

Chapter 1

Introduction and Summary

CONTENTS

	<i>Page</i>
Introduction	3
Summary \$	4
Agency Policies	4
Required Animal Testing.	5
Guidelines for Testing Protocols	5
Risk Assessment Policies	6
Carcinogen Assessment Policies	7
Federal Assessment and Regulation of Carcinogens	9
Type of Evidence: Human or Animal Data	15
The National Toxicology Program (NTP)	16
Regulatory Responses to NCI/NTP Test Results and the Annual <i>Report</i>	18
Future Improvements	22

Figures

<i>Figure No.</i>	<i>Page</i>
I-1. Elements of Risk Assessment and Risk Management.	8
I-2. Agency Actions <i>on Annual Report</i> and Positive NCI/NTP Chemicals	20

Introduction and Summary

INTRODUCTION

Over the years, laws have been enacted to protect the health of Americans, with particular emphasis on protection against cancer. By and large, these laws provide for reducing or eliminating exposures to external chemical carcinogens with which people come into contact—in the food supply; in drinking water; in pharmaceutical drugs and other consumer products; in work environments; in ambient air, water, and soil. Most cases of cancer, however, are not caused by these types of carcinogenic exposures.

Instead, according to the best interpretation of the evidence currently available, most result from “lifestyle” factors, of which the details are only slowly becoming clear. One—tobacco smoking—stands out the clearest of all, and alone is the cause of more than one-third of all deaths from cancer each year in the United States. The more poorly defined lifestyle factors include such items as overall dietary balance and aspects of sexual behavior; others, slightly better defined, include exposure to sunlight (see OTA 1981 for a fuller discussion of causes of cancer). In addition to lifestyle factors, viruses are potentially great, but currently unquantifiable, contributors to the overall cancer burden. Nevertheless, those carcinogenic chemicals that *can* be identified specifically and can be controlled are important for those very reasons: they are avoidable. And often, unlike cigarette smoking, exposure to them is involuntary. Furthermore, the potential for introducing new, potent, carcinogens is very real.

For the laws addressing chemical carcinogens to be effective, there must be means of identifying substances that have caused, or would cause, human beings to get cancer. Once the substances have been identified, regulatory decisions can be made about whether and how to control exposures. Both the process for finding out which substances already in the human environment are causing cancer in the population (through epidemiologic studies) and the process for predicting carcinogenicity in humans *before* people are exposed (by testing in the laboratory and in ex-

perimental animals) are imperfect, and interpretation of the results of such studies is contentious. While efforts to develop improved methods for identifying carcinogens continue, current and past regulatory decisions have, of necessity, embodied many untested and some untestable assumptions.

This OTA background paper responds to a request from the House Committee on Government Operations and its Subcommittee on Intergovernmental Relations and Human Resources to examine Federal activity in testing chemicals for carcinogenicity and the use of test results by regulatory agencies.

In this background paper, OTA addresses the following specific questions:

- What policies for regulating carcinogens have Federal agencies adopted? What guidance do these policies provide about identifying, assessing, and regulating chemical carcinogens? What kind of evidence, human or animal, do the agencies require to identify a chemical qualitatively as carcinogenic? How do the agencies intend to conduct quantitative risk assessments?
- What chemicals have actually been regulated? What evidence provided the basis for these regulations? How long does the regulatory process take?
- How is Federal carcinogenicity testing organized? How are chemicals chosen for such testing? After the chemicals are tested, are the chemicals that test positive regulated? Have agencies regulated the chemicals listed in the Federal Government's *Annual Report on Carcinogens*?

Chapter 2 of this background paper compares the formal Federal policies for identifying and assessing the risks from carcinogenic chemicals. Chapter 3 lists the carcinogenic chemicals that have been regulated by each Federal regulatory agency. Federal agencies with the greatest roles in regulating chemical carcinogens are the Food and Drug Administration (FDA) for foods, cos-

metics, and human and animal drugs; the Occupational Safety and Health Administration (OSHA) for worker exposure in most industries; the Mine Safety and Health Administration (MSHA) for worker exposure in mines; the Consumer Product Safety Commission (CPSC) for consumer products; and the Environmental Protection Agency (EPA). EPA is charged with regulating air pollutants under the Clean Air Act (CAA); water pollutants under Clean Water Act (CWA); drinking water contaminants under the Safe Drinking Water Act (SDWA); pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA); toxic chemicals under the Toxic Substances Control Act (TCSA); and hazardous wastes under the Resource Conservation and Recovery Act (RCRA) and the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA).

Chapter 4 describes the National Toxicology Program (NTP), the home of the Federal testing program, and its carcinogenicity testing. Chapter 5 examines the regulatory responses to positive results from Federal carcinogenicity bioassays and to the chemicals listed in the *Annual Report*

on *Carcinogens*. Appendix A describes the Federal statutes that have been most important in regulating carcinogenic chemicals.

The scope of this background paper is limited to “chemicals” that have been tested, listed, or regulated by the Federal Government for carcinogenicity. The term “chemical” is used broadly here to encompass substances, mixtures, groups of substances, and exposures. This background paper does not examine the regulation of radiation sources licensed by the Nuclear Regulatory Commission, electronic radiation (including, for example, x-ray machines, which are regulated by FDA), ultraviolet radiation, alcohol, and tobacco. Depending on statutory mandate, Federal regulatory decisions can be based on such factors as control technologies and costs, in addition to risks. Agency procedures for developing information on these factors will not be discussed in this background paper. Moreover, while very important, other related efforts not covered here are those of industry and the private sector to test chemicals for carcinogenicity and implement voluntary controls to reduce exposures to carcinogens.

SUMMARY

Agency Policies

Over the last decade, several Federal agencies have issued guidelines and policies detailing how they intend to identify, evaluate, and regulate carcinogens. These guidelines encompass the design of animal carcinogenicity bioassays, the interpretation of data from human and animal studies, and the assumptions that should or will be made when assessing human risk from such studies.

