ASSESSMENT OF TECHNOLOGIES FOR DETERMINING CANCER RISKS FROM THE ENVIRONMENT

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CONGRESS OF THE UNITED STATES
Office of Technology Assessment
Washington, D. C. 20510

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Foreword

Congressional interest in cancer is long standing and continuing. Programs in basic cancer research, and in treatment and prevention of the disease are now complemented by some two dozen laws directed at reducing exposures to cancer-causing substances. This report examines the technologies used to gather and analyze information about cancer in our society, as well as the ways in which those technologies affect and are affected by the public health and environmental legislative mandates.

The report discusses the strengths and weaknesses of data sources used for determining trends in cancer occurrence and mortality, and reviews estimates of the contribution of various factors—behaviors and exposures—associated with cancer in this country. Evidence linking today's cancers with past carcinogenic influences has come mainly from epidemiology, which continues to scrutinize aspects of the American lifestyle, for possible associations with cancer.

Congressional mandates intended to shield people from new and already-present carcinogens have heightened the need for methods to identify such harmful agents before they have an impact on human health. Laboratory testing technologies currently used to determine the carcinogencity of substances, and technologies that may become important in the near future are discussed and evaluated. The assessment examines the use of extrapolation techniques for estimating human carcinogenic risks from test-derived data; the advantages and disadvantages of the available extrapolation models; and the ultimate use of these techniques in setting standards for controlling exposures under diverse legislation. The report then looks at the problems of decisionmaking in the face of the often-great uncertainties accompanying scientific findings and the proposals for regulatory reform that have grown out of concern for these issues.

In preparing the full report, OTA staff consulted with members of the advisory panel for the study, with contractors who prepared material for the assessment, and with other knowledgeable persons in environmental organizations, Government, industry, labor organizations, research institutions, and universities.

A draft of the final report was reviewed by the advisory panel, chaired by Dr. Norton Nelson, the OTA Health Program Advisory Committee, chaired by Dr. Sidney S. Lee, and by approximately 80 other individuals and groups. We are grateful for their assistance and that of many other people who assisted and advised in the preparation of this report.

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1. Summary

Cancer occupies center stage in American concern about disease because of its toll in lives, suffering, and dollars. It strikes one out of four Americans, kills one out of five, and as the second-leading cause of death, following heart disease, killed over 400,000 people in the United States in 1979. According to estimates from the National Center for Health Statistics (NCHS), cancer accounted for about 10 percent of the Nation's total cost of illness in 1977. These numbers are distressing, but the impacts of cancer extend beyond the numbers of lives taken and dollars spent. The human suffering it causes touches almost everyone.

Cancer is a collection of about 200 diseases grouped together because of their similar growth processes. Each cancer, regardless of the part of the body it affects, is believed to originate from a single "transformed" cell. A transformed cell is unresponsive to normal controls over growth, and its progeny may grow and multiply to produce a tumor. Studies in human populations and in laboratory animals have linked exposures to certain substances with cancer. This knowledge of cancer's origins has led to the conclusion that preventing interactions between cancer-causing substances and humans can reduce cancer's toll.

CANCER AND "ENVIRONMENT"

Studies over the last two decades yielded a variety of statements that 60 to 90 percent of cancer is associated with the environment and therefore is theoretically preventable. As it was used in those statements and is used in this report, **"environment" encompasses anything that interacts with humans, including substances eaten, drunk, and smoked, natural and medical radiation, workplace exposures, drugs, aspects of sexual behavior, and substances present in the air, water, and soil.** Unfortunately, the statements were sometimes repeated with "environment" used to mean only air, water, and soil pollution.

Relating exposures and behaviors to cancer occurrence is a first step in cancer prevention. Once carcinogenic influences are identified, efforts to control them can be undertaken toward the goal of reducing cancer. This study is intended to illuminate the debates about the importance of environmental factors in cancer occurrence, the laws that require actions to reduce exposures to cancer-causing substances (carcinogens), and describes:

- what is known about the occurrence of cancer and death from cancer in the United States;
- methods to identify cancer-causing substances, exposures, and behaviors;
- methods to estimate the amount of cancer which may result from a particular behavior or exposure;
- Federal laws that provide for regulatory control of carcinogenic exposures; and
- options for Congress.

