse health effects of environmental exposures (box **7-c).**

Basic biomedical research is likely to influence the direction of health risk research in unanticipated ways. For example, if successful, the Human Genome Project now underway will eventually provide information on the entire nucleotide sequence of the human genome, which will in turn contribute to risk assessment by providing information about the molecular basis of disease. Biomedical researchers are expanding our knowledge about the normal relationships of specific human genes, their gene products, and biological functions. That information greatly facilitates the studies of how toxic agents can affect biological processes.

An exciting recent discovery for understanding developmental toxicology has been an understanding of homeobox genes. Studies in mice show that these genes encode proteins that specify the development of, say, the head and neck. Damage to the homeobox genes by environmental agents could lead to abnormal development. Knowledge of the location and function of these genes can focus toxicologists in their research on understanding how chemicals might alter development.

Studies of the biology of diseases in general provide an understanding of the functioning of various organ systems. For example, research related to the acquired immunodeficiency syndrome (AIDS) has revealed much about the immune system; similarly, studies of the lung diseases cystic fibrosis and emphysema have contributed to basic knowledge of pulmonary biology. Studying the behavioral disorders arising from Alzheimers and Parkinson's disease has helped researchers to discern the connection between the functioning of the nervous system and behavior. Such disease-specific research may provide clues for studying how toxicants interact with biological systems and understanding the types and nature of adverse effects that may result from exposure to them.

Data Development and Management

Keeping abreast of the need for toxicity information of new chemicals will require new technologies to generate the data and to manage the burgeoning database. While data development and management are important for advancing health risk assessment, some scientists may not consider it research. Whether or not this activity is considered research, data on the toxic properties of specific compounds and of human exposure is the basis for health risk assessment. With new tools for the study of toxicology and exposure, traditional approaches are constantly being challenged for their information value. Moreover, estimates are that only about 10 percent of the

Box 7-C-Genetic Predisposition to Cancer: The Role of Oncogenes and Tumor Suppressor Genes

Cancer is a multitude of diseases. The nature and the number of genetic and nongenetic changes associated with each type of cancer differ. However, both laboratory and human studies confirm that the pathogenesis occurs in stages and multiple genetic and environmental factors can affect its development.

Most genes in humans come in pairs. Usually both copies of the gene carry out an identical job. The large number of genes in the human genome makes it relatively rare that a damaging alteration will take place in both copies of a gene when the cell is subjected to damaging radiation or chemicals.

Conversion of one of a pair of suppressor genes to an inactive form is not sufficient to cause cancer; the remaining active gene is sufficient to maintain normal growth. When both members of the pair of suppressor genes are made inactive, cancer can result. Such a case occurs with retinoblastoma, a cancer of the retina in children. Carriers of the defective gene are born with one of a pair of the suppressor gene, the rb gene, defective. Such carriers have a much higher risk of retinoblastoma: inactivation of the remaining rb gene in a retina cell results in this cancer. Noncarriers require two such changes to develop retinobtastoma Thus carriers of the defective rb gene, compared with someone who has two working copies of the rb gene, are predisposed or have a greater "susceptibility" for developing retinoblastoma.

Susceptibility can be identified among families. Such at-risk families are susceptible to a specific type of cancer, corresponding to the specific damaged gene that is inherited. Familial polyposis coli is a common hereditary predisposition to colon cancer and has an incidence of about one in every 10,000 individuals.

Oncogenes have not yet become useful tools for identifying an individual's predisposition to cancer. Most identified oncogenes are "dominant;" only one member of the gene pair has to be converted to an oncogene to cause unregulated growth of the cell. These oncogenes are seldom passed from parents to child; even one oncogene of the pair would wreak havoc with the growing embryo long before it could mature to birth.

What is imaginable, however, is that less "dominant" oncogenes might exist and could be inherited in humans. These would probably not be strong initiators of cancer but would act in tandem with other "weak" oncogenes to predispose individuals to a variety of tumors. Such "weak" oncogenes have not yet been tied to any particular location in the human genome.

In contrast to oncogenes, several tumor suppressor genes have become quite valuable in identifying genetic predispositions to specific cancers. Notable among them are the Rb gene discussed earlier and the p53 gene in Li-Fraumeni syndrome. The Li-Fraumeni syndrome predisposes carriers to a wide variety of cancers. The study of a family predisposition for retinoblastoma identified Rb as the first known tumor suppressor gene.

SOURCES: J. Barrett. 1SS3. Mechanisms of multistep carcinogenesis and carcinogen risk assessment. *Environmental Health Perspectives* 100:9-20; H. Evans, J. Prosser and J. Presser. 1SS2. Tumor-suppressor genes: cardinal factors in Inherited predisposition to human cancers. *Environmental Health Perspectives* 98:25; A. Knudson. 1999. *The genetic predisposition* to *cancer. Genetic Susceptibility to Environmental Mutagens and Carcinogens.* March of Dimes. White Plains, NY; J. Marx. 1991. Possible new colon cancer gene found. *Science* 91:1317; E. Solomon, B.J. Borrow, and A.D. Goddard. 1SS1. Chromosome aberrations and cancer. *Science* 254:1153; H. Yamasaki, L. Alexandre, and L. Tomatis. 1992. Perinatal and multigenerational effect of carcinogens: possible contribution to determination of cancer susceptibility. *Environmental Health Perspectives* 98:39.

chemicals in commerce have data available for a risk assessment *(Environmental Health titter,* 1993). Baseline data on human exposure are also lacking because of the limitations of current methods and resources. Toxicity data have been developed through epidemiologic studies or tests using animals or microorganisms. Information on exposure comes from measuring the levels of a chemical agent present in air, food, water, soil, or consumer products. As discussed in other chapters of this report, uncertainty about such data affects the confidence that can be placed in the results of risk assessments. The validity of new methods for toxicity testing and human exposure monitoring must be demonstrated before the methods are adopted. This should be an iterative

process whereby the generation of data is linked to validation.

The explosion of research data applicable to risk assessments combined with a greater need for data to support regulatory action necessitates improving the access to this information. Storing and analyzing that information will require more advanced computational tools. In time, the broad task of data synthesis will play an increasingly important role in characterizing and comparing risks posed by different environmental problems. Scientists are seeking ways to improve the size and reliability of the toxicological database on environmental agents.

With improved techniques for analyzing and managing information, researchers may be able to connect disparate pieces of data, which could lead to conceptual breakthroughs. They could assemble information about metabolic transformations, for example, into a database on metabolism that could anticipate metabolic products of other environmental agents. In addition, ways could be devised to examine and analyze old databases, as well as new data, for useful information that may not be detectable with existing methods.

One example of a new method for analyzing data is meta-analysis. Meta-analysis is a broad label for a variety of statistical and mathematical methods for assessing and summarizing a body of data. In the most restrictive sense, scientists use formal meta-analytic techniques to summarize the information in several studies of very similar design. But methods are also needed to synthesize complex databases to include the results of more methodologically distinct studies involving, for example, data on exposure and health effects in animal and human systems. The science of meta-analysis is still in its infancy. Nevertheless, it offers the potential to help researchers assess data on the health effects of environmental pollutants in new and more meaningful ways. It may also provide opportunities to predict toxicity for a chemical or class of chemicals for which few data exist.

FOSTERING RESEARCH LiNKAGES

Research linkages and collaborations offer enduring benefits to all participants. They bring together researchers with different strengths and expertise, foster the dissemination of knowledge, and permit the sharing of resources. Research linkages also allow researchers to undertake projects that otherwise might not be possible.

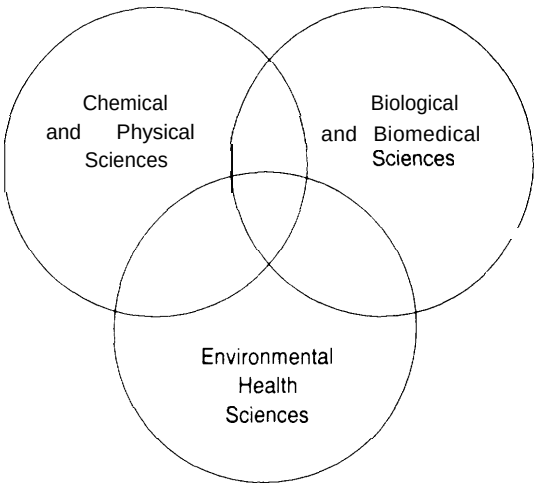
Linkages can occur within and between Federal agencies as well as between Federal and nonfederal institutions. Traditionally, linkages in health risk assessment research were forged between government and university researchers; fewer such linkages exist between government and industry. Although not all areas of health risk assessment research lend themselves to industry linkages, some topics have commercial potential and would benefit from public-private partnerships. The paucity of those linkages also stems, in part, from the primary focus of publicly funded health risk research, which is to identify toxicants and determine risks to public health. Because some of these risks come from industrial activities, those linkages could create conflicts of interest between public and industry concerns.

Building Disciplinary Bridges

Multidisciplinary interactions in most scientific endeavors require various resources—intellectual, personal, and financial. Because the requirements are great and the barriers are high, many collaborations across disciplines do not succeed (Chubin et al., 1986; Klein, 1990). Yet for those that do, the benefits often include establishing new, even revolutionary, frontiers of science, arising from the exchange of information across disciplines (Kuhn, 1962).

Health risk assessment can be viewed as the overlap between chemical- physical sciences, biological-biomedical sciences, and environmental health sciences (figure 7-l). To develop as a field, health risk assessment research must be linked with broader areas of research. From bridges built between different research disciplines, new per-

Figure 7-l—Linking Scientific Disciplines in Health Risk Research



SOURCE: Office of Technology Assessment, 1993.

spectives and insights can emerge. In addition to the invaluable expansion of scientific knowledge, basic science is the basis for developing the 'risk sciences. " Risk science, under appropriate leadership, could be a magnet for collaborative research. It could become analogous to the Human Genome Project, in which collaborations have been formed among scientists working to sequence the human genome. Its goal is different, of course; yet, a similar process could occur. Researchers from many disciplines could work together to improve health risk assessments as a desirable social and scientific goal.

Research is traditionally structured along disciplinary lines and separated conceptually, if not actually, into basic and applied research as away to highlight the goal of the activities. Because research in support of risk assessment is generally multidisciplinary, the differences between basic and applied research are often subtle and difficult to discern. For example, researchers using chemicals as investigative tools for probing fundamental biological systems (basic biological research) are nearly indistinguishable from those investigating the basic underlying mechanisms of the adverse health effects of specific chemicals (applied toxicological research). The objectives and approaches may differ, but the results can be complementary; and, information sharing by the researchers can enhance the value of the results of everyone's efforts for the advancement of knowledge and improving risk assessment. Similarly, because health risk is essentially a composite of toxicity and exposure, health effects and exposure research should be linked and integrated as well, especially when planning research programs and activities.

Partnership With the Private Sector

In addition to scientists' collaborating to improve risk assessments, federally supported researchers can transfer knowledge to the private sector to foster economic growth and competitiveness, now a vital part of the mission of many research agencies. Revenue raised through technology transfers could be used to bolster research in health risk research. Such additional funding could be important because, as this report describes, resources are currently inadequate to provide stable, long-term support for research in this area.

Increasingly, mechanisms are being developed to facilitate the transfer of research results developed with public funds to the private sector. In particular, legislation enacted during the 1980s—the Bayh-Dole Act of 1980 (P.L. 96-517) and the Federal Technology Transfer Act of 1986 (P.L. 99-502)-provides Federal agencies with incentives to promote technology transfer. That legislation encourages the commercialization of research by permitting Federal grantee institutions, contractors, and laboratories to retain the rights to inventions that they develop with Federal funding. In addition, scientists at those institutions can collect a portion of the royalties. The legislation also authorizes Federal agencies to enter into research with the private sector through cooperative research and development agreements (CRADAs). Those agreements can be put into place very early in the development process—well before the invention stage. Although conflict

of interest is still of concern in some circumstances, public and commercial interests converge in selected areas of health risk assessment research. Examples include toxicological tests and exposure monitoring technologies that will be quicker, more accurate, and less expensive. To date, only a few such cooperative ventures have been established.

Ties to Universities

Many areas of health risk assessment research do not lend themselves to product development. Basic research is an example, but basic research is ripe for collaborative efforts between and within agencies of the Federal Government and between Federal agencies and universities (box 7-D). Many of the specific research opportunities in health risk assessment research described in the previous section would benefit from linkages and collaborations between Federal and university researchers.

This need to exchange views, results, developments, and insights led to calls for a forurn of coalescing research interests. One result was the Society for Risk Analysis, which was founded in 1982 to focus on the risk analysis debate and publish relevant work on the topic. Interest in the society has grown over time, as has the number of papers submitted to its publication, *Risk Analysis; An International Journal* (Travis, 1993), and health risk research articles are frequently published in the journal. Other avenues of expression are opening up as well. Of note is a recent conversion by ***Environmental Health Perspectives,*** a journal published by the National Institute of Environmental Health Sciences. That journal traditionally published scientific articles on environmental health and toxicology. In April 1993, the journal began incorporating news features, editorials, commentaries, and perspectives relevant to health risk, including policy. The editors say they want the journal to be a printed nexus of the various perspectives in the environmental health sciences (Lucier, 1993). In the final analysis, perhaps an integrated risk assessment culture may be emerging from the disparate strands of its disciplinary origins.

