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# Summary

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# 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-

suited from improvements in public health and medical care. In yearn 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 opportunities 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 | 3.3 |
| 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 lo-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 potentate 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 patients. 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, b/adder, 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 7-3 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]Est imat s are listed under th 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" Off Ice 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 bioassa, 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-

cals in fiscal year 1980; the number will drop to about 30 in fiscal year 1981 because of budgetary limitations.

Government-sponsored cancer epidemiology is supported principally by the National Institutes of Health, with the National Institute of Occupational Safety and Health, and other agencies carrying out some research. Epidemiologic research is marked by flexibility in experimental design, and it has not been placed under an umbrella organization like NTP.

### Nongovernment Programs

Many chemical, drug, and petroleum companics have large, active, inhouse toxicology and epidemiology units. These resources are employed to develop information about substances of concern to the companies and also to supply data to Federal regulatory agencies. One of the most modern toxicology laboratories is that of the Chemical Industry Institute of Toxicology (CIIT). This laboratory recently completed extensive testing of formaldehyde, which demonstrated that the chemical causes nasal cancer in rats. CPSC and other agencies have proposed regulations to curtail exposures to formaldehyde based on information from CIIT studies.

Many epidemiologic studies and much of the development of test procedures take place in academic institutions. Funding for these activities *comes* from both Federal and non-Federal sources, and these institutions have been important in gaining knowledge and improving techniques.

## ANALYSES OF TEST RESULTS

Results from tests are conveniently discussed as being "positive," "negative," or "inconclusive." A "positive" test is sufficient to convince all (or most) experts that the tested substance causes the measured effect —e. g., cancer in bioassay. Similarly, a "negative" result is one that convinces all (or most) experts that the tested substance does not exert the effect measured in the test. "Inconclusive" means that no conclusion can be drawn from the test. Test results are analyzed initially by the scientists who conduct the tests. Their conclusions may be reviewed by other experts later on, and such peer review is important for the acceptance or rejection of the conclusions.

Positive epidemiologic results show an association between an exposure or behavior and human cancer. When they are available and based on a valid study, they tend to dominate any decision to be made about carcinogenicity. When no or limited epidemiologic data are available, bioassays which measure carcinogenicity in intact animals are the most important source of information. The last decade saw Government organizations, Congress, executive agencies, and the courts, as well as private sector organizations endorse bioassays and agree that they can be used to identify potential human carcinogens. For instance, IARC concluded:

> . . . it is reasonable, for practical purposes, to regard chemicals for which there is sufficient evidence of carcinogenicity . . . in animals as if they presented a carcinogenic risk for humans.

The use of short-term test results varies depending on whether the substance being tested is *in use* or *new*. When making decisions about currently used chemicals, short-term test results are used to decide whether or not to proceed to a bioassay, and they are accorded a supporting role in making decisions about carcinogenicity.

In industry, short-term tests play a role in making decisions about whether or not to proceed with *development* of a new chemical. A positive result, indicating that the cost of developing the chemical for market might have to include extensive and expensive toxicological testing, may be factored into a manufacturer's decision to develop or not to develop a chemical. A risky chemical may be dropped from consideration for further development.

A problem that bedevils decisionmaking is the existence of both "positive" and "negative" results from tests of the same substance. Careful analysis of the design and execution of the "pos-

itive" and "negative" tests sometimes resolves the discrepancies and allows reconciliation of the results. When the conflicting results cannot be explained, more importance is attached to the positive results.

It is not possible to say how many of the 55,000 chemicals in commerce are carcinogens. About 7,000 have been tested in bioassay, and 10 to 16 percent were "positive." However, this percentage has little meaning when discussing all chemicals. There is a strong bias toward testing risky chemicals, as is shown by the fact that about half of 190 chemicals tested in NCI's bioassay program were reported to be positive. On the other hand, many tests done years ago are insensitive by today's standards and that would tend to decrease the percentage of substances detected as carcinogens.

The IARC list of 18 human carcinogens, plus tobacco smoke, alcohol, radiation, and the 18 probable human carcinogens, provide a minimal answer to the question of how many substances are known to cause or probably cause human cancer. The IARC list of 121 substances that produced "sufficient" evidence for carcinogenicity in animals expands the number of substances that must be considered as carcinogenic hazards for humans. These two lists add up to the "rock-bottom" number of about 160 substances. How many more carcinogens will be identified is uncertain, and what is known about the tested chemicals may be overshadowed by what is unknown both about untested chemicals and about complex human exposures and behaviors that are not amenable to laboratory testing.

## EXTRAPOLATION FROM TEST RESULTS TO ESTIMATES OF HUMAN CANCER INCIDENCE

Extrapolation techniques are used to estimate the probability of human cancer from study-derived data. Extrapolation can be divided into two parts. "Biologic extrapolation" involves the use of scaling factors to make adjustments between biologic effects in small, short-lived laboratory animals and in humans. "Numeric extrapolation" models are used to estimate the probability of cancer at doses below those administered to animals in a test and to estimate cancer incidence at exposure levels other than those measured in epidemiologic studies.

Some extrapolation models assume a "threshold" dose, a nonzero dose below which exposures are "safe" and not associated with risk. Individual thresholds may exist, because not all individuals exposed to similar levels of carcinogens develop cancer, but such differences in sensitivity may also be explained by differences in luck rather than in biology. However, it is generally accepted that a population threshold which would define a "risk-free" dose for a group of people composed of diverse individuals, if it exists, cannot now be demonstrated. Federal agencies do not accept the idea of thresholds in making decisions about carcinogenic risks.

Numeric extrapolation models differ in the incidence of cancer that they predict from a given exposure. Extrapolation models which assume that incidence at low-exposure levels is directly proportional to dose generally estimate higher incidence. Such "linear" models are "conservative" in that, if they err, they overestimate the amount of disease to be expected. All governmental agencies that use extrapolation employ linear models for predicting cancer incidence. Other models project risks that decrease more rapidly than dose, and they are advanced as alternatives to the linear model. The choice of a model is important because, if an acceptable level of risk were decided on, almost any other model would allow higher exposures than do linear models.