CANCER MORTALITY AND INCIDENCE

Nationwide mortality data are used to answer questions about the number of deaths caused by cancer in the United States. Without doubt, the number of Americans dying from cancer has increased during the last century. Paradoxically, a major part of this increase re-

sulted from improvements in public health and medical care. In years past, infectious diseases killed large numbers of people in infancy and during childhood. Now that improved health care has softened the impact of those diseases, many more people live to old ages when cancer causes significant mortality.

Cancer deaths are not evenly distributed among all body sites, the lung, colon, and breast accounting for over 40 percent of the total (see table 1). Changes in cancer rates over time also vary by body site. For this reason, discussion of cancer rates at particular body sites is more revealing than discussion of overall trends which mask changes at individual sites. Moreover, because some cancer-causing substances act at specific sites, more information about oppotunities for prevention is obtained from the analysis of particular sites.

To permit the examination of cancer rates over time, standardization, a statistical technique, is applied to make allowances for a changing population structure. Standardization allows the direct comparison of single, summary statistics, e.g., the mortality rates from lung cancer for the entire population in 1950 and 1981. In this report, mortality rates are standardized to the age and racial structure of the 1970 U.S. census, unless otherwise specified.

Age-specific rates are also used extensively for examining trends. These rates measure the *proportion* of people in defined age classes who have developed or died from cancer, and are unaffected by changes in the age structure of the population. Of greatest importance in detecting and identifying carcinogens, changes over time in younger age groups often presage future, larger changes in that group of people as they enter older age groups.

In general, cancer mortality rates are higher among nonwhite males than among white males. Differences between nonwhite and white females are less pronounced. The observed greater fluctuations in rates from year to year for nonwhites is consistent with the conclusion that reporting of vital statistics is poorer for nonwhites than for whites.

Greatest concern is expressed about the increasing trends. The largest increases since 1950 are in respiratory cancers (mainly of the lung, larynx, pharynx, trachea), which are largely ascribed to the effects of smoking. Male respiratory cancer rates began to rise about 25 years earlier than female rates, which reflects the difference in time when the two sexes adopted smoking. Further evidence for the importance of smoking in lung cancer is the recent decrease in lung cancer mortality among males younger than 50. The percentage of males who smoke is known to have decreased during the last 20 years, and studies have shown that smoking cessation reduces lung cancer occurrence. Addi-

Table 1.—Mortality From Major Cancer Sites in the United States, 1978, All Races

Anatomic site	Number of deaths			Percentage of total		
	Male	Female	Total	Male	Female	Total
All malignant neoplasms	215,997	180,995	396,992	100%	100%	100%
Lung, trachea, and bronchus	71,006	24,080	95,086	32.9	13.3	24.0
Colon	20,694	23,484	44,178	9.6	13.0	11.1
Breast	280	34,329	34,609	0.13	19.0	8.7
Prostate	21,674	—	21,674	10.0	—	5.5
Pancreas	11,010	9,767	20,777	5.1	5.4	5.2
Blood (leukemia)	8,683	6,708	15,391	4.0	3.7	3.9
Uterus	—	10,872	10,872	—	6.0	2.7
Ovary, fallopian tubes, and broad ligament	—	10,803	10,803	—	6.0	2.7
Bladder	6,771	3,078	9,849	3.1	1.7	2.5
Brain and other parts of nervous system	5,373	4,362	9,735	2.5	2.4	2.5
Rectum	5,002	4,089	9,091	2.3	2.3	2.3
Oral: Buccal cavity and pharynx	5,821	2,520	8,341	2.7	1.4	2.1
Kidney and other urinary organs	4,809	2,916	7,725	2.2	1.6	1.9
Esophagus	5,552	2,030	7,582	2.6	1.1	1.9
Skin	3,537	2,511	6,048	1.6	1.4	1.5
All other	45,785	39,446	85,231	21.2	21.8	21.5

SOURCE: Office of Technology Assessment.

tionally, changes in cigarette composition are thought to contribute to a reduced risk of lung cancer. Decreases among men now over 50 are not expected because those populations include a large proportion of long-time smokers who remain at high risk.

