

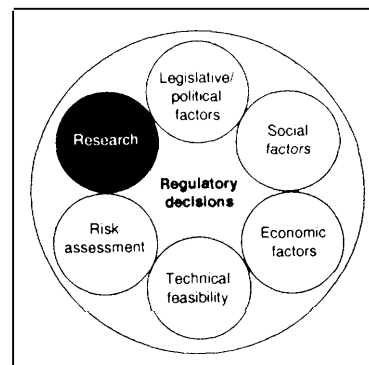
# Structuring the Future of Health Risk Assessment Research

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**R**esearch 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 innova-

tion 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 a broad 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**

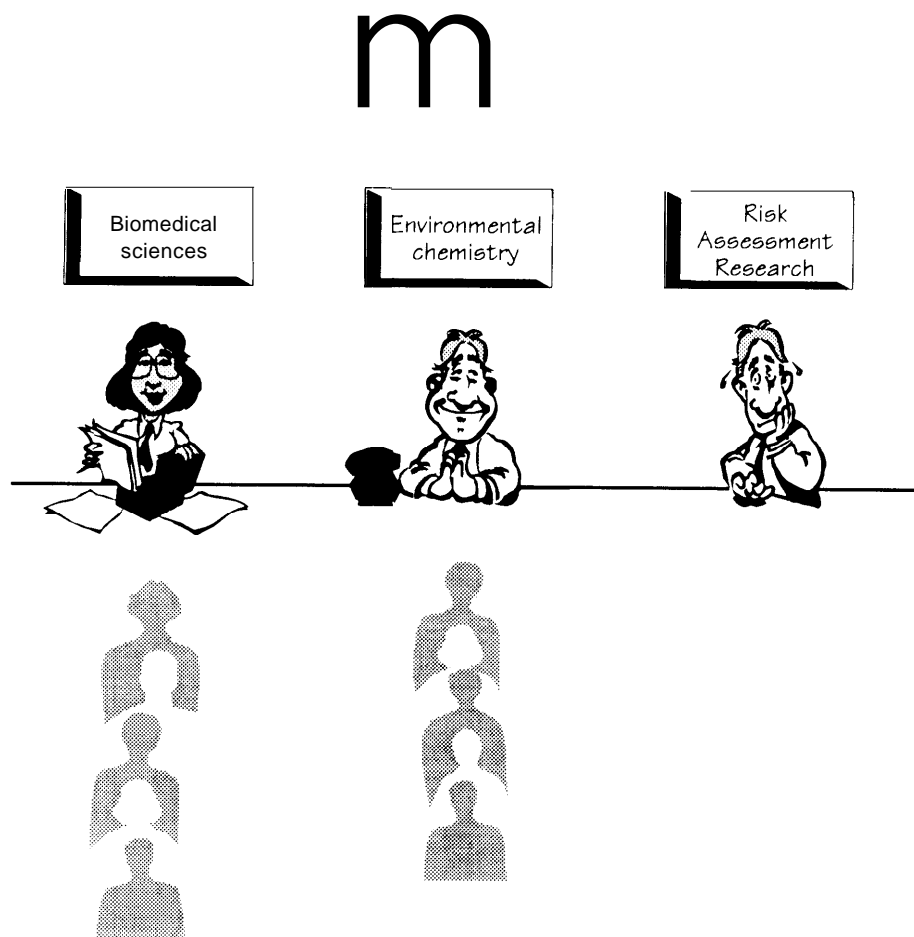
Health risk assessment research encompasses a broad spectrum of scientific disciplines, Coordi-

nation 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).



### 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 mi-

croelectronics 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 identifying agents 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 acetylcholinesterase levels following 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 polyposis coli gene in people with familial adenomatous polyposis 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. 1990. *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. 1995. *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 tetrachlorodibenzo-dioxin (TCDD) (Vanden Heuvel and Lucier, 1993).

Physiologically based pharmacokinetic (PBPK) models estimate both the concentration of a toxicant, or an active metabolite 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 cell 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 cell 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. 1981. Growth factors and cancer. *Science* 254:114S; J. Barrett. 1995. 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. 1992. Dying cells reveal new role for cancer genes. *Journal of NIH Research* 4:48; H. Varmus. 1987. 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 decision-makers interviewed by OTA stressed the importance of the relationship between conducting basic research and improving risk assessment methodology. Of arguably the greatest long-term significance 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 retinoblastoma. 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. 1983. Mechanisms of multistep carcinogenesis and carcinogen risk assessment. *Environmental Health Perspectives* 100:9-20; H. Evans, J. Prosser and J. Presser. 1982. 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. Borow, and A.D. Goddard. 1981. 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.

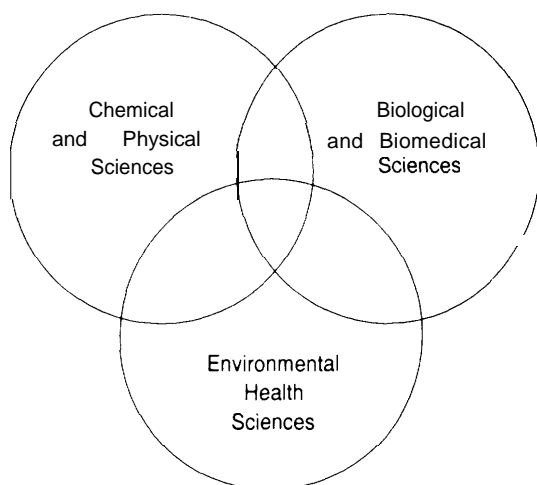
Linkages can occur within and between Federal agencies as well as between Federal and nonfederal institutions. Traditionally, linkages in health risk assessment research were forged between government and university researchers; fewer such linkages exist between government and industry. Although not 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 7-1). 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-I—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 forum 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 analy-

sis, 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, whole 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 fields (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 differently 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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