Opinions differ about whether and how extrapolation methods should be used in estimating the amount of human cancer that might be caused by exposure to a carcinogen:

- Some individuals object to any use of numeric extrapolation. For them, identification of a substance as a carcinogen is enough to justify efforts to reduce or to eliminate exposure.
- Other people see extrapolation as useful to separate more risky from less risky substances.
- The most extensive use of extrapolation is recommended by people who urge that extrapolation methods be used to estimate quantitatively the amount of human cancer likely to result from exposures. Such estimates are seen as necessary by those who wish to compare quantitatively the risks and benefits from carcinogens.

The disagreements among the groups who hold different opinions about use of extrapolation are vocal and current. A particular problem in quantitative extrapolation arises from the fact that different extrapolation models produce estimates of cancer incidence that differ by factors of 1,000 or more at levels of human exposure. Given such uncertainty, some labor and environmental organizations and many individuals refuse to choose one model or another for estimating the impact of a carcinogen on humans, and oppose the use of quantitative extrapolation. Fewer objections are raised against choosing a model to order carcinogens on the basis of their likelihood of causing cancer. Regardless of which particular model is chosen, it should produce approximately the same relative ranking as any other.

Proponents of quantitative extrapolation argue that careful attention to the available data aids in choosing the correct model and reduces chances for error. Arguments about the applicability of these techniques will continue, especially because efforts to apply cost-benefit analysis to making decisions about carcinogens will require quantitative estimates of cancer incidence.

There are now no convincing data to dictate which extrapolation model is best for estimating human cancer incidence, whether from epidemiologic data or animal data, or even that one model will be consistently better than all others. However, one particular model for estimating human incidence from animal data (linear, no threshold extrapolation and relating animal and humans on the basis of total lifetime exposure divided by body weight) has been reported to estimate human cancer incidence within a factor of 10 to 100 when compared to incidence measured by epidemiologic studies. While this agreement is gratifyingly good, data exist to make these comparisons for fewer than *20* substances.

## STATUTORY AND REGULATORY DEFINITIONS OF “CARCINOGEN”

Regulation of carcinogens has been marked by repeated arguments about the amount and kind of evidence necessary to make decisions to regulate substances as carcinogens. Several Federal documents describe the types of tests agencies will consider and the criteria they will apply to make such decisions. Statements of regulatory agency policy are found in EPA’s Interim Guideline for Carcinogenic Risk Assessment, EPA’s air carcinogen policy statement, OSHA’s generic cancer policy, and the Regulatory Council’s policy statement, which drew heavily on recommendations of the Interagency Regulatory Liaison Group (IRLG). IRLG now coordinates Federal regulatory agency discussion about identifying and characterizing toxic substances, including carcinogens.

All Federal agencies accept positive epidemiologic studies as strong evidence for carcinogenicity, and a positive bioassay result in a single species as evidence that the substance is a potential human carcinogen. All relegate short-term tests to a supporting role. Trade associa-

tions, such as the American Industrial Health Council (AIHC), fault the regulatory agency policies. AIHC insists that positive bioassays in two different species should be required to define a carcinogen.

The importance of the dispute about whether a positive test in only one of two test species or positive tests in both species is necessary to reach a conclusion about potential human carcinogenicity is illustrated by an analysis of NCI bioassay data. Of 190 chemicals tested, 98 were judged positive in either one or two species. While 44 were positive in both species, 54 were positive in either the rat or the mouse, but not both. Although different analytical techniques can reduce the number of discrepant results, there is now no resolution to the arguments raised by one positive result in a two-species test. The agencies take the position that public health considerations require that results from the more sensitive animal be taken as indicating the substance is a potential human carcinogen, and others disagree.

An epidemiologic study that is not positive demonstrates that no excess cancer was detected in that study. Clearly a study that examines large numbers of people over a long period of time is more likely to detect carcinogenic risks than a smaller, shorter study. In general, epidemiology cannot detect risks at the level predicted from animal tests, and agencies specify stringent requirements under which they would weigh negative epidemiologic data against positive animal data. Judicial decisions have supported the prominent role given to "positive" animal tests.

AIHC urges that all epidemiologic evidence be considered because of uncertainties in extrapolating from animals to humans, and because human response may differ from that of test animals. Furthermore, AIHC sees epidemiologic studies as useful for putting a limit on the amount of risk associated with a substance.

## FEDERAL GOVERNMENT DECISIONMAKING ABOUT CARCINOGENICITY

Scientists in each regulatory agency review study designs and results to decide for their own agency whether or not a substance is a carcinogen and, in some cases, to estimate the number of cancers it may cause.

Suggestions have been made by the various groups to change the process used in deciding whether or not a substance is a potential human carcinogen for regulatory purposes. The suggestions propose that a single panel of scientists evaluate study results for all Government agencies. A panel, depending on the. particular proposal, might be composed of Federal scientists, non-Federal scientists, or both. The panel would report its finding to all regulatory agencies. These proposals separate the "scientific" decisions about the toxicity of the substance and its possible impact on humans from the "policy" decision about how to reduce risks it may pose to humans. Policy actions to be taken on the results of the scientific decision would remain the responsibility of the regulatory agencies.

Proponents claim a panel would improve the efficiency of the regulatory process. It would make technical decisions for all the agencies, rather than each agency making its own, Secondly, a time limit could be imposed on panel deliberations to ensure that its work is completed quickly. Finally, under some proposals, a regulatory agency would initiate the panel review of data about a suspect substance, and therefore the review could take place when it best fits the agency schedule.

Public interest, labor, environmental organizations, and Federal regulatory agencies oppose

these suggestions. They see the regulatory agencies as the appropriate and lawful locations for making decisions about risk. In general, they see a science panel as another layer of bureaucracy that might hinder regulatory activities, and worry that a single panel might be more sensitive to pressure from interested parties. Furthermore, they see the division between "science" and "policy" in decisions about cancer as illusionary. They argue that such a panel might have the power to delay decisions by imposing a higher standard of proof that a substance is a carcinogen than is required by law. This, they say, would stymie preventive "precautionary" governmental action that they view as necessary to protect lives and health when certainty cannot be achieved.