Death rates from prostate and kidney cancers among males have risen somewhat, and mortality rates from malignant skin tumors (melanomas) have increased in white males and females. Mortality from breast cancer, the number one cancer killer of women, has remained relatively constant. Overall mortality from nonrespiratory cancers (i.e., excluding most cancers generally associated with smoking) has decreased in females and remained constant in males during the last 30 years.

The more satisfying trends are those that are decreasing. The most striking, among both men and women, has been the great decrease in stomach cancer since 1930. Although generally ascribed to changes in diet, the reasons for the decrease are not known with any certainty. A decrease in uterine cancer within the last few decades is attributed to higher living standards, better screening tests for early cancer, and an increase in hysterectomies, which reduces the number of women at risk.

In general, mortality data (numbers of deaths) are considered more reliable for deciding about trends in cancer occurrence than are data about cancer incidence (numbers of new cases). This is largely because nationwide mortality data have been collected on a regular basis for almost 50 years. In contrast, incidence data for a sample of the entire country have been collected systematically only since 1973 by the National Cancer Institute's (NCI's) Surveillance, Epidemiology, and End Results (SEER) program. Before that, incidence data are available only for three points in time since 1937. The 10-percent sample of the population included in the SEER areas is not representative of the entire population. Some groups—orientals—are overrepresented in the data collected, and some groups—rural blacks—are underrepresented. Incidence rates for nonwhites, at least during the first 4 years of the SEER program, were considered too unreliable for meaningful analysis.

Incidence data are important because they provide information not captured in mortality data. They record each new case of cancer whether the person dies from cancer, is cured, or dies from other causes.

Followup studies of SEER program participants have provided information about survival from the various types and stages of cancer. A problem encountered in such studies was that people who move from the registration area after treatment are sometimes lost to further study, making it difficult to ascertain whether they eventually succumb to cancer or if treatment cured them. Use of the newly established (1981) National Death Index, by which deaths can be identified through a single query to NCHS rather than through a request to every State, is expected to facilitate SEER program followup studies. If this expectation is realized, information from the "End Results" component of SEER should be improved.

Data collected in the SEER program (1973-76), in combination with data from the Third National Cancer Survey (TNCS), carried out from 1969 through 1971, have been interpreted as showing an increase of more than 10 percent in cancer incidence during the last decade. The major changes seen in the incidence data parallel those seen in mortality data—increases in lung cancer and decreases in stomach and uterine cancers. However, publication of this analysis sparked a controversy about the true nature of incidence trends, since only 2 years earlier an analysis of data from the three national cancer surveys had shown an overall decrease of about 4 percent between 1947 and 1970. Some observers are concerned about the possibility that, after at least half a century of stable or declining rates, cancer incidence has gone up and that the increase might result from newly introduced chemical carcinogens. Those who dispute the importance of the observed increase contend that it reflects changes in the reporting of cancer incidence between TNCS and SEER (1973 through 1976), and not real changes in cancer incidence. As more data are collected during the next few years, a clearer picture of incidence trends may emerge.

INITIATION, PROMOTION, AND SYNERGISM

Cancer causation is thought to involve at least two steps: an early initiation step and a later promotion effect. A single agent may cause both events, or two or more separate agents working in the proper sequence may be necessary. Initiation is generally thought to involve a genetic change in the cell, but that change is not expressed and does not result in a tumor unless a promotion event follows it. The latent period of most cancers—the time between exposure to an initiator and appearance of the disease—is often 20 years or more. This long latent period is the cause of a great deal of apprehension among policymakers, scientists, and the general public because new substances and living habits are continually introduced, and today's harmful exposures may not cause ill effects for years.