SUMMARY AND CONCLUSIONS

Recognizing the potential of research to narrow the uncertainty of risk assessment, OTA noted several characteristics common to high-quality research programs that should be considered in structuring future research efforts. These include leadership, well-defined objectives, investigator initiation of research, competitive awards and peer review, planning and criteria for evaluating success, collaboration and coordination, training, and advisory input.

OTA identified several areas that promise to improve risk assessment. They include research into new methods for toxicity studies; biomedical and molecular epidemiology; mechanistically based effects and dose-response extrapolation methods; improved methods for measuring or estimating human exposures; mechanistic studies of the actions of toxic substances; attention to methods evaluation and validation; techniques for characterizing and communicating risks; and information management.

Exploitation of the many promising research avenues for improving health risk assessment requires establishing linkages not only within and among various scientific disciplines but also with various organizations. Furthermore, as discussed in chapter 5, an important criteria to judge success for health risk research is that it be useful for decisionmaking . Linkages with risk assessments and decisionmaking too should be fostered. No one category of research can be classified as most useful for decisionmaking. Instead, risk assessments will increasingly require multidisciplinary approaches and analyses of all available information. Moreover, the nature of the health risk being addressed, the nature of the information already at hand, and other factors that affect decisionmaking should be considered when structuring a research program for solving health risk problems.

Box 7-D–The Environmental Health Sciences Center at the Johns Hopkins University

The Environmental Health Sciences Center at the Johns Hopkins School of Hygiene and Public Health is supported by the National Institute of Environmental Health Sciences (NIEHS), through an NIEHS Centers Grant. The goals of the center focus on understanding the impact of potentially toxic environmental agents on health by investigating mechanisms of action at the molecular, whale animal, and human levels of interaction. In addition, the center attempts to stimulate research interactions between individual faculty and faculty of other existing environmental and occupational health-oriented centers throughout the university, such as the Educational Resource Center, supported by the National Institute for Occupational Safety and Health, and the Injury Prevention Center, supported by the Centers for Disease Control and Prevention.

An underlying theme of the center is "molecules to man." This theme is in accord with the concept that it is critical to understand the basic biological and molecular mechanisms by which environmental agents cause disease in man so that they can be prevented. Currently, the center draws upon the Departments of Biochemistry, Biostatistics, Environmental Health Sciences, Epidemiology and immunology and Infectious Diseases for its members. The rationale for the Johns Hopkins NIEHS Center is that the many scientific disciplinary investigatory talents at the university benefit from an environment which promotes collaborative, interdisciplinary research.

The center also provides a suitable environment for the education and training of future Environmental Health Research Scientists by incorporating pm-and post-doctoral students and fellows, respectively, into the research activities of the center. The center also conducts outreach programs for the continuing education and training of environmental health professionals.

The center is organized into six research core units each having its own area of emphasis and specific aims: Epidemiology and Exposure Assessment; Molecular Dosimetry and Biological Monitoring; Environmental Carcinogenesis; Physiologic Responses to Inhaled Pollutants; Cellular and Immune Defense Mechanisms; and Neurotoxicology. These programs conduct studies on a spectrum of environmental agents as well as a number of human diseases.

Some highlights of the scientific accomplishments include the research findings made by the Environmental Carcinogenesis program in the area of chemoprevention. Aflatoxin, a widespread contaminant in the environment, particularly in Africa and Asia has been associated with increased incidence of hepatocellular carcinoma Center researchers found that an antioxidant known as oltipraz can prevent hepatotoxicity and the ultimate appearance of liver tumors when given at the same time as aflatoxin. This research provides new insights into the mechanism of the protective action of oltipraz, which may represent a compound that could be given to individuals at high risk of aflatoxin exposure.

Another center project collected data about exposure to electromagnetic fieids (EMF), as part of a national case-control study of telephone linemen. The study identified individuals working in telephone switching offices who had electric and magnetic field exposures that were different from those produced by 60-HZ alternating current. Some studies suggest that complex electromagnetic field exposure environments may impact biological activity differenty than fields produced by 60-Hz alternating currents. The center investigation found that telephone linemen working in switching offices had an increased risk to male breast cancer.

SOURCE: The Johns Hopkins University School of Hygiene and Public Health, 1993.

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Appendix A: International Risk Assessment

This appendix provides a snapshot of how other countries and international agencies practice health risk assessments. It highlights the risk assessment of chemical carcinogens because the methodologies for that type of assessment are better developed than those for other health endpoints. It also focuses on the various types of health risk assessment used by different countries and international bodies, specifically noting those cases in which quantitative risk assessments (QRAs) are employed. The definition of a QRA is subject to controversy and differs from country to country. For the purposes of this discussion, a risk assessment is characterized as quantitative when it generates numerical estimates relating the risk of developing cancer to particular levels of exposure to a chemical. Adding to the lack of uniformity internationally is the fact that countries and international bodies involved in monitoring human exposure to chemical carcinogens and other toxic substances have adopted their own processes of health risk assessment. The differences in their methods and definitions are due to a number of variables, including legislative and regulatory histories, government structure, public involvement, research and development, and cultural characteristics.

The information used to generate this appendix was obtained through written and oral correspondence with the relevant officials in each of the countries and international bodies that the Office of Technology Assessment (OTA) surveyed. OTA chose the countries and organizations that participated based on their activity in the field of risk assessment and availability of resources. A minimum of three sources for each country or body was examined; the same sources also had an opportunity to review and comment on a draft of this text.

How do these countries approach risk assessment? An important prerequisite for many of them in conducting QRAs is knowledge about the mechanism of carcinogenic action of a substance. Usually, only QRAs are performed for genotoxic carcinogens.[1] In addition, many industrialized nations that regulate chemical carcinogens tend to use a case-by-case approach: each chemical is subjected to an individual review that considers cancer mechanisms. Such countries as the United Kingdom and Germany rely primarily on expert judgment in risk assessments and regulatory decisionmaking, The risk assessment process in those nations involves the formation of expert advisory committees that make the actual decisions regarding exposure standards or regulations instead of the agencies. Those advisory bodies commonly use a ‘‘ weight-of-the-evidence’ approach, in which all of the available information and test data are evaluated in formulating a decision concerning a carcinogen.

Finally, the countries OTA surveyed support a variety of regulatory agencies, a characteristic common to the United States as well. As a result, just as the

[1] When a carcinogen acts by a genotoxic mechanism, it damages DNA and causes genetic changes (e.g., mutation of a gene), which may in turn lead to the abnormal development of human cells that may serve as a precursor for cancer (see ch. 2).

use (or nonuse) of QRA may differ among countries, QRA policies among a country's regulatory organizations may also vary. Because one agency uses QRA does not mean that other regulatory bodies in the same country also practice it. Moreover, regulatory organizations may use QRA for different purposes to develop standards of exposure or to establish regulatory or research priorities.

INTERNATIONAL BODIES AND RISK ASSESSMENT

Their increasing awareness of the risk of exposure to toxic chemicals has led several international bodies to develop programs addressing the need to identify, monitor, and assess toxic agents. The focus of each program differs, based on its structure and clientele. Nevertheless, these international bodies, along with regulatory agencies in the United States and other countries, have developed significant collaborations in fulfilling their overall missions to protect humans from exposure to hazardous substances.

The activities of these organizations encompass collecting data on hazardous chemicals, evaluating additives and pesticide residues in food, labeling and classifying both new and old chemicals, reviewing occupational exposure to hazardous chemicals, and promulgating guidelines for assessing chemicals. Much of the work of these international organizations is targeted at improving trade between countries by promoting the use of standardized testing, classification, and labeling procedures. OTA, in the following discussion, focuses on the more prominent chemical risk reduction programs and highlights any use of human health risk assessment, either qualitative or quantitative. The United States makes a substantial contribution to many of these organziations (table A-l). We emphasize the regulation of exposures to carcinogens, but not to the exclusion of noncarcinogenic chemicals.

International Agency for Research on Cancer

As part of the World Health Organization (WHO), the International Agency for Research on Cancer (IARC) was established in 1965 to promote international collaboration in cancer research. The main activities of IARC currently encompass collecting and disseminating data on cancer occurrence, searching for the causes of cancer, and conducting research aimed at preventing cancer. IARC is also exploring other aspects of cancer, including mechanistic aspects of carcinogenesis, genetic disposition toward cancer, and quantitative estimation and prediction (QEP) of cancer risks. QEP is IARC's approach to quantitative risk assessment.

Currently, 16 participating nations contribute resources for research and provide expert advice to IARC (IARC, 1991). Participating states also make financial contributions. Yet, despite that assistance, the agency reports that it is experiencing financial difficulties, which makes it difficult to recruit additional personnel to pursue all of its objectives. Notwithstanding these problems, the agency has initiated some new projects and is continuing those already under way (IARC, 1992b).

In addition to its affiliation with participating countries, IARC is also involved in numerous collaborations with other international agencies and national institutes. Numerous countries, especially those lacking resources, use publications containing the agency's evaluations and classifications of chemical carcinogens in formulating their policies on carcinogens.

Although IARC does not perform risk assessments in their entirety, it serves an important role in the initial stage of risk assessment—that is, in hazard identification of carcinogens using rodent bioassays. Participating countries, including the United States, conduct them and submit the results to IARC for review, evaluation, and publication in its series ***Monographs on the Evaluation of Carcinogenic Risks to Humans. During*** its review and evaluation process, IARC subjects chemicals to a classification scheme it developed to characterize their degree of carcinogenicity. One of the agency's major accomplishments has been establishing a process for evaluating and analyzing data based on the consensus of multidisciplinary experts and not on the basis of administrative or political concerns (Richter and Goldsmith, 1991).

IARC's *Monographs series is* one of its most important contributions to cancer research, To date, IARC has published 57 volumes of the series, which qualitatively evaluates and classifies more than 750 agents and complex exposures for carcinogenicity (IARC, 1993). The process begins by choosing candidates for hazard identification and classification from

Table A-l—Assessed and Voluntary Contributions by the United States to International Organizations

	1991 assessed (millions of U.S. dollars)	Percentage of total budget	Voluntary[b]	1992 assessed (millions of U.S. dollars)	Percentage of total budget	Voluntary
World Health Organization	$78.3	25%	N/A	$94.2	25 %	N/A
Organisation for Economic Cooperation and Development. . . .	45.6	25	$0.015	44.6	25	$0.005
International Labor Organisation	61.8	25	N/A	N/A	N/A	N/A
Food and Agriculture Organization . . .	70.0	25	N/A	N/A	N/A	N/A
Pan American Health Organization . .	42.0	61	N/A	45.4	61	N/A
International Agency for Research on Cancer	1.4	10	N/A	1.5	11	N/A

NOTE: N/A- not available.
[a] In many cases, there is a cap of 25 percent on the total budget percentage that the United States may contribute to an organization.
[b] Totals are incomplete. Voluntary contributions originate from a variety of sources, not necessarily the Federal Government.

SOURCE: U.S. State Department, World Health Organization/International Programme on Chemical Safety, 1993.

the results of surveys sent to governments of participating countries and to cancer experts (Richter and Goldsmith, 1991). IARC then uses international working groups of experts to evaluate a selected number of agents or exposures. The categorization of an agent or exposure is a matter of scientific judgment, reflecting the strength of the evidence derived from studies in humans, studies in experimental animals, and other relevant data. In cases in which there is sufficient evidence of human carcinogenicity, an agent or exposure is classified as carcinogenic to humans. Subsequent categories characterize agents as probably or possibly carcinogenic to humans, impossible to classify, and probably noncarcinogenic to humans (IARC, 1992a).

In the area of quantitative risk assessment, IARC is planning a workshop entitled 'Scientific Principles of Quantitative Risk Estimation and Prediction of Carcinogenic Risk' in October 1993. The workshop's main product will be a comprehensive publication on the scientific bases and state-of-the-art of QEP. Its main focus will be to review existing methods, but it will also describe the relevance of QEP for policy setting and attempt to provide some scientifically based guidelines for the use of QEP. The publication will be designed for a wide audience, including the scientific community, regulators, and national governments (IARC, 1992c). In addition, the workshop will serve as a forum to discuss and recommend the extent to which IARC should be involved in developing and conducting QEP (specifically, whether the state-of-the-art allows the definition of a scientific procedure) (IARC, 1992c).

The European Community

The European Community's (EC) pursuit of a unified internal market has forced it to address environmental issues directly. As a consequence, the EC has been working toward the "harmonization' of health, safety, and environmental regulations, to reduce competitive imbalances among EC countries and keep regulations from acting as trade barriers (U.S. Congress, OTA, 1992) (box A-l). The EC has also sought to protect the public and the working population from exposure to hazardous chemicals. With all of this in mind, the EC has turned to risk assessment for determining g standards of exposure and levels of risk and for harmonizing testing standards for chemicals.

EC legislation pertaining to human health risk assessments has been mainly directed at: chemical safety, pesticide residues, food additives, and occupational exposure to chemicals. A common characteristic of most of the directives passed or proposed in those fields is that the member states or individual employers are responsible for performing any risk assessments, not the EC, Bodies of experts are used throughout this process, both by those performing the risk assessments and by the EC to design its directives and evaluate the end results.

EC directives mandate both qualitative and quantitative risk assessments, depending on the type of chemical and its usage. In the area of chemical control

Box A-l-Organization of the European Community

The European Community, which was established by a series of treaties in the 1950s, currently has 12 members, all Western European countries. Representatives of these member states serve on the various committees and institutions that comprise the EC. In addition to its select membership, the EC is unique among international bodies in that it has the power to mandate the adoption of its legislation by member states.