The assumptions in these documents represent scientific views and policy judgments about carcinogen assessment. Some assumptions are made because, though appropriate data might be obtained with current techniques, the data are simply not available in a particular case. Other more general assumptions take the place of experimental evidence that may be developed with further research. Finally, some assumptions are employed because of ethical considerations and the inher-

ent limits of experimental methods. The use of assumptions, the frequent absence of data, the potential economic implications of government regulation, and underlying political disputes about the desirability of regulation, combine to make the assessment of carcinogenicity and the development of corresponding regulations subjects of intense debates.

It is now common to distinguish between risk assessment and risk management: risk assessment characterizes the adverse health effects of human exposures to environmental hazards; risk management is the choosing of regulatory options. Both risk assessment and risk management incorporate policy choices and reflect the values of the risk assessors and managers. Some agencies have attempted to establish separate staffs for the two tasks, but this separation does not eliminate the need to make policy choices about the assumptions used in risk assessments.

The values and policy preferences of decision-makers, risk assessors, and representatives of industry, labor unions, environmental organizations, and public interest groups often differ. Scientists disagree about the nature of scientific evidence. These differences explain some of the past controversies over the regulation of specific carcinogenic chemicals and the development of agency policies.

In 1983, a committee of the National Research Council recommended the development of uniform guidelines for conducting risk assessments. The committee described several advantages and disadvantages of such guidelines. They have the advantages of promoting quality control, consistency, predictability, public understanding, administrative efficiency, and improvements in methods. In addition, guidelines serve an important role within agencies in training new staff in agency practices. The potential disadvantages of such guidelines include oversimplification, inappropriate mixing of scientific knowledge with risk assessment policy, misallocation of agency resources to the task of developing guidelines, and insensitivity to scientific developments. Some have hoped that policies for assessing and regulating carcinogens would speed regulatory activity. Others have tried to use such policies to change the direction of risk assessment and regulation.

While much effort has been devoted to developing guidelines and policies for carcinogen assessment and regulation, it is not clear how much effect they have actually had. They do provide points of reference for discussions on particular regulatory issues. Nevertheless, while there are important disagreements among regulatory agencies, industries, and other groups on general issues, many disagreements concern interpretations of evidence in particular cases. Everyone may agree, for example, that animal data can be used to identify potential human carcinogens, yet they may disagree about the applicability of results from particular animal experiments in assessing particular chemicals, especially commercially important ones. Adoption of general guidelines cannot resolve these specific disputes.

Agency policies and guidelines have varied considerably in their flexibility, formality, and comprehensiveness. They have also evolved, generally becoming more complex and detailed.

This background paper considers two distinct, but related, types of guidelines: agency requirements for animal carcinogenicity studies; and agency policies on identifying, assessing, and regulating carcinogens.

Required Animal Testing

FDA and EPA have required industry to conduct carcinogenicity testing of food and color additives, animal drugs, animals, human drugs, pesticides, and toxic substances.

FDA requires carcinogenicity testing for a proposed food additive only if it falls into certain chemical categories and its expected concentration in food exceeds specified levels. For an animal drug, testing may be required depending on the expected extent of its use in animals, the levels of drug residues, and the potential toxicity of the drug as determined from chemical structure, short-term tests, and other data. FDA requires carcinogenicity testing for new human drugs that are expected to have chronic or widespread use, although this requirement has not been applied to drugs marketed prior to 1968. For some of these older drugs, which are used widely today, FDA has requested studies from NTP rather than from drug manufacturers.

EPA may require animal carcinogenicity studies of pesticides when they generate some toxicologic concern, when they will be used on food, or when their use will result in significant human exposure. Considerable delays have occurred in requiring test data on pesticides marketed prior to 1972. Under TSCA, EPA may require testing for new chemicals or for existing chemicals.

Guidelines for Testing Protocols

OTA compared the bioassay study designs for suspected carcinogens that are specified by several Federal agencies. FDA and EPA have issued guidelines for the design of toxicologic studies, in-

eluding those of carcinogenicity. FDA has relied on nonregulatory guidelines, such as its “Red Book,” for studies required of new food and color additives. For human drugs, a joint workshop sponsored by FDA and the Pharmaceutical Manufacturers’ Association (PMA) discussed the design of studies. Although FDA decided not to issue guidelines under its own name, the guidelines were published by PMA. EPA issued as regulations separate testing guidelines for pesticides and for toxic substances. The National Cancer Institute (NCI) and NTP test guidelines were also considered in this OTA comparison.

Federal agency guidelines are generally consistent about major features of the study design. They specify testing in two animal species, which in practice are usually rats and mice. The two oldest guidelines (those of NCI and PMA) require at least two dose groups in addition to a control group. All other guidelines suggest the use of three dose groups and a control group. The guidelines agree that to maximize the sensitivity of a study in detecting carcinogenic effects, the highest dose in the study must be set as high as possible without shortening the animals’ lives because of non-carcinogenic toxic effects.

Risk Assessment Policies

OTA also compared Federal agencies’ policies on identifying and assessing carcinogens. These policies were issued under a variety of circumstances and are organized in different ways. In some cases, the policies are relatively informal statements of current scientific understanding about how carcinogens might be identified. In other cases, they constitute formally adopted regulations, specifying how an agency will identify carcinogens and limiting the kinds of arguments and evidence to be considered in specific regulatory proceedings. In between these two extremes, some documents outline an agency’s standard procedures and discuss problematic areas of interpretation, including the inference assumptions that the agency will use.

Several agency policies have taken a regulatory form, for example, OSHA’s 1980 policy. OSHA intended to collect evidence and testimony on “generic” issues in carcinogen identification and

regulation, make decisions on these issues, and then rely on these decisions and presumptions in future proceedings. The policy might be termed a “presumption-rebuttal” approach, providing strong presumptions and limited room for rebuttal. The framers of this policy hoped it would limit debate in subsequent regulatory proceedings and thereby speed carcinogen regulation. That hope has not been realized. Two carcinogens with occupational exposures, ethylene oxide and asbestos, have been regulated since the publication of OSHA’s policy.