The time between exposure to a promoter, after initiation has occurred, and the appearance of cancer, can be much shorter. "Initiated cells" may lie quiescent if they are not "turned on" by a promoter, and cancer may never develop if sufficient exposures to promoters do not occur. The practical importance of this property of promoters is illustrated by the change in cancer risk experienced by ex-smokers of cigarettes. Smoking is thought to play both an initiation and promotion role in cancer causation. Because of smoking's promotional properties, the risk of cancer falls off rapidly after a smoker quits.

Synergism, another form of interaction, occurs when two or more substances potentiate each other's effects, producing more cancers than can be accounted for by adding the effects of each. The multiplicative effects of cigarette smoking and exposure to asbestos and smoking and exposure to radiation are well-known examples of synergism.

Unfortunately, relatively little is understood about interacting agents—either synergisms or initiation and promotion. In particular, promoters have not received as much experimental attention as have initiators or complete carcinogens, which both initiate and promote.

FACTORS ASSOCIATED WITH CANCER

The possibility that cancers may be prevented by eliminating or modifying behaviors or exposures has stimulated the continued search for factors important in cancer causation. Importantly for prevention efforts, studies of agents that interact in causing cancer have shown that altering exposure to a single factor may eliminate or greatly reduce the risk of cancer.

Evidence for the associations between various "factors" and cancer ranges from very strong to very weak. Regardless of the strength of the association, the estimated magnitude of the amount of cancer associated with factors also varies. For instance, the strongest associations include those between smoking tobacco and respiratory cancers, between asbestos and cancer of the lung and other sites, and between ionizing radiation and cancer at many sites. While each of the three associations is strong, the percentage of cancer associated with each is different. Smoking is associated with more than 20 percent of cancer, asbestos with between 3 and 18 percent, and natural radiation with less than 1 to 3 percent.

Table 2 (pp. 8-9) presents information about associations between several factors and cancer. The associations between some aspects of human biology and reproduction and a proportion of cancer, especially in women, are well-established, as is the association of a small percentage of cancer with medical drugs. The specifics of the association between human diet and cancer are not understood, but diet is generally considered to be associated with a large percentage of cancer. Infection, especially viral infection, is associated with particular tumors that occur mainly in people in other parts of the world, and is also thought to be associated with some urogenital cancers in the United States.

The magnitude of associations between air and water pollution and cancer are argued and studies to examine the associations are difficult to design and execute. The same is true of associations between consumer products and cancer.

There is no disputing that occupational exposures to asbestos and some chemicals have caused human cancer, and table 2 presents estimates both for asbestos-caused cancer and total occupationally associated cancer. As the data in the table show, there is significant disagreement about how much current cancer and cancer in the near future is to be associated with occupational exposures.

Associating a high or low percentage of cancer with a factor does not reflect the present-day opportunities for prevention. For instance, diet is considered very important, but because associations with specific elements and cancer are poorly understood, there are few practical preventive measures now available.

The opportunities for prevention of occupation-related cancers at this time are better. Identification of a cancer-causing substance in the workplace can lead to reductions in exposure either by regulation or through voluntary activities on the part of industry. While reducing or eliminating occupational exposures to carcinogens might only slightly reduce the overall cancer toll, it could have a profound effect on the amount of cancer among workers who may now be at risk. A reduction of only 1 percent in cancer mortality means 4,000 fewer cancer deaths each year, so that even small reductions translate into relatively large numbers.

IDENTIFICATION OF CARCINOGENS

The Federal Government has centered efforts to control cancer on reducing exposures to chemical and physical carcinogens.

Carcinogens can be identified through epidemiology—the study of diseases and their determinants in human populations—and through various laboratory tests. Currently 18 chemicals and chemical processes are listed as human carcinogens and an additional 18 listed as probable human carcinogens by the International Agency for Research on Cancer (IARC), a World Health Organization agency. IARC conclusions, based on reviews of the worldwide literature, are accepted as authoritative by government agencies and many other organizations.

In the United States, Congress has directed the National Toxicology Program (NTP) to produce an annual list of carcinogens. The first list, published in 1980, was composed of the substances identified as human carcinogens by IARC. The next publication is to be considerably expanded and will include usage and exposure data and information on the regulatory status of over 100 chemicals either considered to be carcinogens or regulated by the Federal Government because of carcinogenicity.