The EC legislates through regulations, directives, decisions, and recommendations. Regulations, the most stringent of the EC's legislation, mandate compliance by EC member states in direct accordance with the language of the regulation. Directives, which are the most common form of environmental legislation, are also binding on member states. However, member states have varying degrees of technological capability for complying with EC directives and in addition are free to choose a method of national implementation. Those factors and the EC's limited enforcement mechanisms can lead to significant time delays in a member state's compliance with a directive, despite assistance provided through temporary exceptions or financial support.

The original Treaty of Rome, which created the EC, did not include an explicit legal basis for addressing environmental issues. That deficit was remedied by the adoption of the 1987 Single European Act (SEA). The SEA, which amended the Treaty of Rome, addressed further areas of fragmentation and noncooperation within the EC and included an environmental amendment to the original treaty. The act codified a basis for the EC to require that members harmonize their national environmental regulations. It also allowed the EC to create environmental laws when the preservation of the environment was better ensured by its actions than by those of individual countries.

Before and after the existence of the SEA, the EC has approached the growing need for environmental legislation by developing environmental action programs. The first program was ratified in 1973, and the fifth was adopted in 1992. These programs have addressed a wide range of environmental regulation, including air, water, chemicals, waste, wildlife, environmental assessments, and site safety. To date, nearly 300 environment-related directives have been passed, but fewer have actually been implemented by the member states.

EC policy is executed by the European Commission, which has about 20 divisions or directorates-generals. The Environment Directorate-General is knownasDG-XI(11) and is somewhat similar to the U.S. Environmental Protection Agency. But, in response to a growing need for a centralized body to deal with environmental matters, an European Environment Agency (EEA) has been planned since 1990, with the role of collecting information and providing objective and comparative data on the state of the environment in member states. Unlike the U.S. EPA EEA is not designed to have enforcement power and will operate on a first-year budget of only $1.4 million, compared with to the U.S. EPA's current $6.5 billion. The EEA also lacks the authority to fund research, but supporters hope that it will eventuality be able to direct projects aimed at filling gaps in its database. Ironically, EEA has yet to begin collecting and disseminating data because of an ongoing debate about its geographic location.

SOURCES: Commission of the European Communities, 1990. Completing the single market: The removal of technical barriers to trade within the European Economic Community (Brussels); Hurwitz, L. 1992. The European Community and the Single European Act of 19S7: What Does It Mean? *Phi Kappa Phi Journal*, spring; Keyes, C. 1991. The European Community and Environment Policy: An Introduction for Americans (Baltimore, MD: World Wildlife Publication, 1991).

and safety, very basic qualitative risk assessments are used in evaluating "new' chemicals. The EC's initial effort at environmental policy came in this area with the 1967 directive on classification, packaging, and labeling of dangerous substances. After the passage of this directive, chemical control and safety became a prominent issue in EC environmental policy. An important addition to the 1967 directive came in 1979: known as the "sixth amendment, " this document established a harmonized testing and notification scheme for new chemicals. A seventh amendment, which further updates EC guidelines for chemical testing and assessment, was approved in April 1992 (Official Journal of the EC, 1992).

The EC's procedure for chemical testing was an important advance in harmonizing the chemical assessment guidelines of the various member nations, and, subsequently, the 1967 directive and its compo-

nents have served as a model for environmental regulation in other countries and through international organizations (e.g., the Organisation for Economic Co-operation and Development (OECD)) (CEC, 1987). The EC's tests mainly identify hazardous chemicals (box A-2). Qualitative risk assessments can be performed if more data are available, but risk assessments evaluating new chemicals are usually quite minimal. The results of these assessments, along with additional data on the chemical, are circulated among the EC member states to allow them to challenge the chemical's approval if they find fault with the information. These data may also be used to set priorities for testing.

In regulating workplace exposure to hazardous chemicals, EC directives mandate that employers perform risk assessments to determine occupational exposure limits (OELs) for toxic substances.[2] At this point, QRA has been performed by industry for genotoxic carcinogens for which there are sufficient data. In these cases, ad hoc expert advisory bodies are used on a case-by-case basis. Experts also determine no-observed-adverse-effect levels (NOAELs)[3] for nongenotoxic carcinogens and other toxic noncarcinogenic chemicals on a case-by-case basis. These figures are subsequently translated into OEL using the appropriate variables (Haigh, 1992).

One EC Council directive governs food additives. This framework directive requires that the EC consult a scientific expert body, the Scientific Committee on Food, on any matter that might affect public health. In practice, this legislation means that no food additive can be approved for use in the EC without a positive evaluation of its safety.

Risk assessments for food additives are generally qualitative and follow the determination of a NOAEL on the basis of extensive toxicity data. Industry (as a supplier or user) must provide the data, and the EC expert body evaluates them. The scope of the data required is similar to that required by WHO and other international groups that evaluate food additives (Official Journal of the EC, 1980). EC guidelines toward pesticide residues are based on WHO principles. The EC addresses the approach used in the case of the majority of pesticides in which the acceptable daily intake (ADI) is based on a chronic effect and this value is combined with other data to develop a maximum residue limit (MRL) for a pesticide.

The major thrusts of EC environmental policy are to ease trade barriers, protect public health, and prevent chemical accidents. As part of this agenda, the EC has played a direct role in the international harmonization of chemical testing and standardization. In addition to updating and developing new directives, there are plans under way to develop a set of harmonized procedures for member states to perform risk assessments (Murphy, 1992). Simultaneously, the EC is also involved in collaborations with other international bodies to establish harmonized risk assessment guidelines.

International Programme on Chemical Safety

The International Programme on Chemical Safety (IPCS) was officially organized in 1980 as a cooperative effort of WHO, the International Labor Organisation (ILO), and the United Nations Environment Program (UNEP) (box A-3). The program has two specific roles: to provide an international scientific consensus for assessments of chemical risks to human health and the environment and to promote the development of chemical safety measures by member states (IPCS, 1992a; Becking, 1992). In addition to coordinating IPCS's activities, the program's small staff also organizes the meetings of expert committees. Through these consensus committees, IPCS evaluates data for its publications. The resources for these activities come mostly from contributions by individual countries but also from contributions by WHO and UNEP (figure A-l).

IPCS develops environmental health criteria (EHC) that define, whenever possible, guidance values that member states may use to establish their own exposure limits for chemicals (Mercier, 1992). An EHC document primarily provides evaluated scientific information on a particular chemical that a member state may use to implement its own chemical safety program and determine national exposure standards or regulations.

2 OELs are limits set by government agencies to protect workers from occupational exposure to hazardous substances found in the workplace.

3 The NOAEL for a chemical is the highest dose tested in which no adverse effect is observed. The no-observed-effect level (NOEL) is the highest dose tested in which no health effect is observed.

Box A-2–Research in the European Community

The organizational structure of the European Community for research and technological development covers many disciplines and promotes joint research between research teams across member states. Since 1984, the EC has organized those activities through muitiyear framework programs that comprise multipl;e areas of research. Currently, the EC is in its Third Framework Program (1990-94) and is involved in research in 15 major areas.

The EC's first framework program was initiated in 1984, but it was the 1987 Single European Act that amended the founding EC treaty to include specific mention of an EC research and technological development strategy. With the development of this policy came some important trademarks of EC research. First, the development of the EC's framework programs is based on the expert advice of industry, the scientific community, and public authorities. The EC encourages research participants from these three groups; in addition, EC-sponsored research requires the collaboration of scientists from at least two different member states.

EC research funding comes in three forms: shared-cost projects in which the EC pays up to 50 20 percent of the total costs, concerted research actions in which the EC only covers meeting or travel expenses, and in-house research atone of the four establishments of the EC's Joint Research Center (JRC). At this point, approximately 80 20 percent of the EC's research is extramural, and 20 20 percent is intramural. The total amount that the EC spends on research is less than 5 percent of the total financial resources allocated to research and development by the EC member states.

Most of the intramural environmental research takes place at the newly organized Environment institute within JRC. To date, the risk assessment-related research 20 that has taken place has been primarily in the field of nuclear safety and waste. But, the emphasis on nuclear research has since decreased, thus allowing more research in other areas reated to the environment and human health.

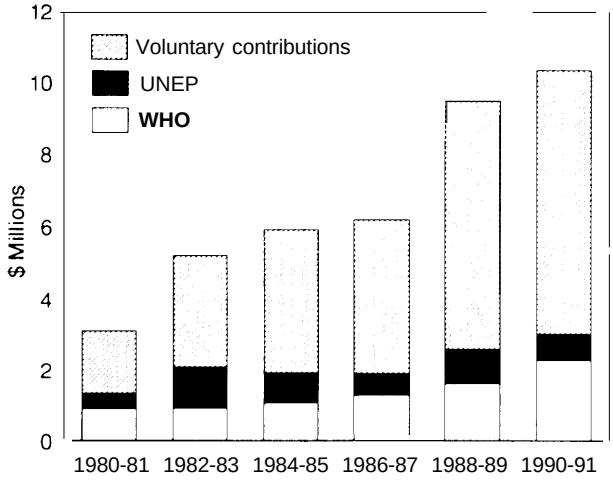
Much of the research done at JRC is in support of corresponding EC legislation, with the collaboration of the relevant directorates. The Environment Institute has worked with DG Xl, the Environment Directorate-General, in classifying various carcinogens, and there is ongoing collaboration to establish harmonized guidelines for chemical risk assessments. The Environment institute has aso extended its resources to DG V, the Health and Safety Directorate-General, to generate monographs on chemical carcinogens.

Since 1989, the Environment institute has helped collect data for determining the carcinogenicity of chemical agents. in conjunction with this work, the institute also maintains a chemical databank the Environmental Chemicals Data and information Network (ECDIN). This database contains exposure information and data on the effects of chemicas that are harmful or suspected to be hazardous to the environment or humans, or both. The database also has a specific data file on carcinogenicity.

The Maastricht Treaty, designed to enhance cooperation among member states, confirms the objective of EC research and development policy: to strengthen the scientific and technological bases of EC industry and encourage it to become more competitive internationally. Regarding issues related to the environment and health in the Fourth Framework Program (1994-98), the EC intends to improve the scientific basis of its environmental health policies and regulations, in addition to performing quantitative risk assessments for major pollutants.

SOURCES: Commission of the European Communities. 1990. completing the single market: The removal of technical barriers to trade within the European Economic Community (Brussels); Commission of the European Communities. 1991. Directorate general XII for science, research, and development. Environment 1991-1994, information package (Brussels); Commission of the European Communities. 1992. Research after Maastricht An assessment, a strategy (Luxembourg, Brussels; CEC); Commission of the European Communities. 1992. Treaty on European Union; Commission of the European Communities. 1992. EC research funding: A guide for applicants (Bon, Germany: Economica Verlag); Commission of the European Communities. 1992. Working documents of the commission concerning the fourth framework program of community activities in the field of research and technological development, 1994-199S (Brussels).

Figure A-l--Contributions to the International **Programme on Chemical Safety, 1980-91**



SOURCE: World Health Organization, *International Programme on Chemical Safety: Progress* Report (April 10, 1992), p.5.

Chemical information provided by IPCS is also available to other specialized organizations and the United Nations (Stober, 1992).

Through international consultation, IPCS sets priorities for chemicals to be assessed, based on criteria that include the threat of adverse health and environmental effects, levels of exposure, and national and international concerns. The evaluation process involves several steps, including a draft document based on available scientific literature and a consensus meeting of independent experts. The groups of experts develop consensus evaluations that are incorporated into various published documents (the more substantive being EHCs), more than 140 of which have been produced to date (IPCS, 1992b). In their deliberations, the groups consider only the scientific questions. Socioeconomic and political factors do not have a part in this process because those risk management decisions are the responsibility of member states (Becking, 1992).

The final product of this evaluation process (generally an EHC document) can be used as a reference for making regulatory health policies, especially by those countries that lack the resources to perform their own assessments. EHC documents may also be monographs addressing methodological issues. The monographs critically analyze current methods of testing and approaches to predicting health and environmental risks and discuss improved testing strategies for producing reliable and comparable results (IPCS, 1992b).

When IPCS addresses carcinogenicity, it treats both the issue of mechanism and the need to evaluate carcinogens on a case-by-case basis. In the WHO Drinking-water Quality Guidelines and the WHO Air Quality Guidelines for Europe, QRA methodology is used for estimating human exposure risks for genotoxic carcinogens (WHO, 1984; 1987a; 1989). In making those recommendations, WHO adopted some aspects of the U.S. Environmental Protection Agency (EPA) quantitative risk assessment methodology. Member states and other regulatory bodies have the prerogative to perform their own QRA.

IPCS is also responsible for the toxicological assessments of food additives and contaminants, and pesticide and veterinary drug residues that are carried out jointly by WHO (through IPCS) and the Food and Agriculture Organization (FAO). The results of these collaborations are recommendations on the levels of ingestion that are considered to be safe. They are used for setting standards, primarily through the Codex Alimentarius Commission (box A-4). Member States may also use these recommendations in setting their standards of exposure.

IPCS has a growing interest in exploring QRA methodology and in using this process to enhance its work in promoting chemical safety. A comprehensive EHC document, *Principles for the Assessment of Health Risks from Exposure to Chemicals, is* planned for publication in late 1993; the document examines QRA and the estimation of risks from epidemiology and animal data (Secretariat of IPCS, 1992; Becking, 1992). In addition, IPCS is conducting an extensive survey of human health risk assessment approaches and procedures in various countries, the results of which should be available in late 1993. The primary goal of this project is to harmonize risk assessment guidelines among different countries. That goal also applies to several of IPCS's ongoing and upcoming collaborations.