CPSC attempted to adopt carcinogen assessment guidelines in 1978. CPSC was sued, and the guidelines were struck down by a reviewing court. Subsequent to this decision, CPSC formally withdrew its policy.

FDA has been working on a regulatory definition of allowable animal drug residues in human food since 1973. This definition specifies how sensitive an analytic technique must be, hence the definition is called “sensitivity of method” (SOM). It was first proposed in 1973, made final in 1977, challenged in court and sent back to FDA, re-proposed in 1979, then proposed for a third time in 1985. The final rule has still not been issued.

Other agency policies provide guidelines for conducting risk assessments. EPA’s 1976 “interim” guidelines and its 1986 carcinogen risk assessment guidelines are examples of this approach, which discusses scientific issues, sets forth flexible assumptions, and specifies an analysis based on the weight of the evidence.

A 1979 Interagency Regulatory Liaison Group (IRLG) policy and a 1985 guideline issued by the White House Office of Science and Technology Policy (OSTP) both discussed current knowledge of carcinogenesis and related risk assessment techniques. These documents are important because they represent the results of extensive discussions among scientists from many agencies. One goal of these discussions was to develop a consensus among the agencies on these issues.

Not all agency programs have adopted policies on risk assessment. For example, FDA does not have a formal risk assessment policy on food and color additives. However, FDA’s Center for Food

Safety and Applied Nutrition has established a formal committee for considering evidence on the carcinogenicity of food and color additives. FDA has published a policy on regulating additives with carcinogenic impurities and has developed a policy incorporating a de minimis approach to regulating the safety of food and color additives. For evaluating the safety of human drugs, FDA requires different kinds of tests depending on the expected duration of human use of the drug, but it has never issued guidelines for evaluating or assessing animal carcinogenicity test results. It does provide guidance, however, on preparing data for statistical analysis.

Carcinogen Assessment Policies

A National Research Council committee divided risk assessment into four distinct parts: hazard identification, dose-response assessment, exposure assessment, and risk characterization (137). Hazard identification is the qualitative identification of a substance as a human or animal carcinogen. In dose-response assessment, the relationship between the level of exposure or the dose and the incidence of disease is described. The two most important aspects of the second step are extrapolating from information on incidence at high doses to predict incidence at lower doses and, in the case of risk assessments based on animal data, converting animal doses into equivalent human doses. Exposure assessment estimates the frequency, duration, and intensity of human exposures to the agent in question. Finally, risk characterization relies on information from both dose-response and exposure assessments to estimate the expected risk, as well as to explain the nature of the risk and any uncertainties in assessing it.

Figure 1-1 illustrates these steps, which eventually lead to information useful for risk management decisions. Each step involves some uncertainty, owing either to inadequate data on the particular agent or to uncertainty about its mechanisms of toxicity.

Hazard Identification

In many situations of regulatory interest, there are few toxicity data of any sort. When data are

available, the agencies value epidemiologic studies as the most conclusive evidence for human carcinogenicity, presume that substances found to be carcinogenic in animals in long-term bioassays present carcinogenic hazards to humans, and use short-term test results as supportive information. Analyses of structure-activity relationships (analyses based on the structural similarity of a substance to other known carcinogens) are used mostly when there are no other data (e.g., to identify new chemicals that should have additional testing prior to large-scale manufacture).

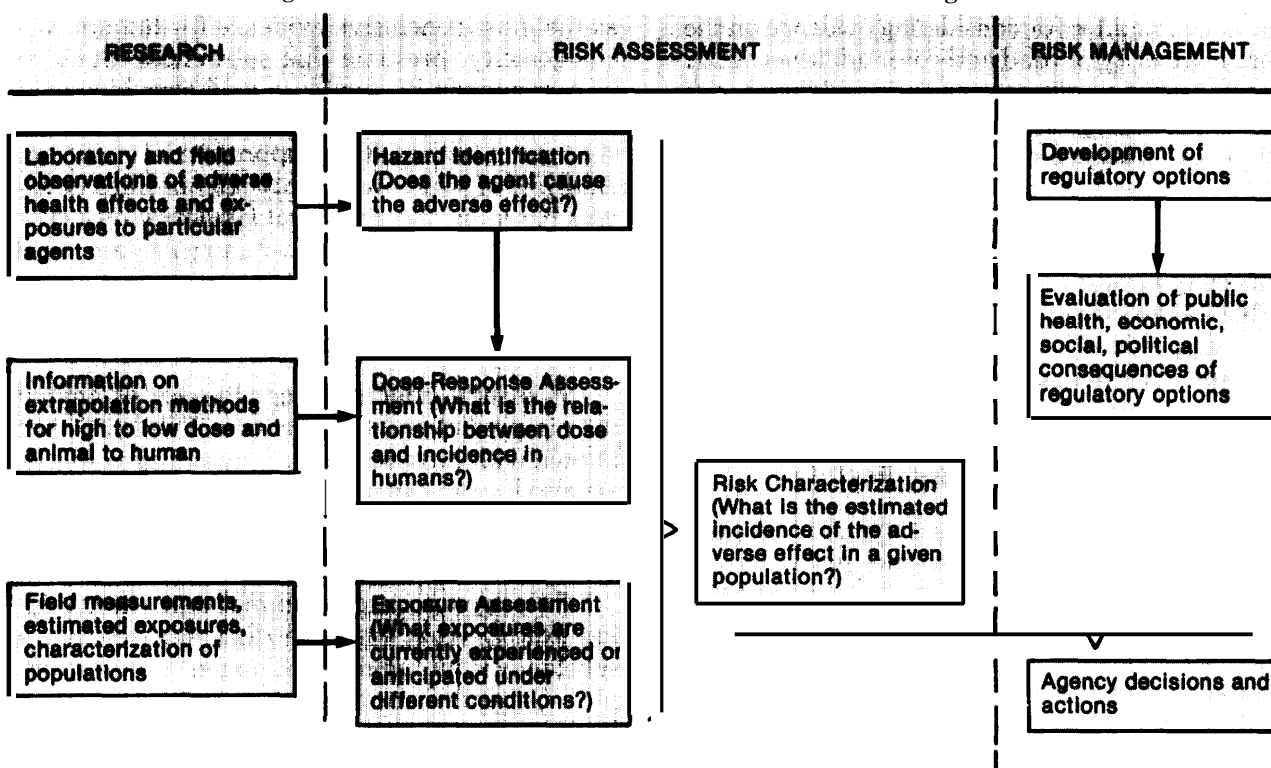
All Federal policies accept the use of animal data in predicting human effects. While it is not known with certainty that all animal carcinogens are also human carcinogens, most well-studied human carcinogens show some evidence of carcinogenicity in animals.