The number of proposals for risk-determination panels almost guarantees that the panels will remain an issue in Federal policy about carcinogens. Establishment of such a panel would represent a significant change in how the Federal Government makes decisions about health risks and would probably require specific legislation. In November 1980, Congress provided $0.5 million to the Food and Drug Administration (FDA) to place a contract to investigate the feasibility of a panel. The report from the study is expected by the end of 1982.

## REGULATED CARCINOGENS

Approximately 96 substances have been regulated as carcinogens or suspect carcinogens, and an additional 49 toxic chemicals which have been identified as carcinogens by EPA are required to be considered for regulation under the 1977 Clean Water Act Amendments. When overlaps between the list of already regulated substances and those required for regulation are taken into account, there is a total of approximately 102 substances. Fifty-seven of those substances are regulated under more than one law. This is expected because exposures to a carcinogen may occur in air, in water, from solid waste on land, and in the workplace so a carcinogen may be regulated under several statutes. Twenty-one of the substances that are regulated under a single law are FDA-regulated components of food.

## COLLECTION AND COORDINATION OF EXPOSURE AND HEALTH DATA

Congress has enacted several pieces of legislation that require Federal agencies to control carcinogenic chemicals. OSHA is responsible for the occupational setting; CPSC, consumer products; FDA, some food, drugs, and cosmetics; EPA, the "environment" (air, water, and soil); and the Department of Agriculture, food. In order to meet their responsibilities, agencies must collect information and assess risks.

Data about exposure histories and health status are useful in assessing associations between the environment and cancer. Both types of information are collected by Federal agencies but often in separate data systems in different agencies. Because of privacy and confidentiality restrictions, these records can seldom be brought together to "link" information pertaining to an individual. In general, these records either cannot be made available to researchers or can be made available only without personal identifiers, which makes linkage impossible. Efforts to ease these restrictions are being pursued.

Federal, State, and local groups collect environmental data for a multitude of reasons, and individual programs periodically review their monitoring capabilities and directions. However, there is no federally coordinated focus to review the quality and quantity of data that are collected. Thus, there is no assurance that adequate exposure data are collected for identifying and estimating carcinogenic risks.

The Toxic Substances Control Act (TSCA) of 1976 was designed to strengthen the ability of the Federal Government to accumulate information on potentially hazardous substances and to protect the public from their risks. TSCA required establishment of new programs at EPA, and, not unexpectedly, there have been difficulties. A 1980 General Accounting Office (GAO) review concluded that EPA's "disappointing" progress in implementing TSCA was partly because of too few staff members and recruitment problems.

TSCA's authority for acquiring information to assess carcinogenic risks differs, depending on whether chemicals are "new" or "existing" in commerce. Companies must notify EPA in a "remanufacture notice" (PMN) of their intention to manufacture or import a new substance at least 90 days in advance. Based upon information submitted by industry, EPA then decides if the new substance "may present an unreasonable risk" to health or the environment. If EPA concludes such a risk may exist, it can require additional information before allowing manufacture.

EPA has been hampered in evaluating PMNs because more than *60* percent of the first 199 PMNs contained no toxicity data. EPA has had to rely on molecular-structure analysis and, when available, short-term test results to make premanufacture decisions. EPA has twice asked for additional information that was not included on the PMN, and each time the company decided not to generate the data and not to manufacture. To improve the availability of data, EPA is considering following the lead of the Organization for Economic Cooperation and Development and requiring submission of a base set of data including short-term test results before it will permit manufacture. However, requiring testing of chemicals simply because they are "new" is not now possible, and TSCA would have to be amended to permit it.

If EPA does not take regulatory action on a PMN, the substance maybe produced and used as desired. However, it does not mean that the substance is safe or approved. Once production of the chemical is initiated, it is no longer classified as new, and EPA can require testing under the provisions for existing chemicals. EPA can also issue a "significant new use rule" (SNUR) for a new chemical when there is concern that specific uses of the chemical, other than those specified in the PMN, might pose a risk. An SNUR requires that EPA be notified before the substance is used in a manner covered by the SNUR. To date, one SNUR has been proposed, and EPA is considering SNURs on more than *40* chemicals for which PMNs were received.

One of TSCA's first activities related to existing chemicals was the compilation of an inventory of chemical substances manufactured in the United States. The initial inventory, published 18 months late in June 1979 and updated in July 1980, lists about 55,000 chemicals. EPA can, by rule, require industry testing of potentially harmful chemicals present in commerce if the available information, while insufficient for an evaluation of risk, supports the finding that the chemicals "may present an unreasonable risk" or may result in substantial or significant exposure. Screening all chemicals in commerce to choose those few most needing testing is a large task, and TSCA established the Interagency Testing Committee (ITC) to make recommendations about which chemicals should be tested. ITC has recommended about 50 chemicals to EPA, but EPA has been unsuccessful in meeting deadlines for ordering tests to be done. EPA was sued by the Natural Resources Defense Council because it failed to meet TSCA-specified deadlines, and it is now developing test rules under a schedule that was produced in response to a court order.

A *1980* GAO report estimated that the initiation of a rule to require testing can take as long as 5 years, and up to 54 months is then allowed to complete a chronic bioassay for carcinogenicity. Hence, 9 years or more may elapse before information about a chemical's potential carcinogenicity is available under the testing provisions of TSCA.

Environmental groups are critical of EPA's slow progress in test-rule development and argue that EPA could move more quickly. In particular, they cite EPA's exhaustive review of the literature about a substance as being unnecessarily thorough for test-rule development. EPA

cites problems that it anticipates if its literature reviews are not so complete, as well as problems it has faced in establishing the new program, as reasons for its slow progress. From the other side, industry objects to some EPA procedures, including the agency's intention to require testing of some chemicals as representative of "chemical categories." Industry suggests that identifying members of a category as carcinogens will falsely prejudice attitudes towards other members of that category. EPA counters that testing certain representative members of categories will be more efficient than testing chemicals on a one-by-one basis and that the public is better served by testing the wider range of chemicals that can be accomplished under a category approach. EPA's first proposed test rule specified testing of 5 chemicals from a category that included 11 chemicals.