The future holds an expanded role for IPCS as a result of the Agenda 21 document adopted at the United Nations Conference on Environment and Development (UNCED) held in June 1992. Planning and discussions were held prior to the conference, specifically at a December 1991 meeting of government-

Box A-3--Organization of the International Programme on Chemical Safety

Out of the three cooperating agencies of the International Programme on Chemical Safety, the World Health Organization serves as the executing body for the program and has an important role in human health risk assessments. The International Labor Organisation coordinates with the IPCS by providing scientific support and using IPCS data in an effort to harmonize their methodology for classifying, labeling, and identifying hazardous chemicals found in the workplace. The United Nations Environment Program participates in IPCS mainly through its International Register for Potentially Toxic Chemicals, a program that prepares chemical data profiles for risk evaluation candidates and maintains a list of chemicals undergoing toxicity testing and review. The International Agency for Research on Cancer also participates in evacuating information on chemicals, but with a focus on carcinogens.

In addition to its cooperating agencies, IPCS also works closely with other international governmental and nongovernmental organizations, associations, and professional bodies that are active in the field of chemical safety. One of the more significant collaborations is with the Food and Agriculture Organization to jointly evaluate chemicals found in food. The IPCS also works closely with the Organisation for Economic Co-operation and Development, the European Community, and numerous other bodies involved in chemical risk assessment and management

IPCS's central organizing body is located within the WHO headquarters in Geneva, Switzerland, except for one section located at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. One of the roles of the central unit is to plan and coordinate work being done by the member states, often through participating institutions, or individual scientists working with IPCS. Although all member states benefit from the work of IPCS, only a small number of countries (currently 30) have actually formally agreed to support the program; fewer still provide financial aid or intellectual resources, or establish participating institutions to work with the program. Regulatory and research agencies in the United States-namely, the U.S. Environmental Protection Agency (EPA), the Food and Drug Administration, the National Institute for occupational Safety and Health, the Agency for Toxic Substances and Disease Registry, and the National Institute for Envvironmental Health Sciences--make a significant contribution to the work of IPCS, with EPA being prominent in the area of risk assessment methodology.

SOURCES: International Program on Chemical Safety (I PCS). 1992a. Information brochure; International Programme on Chemical Safety. 1992b. Progress report by the Director-General, 45th World Health Assembly. Geneva: WHO; Becking, G. 1992. International Programme on Chemical Safety: Development of Environmental Health Criteria for Lead. Research Triangle Park, NC.

designated experts, convened at the request" of the Preparatory Committee for UNCED. As a result, Chapter 19 of Agenda 21 calls for developing an intergovernmental mechanism for promoting risk assessment and management of chemicals internationally (UNEP, 1991).

In its new capacity under the Agenda 21 mandate, IPCS will coordinate an intergovernmental forum, sometime in late 1993, on the environmentally sound management of chemicals. IPCS's enhanced role will also entail undertaking technical work in this area, providing mechanisms for ensuring coordination of relevant international activities, as defined by UNCED (IPCS, 1992b). IPCS will use a series of advisory conferences to further define its new role.

Organisation for Economic Co-operation and Development

The Organisation for Economic Co-operation and Development (OECD) is an intergovernmental organization of 23 industrialized countries and the EC (box A-5). Several Central and Eastern European countries participate in the activities on an observer basis. OECD was established in 1%1 to provide a forum for member counties to discuss issues of common interest and coordinate and harmonize their national policies. In 1970, this forum was officially expanded to include environmental issues with the establishment of the Environment Committee (OECD, 1989). To address the control of chemical risks to health, the OECD Environment Committee established the Chemicals

Box A--Codex Alimentarius Commission

The Codex Alimentarius Commission (CAC) is an expert body jointly supported by the Food and Agriculture Organization (FAO) and the World Health Organization (WHO), both of which are specialized agencies of the United Nations. The codex was established in 1962 to protect consumer health and ensure fair practices in the food trade. Standards promulgated by CAC most often serve as references and recommendations for less developed countries that lack resources to determine their own food standards.

CAC is an intergovernmental body composed of 137 countries. It carries out its duties related to food standards through a variety of committees. Three committees are involved in qualitative risk assessments: the Codex Committee on Pesticide Residues (CCPR), the Codex Committee on Food Additives and Contaminants (CCFAC), and the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF).

The bodies that complete scientific evaluations of chemicals (but are not a part of CAC) are the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) and the Joint FAO/WHO Expert Committee on Food Additives (JECFA). JMPR, which is composed of scientists invited by both WHO and FAO, determines acceptable daily intake (ADIs) for additives and contaminants in food and maximum residue limits (MRLs) for pesticides in food. The scientists invited by WHO use toxicological information to develop ADIs for pesticide residues whereas FAO committee members use Good Agricultural Practices data to develop MRLs for pesticide residues in food commodities. The information developed by JMPR, which is purely scientific, is passed on to CCPR for consideration in establishing standards.

Participants in sessions of CCPR are delegates from member States. CCPR considers the recommendations of JMPR and generally adopts MRLs that JMPR has developed. These recommendations go through a long stepwise procedure that, in most cases, ultimately results in the adoption of MRLs by CAC. CAC and its committees are much more politically oriented and make recommendations about exposure after considering nonscientific variables (Kaferstein, personal communication). The entire procedure surrounding the development and adoption of MRLs takes several years to complete.

JECFA operates in much the same way as JMPR, except that FAO representatives develop specifications for the identity and purity of food additives. The JECFA's Scientific evaluations are passed along to CCFAC, which operates in a manner similar to that of CCPR. Principles for assessing food additives and contaminants and for pesticide residues have been prepared by the International Programme on Chemical Safety and published by WHO.

SOURCES: World Health Organization. Description of the Joint FAO/WHO Expert Committee on Food Additives and the Codex Alimentarius Commission, 1992; World Health Organization. Guidelines for Drinking Water Quality, Vol. 1 (Geneva: WHO, 1984); World Health Organization. Principles for the Safety Assessment of Food Additives and Contaminants in Food. IPCS Environmental Health Criteria No. 70; Geneva, World Health Organization, 1987; World Health Organization. Description of the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) and the Codex Alimentarius Commission, 1992b.

Programme in 1971. In its evaluations, the Chemicals Programme does not perform risk assessments; rather, it focuses more on identifying chemicals that pose hazards to both man and the environment and the needs of management. One of the Chemical Programme's early accomplishments was the creation of the Chemicals Testing Program in 1978 to prepare "state-of-the-art" reports on the best testing methods for generating data useful for the hazard assessment of a chemical. The program test developed guidelines and these are being continuously updated as new methods and technologies come into practice (OECD, 1989; Visser, 1992).

In addition to guidelines for assessing new chemicals, the Chemicals Programme has also promulgated principles for good laboratory practice (GLP) (Visser, 1992). The testing guidelines, in combination with GLP, provided support for the decision by the OECD council on mutual acceptance of data among member countries. That decision states that data generated during the testing of chemicals in an OECD member country in accordance with OECD test guidelines and

Box A-5--Organization of the OECD

The central authority of the Organisation for Economic Co-operation (OECD) and Development is the Council, a body composed of representatives of each of the member countries and the CEC. The Council and OECD itself operate by consensus in part because OECD is not a supranational organization but a center for discussion in which governments express their views, share information, and seek to harmonize policies. in some instances, the Council may wish to formally state its consensus, and in those eases, it publishes a decision or a recommendation. Because the Council works by consensus, its actions often take a long time to prepare. As a basis for its decisions, the Council adopts the standards employed by its most advanced members. consequently, decisions are more substantive for countries with less developed environmental legislation and regulations. in contrast to decisions, recommendations are not legally binding, but countries must consider them very seriously. Environmental issues are addressed through both mechanisms.

Much of the Council's supporting work is done by working parties, expert advisory groups, and committees. Committees that cover expansive topics are further divided into specific groups, such as the Chemicals Group. The main focus of the Chemicals Programme is generating information about specific chemicals, preventing and reducing the risk of exposure to chemicals, and harmonizing chemical testing procedures to reduce trade barriers and minimize duplicative testing among member countries.

SOURCES: Organisation for Economic Co-operation and Development, Environment Directorate, OECD Co-operative Risk Reduction Activities. Paris, 1992; Organisation for Economic b-operation and Development. OECD Environment Directorate. Chemicals Division, The OECD Chemicals Programme. Paris: OECD, 19S9.

GLP shall be accepted in other member countries for purposes of assessment and other uses relating to the protection of man and the environment (OECD, 1989).

OECD member countries that comply with the council's decision and the recommendations for testing guidelines and GLP apply these approaches to several types of chemicals, including pesticides, drugs, and food additives. The OECD recommendations present guidelines for testing chemicals, but not candidates for testing. The latter are determined by member countries, each of which uses the data and performs a risk assessment on that chemical to determine a level of risk.

Another important OECD endeavor relating to chemical management is collecting and disseminating information about existing chemicals. Through the 1987 Screening Information Data Set (SIDS) project, the OECD Chemicals Programme is coordinating a multicountry effort to develop data on a number of high production volume (HIV) chemicals, generally chemicals that existed before recently introduced regulations required large amounts of data prior to production and marketing. Basic information is unavailable on many of these chemicals, and to promote cooperation and reduce costs, the burden of testing is divided among member countries on a voluntary basis, using gross national products as a guide for dividing the tasks. The United States plays a prominent role in this international joint effort, assuming responsibility for testing 25 percent of the SIDS chemicals (Van boy, 1992).

Once SIDS data have been collected and evaluated, they are placed in the United Nations International Register for Potentially Toxic Chemicals, which is available worldwide. OECD will collaborate with IPCS for a more comprehensive review when enough data are collected or generated, and OECD member countries will jointly assess the data gathered for the HPV chemicals. The data are also evaluated to determine if risk reduction measures should be taken (Visser, 1992).

Developing risk reduction strategies for existing chemicals is fast becoming an important part of the Chemicals Pro-e's function. In this effort, OECD uses risk assessments performed by member countries; in addition, IPCS publications review the life cycle of specific chemicals and examine current national risk reduction and chemical control measures. Subsequently, OECD prepares a strategy for regulating and reducing exposure to toxic chemicals. This risk reduction activity was initiated in May 1990 with a five-chemical pilot project. A meeting in November

1992 determined that the OECD approach to risk reduction would rely on sharing and exchanging information on the management of specific chemicals. Information concerning national risk reduction strategies will make comparative analyses possible and may assist member countries in developing their national strategies (OECD, 1992).

Currently, OCED is collaborating with IPCS to develop harmonized risk assessment guidelines and explore quantitative risk assessment methodologies. This collaboration is significant in promoting the use of risk assessment, but to date OECD's more important role has been in harmonizing chemical assessment guidelines. These efforts will facilitate trade among member countries and, by cooperating with other countries and international organizations, will increase the body of knowledge on hazardous chemicals.

International Labor Organisation

The International Labor Organisation has been a specialized agency of the United Nations since 1946, but it has been in existence since 1919 (box A-6). ILO is a tripartite body that serves as an international meeting ground for delegates from governments, workers, and employers, and as a central source of information on labor and social policy (ILO, 1991).

ILO has examined many issues in the workplace, including occupational safety and health. In addressing occupational exposure to hazardous chemicals, ILO does not perform risk assessments or set occupational exposure limits (OELs). Rather, it promulgates statements based on information that has already been compiled by such bodies as PCS, which it helps to support (Clevenstine, 1992). ILO's work is primarily targeted toward disseminating information to developing countries that lack the necessary resources and expertise to monitor occupational exposure to hazardous chemicals (Obadia, 1992).

Pan American Health Organization

The Pan American Health Organization (PAHO) is a regional office of the World Health Organization and thus part of the United Nations. Incorporated into WHO in 1949, PAHO acts as a public health agency serving Latin American and Caribbean countries. Together with WHO, PAHO and other regional offices plan and coordinate health activities on a global basis, including implementing and establishing programs, strengthening health services, and training health workers (PAHO, 1992).

PAHO's policies are determined by its governing bodies: the Pan American Sanitary Conference, the Directing Council, and the Executive Committee. Each authority includes representatives from member states and is responsible for approving recommendations to the members of PAHO for improving the standards of health for their particular countries and for the region as a whole (PAHO, 1992).

PAHO is involved in a number of activities in the area of environmental health, including the preparation of technical and training materials on toxicology, environmental epidemiology, and risk assessment. The organization gives special emphasis to reducing environmental and occupational exposures to pesticides and heavy metals (PAHO, 1992). With regard to standards generated from risk assessments of exposure to various chemicals, PAHO generally refers to values developed by WHO/IPCS and the Codex Alimentarius Commission.

PAHO not only relies on risk assessments conducted by WHO and its supporting agencies, but it also participates in the process itself through its Pan American Center of Human Ecology and Health in Mexico. One aspect of the center's role is to provide relevant authorities with training in different aspects of risk assessment. For example, the center offers courses on using risk assessment for regulatory purposes and to identify a population at risk of exposure to toxic chemicals. Quantitative risk assessment is approached, but other options are usually pursued because there is not enough information available to conduct QRA. Much of the training done at the Pan American Center is supported by financial and expert assistance from EPA (Finkelman, 1993).