While agencies accept animal data, determining exactly what evidence demonstrates that a substance is an animal carcinogen is more complex. Generally, the agencies accept data derived from use of the maximum tolerated dose, and then use the increased incidence of malignant or benign tumors to demonstrate carcinogenicity. Policies usually state that positive results in animals outweigh negative epidemiologic results, and that positive results in one species outweigh negative results in another.

Dose-Response Assessment

Prior to 1970, there was considerable doubt about the utility of quantitative assessments. During the 1970s and 1980s, the agencies began using these assessments for carcinogens. In 1973, FDA specified the use of quantitative risk assessment in the proposed SOM for evaluating animal drugs. In 1978 and 1979, FDA conducted risk assessments for the environmental contaminants aflatoxins and polychlorinated biphenyls (PCBS). FDA first used risk assessment to determine the risk of carcinogenic impurities of color additives in 1982 and of food and color additives themselves in 1985 and 1986. The first EPA risk assessment, in 1975, concerned vinyl chloride. In 1976, EPA established its Carcinogen Assessment Group and published its "interim" guidelines on risk assessment. CPSC's first use of risk assessment came with its evalua-

Figure 1-1.—Elements of Risk Assessment and Risk Management



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

tion of tris(2,3-dibromopropyl)phosphate (Tris) in 1977. While OSHA had first prepared a quantitative risk assessment in 1976 for worker exposure to coke oven emissions, it resisted calls for increased use of these assessments until the Supreme Court's 1980 decision on the benzene standard. Today, although there are still many uncertainties associated with quantitative risk assessment, all of these agencies use it.

The agencies all assume that human risk estimates can be derived from animal data, that carcinogenic chemicals do not have no-effects thresholds, and that risk estimates should be based on results from the most sensitive animal species. All the agencies use mathematical models that assume low-dose linearity for extrapolating from the doses tested in the animal experiment to the doses of regulatory interest, although they differ on the mathematical technique to use, whether the focus should be on the "upper confidence limit" or the "maximum likelihood estimate," and the

method of converting animal doses into human doses. The general approach is to develop risk estimates with assumptions designed to err on the side of safety. The agency policies do not distinguish among chemicals thought to have different mechanisms of action (e.g., between "initiators" and "promoters"). The agencies are only beginning to explore the use of pharmacokinetic modeling techniques, and thus have not discussed these in detail in their policies.

Exposure Assessment

Agency policies give much less detailed guidance on how human exposures to specific chemicals should be estimated. While EPA has issued exposure guidelines, the predominant approach in those guidelines and in actual agency practice is to make evaluations case by case. The lack of detailed guidelines does not diminish the great importance of considering exposure in estimating human risk.

Risk Characterization

Several policies discuss risk characterization, mentioning alternative ways to describe estimated risk and various sources of uncertainty. Some policies also specify a method of classifying carcinogens, for example, by the weight of evidence for carcinogenicity. Considering the weight of evidence, that is, using all available information on a chemical's effects, has received more attention in recent policies.

Federal Assessment and Regulation of Carcinogens

Federal statutes authorize agencies to set exposure standards, residue limits, tolerances, and emissions standards for carcinogenic chemicals found in air, water, food, and the workplace. Some statutes authorize or require the outright banning of carcinogenic substances or products containing them; in other cases, agencies may set rules for a product's use.

Under this authority, a number of carcinogens have been regulated, although the agencies have not acted on all of the exposures known to present carcinogenic risk. While some time is required to prepare the analyses necessary for regulatory action and to respond to public comment, there have also been lengthy delays between knowing the outcome of human epidemiologic studies or animal bioassays and publishing proposed regulations, and delays between the publication of proposed and final rules. Regulations on carcinogens have frequently been challenged in court by industry, labor unions, environmental organizations, or other groups. In some cases the courts have ruled that the agencies exceeded their authority, although in other cases the courts have compelled the agencies to act.

Many chemical exposure limits set by the government or recommended by private individuals and organizations were established primarily to protect people from noncarcinogenic toxicities—effects that manifest themselves at the time of exposure or shortly thereafter. But cancer is an insidious disease. People can be exposed to carcinogens at levels that do not cause any immediately apparent adverse effects. These exposures, how-

ever, can crucially injure individual cells, leading to cancer many years later. Thus, regulatory standards to protect the public from carcinogen exposures will need to be set at levels much lower than those designed to protect against acute toxicities.

In general, a standard that reduces exposures based on concern for one health effect will do so for all health effects associated with that chemical. But a standard based on noncarcinogenic toxicities may not reduce exposures sufficiently to protect against cancer. Significantly, many Federal standards regulating carcinogenic chemicals were set originally to protect against noncarcinogenic toxicities and have not been updated to take account of carcinogenic effects.