Cancer epidemiology established the associations between the 36 substances and human cancer listed by IARC as well as the carcinogenicity of smoking, alcohol consumption, and radiation. However, **epidemiology is limited as a technique for identifying carcinogens because cancers typically appear years or decades after exposure.** If a carcinogen were identified 20 years after its widespread use began, many people might develop cancer from it even though its use is then immediately discontinued. Certainly, those people who were identified in the study as having had their cancer caused by the substance would have been irreparably harmed. Epidemiology is complicated because people are difficult to study; people move from place to place, change their type of work, change their habits, and it is hard to locate them and to estimate their past exposures to suspect agents.

Laboratory tests, which do not depend on human illness and death to produce data, have been developed to identify carcinogens. Currently, the testing of suspect chemicals in laboratory animals, generally rats and mice, is the backbone of carcinogen identification. The suspect chemical is administered to the animals

Table 2.—Summary of Cancer-Associated Environmental Factors[a]

Factor[b]	Sites considered in drawing the estimates	Range of estimates associated with factor
Diet	***Digestive tract, breast, endometrium, ovary***	***35–50 percent***
Associations between diet and cancer are suggested by epidemiologic and experimental laboratory studies. Significant differences in cancer rates are observed between different population groups with varying eating habits. Dietary components, such as high-fat and low-fiber content, and nutritional habits that affect hormonal and metabolic balances are believed more important than additives and contaminants. The magnitude of the estimates reflect observed relationships between diet and prominent cancer sites, e.g., breast and colon.		
Tobacco	***Upper respiratory tract, bladder, esophagus, kidney, pancreas***	***22–30 percent***
Tobacco is associated with cancer at many anatomical sites, principally the lung. Many estimates of the proportion of overall cancer mortality associated with tobacco smoking are firmly based on epidemiologic studies that compared cancer mortality among individuals with varying smoking habits. Several carcinogens act synergistically with tobacco, e.g., asbestos, alcohol, radiation.		
Occupation, asbestos	***Upper respiratory tract, others***	***3–18 percent***
Several occupational exposures are firmly linked to cancer occurrence, the most important of these is asbestos. Estimates for the contribution of asbestos to current cancer deaths and cancers in the near future range from 3 percent (1.4–4.4 percent) to an upper estimate of 13–18 percent. Most estimates lie toward the lower end of the range. The exposures responsible for these cancers occurred primarily in the 1940's and 1950's and the resultant cancers are expected to peak in the early to mid-1980's.		
Occupation, all exposures	***Upper respiratory tract, others***	***4–38 percent***
Estimates of the proportion of cancer associated with all occupational exposures range from 4 percent (2–10 percent) to a high of 23–38 percent. The higher estimates are from a paper that estimated that asbestos is associated with 13–18 percent of all cancer and added to that estimates of cancer associated with five other occupational exposures. Almost all other estimates are near the lower end of the range.		
Alcohol	***Upper digestive tract, larynx, liver***	***3–5 percent***
Alcohol consumption is associated with cancer in the upper digestive tract and in the liver. The digestive tract cancers occur more frequently in smokers than nonsmokers, and therefore many of these cancers could be prevented if either tobacco or alcohol were discontinued. The majority of reliable estimates are based on apportioning a percentage of the cancers at the alcohol-related sites to alcohol, and the numerical estimates are very similar.		
Infection	***Uterine cervix, prostate, and other sites***	***1–15 percent***
Epidemiologic data strongly suggest an association between a virus and cervical cancer, and cancer at that site accounts for the lower numerical estimate. The higher estimate is much more tentative and associates all urogenital cancers in both sexes with infections of venereal origin. Some other cancers which occur commonly in other parts of the world are strongly associated with viral infection. They are rare in the United States.		
Sexual development, reproductive patterns, and sexual practices	***Breast, endometrium, ovary, cervix, testis***	***1–13 percent[c]***
All of the hormonally related cancers in women, breast, endometrial, and ovarian are believed associated with sexual development and reproductive patterns. The important characteristics are: 1) age at sexual maturity; 2) age at birth of first child; 3) age at menopause. The higher numerical estimate includes the large number of breast cancers. Testicular cancers are associated with developmental and hormonal abnormalities.		
Pollution	***Lung, bladder, rectum***	***Less than 5 percent***
Air pollution: Several epidemiologic studies of the effects of air pollution demonstrate an increased risk of lung cancer in heavily polluted areas, but these conclusions are weakened because smoking and occupational exposures were not always taken into account. The most important carcinogens are believed to be combustion products of fossil fuels. There is continued concern that chlorofluorocarbons introduced into the atmosphere may deplete the ozone layer. This would result in more ultraviolet light reaching the surface of the Earth and increase the number of cases of skin cancer.		
Drinking water pollution: Many carcinogenic chemicals have been identified in drinking water but the extent to which past and present levels contribute to the overall cancer rate is uncertain. Several descriptive epidemiologic studies have suggested an association with an increased risk of cancer but the studies are plagued by confounding variables. A soon to be released NCI epidemiologic study is expected to provide more definitive evidence regarding the association between quality of drinking water and bladder cancer.		
Medical drugs and radiation	***Breast, endometrium, ovary, thyroid, bone, lung, blood (leukemia)***	***1–4 percent***
Drugs known to be carcinogenic are used in the treatment of diseases, including some cancers. In addition, hormonal therapies, particularly the estrogens, are firmly linked to an increased cancer risk. Medical radiation exposures are known to have caused cancer and while dosage levels can be estimated, the level of risk from present day exposures is uncertain.		