## LAWS THAT PROVIDE FOR THE REGULATION OF CARCINOGENIC RISKS

Reflecting public concern about cancer, Congress has enacted laws to regulate exposures to carcinogens in order to protect public health. The laws were written at different times by different Congresses and are directed at controlling exposures from different sources. Not unexpectedly, the laws differ in the amount and type of evidence they require, and some do and some do not require that benefits of the carcinogen be balanced against its risks in making decisions about regulation. "Zero-risk" laws, such as the Delaney clause of the Food, Drug, and Cosmetic Act, and the Resource Conservation and Recovery Act, direct regulatory agencies to eliminate risks without consideration of other factors. Because the Federal Government does not accept a threshold level for carcinogens, a strict interpretation of these laws would require that risk be entirely eliminated. Proponents of these laws point to the limited benefits associated with food additives or pollutants escaping from dumps and argue for allowing no risk from such exposures. The opponents suggest that consumers might choose an additive in spite of its risks and that reducing low-level risks from dumps may cost too much.

The "technology-based" laws, such as the Clean Water Act, direct EPA to impose specific levels of control, considering technical and economic feasibility. The Clean Air Act and the Occupational Safety and Health Act are also largely technology based. In practice, regulations from these laws direct that pollutants or exposures be controlled by installation of specified control devices.

The "balancing" laws, the Federal Insecticide, Fungicide, and Rodenticide Act, TSCA, and the Consumer Product Safety Act direct agencies to consider other factors in addition to health risk in promulgating regulations. For instance, TSCA directs EPA to control "unreasonable risks" and gives the agency some leeway in deciding what to regulate and how stringently to regulate.

An example of the complexity of the laws and of regulations based on them is provided by the Clean Air Act. The section of the Act providing for the regulation of airborne toxic substances from stationary sources was written as "zero-risk." However, EPA's proposed airborne carcinogen policy concluded that such stringent control was not always feasible because elimination of exposure to some carcinogens might cause too much economic disruption. EPA has proposed that it will first apply a technology-based standard for control and then, if necessary, balance risks and other factors in making a decision about whether any residual risk is "unreasonable" and requires further regulation. The "unreasonable-risk' decision is analogous to EPA requirements under TSCA. The Clean Air Act, then, was written as zero-risk, but regulations from it are first technology based and then balancing.

Congress, reflecting; the difficulties inherent in regulating when risks and benefits are uncertain and difficult to quantify, delegated to the agencies the task of operationally defining certain key balancing terms. Words in the laws, for instance, those requiring EPA to regulate "unreasonable risks" under TSCA, were purposefully left undefined. The agencies and the courts, by their decisions, are now defining those terms.

Some regulatory agency lawyers have been asked about the ability of the agencies to work within the confines of the present laws. They expressed confidence that the agencies can administer the balancing laws (such as TSCA) and apparently appreciate the flexibility of the laws as they are now written.

Other observers are of the opinion that greater attention to the balancing terms in the law would improve the regulatory processes. To some extent, defining a balance may mean accepting a specified risk, and Congress, composed of elected representatives, is most often seen as the body to decide on such a level. Congress already avails itself of opportunities during oversight and reauthorization hearings to question agencies and other organizations about difficulties in implementing the laws. Continuation of these activities may be sufficient to satisfy Congress that the language of the laws does or does not present a problem that can be rectified by congressional action.

## BALANCING RISKS, COSTS, AND BENEFITS IN DECISIONS ABOUT REGULATING CARCINOGENS

Beyond the technical level of deciding whether or not a substance is a carcinogen and estimating the amount of human cancer it may cause is any decision that requires weighing risks against the benefits of its continued use. The decision is complicated by equity considerations. The people who most directly bear risks from exposures to carcinogens are not necessarily the people who most directly benefit from the activities that produce the risk. Depending on conditions, either the risks or the benefits may be accorded greater quantitative importance. Numerous surveys show that society wants protection from health risks and is willing to pay for it. At the same time, economic and other considerations cause society to attempt to spend no more than is necessary. Uncertainties attached to estimates of health risks and economic benefits complicate regulatory decisionmaking. Improvements in cancer risk identification and measurement will reduce the uncertainty, but balancing health risks against costs of control and the benefits of the regulated substance will remain a difficult value judgment.

## REGULATORY REFORM

Concern about increasing regulatory costs and burdens in recent years has produced a push for changes in regulatory decisionmaking. Charges of overregulation or untimely regulation have been leveled at many programs, including those that regulate exposures to carcinogens.

Current procedural reform proposals include:

. more emphasis on regulatory benefit-cost analysis;
- more systematic regulatory review;
- more flexibility in rulemaking;
- appointment of additional administrative law judges and greater involvement of the Administrative Conference; and
- providing financial assistance to public intervenors who are seen to be at a disadvantage when opposed by resources of industry or agencies.

Each of these proposals is directed at improving regulatory decisionmaking, but not all

would have the same effect. Increased emphasis on benefit-cost analysis will impose an additional hurdle for proposed regulations and reduce the number and the cost of regulations. Opponents of this proposal cite problems with the quantification of costs and benefits and its ignoring of equity considerations. They object to it as another barrier against regulations that they see as necessary to protect health and environment.

Systematic regulatory review, whether by the President, Congress, or courts, is also designed to reduce the number and cost of regulations. Opponents again object to the imposition of an additional hurdle to the promulgation of what they see as desirable regulations. Additionally, they see the review as stripping the agencies of some of the authority delegated to them by Congress and putting technical decisions into organizations which lack the necessary experience and knowledge to deal with them.

More flexibility in rulemaking would alter agency regulatory proceedings. The first stage of proceedings might be conducted as an informal hearing, without employing trial-type procedures. The right of cross-examination and use of the full adversary process would be reserved only for those issues which warranted further proceedings, as determined by the presiding hearing officer. Such increased flexibility might significantly expedite the entire administrative decisionmaking process.

Appointment of more administrative law judges and greater involvement of the Administrative Conference in reviewing judicial performance is intended to make the current regulatory process more responsive. Systematic regulatory review by the courts might increase the need for administrative law judges.