OSHA

Congress passed the Occupational Safety and Health Act in 1970. In 1971, OSHA adopted a large number of startup standards, setting exposure limits on about 400 specific chemicals. These exposure standards consisted largely of the 1968 recommendations of the American Conference of Governmental Industrial Hygienists (ACGIH) and had been developed primarily to protect workers from noncarcinogenic toxicities. While the ACGIH recommendations are updated annually, OSHA standards are not.

From 1972 to 1986, OSHA issued health standards covering 22 carcinogens, many of which had been regulated by the 1971 standards. Most of these carcinogen standards have aroused controversy. Of 9 final actions on carcinogens regulated individually (including 2 on asbestos), 7 resulted in court challenges. In OSHA's regulation of a group of 14 carcinogens, the final standards for 2 chemicals were challenged. Permanent standards for 2 chemicals were struck down as a result of such challenges.

National Institute for Occupational Safety and Health (NIOSH)

One role of NIOSH is to identify substances that pose potential health problems and recommend exposure levels to OSHA. However, OSHA has not responded to many NIOSH recommen-

dations. Since 1971, NIOSH recommendations have addressed 71 different chemicals or processes that they determined to be carcinogenic. OSHA has issued health standards for 21 of the 71 chemicals or processes. Two of these OSHA standards were struck down by the courts. Thus, 19 of the 71 NIOSH recommendations on carcinogens have actually been addressed by OSHA regulations. Of the 50 chemicals or processes that are not the subjects of a final OSHA standard based on carcinogenicity, many are still regulated under the 1971 startup standards. OSHA has proposed regulations for four, but is actively working on a final standard for only one. No OSHA proposals have been issued for the remaining 46 chemicals or processes.

OSHA has criticized the quality of early NIOSH criteria documents, yet OSHA's failure to respond with standards highlights OSHA's regulatory difficulties. Increasingly, OSHA's regulatory agenda is being set by outside groups, in the form of petitions, court orders, congressional directives, and EPA referrals, including those on seven chemical carcinogens that EPA formally or informally referred under TSCA. OSHA has proposed a standard for one of these referred substances.

MSHA

MSHA regulation covers coal mines and metal and nonmetal mines. Regulation of toxic exposures in mines consists largely of reference to the 1972 and 1973 recommendations of ACGIH, depending on the type of mine. The ACGIH recommendations are updated annually, while MSHA has changed few of its standards.

In the late 1970s, MSHA regulated asbestos exposures for surface mines (using the exposure limit OSHA issued in 1972) and the chemicals OSHA included in its "14-carcinogens standard." MSHA has also proposed revised standards for underground exposure to radon daughters.

OSHA set a stricter standard for asbestos in 1986, but MSHA has not followed suit. Moreover, MSHA's current asbestos standard does not apply to exposures in underground coal mines. The increased use of diesel engines in underground coal mines has exposed workers to fumes. While MSHA has standards for such exposures in metal

and nonmetal mines, these standards were not based on carcinogenicity. MSHA is developing a proposed standard for diesel exposures in coal mines.

FDA Actions on Food and Color Additives

Since congressional enactment in 1958 of the Delaney clause, which prohibits the use of food additives determined to cause cancer, FDA has identified over 60 relevant carcinogenic chemicals. They include direct food additives, indirect food additives (chemicals that might migrate from packaging material or manufacturing processes into foods or beverages), color additives, cosmetic ingredients, contaminants or potential contaminants of food or color additives, and environmental or unavoidable contaminants of food.

The regulation of food additives received much public attention when FDA banned cyclamates and proposed to ban saccharin. FDA has actually banned seven direct food additives. Its proposed ban of saccharin was barred by congressional action.

The review of provisionally approved color additives, begun in 1962 under the Color Additive Amendments of 1960, has been lengthy. It has taken until now to obtain required toxicity data and make regulatory decisions about many of the substances on the list. FDA has banned a total of 10 color additives, while a number of other color additives were withdrawn from the market by their sponsors who sometimes chose not to conduct the FDA-required testing.

In the last few years FDA policy on regulating food and color additives has also changed. Prior to 1982, FDA banned several color additives because they were shown to be carcinogenic or contaminated with a carcinogen. Since 1982, FDA has permanently listed several color additives even though they contain known carcinogens. The new policy states that, if a color additive itself does not cause cancer in humans or animals, but a contaminant of the additive does, FDA will regulate this color additive based on the general safety provisions of the act. Under this policy, the carcinogenic impurities are not considered to trigger the requirements of the Delaney clause. FDA will estimate potential risk using quantitative risk assess-

ment techniques and if the risk of the impurities is estimated to be low, FDA will permit the use of the color additive.

In 1985 and 1986, FDA took action to allow use of food and color additives that were themselves carcinogenic, basing its action on quantitative risk assessment. In 1985, FDA proposed to allow the continued use of methylene chloride for decaffeinating coffee by limiting the allowable residue, rather than to ban the chemical's use entirely. Several color additives were identified by FDA as carcinogenic in 1982 and 1983 based on the results of animal bioassays. After performing risk assessment calculations, FDA announced in 1986 that it was permanently listing these additives because their estimated carcinogenic risks were low. FDA believes such actions are legally permissible under the interpretation that the Food, Drug, and Cosmetic Act allows FDA to ignore de minimis risks, despite the seemingly absolute language of the Delaney clause. In February 1987, FDA argued further that because the estimated risk in humans was low, the color additives in question would not be considered, for purposes of the Delaney clause, to be animal carcinogens either.

Indirect food additives are generally packaging material—various plastics and adhesives used to hold foods and liquids—and materials that contaminate foods in the manufacturing process. FDA has banned two indirect food additives. Other indirect additives containing carcinogenic impurities have been regulated by prescribing conditions for “safe use.”

In the mid-1970s, FDA prohibited the use of bottles made from polymers of acrylonitrile and vinyl chloride, because these chemicals might leach into liquids. FDA's position was rejected by the courts. In the 1980s, FDA issued a rule to allow acrylonitrile copolymer bottles and proposed to allow polyvinyl chloride bottles, arguing that new manufacturing technology can ensure minimal leaching from these bottles.