Table 2.—Summary of Cancer-Associated Environmental Factors[a]—Continued

Factor[b]	Sites considered in drawing the estimates	Range of estimates associated with factor
Natural radiation	***Skin, breast, thyroid, lung, bone, blood (leukemia)***	***Less than 1-3 percent***
There is no doubt that natural radiation, consisting of ionizing radiation from cosmic rays and radioactive materials, can cause cancer. While disagreements persist regarding the amount of risk associated with low-level ionizing radiation, the estimates generally agree within one order of magnitude. Ultraviolet radiation from the Sun is believed responsible for most of the 400,000 nonmelanoma skin cancers. These tumors are not usually included in quantitative estimates of cancer rates because they are poorly recorded and generally curable. They are not included here.		
Consumer products	***Possibly all sites***	***Less than 1-2 percent***
Substances known to be carcinogenic are present in consumer products at usually very low levels. The extent to which they contribute to the overall cancer rate is uncertain.		
Unknown associations	***All sites***	***(?)***
Many substances have not been tested for carcinogenicity and associations between some of those substances and cancer may exist. Furthermore, substances newly introduced into the environment may have an impact in the future. In particular, there is concern that point sources of pollutants, such as dumps, may be contributing to cancer. Because the associations are unknown, the estimate is uncertain but it is certainly not zero. Additionally, stress, which may be manifested by overeating, smoking, or in other ways, probably plays a role in cancer causation.		

[a]Many cancers may be associated with more than one factor. Factors are not mutually exclusive, and the total, if all associations were known, would add to much more than 100 percent.
[b]Estimates are listed under the factors that most closely approximate the description published with them. The estimates are detailed and their sources referenced in ch. 3.
[c]Range of single estimate.

SOURCE: Office of Technology Assessment.

either in their food, water, air, or (less frequently) by force feeding, skin painting, or injection. As the animals die, or when the survivors are killed at the end of the exposure period (which is generally the lifespan of the animal), a pathologist examines them for tumors. The number of tumors in the exposed animals is then compared with the number in a group of "control" animals. The controls are treated exactly as the experimentals except that they are not exposed to the chemical under test. The finding of a significant excess of tumors in the exposed animals compared with the number found in controls in a well-designed, well-executed animal test for carcinogenicity leads to a conclusion that the chemical is a carcinogen in that species.

