Federal Research in Health Risk Assessment

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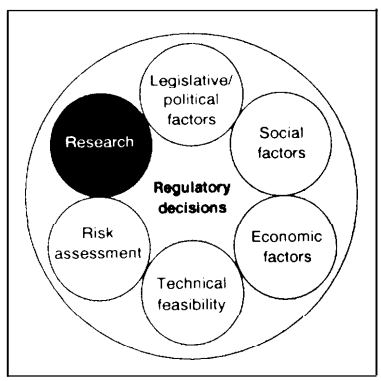
This chapter describes the research that the Federal Government is now conducting to improve health risk assessments. It summarizes the results of the Office of Technology Assessment's (OTA) survey of such Federal research efforts and identifies their strengths, weaknesses, and trends.

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).

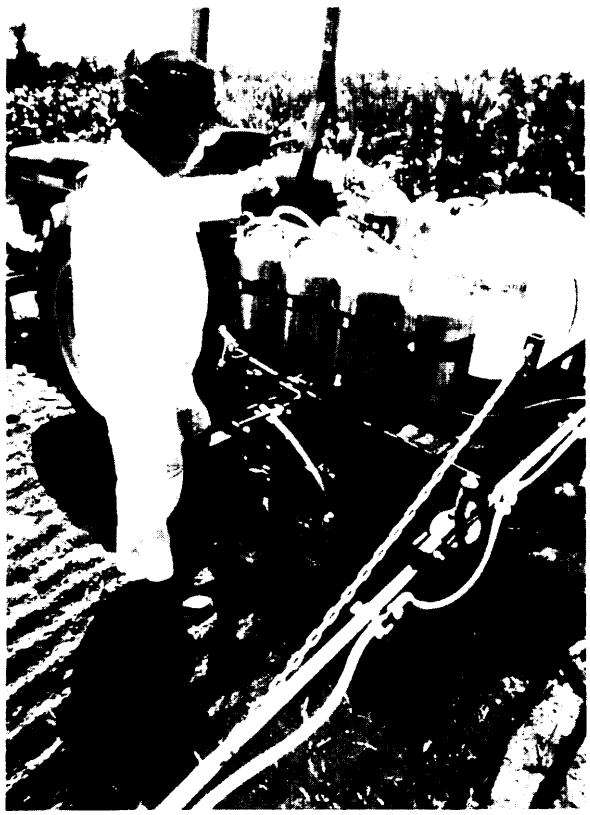
OTS is split into a research component and a regulatory review group, both of which report to the office manager.[5] The office sets priorities informally, and there is no external review of research plans or activities. Upper management establishes priorities for research, which are based on regulatory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