FDA can set regulatory tolerances or action levels for environmental or unavoidable contaminants. It has set tolerances for PCB contamination of fish and action levels for aflatoxins,

dimethylnitrosamines (in malt beverages), and N-nitrosamines (in baby bottle nipples).

FDA Actions on Animal Drugs

FDA has identified 14 chemicals associated with animal drugs that might leave carcinogenic residues in animal tissues. Such residues had been subject to the Delaney clause, but in 1962 Congress amended the Food, Drug, and Cosmetics Act to permit the use of carcinogenic drugs in animals, providing carcinogenic residues cannot be detected in meat or milk using FDA-approved methods. FDA has banned diethylstilbestrol (DES) from use in animals and has required residue studies on six other substances. FDA has proposed to withdraw approval for seven. One animal drug was withdrawn by the sponsor and there is no reported action for several others. As mentioned above, FDA has been working for 14 years on regulatory guidelines specifying the SOM for determining the presence of harmful animal drug residues.

FDA Actions on Human Drugs

In regulating carcinogens in human drugs, FDA has issued rules on six substances or groups of substances. Two were removed from the market, one was voluntarily recalled, and cautionary labeling was required on three. When a drug is determined to be carcinogenic, the drug's labeling for physicians is usually updated informally. Many, but not all, carcinogenic drugs on the market are, in fact, anticancer drugs. Treatment in these cases involves balancing the risk of future cancer against the benefit of treating a diagnosed cancer today.

CPSC

Since its creation in 1970, CPSC has evaluated and attempted to regulate or begun to regulate eight chemicals (or groups of chemicals) for carcinogenicity. CPSC regulations have often been overruled by the courts, although in the case of Tris-treated children's pajamas, CPSC developed an alternative strategy to remove the product from the market. In 1981, CPSC issued a rule regulating hazardous urea-formaldehyde foam insulation (UFFI), a rule that was also struck down by the courts.

In other cases, use of chemicals in consumer products stopped, even though regulation was not final or had been overturned in court. In some cases, CPSC has been able to negotiate voluntary actions by manufacturers, such as the 1979 voluntary recall of hairdryers containing asbestos shields.

EPA Actions Under the Clean Air Act

Since the 1970 enactment of the Clean Air Act, EPA has, often under legal pressure, listed seven carcinogens and issued hazardous air pollutant emission standards on six, although one of these actions was based on noncarcinogenic toxicity.

Although the Clean Air Act provides EPA one year to issue regulations after a substance is listed, this deadline was met only in the case of vinyl chloride. EPA has taken an average of almost 4 years from the date of listing to final action for the six carcinogens on which it has issued final rules. During the time between the listing and regulation of benzene, one major industrial source of benzene had changed its process and eliminated release of the chemical.

EPA has created a new type of action in addition to listing: an "intent to list" decision. According to EPA, the intent to list a substance as a hazardous pollutant does not legally bind the agency as does a listing decision. EPA has indicated the intent to list for 10 substances, but none as yet has been listed and therefore none regulated.

EPA Actions Under the Clean Water Act

Important amendments to the Clean Water Act were enacted in 1972, 1977, 1981, and 1987. From 1972 to 1975, EPA issued toxic effluent standards for six categories of pollutants, under court order. In a consent decree, EPA agreed to regulate toxic pollutants by industry and by specifying the technology to be used. EPA agreed to issue effluent limitations for 65 categories of toxic substances, including 29 judged to be carcinogenic according to the water quality criteria documents that were also developed under this decree.

EPA has focused on 126 chemicals within these 65 classes of pollutants, but not all of these chemicals are regulated for every industry. In addition,

EPA has not established effluent limitations for toxic pollutants from the organic chemicals industry, and current regulation of the pesticides industry does not limit the discharges of most toxic pollutants in that industry. EPA had issued new regulations for the pesticides industry, but they were challenged in court and are now being reconsidered by EPA. Again, this regulatory activity has taken considerable time (from the 1976 consent decree until today), has involved the courts on a number of occasions, and is not yet finished. Further, while the list of 126 chemicals was chosen based on known toxicity and probable presence in water, and represented the best efforts of the participants at the time, more recent data reveal that many of the chemicals most commonly found in industrial discharges are not on this list.

EPA has also prepared nonbinding water quality criteria documents for States to use in developing water quality standards and requirements for specific discharge permits. However, only 7 of the 29 water quality criteria set for carcinogens have been adopted by one or more States. For only one of these substances (arsenic) have more than one-fourth of the States issued a water quality standard, although in some States that have not taken legislative action, individual discharge permits impose limitations based on the water quality criteria.

EPA Actions Under the Safe Drinking Water Act

In 1975, EPA issued the "interim" drinking water standards still used today for several inorganic and organic chemicals and for microbial contaminants. These standards were based on the 1962 recommendations of the U.S. Public Health Service for noncarcinogenic toxicities. EPA also issued regulations for radionuclides in 1976 and for total trihalomethanes in 1979, two groups of substances presenting carcinogenic hazards.

Following the congressionally mandated reports on drinking water by the National Academy of Sciences (the first of six volumes was published in 1977), EPA was required to publish proposed recommended maximum contaminant levels (RMCLs) and then to issue maximum contaminant levels (MCLs) for particular chemicals found in drink-

ing water. The MCLs are to be set as close to the RMCLs as is feasible. After considering a 1978 proposed regulation to set generic standards for treating surface water supplies, EPA decided to continue focusing on individual substances.

In 1982 and 1983, EPA published two Advanced Notices of Proposed Rule-making (ANPRMs) listing 83 chemicals of concern. In 1983 and 1985, it proposed RMCLs for inorganic substances, volatile organic compounds, and synthetic organic compounds. EPA issued final RMCLs for eight volatile organic compounds in November 1985. It has not yet issued final RMCLs for the inorganic substances and the synthetic organic compounds, and has not proposed RMCLs for radionuclides. To date, EPA has issued final MCLs for nine chemicals, five of which are judged to have sufficient evidence for carcinogenicity, and one to have limited evidence.