IARC has reviewed the literature concerning 362 substances which have been tested in animals and considers the data "sufficient" to conclude that 121 are carcinogens. For about 100 others, there was "limited" evidence of carcinogenicity, indicating that further information is desirable, but that the available evidence produces a strong warning about carcinogenicity. Data were "insufficient" to make decisions about the carcinogenicity of the remaining substances. The IARC review program is active and continuing and updates it findings periodically.

The reliability of animal tests, bioassays, depends on their design and execution. NCI published guidelines for bioassays in 1976. Bioassays now cost between $400,000 and $1 million and require up to 5 years to complete. Clearly such expensive tools should be used only to test highly suspect chemicals, and much effort is devoted to selecting chemicals for testing.

Molecular structure analysis and examination of basic chemical and physical properties are used to make preliminary decisions about the likelihood of a chemical being a carcinogen and whether or not to test it. For instance, greater suspicion is attached to chemicals that share common features with identified carcinogens. Unfortunately, not all members of a structural class behave similarly, which places limits on this approach. In making decisions about whether chemicals should be tested further, scientists consider other data, including any available toxicological information. These preliminary decisions may be critical, because if a decision is made not to test a substance, nothing

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more may be learned about its toxicity. The wrong decision might result in a carcinogen entering the environment and being ignored until it causes disease in a large number of people.

The most exciting new developments in testing are the short-term tests, which cost from a few hundred to a few thousand dollars and require a few days to months to complete. Such tests have been under development for about 15 years, and most depend on biologically measuring interactions between the suspect chemical and the genetic material, deoxyribonucleic acid (DNA). The best-known test, the "Ames test," measures mutagenicity (capacity to cause genetic changes) in bacteria. Other short-term tests use micro-organisms, nonmammalian laboratory animals, and cultured human and animal cells. Some measure mutagenicity and some the capacity of a chemical to alter DNA metabolism or to transform a normal cell into a cell exhibiting abnormal growth characteristics.

Many chemicals that have already been identified as carcinogens or noncarcinogens in bioassays have also been assayed in short-term tests to measure congruence between the two types of tests. Results from these "validation" studies vary, but up to 90 percent of both carcinogens and noncarcinogens were correctly classified by short-term tests. These figures are sometimes questioned because they were derived from studies that excluded classes of chemicals known to be difficult to classify by the short-term tests being evaluated. However, the International Program for the Evaluation of Short-Term Tests for Carcinogenicity concluded that the Ames test, in combination with other tests, correctly identified about 80 percent of the tested carcinogens and noncarcinogens. That study purposefully included some chemicals known to be difficult to classify by short-term tests, and it further demonstrates the promise of short-term tests.

Short-term tests now play an important role in "screening" substances to aid in making decisions about whether or not to test them in animals. The role of short-term tests is expected to increase in the future as more such tests are developed and validated. However, the eventual replacement of animal tests by short-term tests is probably some time away.

One factor likely to retard replacement of animal tests by short-term tests is the poor quantitative agreement between the two kinds of tests. Qualitative agreement, as measured in validation studies, is good—i.e., a mutagen is very likely to be a carcinogen—but poor quantitative agreement means that a powerful mutagen may be a weak carcinogen or the other way around. Additionally, because there is some evidence to support the idea that the potency of a carcinogen in animals is predictive of its potency in humans, the poor agreement about potency between animal and short-term tests may inhibit wider use of the latter tests.

PROGRAMS TO IDENTIFY CARCINOGENS

Government Programs

The most important recent development in governmental management of test development and implementation is the establishment of NTP by the Department of Health, Education, and Welfare in 1978. The program encompasses the short-term and bioassay testing activities of the Department of Health and Human Services (DHHS) but not the testing programs that exist in other executive branch departments. Other agencies with a stake in carcinogen testing, the Environmental Protection Agency (EPA), the Consumer Product Safety Commission (CPSC), and the Occupational Safety and Health Administration (OSHA), participate in the selection of substances to be tested by NTP. Each of these agencies retains responsibility for development of policies and guidelines for testing and interpretation of results under the laws that they administer.

NTP has assumed the management of the carcinogen bioassay program that was formerly located at NCI. This is the largest single test program, and began the testing of about 50 chemi-