Public interveners from consumer, environmental, or other groups often have interest in regulations. They are sometimes hampered in their efforts to participate in regulatory hearings because of lack of finances. Providing such groups with financial assistance would allow them to be heard. This proposal is opposed by those who believe public financing should not be provided to private "public interest" groups.

The regulatory reform proposals reach to the heart of the Federal Government's role in protecting the health and the economic interests of the public, both as a whole, and as composed of diverse groups, such as labor and industry. The decision that its current activities are appropriate and sufficient or that they should be curtailed or expanded will involve profound and basic social, political, and equity considerations. Cancer may be the focus for such debates about health regulation. Its toll in death and suffering is large, it is widely feared, efforts to gain knowledge of its causes often depend on measures with wide margins of error, and payoffs from reduced exposures may be years or even decades away. The debate will involve more than technical issues.

## OPTIONS

Options for improving technologies for determining cancer risks from the environment are divided into four groups. The first group (options 1 through 4) is concerned with gathering information about the occurrence and distribution of cancer in the population and carcinogenic risks in the environment. The second group (options 5 through 7) is related to testing substances for carcinogenicity. Options 8 through 10 relate to TSCA and its implementation. The final option is concerned with possible changes in the process used by regulatory agencies in making technical decisions about carcinogens.

Methods for obtaining better information about the occurrence, distribution, and outcome of cancer.

These four options are discussed separately and can be considered for implementation separately. Adoption of any or all of the options would improve the quality and quantity of data available to draw conclusions about the occur-

rence and distribution of cancer. This information would allow more precise estimates to be made about the incidence of cancer and therefore allow accurate monitoring of cancer trends. Results from the specific studies in option 3 might clarify many questions about relationships between particular exposures and behaviors and cancer. They would be immediately useful for prevention programs.

### OPTION 1

Expand the operation of NCI's SEER program to collect cancer incidence and survival data representative of the entire country and design programs to assess validity of collected data.

The SEER program, which started in 1973, is the first continuous cancer incidence reporting program in the United States and provides an approximation of cancer incidence and survival rates for the country as a whole. The SEER program has been and should continue to be a useful source of identified cancer cases which greatly facilitates studies about the disease. Detailed diagnostic information is available on each case recorded by the SEER program, and patients, family members, and friends can be queried to learn more about exposures, behaviors, and occurrence of cancer.

SEER program data are collected from about 10 percent of the total population, but the geographical regions covered by the SEER program do not closely represent the demographic makeup of the entire country. A slightly expanded SEER program could encompass more of the country and be constructed so as to collect data representative of the entire population. Expanded coverage would generate data for a more careful and detailed examination of cancer rates over time than what is now possible. An important component of an expanded SEER program could be rigorous examination of the validity of the collected data. For instance, the accuracy of diagnoses and transfer of the diagnosis information to the SEER program data could be monitored to reduce uncertainties about data. Such attention to data reliability would make conclusions drawn from the data more convincing and accepted.

The current SEER program costs about $10 million annually out of the total NCI budget of about $1 billion. Expanding the program would cost more money and would also require cooperation of additional local medical organizations to establish new SEER data collection areas. Balanced against these costs are opportunities to gather incidence and survival data representative of the whole country and to learn more about cancer in the U.S. population.

### OPTION 2

**Establish a National Cancer Registry (NCR) to record all new cases of cancer** in the United States.

An NCR would provide the most comprehensive data possible on cancer incidence in this country. With a national registry, cancer would become a reportable disease, as are some infectious diseases. This data base would be useful for trend analysis and for identifying cancer cases for epidemiologic study. The NCR would record the date on which cancer was diagnosed and could be used in conjunction with the National Death Index to generate information about survival.

An NCR would collect less detailed information on each case than is now collected by the SEER program, but would record on the order of ten times more cases. Establishing an NCR would not reduce the need for the SEER program, but rather would add to the cancer incidence data base.

About 30 States presently have enacted regulations or laws requiring that cancer cases be reported to a central authority, but most of those States have not yet initiated programs to implement the laws. Establishment of an NCR which would invite States to participate might provide incentive for States to implement their own programs. At the Federal level, the Centers for Disease Control, or another appropriate organization, might serve as the agency for receiving, storing, and disseminating registry data.

The establishment of a well-structured NCR might become a seed project for a comprehensive registry for many chronic diseases of national importance. The interrelationships and

multifactorial nature of chronic diseases make this a worthwhile step towards the goal of understanding major public health problems.

As a new venture, NCR would require much money and, perhaps, a long time before it became useful for truly national studies. However, it would be immediately useful in identifying cancer cases for study. The percentage of cases reported to it, if the experience of other registries is an accurate indication, would increase with time. This increase might produce an artifactual "cancer epidemic" as better reporting showed an increase in cases regardless of actual trends, but such a development can be anticipa ted.

### OPTION 3

Encourage epidemiologic studies to answer specific questions. Three such studies might be:

- study of workplace-related cancers;
- study of cancer and dietary habits; **and**
- study of respiratory cancer.

Study of Workplace-Related Cancers. —There is a controversy over the amount of cancer associated with occupational exposures. Many currently available study results lend themselves to various interpretations. Additional studies might help resolve the existing controversies and, more importantly, might pinpoint opportunities for regulatory and voluntary reduction in exposures. The National Institute of Occupational Safety and Health now conducts workplace carcinogenicity studies and continuing its support is one mechanism to obtain more information.

Cohort studies identify and follow healthy people with a common characteristic or exposure to look for associations with subsequent cancer occurrence. Such studies could be initiated to examine the cancer risk posed by occupational exposures to chemicals now identified as carcinogens in laboratory tests or suspect for other reasons. Priority consideration might be given to those chemicals perceived to have a higher degree of risk, to which many people are exposed, and for which means of control exist.

Study of cancer incidence and mortality at body sites known or thought to be associated with occupational exposures could be examined in case-control studies, which compare exposures and behavioral histories of people afflicted with cancer (cases) with those of unafflicted persons (controls). Lung cancer is the most common occupationally related cancer. Other types, including nasopharyngeal carcinoma, melanoma, bladder and brain cancers are worthy of study, because of past associations with occupational factors, but no site is free of suspected occupational associations.