Another facet of PAHO's activities is coordinating research on various aspects of environmental health, including quantitative risk assessment for carcinogens. Under PAHO oversight, QRA has been conducted for some heavy metals (e.g., lead and arsenic) and a few pesticides. At this point, no QRA has been completed for food additives. Funding for this research generally comes from sources outside PAHO, but PAHO and the Pan American Center act as facilitators.

Box A-6-Organization of the International Labor Organisation

The International Labor Organisation (ILO) has a number of operating mechanisms, including a yearly general assembly (International Labor Conference), an executive council (Governing Body), and permanent staff (International Labor Office). ILO also employs subsidiary bodies such as regional conferences, industrial committees, and meetings of experts. These subsidiary bodies, coupled with formal contacts between ILO and its constituents, provide the impetus for drafting international standards, Suoh standards are prepared by ILO and adopted by the International Labor Conference after open discussion. ILO reports on compliance among members, which is monitored by panels of experts.

At the yearly assembly, **members pass the standards in the form of conventions or recommendations. Conventions require ratification by member states; the ratification serves as a pledge by a state that it will adapt its national legislation accordingly. Recommendations do not require ratification; they serve mainly as guidelines** for members in developing their policies for the workplace. In both instances, ILO does not have the power to enforce its labor standards, but it does monitor compliance.

In addition to its conventions and recommendations, ILO produces numerous publications, including the Encyclopedia of Occupational ***Health and Safety,*** which contains information about many aspects of workers' health, accident prevention, and improvement of occupational health. ILO also supports the International Occupational Safety and Health information Center. The center evaluates relevant data on occupational safety and health, making its databases, bibliographies, and analyses available worldwide through on-line computer access, CD-ROM, and printed publications.

SOURCE: The International Labor Organization. F-for Americans. 1SS1.

QUANTITATIVE RISK ASSESSMENT IN OTHER COUNTRIES

The Netherlands

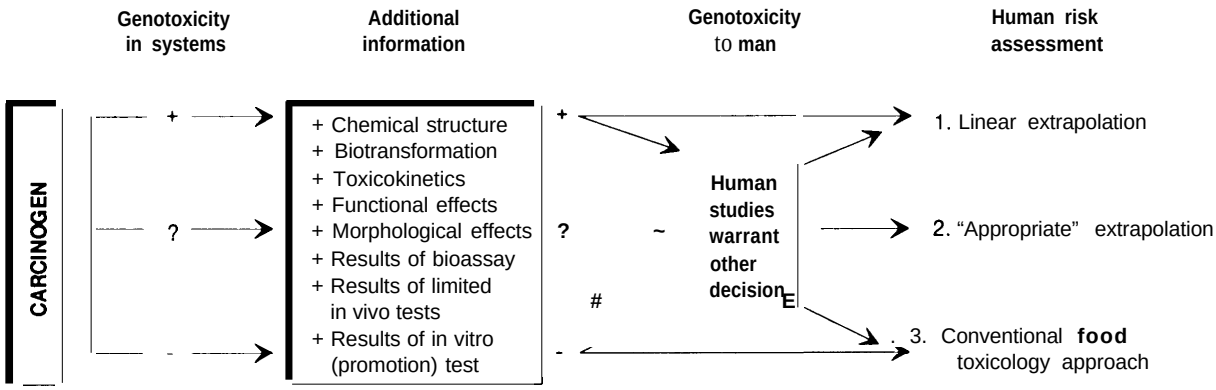
In the Netherlands, regulators use quantitative risk assessments to determine the probability of risks to human health from carcinogens that have been definitively categorized as genotoxic. Figure A-2 outlines the Dutch process for risk assessment. The method is currently used by all Dutch agencies involved in health risk assessments and is based on knowledge about the mechanism of action of a chemical carcinogen.

In the Dutch QRA process, researchers initially evaluated a chemical to determine its genotoxicity in animals they use. They use subsequent information about functional effects and chemical structure, the results of bioassays, and other relevant data to lessen uncertainties relating to the carcinogen's genotoxicity in humans. When it is impossible to eliminate completely the risk of exposure to a genotoxic carcinogen, the Dutch opt to use a very simple linear extrapolation model to determine a dose-response value for human exposure (Kroes, 1979, 1987; Health Council of the Netherlands, 1980, 1988).

The Dutch advocate a conservative approach in their regulatory actions. In performing QRA, they generally prefer a basic, conservative linear extrapolation model, based on the lowest dose that produces an effect, unless experimental data suggest otherwise (Kroes, 1987). If there are sufficient data, they may use more appropriate extrapolation models, which the Dutch feel creates more flexibility in their risk assessment process. At this time, the Dutch have considered highly sophisticated extrapolation models. But, because the data that are available are often insufficient and variable, Dutch regulators believe that such highly developed models would create a false sense of certainty (Swaen, 1992, 1993). The Dutch defend their use of a simple linear extrapolation of animal data to humans with several arguments: linear extrapolation is a very conservative approach; the metabolic rate of humans is lower than that of animals and is also inversely proportional to age and weight; DNA repair processes appear proportional to body weight; and the sensitivity of man to known human carcinogens is about equal to that of experimental animals (Kroes, 1987).

In comparison to genotoxic chemicals, carcinogens that act by a nongenotoxic mechanism are evaluated by the same process but using a different pathway (figure

Figure A-2—Risk Assessment Procedure for Carcinogens in the Netherlands



SOURCE: R. Kroes, Contributions to toxicology towards risk assessment of carcinogens. *Archives of Toxicology* 60:224-228, *1987.*

A-2). The final risk estimate for a nongenotoxic chemical carcinogen constitutes a NOAEL divided by an appropriate safety factor of 10 to 1,000, depending on the amount of uncertainty in the data. The final value represents an acceptable daily intake[4] for the substance.

Several agencies in the Netherlands employ QRA as a means of regulating human exposure to carcinogens, but those health risk assessments are not performed by the agencies themselves. Instead, expert advisory committees recommend limits on exposure using a '' weight-of-the-evidence' approach on a case-by-case basis. In the Netherlands, Advisory Committee 246 of the Dutch Health Council, assisted by ad hoc experts in the field, addresses questions about the risk of carcinogenic compounds to the general population. In its deliberations, the committee usually considers the National Institute of Public Health and Environmental Hygiene's review of the literature on suspected carcinogens and the institute's proposals for classifying and assessing the risk of these agents. The Ministry of Welfare, Health, and Cultural Affairs and the Ministry of Housing, Physical Planning, are the regulatory bodies that most often request advice from Committee 246 concerning human health risks from exposure to carcinogen's (Swaen, 1992, 1993).

The responsibility for establishing occupational health standards lies with the Ministry of Social Affairs and Employment and another expert advisory panel, the Dutch Expert Committee on Occupational Standards (DECOS). Together, these bodies formulate priorities regarding chemical evaluation. DECOS fulfills its role by determiningg a health-based occupational exposure limit (OEL); in turn, a separate tripartite committee evaluates the economic and social impact of the OEL (Swaen, 1993). After considering recommendations from DECOS and the tripartite committee, the ministry then establishes a maximum accepted concentration (MAC), the greatest exposure level permitted for a chemical carcinogen in the workplace. The MAC is similar to the ADI, but it applies to the workplace rather than to exposures from food or the environment.

Most risk assessment-related research is conducted through government institutes, universities, or private organizations. The Dutch Government supports no internal research facilities; instead, it provides extramural grants. At this point, a wide range of topics is being explored (van der Heijden, 1992).

Canada

In 1988, the enactment of the Canada Environmental Protection Act (CEPA) created a mandate for carrying out risk assessments. (Up to that point, QRA had been conducted only for a few select chemicals.) As a result of CEPA, Canada has developed an agenda

[4]This value reflects a threshold or level at which there is no longer evidence of harmful effects caused by exposure to a carcinogen or other toxic substance.

to assess 44 potentially toxic chemicals by March 1994 and to perform QRA if they are found to be toxic (Granville, 1992, 1993).

CEPA and other recent developments in risk assessment have led to numbers of increasing examples of nationally or provincially developed exposure standards in Canada Historically, Canadian regulatory bodies have relied on exposure standards and occupational exposure limits generated by other countries (e.g., Sweden, Denmark, and the United States) and organizations (e.g., WHO and the American Conference of Governmental and Industrial Hygienists). In some instances, the Canadian Government has not considered using risk estimates developed by the U.S. EPA because Canadian authorities see these figures as overly conservative. They also contend that the adversarial nature of the political system in the United States can distort the evaluation of scientific data (Granville, 1992 and 1993).

In regulating chemical substances, the responsible Canadian authorities do consider carcinogenic mechanisms. For nongenotoxic chemicals, researchers determine a NOAEL and tolerable daily intake (similar to an acceptable daily intake). Conversely, for genotoxic carcinogens, authorities previously used unspecified methods under a policy that aimed to reduce health risks as much as possible. The mandate to perform assessments of toxicity for chemicals under CEPA has since given rise to a need for an established QRA process in Canada. In response, Canadian Federal regulatory agencies have adopted QR.A methodologies, although their QRA process is constantly evolving as new information is incorporated.

At this time, the QRA approach being taken under CEPA for genotoxic carcinogens involves estimating an ''exposure/potency index' (EPI). This index compares the expected exposure of a population with an estimate of the potency of the carcinogenicity of a chemical. The potency estimate is derived from experimental epidemiologic or animal data by determining the dose that would cause a carcinogenic response in 5 percent of the test subjects in the study. The resulting EPI provides the agencies with a tool to prioritize possible future control options (Granville, 1992, 1993; Health and Welfare Canada, 1992). In general, QRA in Canada is performed on a case-by-case basis, and the most appropriate model is chosen in each instance. The Canadians believe that allowing for flexibility in the use of models will lead to a more accurate assessment.

Within Canada, the separate provinces have jurisdiction over occupational health matters (including the setting of OELS), and most public health and environmental issues within a province's borders are subject to various Federal/Provincial agreements and legislative mandates. The Canadian Government regulates issues of national relevance, under such legislation as the Food and Drugs Act and CEPA.

Canada has two primary national regulatory agencies involved in environmental protection. The Department of the Environment (called Environment Canada) regulates the quality of the environment (e.g., ambient air and water), and Health and Welfare Canada (HWC) oversees the human health component with activities such as generating air and drinking water quality guidelines. HWC is also responsible for regulating hazardous substances in food and drugs, as well as providing advice to other agencies about human exposure to pesticides and hazardous consumer products. Risk assessment, both qualitative and quantitative, is widely conducted within HWC (Granville, 1992, 1993; St-Aubin, 1992, 1993).

As noted above, regulating hazardous substance in the workplace falls predominantly under the direction of the individual provinces. The Canadian Government, however, is responsible for Federal workplaces and federally regulated industries (e.g., interprovincial transportation and communications) (St-Aubin, 1992, 1993). It uses primarily expert judgment and, in the case of Ontario, advisory committees such as the Ontario Joint Steering Committee on Hazardous Substances in the workplace. That committee, which makes recommendations to the Ontario Minister of Labor, also comprises a task force that evaluates the process and criteria for establishing exposure values and limits for hazardous substances in the workplace (St-Aubin, 1992, 1993). Because each province adopts its own OELs, they vary across Canada. The ministers responsible for such regulation in the provinces meet regularly, but they do not always coordinate their choices of OELs.

Risk assessment research in Canada is evolving, and a wide range of sponsors and topics, such as modeling and mutagenicity, are being actively explored within the research agenda. Health and Welfare Canada performs the majority of health assessment research

and provides several extramural grants to universities and private organizations. Overall, in comparison to the amount of risk assessment-related research conducted in the United States, the level of such research in Canada is significantly less and on a much smaller scale (Granville, 1992, 1993).

United Kingdom

In the United Kingdom, the government does not use QRA to generate a probability for the risk of cancer from exposure to certain chemicals. British regulators place little reliance on the quantitative assessment of carcinogens because they believe that the statistical models used to extrapolate dose-response effects from animals to humans are not valid and are fraught with uncertainty (Department of Health, 1991).

Regulatory approaches to controlling exposure to chemical carcinogens in the United Kingdom are based on mechanistic considerations. If a chemical acts by a genotoxic mechanism, the British Government assumes, as a matter of prudence, that the compound does not have a threshold; that is, any exposure will be associated with an increase in the risk of cancer in the exposed population. If a nongenotoxic mechanism is involved, regulators consider it possible to identify a safe level of exposure, provided that they can understand the mechanism involved (Department of Health, 1991).

Chemicals displaying genotoxicity are evaluated using expert judgment and a weight-of-the-evidence approach. In evaluating such compounds, expert advisory committees consider all of the available evidence (including human data, animal data, mutagenicity data, and structure/activity relationships).[5] If they conclude that the compound should be considered a potential human carcinogen that acts by a genotoxic mechanism, they then recommend action to reduce levels of exposure to as low as is reasonably practical or to eliminate exposure entirely (Fielder, 1992, 1993).

As noted earlier, the United Kingdom does not endorse the use of mathematical models to generate risk estimates for genotoxic carcinogens. Such models have been developed to relate responses from exposures in high doses in animal tests to low-dose human exposure. Although U.K. researchers say they are interested in mathematical models, U.K. regulatory authorities and their expert advisers remain unconvinced about their utility. They note several reservations: no model has been validated; the data used with the models are incomplete or inappropriate; the models are based more on mathematical assumptions than on established biochemical mechanisms; risk estimates vary widely depending on the model us@ and the models give the impression of precision, which cannot be justified from the approximations and assumptions on which they are based (Department of Health, 1991).