Congress was concerned that drinking water standards were not being set quickly enough, so in the 1986 reauthorization of the act, it set deadlines for EPA to regulate the 83 chemicals that had been identified as candidates for regulation in 1982 and 1983. These 83 substances include 51 in the process of being regulated. In addition, 52 health advisories have been issued by EPA. Many of these provide information on potential carcinogens in drinking water.

EPA Actions Under FIFRA

To prevent unreasonable adverse effects on health and the environment, FIFRA authorizes EPA to screen pesticides before they enter the market and to regulate through reregistration the pesticides that were already on the market in 1972. In both cases, EPA may require manufacturers to conduct toxicity tests, including long-term bioassays for carcinogenicity.

FIFRA was substantially rewritten in 1972. At that time there were about 50,000 pesticide products and 600 active ingredients previously registered by the Federal Government that needed reregistration under the new law. The reregistration process has taken longer than originally anticipated. It was to have been completed by 1976, but in 1975 Congress extended the deadline to 1977, and in 1978 Congress dropped the deadline

completely because of the large number of substances not yet reregistered. This task will OCCUPY EPA for many years.

For a number of active ingredients subject to reregistration, EPA has lacked sufficient information to judge their carcinogenic effects. EPA is taking steps to obtain this information. Still, as of March 31, 1986, it had identified at least 81 carcinogenic active pesticide ingredients. Of these, 18 have been canceled or restricted, Daminozide (Alar) is still undergoing review, and 15 have been voluntarily canceled. However, cancellations often cover only some uses. Other uses of the pesticide continue, although EPA may set additional requirements, for example, requiring workers to wear protective clothing. Special Reviews (SRs) for the substances EPA canceled or restricted required from 13 to 88 months, taking an average of about 44 months.

Another 18 chemicals have also been subjects of SRs. The SRs have been completed for 10 carcinogens, and these chemicals have not been canceled based on EPA judgments weighing risks and benefits. For the remaining 8 chemicals, SRs are not yet complete. Finally, EPA has identified 29 carcinogens, but has not started SR or cancellation proceedings for any of these.

Thus, EPA has identified 47 carcinogenic active pesticide ingredients that have not been canceled. For 13 of these EPA has determined that low exposure, low risk, or the weight of evidence for carcinogenicity suggest no action need be taken.

In addition to considering active ingredients, EPA has indicated that about 55 inert ingredients are of "high concern," with 28 of these showing carcinogenic effects. In 1987, EPA announced for the first time that it was taking steps to address some of the hazards of these ingredients.

EPA Actions Under TSCA

EPA actions under TSCA cover both new and existing chemicals. For new chemicals, the principal focus is the premanufacture review process. If after review of the manufacturer's premanufacture notice (PMN), EPA decides that there is cause for concern, it can request or require that addi-

tional toxicity testing be done, that certain controls be used when working with the chemical, and that the manufacturer notify EPA before beginning a significant new use of the chemical.

From mid-1979, when the PMN program began, until September 1986, EPA received 7,356 valid PMNs. Of these, 80 percent or 5,671 required no further action, according to EPA. Of the remaining chemicals, 523 were subject to some kind of action; an unknown number of these raised concerns about carcinogenicity. About half the time, EPA attention led to the manufacturer's informally and voluntarily agreeing to testing, control actions, or withdrawal of the PMN. For the remaining cases, EPA took more formal action, although often with the manufacturer's consent.

The lack of information in the PMNs is a potential problem. In 1983, OTA found that about half the submitted PMNs reported no toxicity information and "only 17 percent of PMNs have any test information about the likelihood of the substance's causing cancer, birth defects or mutations." Because many PMNs do not provide any toxicity test data, EPA uses information on chemical structure-activity relationships to attempt to predict the hazards that a substance may present.

For existing chemicals, EPA can require toxicity and environmental effects testing, designate the chemical for accelerated review, or require manufacturers to report on production and uses, provide EPA with any studies they have conducted, or report significant new uses. EPA can also issue regulations restricting or banning the production of a chemical or limiting its uses.

TSCA established an Interagency Testing Committee (ITC) to make recommendations on needed testing for toxicity and environmental effects. In the early years of the program, EPA's responses to the ITC recommendations provoked concern, both because of EPA delays in deciding whether to test and because of the particular administrative arrangements chosen for obtaining test data. In addition to the ITC recommendations, EPA could select other chemicals for testing. So far, this has not occurred often, although this may be changing.

A rule issued under section 8(a) of TSCA requires manufacturers to provide information about the production and uses of a chemical, while a rule adopted under section 8(d) requires that manufacturers submit to EPA unpublished health and safety studies. EPA has issued 8(a) and 8(d) rules for all the substances recommended by ITC, but until recently for few additional chemicals. EPA has recently received data from manufacturers as part of its effort to update its inventory on all chemicals in commerce.

Sufficient toxicity information is available on some existing chemicals to show they are carcinogenic. For these chemicals, the issues are determining whether the risks of cancer are "unreasonable" and what actions may be needed to reduce or eliminate such risks. EPA's Office of Toxic Substances, which is in charge of the TSCA program, has identified 38 chemicals or chemical classes as carcinogenic and has prepared risk assessments for 21 of these.

But beyond the development of risk assessments and the gathering of other information, regulatory actions on existing chemicals have been limited. Four chemicals have been designated for an accelerated review under section 4(f) (4,4'-methylenedianiline, 1,3-butadiene, formaldehyde, methylene chloride). Consideration of the regulation of occupational exposures to these chemicals has been referred formally or informally to OSHA since TSCA provides for referrals if EPA believes another agency may be able to address a hazard. Under TSCA authority, EPA began proposing Significant New Use Rules (SNURs) for existing chemicals considered to be carcinogenic. However, actions on carcinogens began in 1984, nearly 7 years after TSCA's enactment. For carcinogenic chemicals, EPA has now proposed six SNURs on eight existing chemicals and has issued four.