The availability of exposure data is a particularly acute problem to be addressed in designing any occupational study. Monitoring in the workplace is now required only for a few chemicals already regulated by OSHA, and although some companies monitor levels of suspect substances, no information is routinely available for many other chemicals. However, OSHA now requires that a company retain ail exposure records that it collects and any collected data can be made available for study. For cohort studies, it may be necessary to initiate and continue monitoring for many years before results are obtainable. Results from such studies are considered very powerful.

Studies of Cancer and Dietary Habits.—Diet is generally considered an important factor in cancer causation, but few specifics are known. Long-term cohort studies could be designed to investigate relationships between dietary variables and cancer. For example, different ethnic populations with distinct eating habits could be followed and their cancer incidence ascertained over the years. Such studies are expensive and time-consuming, but they may provide otherwise unobtainable information about risk factors and protective agents in food.

Large-scale case-control studies also could investigate hypotheses relating diet and particular cancer sites. Congress mandated one such study to investigate whether or not nonnutritive sweeteners cause human bladder cancer. The study involved questioning of 3,000 persons with bladder cancer (cases) and 6,000 others without bladder cancer (controls). The study

showed "that past artificial sweetener use has had a minimal effect, if any, on bladder cancer rates." The same study was used to investigate possible links between water quality and bladder cancer. Results from that part of the study are expected to be published in *1981.* Case-control studies might also associate particular diets with reduced cancer risks which would provide information immediately useful for prevention.

The long latent period between exposures associated with cancer and manifestation of the disease makes associations between them difficult to determine. One possible way to improve this situation, especially for diet-related cancer research, might be to establish a Biological Samples Bank. Such a bank would store samples of urine, hair, blood, feces, and perhaps tissues, as well as answers to questions about diet, recreation, and work from as many as a quarter-million people. An additional activity of the bank would be to obtain a copy of the death certificate for each person represented in the bank. The certificate would be included in the individual record. The data could be stored on microfiche, and the biological samples would be stored under the best possible conditions. No additional processing of the sample and data would be undertaken by the bank, but they would be held until requested by researchers. A researcher investigating a particular illness or cause of death could request questionnaire data and biological samples collected from people who became sick with or who died from that disease. The same information and samples obtained from people who were not afflicted would provide control data.

The Biological Samples Bank would have some of the advantages of large-scale cohort studies but at lower cost. Money would not be expended in following individuals for long periods of time or in carrying out analyses that would not be utilized, and a charge levied for each sample provided to a researcher would offset some of the costs of the program. The bank would allow both Government and non-Government scientists to test hypotheses in a wide range of areas. The program would be far larger than anything like it ever attempted, and its management would have to be carefully planned or access to samples might be so cumbersome that the bank would be unusable.

**Studies of Respiratory Cancer.—Cancers of the respiratory tract, breast, and** colon account for the majority of cancer cases and deaths. Studies which could relate exposures and behaviors with cancer at these sites might produce important information for prevention. In particular, a large case-control study of respiratory cancer would answer several important questions. A sufficiently large study should include on the order of 10,000 cases, about one-tenth of 1 year's total respiratory cancers, and ideally, twice that number of controls. Each case and control would be interviewed to determine smoking habits, place of residence, types of jobs, and eating habits. Case finding and selection of controls could be carried out in a fashion similar to the congressionally mandated study of the effects of nonnutritive sweeteners, which focused on bladder cancer.

This size study should be sensitive enough to detect all numerically important influences in respiratory cancer causation. The major goals of the study, which could be completed in 2 or 3 years, would be to:

- generate an estimate of the contribution of occupational factors and cigarette smoking to respiratory cancer;
- identify hitherto unrecognized occupational respiratory tract carcinogens;
- determine more accurately the effects of "passive smoking" on nonsmoking spouses and children;
- generate a direct estimate of respiratory cancer onset rates in those not exposed to tobacco, either through smoking or passive smoking; and
- obtain direct evidence about different types of cigarettes, including the various low-tar brands, on carcinogenesis.

### OPTION *4*

**Consider for implementation the reccommendations made by congressionally mandated commissions and studies for** the improvement of Federal environmental health data collection activities.

Congressional and executive branch concern about the adequacy of environmental health data has resulted in the establishment of several advisory groups and studies. Although relatively new, they have already made numerous recommendations for improving Federal environmental health data collection and management. In particular, consideration might be given to recent recommendations made by the Task Force on Environmental Cancer and Heart and Lung Disease and in the NCHS report, *Environmental Health.*

The Task Force recommended:

1. Additional research on methodology to achieve less expensive study design and to improve the collection and evaluation of scientific data.
2. Research on the relative contribution to disease made by substances in air, water, and soil, in order to quantify the toxicological effects and the risks to human health, and to develop strategies for control.
3. Support for environmental and occupational health education and development of career opportunities in primary, secondary, and vocational schools, and better coordination of these activities.

NCHS suggested:

1. Several recommendation.~ concerned with developing interagency data systems and other data-linkage activities to improve epidemiologic study capacity.
2. Procedures and legislation to facilitate the sharing of data among Federal agencies while safeguarding the rights of all individuals.
3. Establishing a mechanism for evaluating priorities in Federal environmental health activities.

Additional recommendations for improved data collection are contained in a report of the Institute of Medicine to DHHS. This planning document on the *Costs of Environment-Related Health Effects* will serve to guide DHHS in its ongoing study mandated by the Health Services Research, Health Statistics, and Health Care Technology act of 1978.

Specific comments about the effects of the Privacy Act and the Tax Reform Act of 1976 on epidemiologic research are to be found in the Report of the Work Group on Records and Privacy of the DHEW Interagency Task Force on the Health Effects of Ionizing Radiation. In addition to suggesting changes in those two acts, the Work Group also discussed changes in the medical records law and the advantages of extending the National Death Index back in time to include deaths that occurred before 1979. Although the report was concerned with radiation risks, its recommendations are applicable to cancer epidemiology in general.