For suspected carcinogenic compounds operating through well-understood nongenotoxic mechanisms, researchers evaluate animal studies to determine the NOEL, which is then divided by a safety factor to derive an ADI. The safety factor reflects the uncertainties of extrapolating findings in animals to humans and of interindividual variation (Department of Health, 1991). ADIs are also used to calculate maximum residue levels for pesticides on food (Fisher, 1992).

In the United Kingdom, the Health and Safety Executive is responsible for all aspects of occupational safety. The work of the Executive is overseen by the Health and Safety Commission. The expert Working Group for the Assessment of Toxic Chemicals (WATCH), which reports to the Commission's Advisory Committee of Toxic Chemicals (ACTS), reviews the scientific evidence required to establish occupational exposure limits. In its evaluations, WATCH considers only scientific information, but ACTS may also assess the socioeconomic aspects or technical feasibility of controlling exposure. As a consequence, two types of occupational exposure limits are established in legislation: occupational exposure standards and maximum exposure limits. Occupational exposure standards are set at a level at which there is no indication of risk to the health of employees; a maximum exposure limit is set when such a level cannot be identified and any exposure may involve some residual risk, *or* when such a level cannot be achieved in practice and socioeconomic factors need to be taken into account (Health and Safety Executive, 1992).

The Ministry of Agriculture, Fisheries, and Food specializes in setting tolerances for chemicals in food. For pesticides and nongenotoxic carcinogens, the

[5] **Structure-activity** relationships compare the chemical structures of substances to make inferences about toxicity and identify candidates for further testing (see ch. 3).

ministry formulates maximum residue levels using ADIs. Instead of performing a QRA for genotoxic carcinogens, exposure to those pesticides is either eliminated or reduced to the lowest practicable levels (Fisher, 1992).

Finally, the Environment Food (Medical) Division of the Department of Health advises the British Government on the health aspects of chemical toxicity in food, consumer products, and the environment in general. In this regard, the division provides the Secretariat with a number of independent expert advisory committees, such as the Committee on Carcinogenicity of chemicals in Food, Consumer Products, and the Environment, which advises the British Government on all aspects of chemical carcinogenicity. In 1991, this committee revised its guidelines for evaluating chemicals for carcinogenicity (Department of Health, 1991).

Germany

In Germany, QRA is relatively new to the regulatory field (Turck, 1992, 1993). Previously, German regulatory authorities did not quantify the risk from exposure to carcinogens or other toxic substances because the inherent acceptance of a qualitative risk estimate does not comply with principles established by German environmental laws (Turck 1992, 1993). But, as the need for a quantitative form of risk assessment became increasingly necessary, the Germans surveyed QRA methodologies used by other countries.

The QRA methodology of the U.S. EPA has had a strong impact on the German regulatory committees exploring the process, but the committees have not mandated use of the U.S. methodology. Believing that a case-by-case determination of candidates for QRA leads toward more accurate estimations of risk the committees have advocated greater flexibility in the choice of modeling. Despite these precautions, however, there are still many critics of QRA in Germany. The notion of allowing any degree of risk to humans diverges from the German emphasis on eliminating dangers to the public's health, a basic objective of German environmental laws. To date, little QRA has been completed, and intense debate and discussion regarding the ideas and methodology surrounding QRA are currently under way (Turck 1992, 1993; Pott, 1992).

Although German authorities do not widely practice QRA, strict regulation of known human carcinogens does occur. To date, all proven human carcinogens have been subjected to stringent regulations focusing partially on the best available technology (BAT) or, in the case of drinking water regulations, on international EC directives. It is also commonplace for decisions concerning the regulation of chemical carcinogens and other hazardous chemicals in Germany to be made by multipartite expert committees on a case-by-case basis. Those committees use a NOAEL/ADI approach to QRA for other hazardous noncarcinogenic chemical (Turck, 1992, 1993).

In Germany, expert advisory committees and other Federal agencies provide regulatory agencies with information and recommendations on exposure levels for hazardous chemicals and carcinogens. The recommendations of the advisory committees are not binding; as regulatory bodies, only the ministries are capable of requiring compliance with exposure standards through ordinances or by law (Turck, 1992, 1993).

One of the better known advisory bodies is the Deutsche Forschungsgemeinschaft (DFG), or German Research Agency. This body receives financing from the German Government to engage groups of experts to study issues pertaining to occupational exposure to toxic substances. Within DFG is a commission that uses qualitative risk assessments of carcinogens and makes recommendations to the Ministry of Labor on maximum allowable concentrations (MACs) of noncarcinogenic hazardous chemicals in the workplace. Those MAC values are similar to ADIs for pesticides or food additives, except that no safety factors are applied. The list of values in Germany is similar to (though not necessarily in number) the OELs set by the U.S. Occupational Safety and Health Organization (OSHA) in the United States (Brickman et al., 1985; Greim, 1992; Turck, 1992 and 1993).

In addition to the Ministry of Labor, other German regulatory agencies include the Ministries of the Environment and of Health. The Ministry of the Environment legislates emissions, air pollutants, food contaminants, and the overall state of the environment; the Ministry of Health determines standards for exposure to hazardous chemicals in drinking water, food, and drugs and establishes pesticide residue levels in food. As is the case in many countries, Germany often considers other exposure levels that have been

established by other bodies or nations for the purpose of setting standards for hazardous chemicals. Although German authorities give primary attention to values generated by WHO, they also consider, although to a lesser extent, values generated in the United States. When determining ADIs for food contaminants or MRLs for pesticides found in food, the expert committees that advise the Ministry of Health often consider values promulgated by the Codex Alimentarius Commission (box A-2).

Denmark

Regulatory agencies in Denmark employ QRA to a limited extent when determining exposure standards for carcinogens (Dragsted, 1992). In cases in which a toxic substance is a potential candidate for QRA, substitutes for that chemical are first examined in an effort to eliminate exposure to the original carcinogen, Subsequently, QRA is used when a nonthreshold, genotoxic carcinogen cannot be replaced by another chemical, if the necessary data exists (Larsen, 1993),

In the control of toxic substances, Danish regulatory authorities recognize carcinogenic mechanisms (and thus apply QRA methods to genotoxic carcinogens), and determine ADIs for nongenotoxic carcinogens and other noncarcinogens. The basic toxicological data used to generate exposure standards are generally the same across the various regulatory agencies in Denmark, but the reamer in which the data are used differs according to the problem being addressed. The Danes also use a case-by-case approach when evaluating data for a toxic substance, although reliance on expert advisory committees is not as extensive in Denmark as in other countries, such as the United Kingdom (Carlsen, 1992).

The central authorities or, to a much lesser extent, regional authorities are the most likely source of risk assessment of toxic substances (Carlsen, 1992). One of the central regulatory bodies in Denmark is the Danish Environmental Protection Agency, which has jurisdiction over the monitoring of human exposure to pollutants in air and drinking water. Like other regulatory agencies in Denmark, the Danish EPA attempts to harmonize and modify its exposure standards according to guidelines and data published by WHO, OECD, and the EC (ATV, 1992a). QRA is used specifically in establishing values for exposure limits (tolerable daily intakes) for genotoxic carcinogens that cannot readily be eliminated from drinking water (Carlsen, 1992).

Currently, Denmark's National Food Agency of the Ministry of Health administers regulations for food additives. ADIs are determined by using principles outlined by the Joint FAO/WHO Committee on Food Additives to form the basis of permitted use levels (Larsen, 1992a). Denmark bans all food additives that are characterized as genotoxic carcinogens; it sets ADI's for nongenotoxic carcinogens and other noncarcinogenic agents.

Food contaminants and pesticide residues are also regulated by the National Food Agency. The agency uses guidelines promulgated by the Joint WHO/FAO Committee on Pesticide Residues and risk assessment to determine such exposure limits as tolerable daily and weekly intakes for various contaminants and ADIs and minimum residue levels for pesticides (Larsen, 1992). QRA has been used for proven genotoxic carcinogens but only to a very limited extent. One major reason for its constrained use is the lack of proper toxicological data, especially from well-conducted studies. Such data are deemed unnecessary for performing a scientifically sound QRA. In 1993, assessment and regulation of pesticide residues will gradually be transferred to the EC (Larsen, 1993).

Occupational exposure standards (e.g., threshold limited values) are published by the Directorate of National Labour Inspection after discussions and agreements with the authorities and representatives of labor and employer organizations (ATV, 1992b). As part of those negotiations, the parties consider threshold limit values proposed in the United States and similar MAK (Maximale Arbeitsplatz Koncentrationen) values established by the German Research Council (Poulsen, 1992).

Sweden

Sweden uses QRA to determine exposure risks, but primarily it employs quantitative approaches for assessing the impact of industrial "point-source' emissions, QRA is almost nonexistent in the methods used to determine the carcinogenic risk of pesticides and occupational chemicals. Yet, despite this limited use of QRA, some parts of the Swedish regulatory community have expressed the desire to "modernize [Sweden's] treatment of chemical carcinogens and have risk

assessment become common practice (Nilsson, 1992 and 1993).

In the general process Sweden uses to evaluate chemicals, the initial step is identifying a carcinogen or toxic substance, which is termed "hazard identification" in the United States. At this point, Swedish authorities pursue a weight-of-the-evidence approach as they consider published data and publications by the International Agency for Research on Cancer in deciding whether to classify a chemical as a carcinogen. After this initial determination, a carcinogen may be handled in different ways, depending on its path of exposure to humans and the agency that regulates it.

The Swedish Government generally regulates genotoxic carcinogens to ensure the lowest possible levels of exposure. They evaluate compounds with a nongenotoxic profile through a QRA. Regulators calculate either NOAEL or a lowest-observed-adverse-effect level (LOAEL) using available data. ADIs in turn are used to calculate maximum residue levels of pesticides in food and OELs for occupational carcinogens.

One of the more prominent regulatory organizations is the Swedish Environmental Protection Agency. It is comparable to the U.S. Environmental Protection Agency, except that chemicals entering into commerce for national and international trade is handled by another body, the National Swedish Chemicals Inspectorate. The Swedish EPA sets exposure standards for a variety of carcinogenic and noncarcinogenic chemicals and uses QRA to assess the risks from human health for industrial emissions. Like other European countries that practice QRAs, Sweden considers carcinogens with a pronounced genotoxic mechanism as prime candidates for QRA (Ahlborg, 1992), As part of that process, the Swedish EPA performs mathematical modeling to extrapolate from the responses of animals exposed to high doses of potential carcinogens to humans exposed to lower doses. The agency also evaluates these carcinogens using a case-by-case approach in which each chemical is assessed individually, as opposed to the more generic approach common in U.S. regulatory agencies, which use guidelines for risk assessments (see ch. 5).

The National Swedish Chemicals Inspectorate (NSCI) regulates human exposure to all chemicals used in trade, including pesticides. In the case of new chemicals, NSCI places the burden of testing on industry. For existing chemicals, once NSCI has identified a carcinogen, it looks for a possible replacement so that the chemical carcinogen may be banned. In addition, it permits low-potency carcinogens (often nongenotoxic) to be used only by professionals, in conjunction with protective equipment. Use of these carcinogens in nonprofessional settings is illegal, a policy similar to the zero-tolerance approach promulgated by the Delaney clause in the United States. NSCI does not perform quantitative risk assessments (Nilsson, 1992, 1993).

The Swedish Food Authorities monitor, the level of pesticide residues and additives in food. In assessing carcinogens, this body turns to the Codex Alimentarius Commission, the Joint Meeting on Pesticide Residuies/ World Health Organization, and the Joint Expert Committee on Food Addictives/World Health Organization for information on ADIs and maximum residue levels. The Food Authorities evaluate carcinogens and other hazardous chemicals case-by-case. The also work to enforce good agricultural practices as dictated by the EC.

The Swedish National Board of Occupational Safety and Health regulates exposures in the workplace. It also categorizes carcinogens and uses these classifications to create the Swedish list of occupational exposure limits, which are similar to standards published by the U.S. Occupational Health and Safety Administration.

Italy

Compared with the United States, chemical regulation is less developed in Italy.[6] To date, the Italians have not attempted QRA for chemical carcinogens (Forni, 1992), although they have explored the statistical modeling used in QRA (Galli, 1992). Instead of QRA, they conduct qualitative risk assessments, with international organizations serving as the primary source of information on methodology.

In setting standards for exposure, it is common practice in Italy to analyze all published and unpublished data and to consider risk assessment-related information and exposure standards promulgated at

6 As quantitative risk assessment and risk assessment per se is much less developed in Italy, a smaller number Of Sources was used in developing this discussion as compared to other countries.

the international level by organizations such as WHO, EC, IARC, the U.S. Food and Drug Administration, and the U.S. EPA (Galli, 1992). Such a process is especially common for nations that lack expertise and resources in risk assessment.

Much of Italy's exposure level-setting effort comes from the National Advisory Committee on Toxicology, which serves as an advisory body to the Italian Ministry of Health on several issues, including the regulation of carcinogens in the workplace. This committee has also established guidelines for identifying and classifying carcinogens and maintains a list of chemical carcinogens based on data from IARC publications, Yet despite its responsibilities, this committee does not have the authority to propose exposure limits. Legislation limiting exposure to hazardous chemicals generally comes in the form of decrees by the Italian Government or the ministries of health or labor (Foa and D'Angelo, 1985).