One means of centralizing environmental health data collection activities is to establish a center to coordinate the data collection activities of the Federal Government. With representation from various research and regulatory agencies, the center could provide a mechanism for setting national monitoring priorities. The center would also be in an ideal position for directing research to improve technologies for measuring exposure to environmental agents and to reduce information gaps and duplicative efforts.

The congressionally mandated coordination and review efforts have already been productive, and continuing them has the advantage of building on a base of experience. Congress requires periodic reports from them, and through those and its other oversight responsibilities, Congress can monitor the performance of the advisory groups and studies.

Alternatives for fostering development of short-term tests and an option to expand support of NTP.

### OPTION 5

Encourage NTP to pursue the development of tests to replace the long-term carcinogenicity bioassay in **small** mammals.

Improvements in the design and execution of carcinogenicity bioassay in small laboratory animals have been accompanied by increased acceptance of the results as being predictive for human effects. The tests are used worldwide,

scientists continue to discuss and refine them, and in the United States, NTP has improved the management of the Government test program. Despite all this progress, no improvements are expected in two aspects of the tests: they are expensive (up to $1.0 million for each substance tested) and they require a great length of time (from 3 to 5 years).

In its first annual plan (1979), NTP identified the development and validation of less expensive, quicker tests as a priority goal. NTP has outlined a testing scheme involving both short-term and long-term tests and is working to decide which short-term tests work best for identifying a number of toxics, including carcinogens. The attention paid to short-term tests by NTP promises that progress will be made. The concentration of DHHS toxicological expertise in NTP and the development of NTP's working relationships with agencies outside DHHS assure that the program can call on the appropriate people in pursuing the goal of new tests.

Congress might encourage short-term test development and validation in its oversight activities, and it might consider additional funding for the programs. There is currently a great deal of interest in the short-term tests and additional congressional support might have a profound effect on their development.

A potential disadvantage of relying on NTP for guiding and directing this research and development effort is that NTP has many other responsibilities. As discussed in this assessment and in option 7 below, NTP also is responsible for the management of large animal test programs. As a part of a multipurpose program, short-term test development has to compete for resources with other parts of the NTP. If it were decided that short-term tests are sufficiently important to be set apart from other NTP activities, the following option might be considered.

### OPTION 6

**Establish a commission to advise the Federal Government about optimal methods for development of short-term tests.**

A commission, composed of experts from academe, industry, public interest groups, and Government agencies could be established to make recommendations about short-term tests. This would have the advantage of concentrating the talents of diverse people on test development and bringing increased attention to the tests.

The existence of a commission would probably result in short-term tests being given higher priority in NTP. The exact tasks of the commission would be decided by NTP and other parties with interest in the tests. However, one task might be the serious consideration of which, if any, tests offer promise as substitutes for long-term animal carcinogenicity bioassays when making regulatory decisions. The establishment of criteria that a single test or a combination of tests would have to meet to be considered for regulatory decisionmaking would be a spur and a guide to test development. The possible disadvantage of a commission is that it may provide nothing different from what NTP (as in the previous option) might provide.

The commission could focus attention on the tests, the most likely ways for their employment and what criteria they must meet. Adoption of this option would reinforce the conclusions already reached by many experts that the short-term tests show great promise. In a major way, the commission might answer the question "promising for what?"

### OPTION 7

Expand support of the National Toxicology Program.

NTP has made a promising start at managing DHHS' short-term testing and animal toxicology. Programs. As mentioned above, it has identified the desirability of obtaining alternatives to the current carcinogenicity bioassay, and whether the direction of that effort remains within NTP (option 5) or is shared with a commission (option 6), NTP personnel will continue to be involved in test development. In addition to short-term test research, NTP administers the largest animal test program for carcinogenicity. Those expensive and time-consuming tests are used for two general purposes: to test substances that are of interest to regulatory agencies and to provide information useful in developing and validating possible new tests.

NTP has been successful in organizing expert advice for its programs. It has assembled a board of non-Government scientists to advise the overall program, a panel of regulatory agency representatives to aid in selecting chemicals for animal carcinogencity bioassay, and, most recently, a panel of nongovernmental experts to review the results of animal tests for carcinogenicity. Each of these efforts increases the sources of advice for NTP, and assures NTP higher visibility.

Arguments for encouraging and expanding NTP center on its promising start, its attention to immediate testing needs through the bioassay program, and from the possibility of future payoffs from new test development. Its establishment of advisory committees of Government and private sector representatives helps assure that it will remain responsive to national needs. A possible disadvantage of NTP is that its wide purview and efforts both to develop test methods and to serve the needs of the regulatory agencies may stretch it too thin. Continued congressional interest and oversight can help avoid this possibility.

Options concerned with EPA's implementation of TSCA:

The following three options discuss collection of sufficient information to protect the public from unreasonable risks, as required by TSCA. The first option is to provide additional support to EPA, The second and third options consider changes in TSCA.

### OPTION 8

Increase the resources available to EPA to enable it to assess more effectively potential risks from substances before they are introduced into commerce and from substances already present in commerce.

One of the most important tools for protecting the public from toxic substances is provided in the sections of TSCA which enable EPA to gather information about substances before they are introduced into commerce. The mechanism for obtaining this information is the PMN which must be submitted to EPA 90 days before a manufacturer or processor can produce or import a substance. EPA must then evaluate the PMN to determine whether or not the submitted information supports a conclusion that the substance "may present an unreasonable risk. " If the decision is made that a substance may present such a risk, EPA can then require submission of additional information before allowing introduction of the substance into commerce.

EPA, which bears responsibility for evaluation of PMNs, is overburdened. EPA estimated that 1,500 people were necessary for the program in fiscal year 1979; 382 permanent positions were authorized; 313 were filled.

A GAO report characterized EPA's progress in implementing TSCA as "disappointing," and drew attention to too few staff members as part of the problem. If more resources are not made available, review of PMNs will likely become less complete, because more are being submitted. EPA estimates that 800 PMNs, almost twice the number in fiscal year 1981, will be submitted in fiscal year 1982.