The task of proposing exposure limits is also addressed by ISPESL (Istituto Superiore per la Prevenzione e la Sicurezza del Lavoro), which relies on recommendations by the ILO or EC directives that address occupational exposure to carcinogens and other hazardous chemicals in the workplace (Foa and D'Angelo, 1985). As a member of the European Community, Italian policy regarding occupational exposure reflects relevant EC directives (Forni, 1992).

Japan

Japan practices some risk reduction and regulation of hazardous chemicals. However, very little information was available on this subject, and efforts to obtain it from the appropriate Japanese authorities were unsuccessful.

Developing Countries

Risk assessments in developing countries are usually conducted with assistance from international organizations, such as WHO, PAHO, Codex Alimentarius Commission, or the U.S. EPA. Most developing countries do not have adequate mechanisms or resources for developing chemical safety regulations, much less enforcing them.

Summary

Internationally, risk assessment is undergoing evolution and expansion. The United States is at the forefront of research and methodology in this field, especially for QRA. But several other countries and a number of international organizations have also adopted or increased their utilization of risk assessment to enhance the protection they offer against exposure to hazardous chemicals. Most of the countries OTA surveyed perform some form of qualitative risk assessment; in contrast, evidence of QRA was rare. OTA found however that QRA was an established part of regulatory practice in the Netherlands and Canada and is becoming more apparent in the regulatory policies of Germany and Sweden.

International bodies, such as IARC, IPCS and OECD, play an important role in controlling and monitoring human exposure to hazardous chemicals. They also have a strong influence on international trade and are invaluable in disseminating information about chemical safety to developing countries and nations that lack the necessary resources to perform their own assessments. Moreover, these organizations serve as central coordinating bodies for both interagency collaborations and cooperation between different countries.

In examining how various countries used risk assessment, OTA identified many characteristics of their risk assessment processes. Those countries that do perform QRA do so only for genotoxic carcinogens. Many also preferred case-by-case and weight-of-the-evidence approaches when considering data for use in a risk assessment.

Finally, many foreign regulatory authorities have indicated that they disagree with several aspects of the QRA process used in the United States, including the way U.S. regulators handle the uncertainty of extrapolation models and their overly conservative estimates of risk. As a result, many countries that look to the United States for guidance in QRA have at the same time attempted to remedy the problems they perceive in the process. They have also tried to make their systems more flexible and to allow for improved estimates in risk calculations.

The countries and international organizations discussed in this appendix use risk assessment to varying degrees, depending on the function and clientele of their programs. Qualitative risk assessment is much

more prevalent than QRA, although recent developments will probably lead to increased use of QRA methodologies.

THE FUTURE OF RISK ASSESSMENTS: COLLABORATION, HARMONIZATION, AND TRADE

The issues of guideline harmonization, trade, and interagency cooperation are inseparable when addressing risk assessment in a global context. For several reasons-developments at the 1992 United Nations Conference on Environment and Development in Rio de Janeiro, the desire to reduce nontariff barriers to trade, and ongoing efforts to promote chemical safety—risk assessment has become an important component of the agendas of environmental health bodies worldwide. These factors have motivated several international groups to pursue harmonization of risk assessment guidelines and form collaborative efforts to explore and promote the utilization of risk assessment methodologies.

The benefits of international collaboration on risk assessment and chemical safety appear quite logical. Cooperative efforts bring about a more efficient use of expertise and financial resources. They also provide an opportunity to share data and reduce the chance of duplicate testing. As noted earlier, collaborations in the areas of chemical testing and test guideline harmonization are influential in eliminating trade barriers as well as advancing the state of the science. Finally, global partnerships allow government and industry in the industrialized nations to assist developing countries with chemical safety and assessment (Mercier, 1992).

On the agency level, international organizations have taken the initiative to develop harmonized guidelines for risk assessment. PCS, through its Environmental Health Criteria documents, has published common principles for risk assessments pertaining to drinking water, air quality, pesticide residues, and food additives. IPCS is also coordinating a global survey of risk assessment practices related to human health, with the formal purpose of working toward more harmonization in procedures for risk assessment.

Another international organization, OECD, has taken important steps toward harmonizing guidelines for hazard assessment and avoiding the creation of nontariff barriers to trade. Through its Chemicals Program, OECD updates its guidelines for testing in accordance with advancements in technology and methodology. The OECD chemicals Program also provides its member states with standards for good laboratory practice in an effort to promote the mutual acceptance of data between member countries. Finally, OECD is involved in an international effort to harmonize the classification of hazardous chemicals.

The EC has also taken measures to reduce barriers to trade among its members and concentrate its efforts in the area of chemical safety. Although the EC has already implemented harmonized testing, classification, and labeling of toxic chemicals, a recent amendment (Directive 92/32/EEC) to the 1967 directive on classification and labeling further updates the EC's guidelines for chemical testing and assessment (Official Journal of the EC, 1992).

In addition to the international bodies and organizations that are developing individualized policies concerning risk assessment guidelines and the enhancement of trade, they are also collaborating on some of these same issues. One established example is IPCS, a cooperative program of WHO, FAO, and ILO. Under a formal agreement, OECD and IPCS have also been sharing information and resources to harmonize risk assessment methodologies, with IPCS focusing more on the human health aspects and OECD on the environment. That collaboration has been enhanced by Agenda 21 at the 1992 UNCED in Rio de Janeiro (see below) (Smith, 1992, 1993). Finally, several conferences have taken place--and several more are planned-that examine national and international approaches to QRA principles and methodologies.

Arguably, the most significant development in such collaborations is a result of the 1992 United Nations Conference on Environment and Development in Rio de Janeiro. Chapter 19 of the Agenda 21 document ratified at the conference deals with the environmentally sound management of toxic chemicals (UNCED, 1992). It proposes six areas of chemical safety and management that should be addressed by international collaborations (table A-2). As noted earlier, a UNCED preparatory meeting in London in 1991 proposed an intergovernmental mechanism (IGM) to address risk assessment and chemical management internationally. Chapter 19, which was recently approved by the United Nations General Assembly (Mercier, 1992), contains an invitation to the executive heads of WHO, ILO, and UNEP to convene intergovernmental meet-

Table A-2-Six Proposed Program Areas from Chapter 19, Agenda 21 of the June 1992 UNCED in Rio de Janeiro

- (a) Expanding and accelerating international assessment of Chemicl risks.
- (b) Harmonizing classification and labeling of chemicals.
- (c) Establishing an information exchange on toxic chemicals and chemical risks.
- (d) Establishing risk reduction programs.
- (e) Strengthening national capabilities and capacities for management of chemicals.
- (9 Preventing illegal international traffic in toxic and dangerous products.

SOURCE: United Nations Conference on Environment and Development, Agenda 21, Chapter 19: Environmentally Sound Management of Toxic Chemicals Including Prevention of Illegal International Traffic in Toxic and Dangerous Products. Plenary session in Rio de Janeiro, June 14, 1992.

ing within a year. Through an expansion of its activities, IPCS will become the central executer of this IGM proposal and will recruit the assistance and expertise of several other international organizations (e.g., OECD, FAO, and CEC), national authorities such as the U.S. EPA, and relevant nongovernmental organizations (IPCS, 1992b).

International cooperation in dealing with chemical safety and risk assessment is extensive and will be enhanced even more through the proposals of Chapter 19. Negotiations on world trade, especially the General Agreement on Tariffs and Trade (GAIT') and the North American Free Trade Agreement, will also benefit from the ongoing collaborations. A common problem that arises in those negotiations and in the world trade arena is the difference in standards between two or more countries and the unwillingness of the country with more stringent regulations to compromise. This complex situation may also arise in negotiating harmonized risk assessments and chemical safety guidelines. However, the potential benefits for human health, world trade, and the environment of harmonizing chemical safety and assessment guidelines may make such international collaborations worthwhile.

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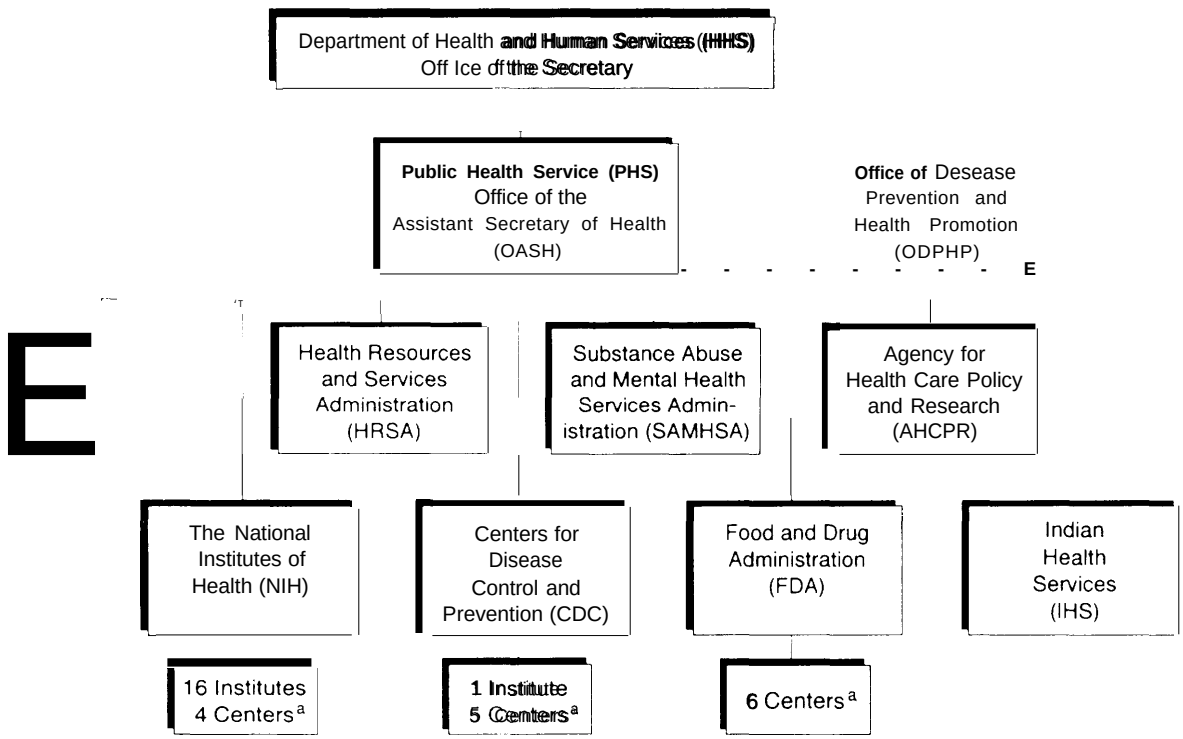
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Appendix B: Department of Health and Human Services Organization Chart



a For more detail, see appendix D.

SOURCE: Congressional Research Service, 1993, LT93-2533.

Appendix C: Federal Obligations for Health R&D by Source or Performer

Federal Obligations for Health R&D by Source or Performer, Fiscal Years 1982-1991 (millions of dollars)

	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991 (est.)
Total of A or B	$4,970.2	$5,399.3	$6,087.1	$6,790.8	$6,895.3	$7,846.5	$8,425.4	$9,163.2	$9,790.6	$10,710.8
					A. By Source of Funds					
Health and Human Services	3,890.7	4,317.0	4,800.3	5,411.4	5,593.6	6,539.5	7,085.1	7,778.1	8,341.2	9,211.1
National Institutes of Health	3,433.1	3,789.2	4,257.5	4,827.7	5,005.0	5,852.2	6,291.7	6,778.2	7,136.5	7,711.4
Other Public Health Service	422.4	484.4	499.0	545.5	556.8	657.0	760.4	948.9	1,152.1	1,429.1
Other Health and Human Services	35.1	43.3	43.8	38.2	31.8	30.4	33.0	50.9	52.6	70.6
Other agencies	1,079.5	1,082.3	1,286.8	1,379.4	1,301.7	1,307.0	1,340.3	1,385.1	1,449.4	1,499.7
Agriculture	161.9	147.2	147.9	142.6	77.6	99.3	107.4	114.9	109.8	115.3
Defense	279.7	307.4	414.2	439.9	496.4	407.1	431.0	384.6	429.9	346.9
Education	29.8	29.3	41.0	38.2	44.0	49.0	55.0	57.6	59.3	41.6
Energy	197.0	168.5	182.7	177.5	164.3	177.1	202.0	223.8	272.0	365.6
Environmental Protection	48.7	39.9	43.5	53.3	32.2	49.3	27.5	53.7	32.4	28.8
International Development (AID)	25.8	31.1	17.7	38.5	29.4	33.7	28.9	29.0	16.7	25.4
Aeronautics & Space	79	76.0	110.2	116.6	129.9	131.6	131.9	36.2	[illegible]	160.4
National Science Foundation	75.3	77.0	86.8	89.3	81.4	89.9	86.3	88.1	82.3	79.8
Veterans	137.3	161.4	190.3	226.6	186.2	209.5	215.3	235.3	237.7	255.5
Other	45.1	44.5	52.4	56.9	60.2	60.5	55.1	62.0	59.0	80.4
					B. By Performer					
Intramural (Federal)	1,446.4	1,574.9	1,739.0	1,867.3	1,845.3	2,039.2	2,209.9	2,158.3	2,399.4	2,812.1
Extramural (non-Federal)	3,523.8	3,824.4	4,348.0	4,923.5	5,050.0	5,807.3	6,215.4	7,004.9	7,391.2	7,898.7
State and local government	295.5	276.4	361.9	363.5	376.5	429.4	436.6	528.5	601.5	578.4
Private nonprofit	3,125.5	3,450.8	3,875.9	4,450.4	4,564.2	5,242.9	5,642.8	6,324.5	6,623.0	7,145.1
Higher education[a]	2,520.2	2,760.4	3,124.9	3,587.6	3,685.3	4,226.8	4,561.2	4,975.7	5,216.1	5,750.1
Medical schools	(1,524.8)	(1,718.9)	1,906.2)	(2,246.7)	(2,327.5)	(2,573.2)	(2,738.6)	3,214.6)	(3,290.8)	(3,527.5)
Other[a]	605.3	690.4	750.9	862.8	878.8	1,016.1	1,081.5	1,348.8	1,406.9	1,395.0
Foreign	45.6	36.9	44.7	47.9	46.0	63.4	58.4	69.9	73.1	74.8

[a] Includes federally funded research development centers.

SOURCE: U.S. Department of Health and Human Services, NIH Data Book (Basic Data Relating to the National Institutes of Health), table 4, p. 5, 1992.

Appendix D: FY 1992 Estimates of Funding Support by DHHS Agencies

FY 1992 ESTIMATES OF FUNDING SUPPORT BY DHHS AGENCIES FOR RESEARCH I RELATED TO CHEMICAL TOXICOLOGY IN BASIC RESEARCH, TESTING AND METHODS DEVELOPMENT[1]

	($ in Thousands)							
	Basic Research		Testing		Methods Development		Total	
NATIONAL TOXICOLOGY PROGRAM AGENCIES	185,773	980[2]	85,023	53,326[2]	50,363	22,603[2]	321,159	79,909[2]
National Institutes of Health	153,337	0	56,870	51,307	26,364	19,935	236,571	71,242
National Cancer Institute	72,984	0	4,622	0	4,404	0	82,010	0
National Institute of Environmental Health Sciences	80,353	0	52,248	51,307	21,960	19,935	154,561	71,242
Food and Drug Administration	19,148	0	4,588	25	19,668	0	43,404	25
Center for Biologics Evaluation and Research	0	0	0	0	0	0	0	0
Center for Drug Evaluation and Research	150	0	0	0	175	0	325	0
Center for Food Safety and Applied Nutrition	3,562	0	4,552	0	3,082	0	11,196	0
Center for Devices and Radiological Health	22	0	11	0	125	0	158	0
Center for Veterinary Medicine	726	0	0	0	89	0	815	0
National Center for Toxicological Research	14,688	0	25	25	16,197	0	30,910	25
Centers for Disease Control	1,085	980	18,280	709	4,331	2,668	23,696	4,357
Center for Environmental Health and Injury Control	105		17,571		1,663		19,339	
Center for Health Promotion and Education	0		0		0		0	
Center for Infectious Diseases	0		0		0		0	
Center for Prevention Services	0		0		0		0	
Center for Professional Development and Training	0		0		0		0	
National Institute for Occupational Safety and Health	980	980	709	709	2,668	2,668	4,357	4,357
Agency for Toxic Substances And Disease Registry	12,203[3]		5,285	1,285[2]	0		17,488	1,285[2]
NATIONAL INSTITUTES OF HEALTH	85,515		52,015		2,158		139,689	
National Eye Institute	2,209		6,778		49		8,856	
National Heart, Lung, and Blood Institute	12,328		4,954		270		17,552	
Heart and Vascular Diseases Program	1,814		2,435		0		4,249	
Lung Diseases Program	8,571		2,245		96		10,853	
Blood Diseases and Blood Resources Program	681		63		95		839	
Intramural Research	1,322		210		78		1,610	
National Institute of Allergy and Infectious Diseases	890		22,020		0		22,910	
National Institute of Arthritis and Musculoskeletal and Skin Diseases	471		2,030		0		2,501	
National Institute of Child Health and Human Development	1,983		5,868		235		8,086	
Center for Population Research	46		3,933		0		3,979	
Center for Research on Mothers and Children	1,937		1,935		235		4,107	
National Institute of Dental Research	2,597		1,367		0		3,964	
National Institute of Diabetes and Digestive and Kidney Diseases	4,999		5,816		0		10,815	
National Institute of General Medical Sciences	8,369		0		0		8,369	
Genetics Program	5,198		0		0		5,198	
Pharmacological Sciences Program	2,595		0		0		2,595	
Minority Biomedical Research Support Program	576		0		0		576	
National Institute of Neurological Disorders and Stroke	36,183		0		0		36,183	
National Institute on Aging	4,371		0		988		5,359	
National Institute on Deafness and Other Communication Disorders	4,198		0		0		4,198	
National Library of Medicine	0		0		0		0	
National Center for Research Resources	7,097		3,182		616		10,896	
ALCOHOL, DRUG ABUSE, AND MENTAL HEALTH ADMINISTRATION	60,811		3,223		0		64,034	
National Institute of Mental Health	4,949		0		0		4,949	
National Institute on Alcohol Abuse and Alcoholism	36,000		0		0		36,000	
National Institute on Drug Abuse	19,862		3,223		0		23,085	
TOTALS	332,009		140,261		52,521		524,882	

[1]Based on the FY 1992 President's proposed budget.
[2]Figures indicate projected commitments to NTP for FY 1992.
[3]The descriptor, "applied research" rather than "basic research" more accurately reflects ATSDR's research mandate and programs under the Superfund Program

Appendix E: List of Abbreviations

AAAS	American Association for the Advancement of Science
ACTS	Advisory Committee of Toxic Chemicals (of Health and Safety Commission, UK)
ACGIH	American Conference of Governmental and Industrial Hygienists
ADI	acceptable daily intake
AIDS	acquired immunodeficiency syndrome
AIHC	American Industrial Health Council
AMS	Agricultural Marketing Service (USDA)
AREAL	Atmospheric Research and Exposure Assessment Laboratory (EPA)
ATSDR	Agency for Toxic Substances and Disease Registry (DHHS)
BAT	best available technology
BBDR	biologically based dose response
BMDs	benchmark doses
CAC	Codex Alimentarius Commission
CAG	Carcinogen Assessment Group (EPA)
CA-HHS	California Department of Health and Human Services
CCFAC	Codex Committee on Food Additives and Contaminants
CCPR	Codex Committee on Pesticide Residues
CCRVFD	Codex Committee on Residues of Veterinary Drugs
CCTN	Italian National Advisory Committee on Toxicology
CDC	Centers for Disease Control and Prevention
CDRH	Center for Devices and Radiological Health
CEC	Commission for European Communities
CEFIC	European Council of Chemical Manufacturers
CEHIC	Center for Environmental Health and Injury Control
CEMBL	Center for Environmental and Molecular Biology of the Lung (UNC)
CEPA	Canada Environmental Protection Act
CFSAN	Center for Food Safety and Applied Nutrition
CIIT	Chemical Industry Institute of Technology
CIRRPC	Committee on Interagency Radiation Research and Policy Coordination
CO	carbon monoxide
CPSC	Consumer Product Safety Commission
CRADAS	cooperative research and development agreements
DBBS	Division of Biomedical and Behavioral Science (NIOSH)
DBRA	Division of Biometry and Risk Assessment (NIEHS)
DCE	Division of Cancer Etiology (NCI)
DECOS	Dutch Expert Committee on occupational standards
DES	diethylstilbestrol

DFG	Deutsche Forshungsgemeinschaft (German Research Agency)
DHHS	U.S. Department of Health and Human Services
DOD	U.S. Department of Defense
DOE	U.S. Department of Energy
DRDS	Division of Respiratory Disease Studies (NIOSH)
DRMS	Decision, Risk, and Management Science (NSF)
DSDTT	Division of Standards Development and Technology Transfer (NIOSH)
DSHEFS	Division of Surveillance, Hazard Evaluations and Field Studies (NIOSH)
EC	European Community
ECAO	Environmental Criteria Assessment Office (EPA)
ECDIN	Environmental Chemicals Data and Information Network (EC)
EEA	European Environment Agency (EC)
EH	Office of the Assistant Secretary for Environment, Safety, and Health
ELF	extremely low frequency
EM	Office of Environmental Restoration and Waste Management (DOE)
EMF	electromagnetic forces
EPA	U.S. Environmental Protection Agency
ER	Office of Energy Research (DOE)
ETD	Environmental Toxicology Division (HERL)
E&M	Division of Energy and Material (NRC)
FACA	Federal Advisory Committee Act
FAO	United Nations Food and Agriculture Organization
FAP	familial adenomatous polyposis
FCCSET	Federal Coordinating Council on Science, Engineering and Technology
FDA	Food and Drug Administration
FHSA	Federal Hazardous Substances Act
FOE	Friends of the Earth
GAC	granulated activated charcoal
GAO	General Accounting Office (U.S. Congress)
GATT	General Agreement on Tariffs and Trade
GLP	good laboratory practice
GTD	Genetic Toxicology Division (HERL)
HEI	Health Effects Institute
HERL	Health Effects Research Laboratory (ERA)
HPAB	Hazard Pollutants Assessments Branch (ECAO)
HPV	high production volume
HSC	Health and Safety Commission (U.K.)
HSD	Human Studies Division (HERL)
HSE	Health and Safety Executive (U.K.)
HUD	U.S. Department of Housing and Urban Development
HWC	Health and Welfare Canada
IARC	International Agency for Research on Cancer
ICO	International Coffee Organization
IGM	intergovernmental mechanism
ILO	International Labor Organization
IOM	Institute of Medicine
IPCS	International Programme on Chemical Safety
IRAA	Indoor Radon Abatement Act
IRLG	Interagency Regulatory Liaison Group
IRPCT	International Register for Potentially Toxic Chemicals (UNEP)
ITB	Irnmunotoxicology Branch (HERL)
ITRI	Inhalation Toxicology Research Institute
JECFA	Joint Expert Committee on Food Additives
JMPR	Joint Meeting on Pesticide Residues
JRC	Joint Research Centers (EC)
LBL	Lawrence Berkeley National Laboratory
LLNL	Lawrence Livermore National Laboratory
LMS	linearized multistage
LOAEL	lowest-observed-adverse-effect level
LOEL	lowest-observed-effect level
LQCB	Laboratory of Quantitative and Computational Biology (NIEHS)
MAC	maximum allowable concentration
MAFF	Ministry of Agriculture, Fisheries, and Food (U.K.)
MEL	maximum exposure standard (OEL)
MIACC	Major Industrial Accidents Council of Canada
MLE	maximum likelihood estimate
MRC	Multi-Media Research committee (RIHRA)
MRI	magnetic resonance imaging

MRL	maximum residue limit
MSHA	Mining Safety and Health Administration
MTD	maximum tolerated dose
NAFTA	North American Free Trade Agreement
NAS	National Academy of Sciences
NATO	North Atlantic Treaty Organization
NCA	National Coffee Association
NCAB	National Cancer Advisory Board (NCI)
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
NCTR	National Center for Toxicology Research
NIEHS	National Institute for the Environmental Health Sciences
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed adverse-effect level
NOEL	no observed effect level
NRC	National Research Council or Nuclear Regulatory Commission
NRDC	National Resources Defense Council
NSCI	National Swedish Chemicals Inspectorate
NSF	National Science Foundation
NTD	Neurotoxicology Division (HERL)
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
OEL	occupational exposure limit
OES	occupational exposure standards (OEL)
OHEA	Office of Health Effects Assessment (EPA)
OHR	Office of Health Effects Research (HERL)
OMB	Office of Management and Budget
OMMSQA	Office of Monitoring Research and Quality Assurance (EPA)
OPPTS	Office of Prevention, Pesticides, and Toxic Substances (EPA)
ORAU	Oak Ridge Associated Universities
ORD	Office of Research and Development (EPA)
OSHA	Occupational Safety and Health Administration
OSH Act	Occupational Safety and Health Act
OST	Office of Science and Technology
OSTP	Office of Science and Technology Policy
OTA	Office of Technology Assessment (U.S. Congress)
OTS	Office of Toxicological Sciences (EEA)
PAHO	Pan American Health Organization
PBPK	physiologically based pharmacokinetic
PCB	polychlorinated biphenyl
PCCDs	polychlorinated dibenzo-p-dioxins
PCDF	polychlorinated dibenzofurans
pCi/L	picocuries per liter
PHS	Public Health Service
PI	participating institution
PIC	products of incomplete combustion
PMA	Pharmaceutical Manufacturer's Association
ppm	parts per million
PTB	Pulmonary Toxicology Branch (HERL)
QEP	quantitative estimation and prediction
QRA	quantitative risk assessment
RAC	Risk Assessment Council (ERA)
RAF	Risk Assessment Forum (EPA)
Rb	retinoblastoma
RCRA	Resources Conservation and Recovery Act
RfC	inhalation reference concentration
RfD	reference dose
RIHRA	Research to Improve Health Risk Assessment program (EFA)
RSAC	Research Strategies Advisory committee (SAB)
RTD&E	Research Development Testing and Evaluation (DOD)
RTP	Research Triangle Park
SAB	Science Advisory Board (EPA)
SAR	structure-activity relationships
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
SEA	Single European Act
SIDS	Screening Information Data Set Project (OECD)
TCDD	tetrachlorodibenzodioxin
TEFs	toxicity equivalency factors
UNC	University of North Carolina
UNCED	United Nations Conference on Environment and Development
UNEP	United Nations Environment Programme

USDA	U.S. Department of Agriculture
VOCs	volatile organic compounds
WATCH	Workplace Assessment of Toxic Chemicals (HSE)
WHO	World Health Organization
WLM	working-level months
WPAFB	Wright-Patterson Air Force Base

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