The premanufacturing review program is designed to screen out risky substances before they enter commerce. Making decisions at that point is more protective of public health, and has the additional advantage of identifying hazards before industry had tied up large amounts of money in manufacture and distribution. Realization of these objectives apparently will require more people as the burden to review PMNs increases at EPA.

Other sections of TSCA specify that EPA can require that industry test substances already present in commerce that "may present an unreasonable risk. " Congress, through TSCA, established the Interagency Testing Committee (ITC) to recommend chemicals for testing, and to date EPA has considered only ITC-recommended substances for testing requirements. Even so, EPA has fallen behind schedule in meeting its requirements to develop test rules.

One criticism leveled at EPA's process of developing a test rule is that it spends more effort than necessary to make the case that a substance "may present an unreasonable risk. " If the criticism is correct, EPA may be able to improve

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its procedures and reduce the time and effort necessary to produce test rules. However, even if that is possible, the same EPA program which is overburdened by the PMN process is also responsible for developing test rules.

A critical problem in implementing TSCA has been understaffing. Additional resources should improve EPA's performance in meeting the requirements of TSCA..

**OPTION** 9

Amend TSCA to require industry to submit to EPA **at** least a minimal amount of information about each new chemical in PMNs.

Implementation of this option would allow EPA to assess more effectively the potential hazards of new chemical substances. It would require manufacturers or processors to provide a "base set" of information including some information about toxicity. Such important information is not required and is often lacking in PMNs that are submitted under the current law. Its inclusion would allow EPA to assess hazards more completely and efficiently. Information requirements could remain flexible to meet varied needs, and EPA might be granted authority to exclude from this requirement those chemical categories not considered to pose a risk.

Requiring industry to generate a base set of information is viewed by some as costly and burdensome. There is also the additional issue of whether the increased costs would retard innovation and keep potentially useful chemicals off the market. However, the system is deemed feasible by other organizations. The Organization for Economic Cooperation and Development, in which the United States participates, has recommended that its member nations adopt a similar system.

OPTION 10

**Amend TSCA to shift from Government to industry the burden of proof for demonstrating that additional testing is unnecessary for existing chemical substances suspected of being toxic.**

EPA is slow in requiring industry to generate toxicity information about chemicals suspected of presenting an unreasonable risk. An amendment to TSCA that shifts much of the burden of proof for demonstrating an "unreasonable risk" from the Federal Government to manufacturers and processors of chemical substances might improve EPA's capability to reach the goals established by TSCA.

To decide about risks associated with pesticides, EPA established the "rebuttable presumption against registration" (RPAR) process which places much of the burden of proof on industry. Under the RPAR process, once a preliminary finding is made that a substance "may present an unreasonable risk" and that available information is insufficient to perform a reasoned evaluation, industry has to produce evidence that the pesticide does not present such a risk or the pesticide is no longer allowed in commerce. TSCA could be amended to permit a similar approach to other substances.

The strength of the RPAR process is that if EPA determines that a pesticide reaches or exceeds specific risk criteria, it is the responsibility of registrants and other interested parties to offer rebuttal evidence within a given time period. A system patterned in concept after RPAR could be incorporated into TSCA to alleviate much of the burden on EPA and speed the process along. The term "concept" is emphasized because the RPAR approach has not so far resulted in an expeditious review of pesticides. Congress may want to examine carefully EPA's current efforts in regard to pesticides and consider the National Academy of Science's recommendations for improving the RPAR process.

A major disadvantage of this option stems from differences between the universe of substances covered under TSCA and the narrower range of substances covered by the Federal Insecticide, Fungicide, and Rodenticide Act. All pesticides are biologically active and, as a class, they are expected to more frequently be toxic than chemicals in general. An RPAR-like process, which requires EPA to develop only a mini-

mal amount of information about hazards posed by substances which are already suspect, may be more appropriate to pesticides than the wide spectrum of substances regulated under TSCA.

An option concerning the mechanism by which technical decisions are made about hazard and risk for regulatory purposes.

OPTION 11

Consider establishment of a central panel for making technical decisions for regulatory purposes.

A number of organizations, including the Office of Science and Technology Policy, the American Industrial Health Council (a trade association), and some members of Congress have proposed the establishment of a panel either to make decisions about carcinogenicity for all regulatory agencies or to review all contested decisions. Consumer, environmental, and labor groups, and the Federal regulatory agencies oppose these suggestions and favor that the regulatory agencies continue to make their own decisions about which substances pose risks. The arguments advanced pro and con about the panel are discussed above and in other parts of the assessment. In brief, proponents hold that scientific decisions about toxicity and risk can be made separately from policy decisions about regulation and find merit in a single panel making scientific decisions for all agencies. The opponents see the division between science and policy as illusionary when making decisions about cancer and see each agency as capable of making its own technical decisions. Furthermore, they view a panel as a layer of unnecessary bureaucracy.

Congress is aware of this controversy and has mandated a study of the feasibility of a panel. The study is to be completed in June 1982, and should produce a great deal of information about the pros and cons of a panel. Congress could require that the study investigate past controversial decisions to see if scientific errors would have been prevented by a science panel.

The objectives of the congressionally mandated study are to:

- assess the merits of an institutional separation of the scientific functions of developing objective risk assessment from the regulatory process of making public and social policy decisions;
- consider the feasibility of unifying risk assessment functions;
- consider the feasibility of developing coherent risk assessment guidelines for use by all regulatory agencies with decisionmaking responsibility; and
- address relevant procedural and institutional issues that may arise in the interaction between the suggested programs of risk assessment and the regulatory process.

In addition to those important subjects, an examination of controversial decisions to determine if scientific or technical mistakes have been made in the past would shed light on the necessity for such a panel.

It may be that Congress is satisfied that hearings and expert opinions have already produced sufficient information to consider the merits of a central technical panel before this study is completed. If a panel were established, it would initiate a new system that will be seen as a turn away from the procedures of the past. In some people's view, those procedures have produced unnecessary regulations, and a panel would be seen as a mechanism to improve regulatory decisionmaking and, perhaps, reduce the regulatory burden. Others would see the panel as a further obstacle in the path of producing regulations to protect the public health.