Section 6 of TSCA provides wide-ranging authority to limit production and uses of chemicals, including the authority to ban a substance. EPA has proposed section 6 action on PCBs, asbestos, chlorofluorocarbons, and metalworking fluids. PCBs were banned by Congress in TSCA itself; EPA regulations cover implementing that ban and arranging for disposal of PCBs. EPA has also banned propellant uses of chlorofluorocarbons,

but it has not yet taken action on the most important uses of this group of chemicals, which are used in refrigeration and air-conditioning. Finally, EPA has issued rules on identification of asbestos in schools and proposed rules to require removal in certain cases. EPA has also regulated asbestos exposures for certain workers not covered by the OSHA asbestos standard, although it has not taken final action on a major proposal to limit and eventually ban asbestos use. The proposal on metalworking fluids is also not yet final.

EPA Actions Under RCRA

RCRA regulates the generators, transporters, storers, and disposers of hazardous wastes. EPA's lists of hazardous wastes cover 361 commercial chemicals and 85 industrial waste processes. When possible, EPA has emphasized waste streams from commercial processes rather than specific hazardous substances, to relieve waste generators of testing burdens and uncertainties in "relating a waste containing many substances to a list of specific substances." EPA has also issued a list of toxic chemicals as Appendix VIII of its RCRA standards. Wastes containing chemicals on this list may be deemed hazardous wastes.

EPA has made limited changes in its list of RCRA hazardous wastes. For example, since 1980 EPA has added five wastes to the RCRA list. In the 1984 RCRA amendments Congress employed "hammers" -congressionally enacted prohibitions against disposal of certain groups of chemicals unless EPA has acted to specify treatment techniques for those wastes. In addition, Congress mandated that EPA review, over a 3-year period, the entire RCRA list of hazardous wastes.

EPA Actions Under CERCLA

Commonly known as Superfund, CERCLA was enacted in 1980. CERCLA requires EPA to identify reportable quantities for hazardous substances and set requirements for notification of environmental releases.

Congress specifically included in the definition of hazardous substances those chemicals already regulated under several environmental statutes. In addition, Congress set reportable quantities for these substances at 1 pound (except for reportable

quantities specified under the Clean Water Act) until EPA could set more appropriate reportable quantities. In May 1983, EPA published its initial list of hazardous substances. Since 1983, 19 substances have been added to the CERCLA list yielding a total of 717 substances. Most of the regulatory activity on the CERCLA list has been in modifying the reportable quantities. In 1987, EPA proposed modified reportable quantities for CERCLA carcinogens. Of the CERCLA hazardous substances, 191 have been identified by EPA as "potential carcinogens" or as substances "having carcinogenic potential."

EPA's Carcinogen Assessment Group (CAG)

As mentioned above, CAG was established in 1976 to centralize the conduct of carcinogen risk assessments at EPA. Major CAG assessments are thorough reviews of the carcinogenic risks of particular chemicals, including both qualitative evaluation of the weight of evidence for carcinogenicity and quantitative dose-response estimates. To date, CAG has prepared full assessments on 57 chemicals.

Office of Management and Budget (OMB)

Although not a regulatory agency, OMB has become an important actor in developing Federal regulations through their review of proposed regulations under Executive order 12291 and the Paperwork Reduction Act. This review has led to delays in proposing and issuing standards on carcinogens. OMB has also publicly questioned some of the regulatory agencies' assumptions in conducting risk assessments. The methods OMB used in commenting on a proposed OSHA formaldehyde standard ran counter to some of the assumptions typically used by the regulatory agencies and incorporated in agency policies on identifying and assessing carcinogens.

Type of Evidence: Human or Animal Data

Agencies use the hazard data available at the time of their action, most generally, data from human or animal studies. OTA has attempted to characterize the evidence that agencies have used in regulating carcinogens.

FDA has relied mostly on animal evidence in evaluating food additives, color additives, human drugs, and animal drugs.

CPSC has used both human and animal evidence, although in its action on Tris and attempted regulation of formaldehyde, it relied upon animal evidence only.

Of the 57 chemicals covered by CAG health assessments, 40 have been assessed based on "sufficient" animal evidence. Nine more were supported by sufficient human evidence and all but one of these were also supported by sufficient animal evidence. EPA judged the remaining 8 chemicals to have inadequate human evidence and limited animal evidence.

Most cancellations and restrictions of pesticides have been based on the results of carcinogenicity tests in at least two animal species. Nearly all TSCA hazard identifications and risk assessments are based on animal data.

There is some evidence of the carcinogenicity of the 35 chemicals proposed for regulation under the Safe Drinking Water Act, but EPA believes that the evidence for the carcinogenicity of 8 of these in drinking water has not been established and thus is basing RMCLs for these chemicals on noncarcinogenic effects. EPA's classification of the other 27 drinking water contaminants as carcinogens relied mostly on animal evidence.

The original RCRA list of hazardous wastes and CERCLA list of hazardous waste reportable quantities were developed largely without specific concern for carcinogenicity, although the original regulations on which these lists were based may have had this concern. Recently proposed adjustments in the CERCLA list of reportable quantities classify 191 chemicals as potential carcinogens: 14 based on sufficient human evidence, 110 on sufficient animal evidence, and 20 on limited animal evidence. Most (40) of the remaining chemicals were classified based on a parent element (e.g., inorganic compounds of arsenic were classified based on the carcinogenicity of arsenic), although for 7 chemicals EPA had no evidence of carcinogenicity.

OSHA and EPA's Clean Air Program have based regulation on human data most of the time, though there are indications this may be changing.

Of OSHA's eight regulations on individual carcinogens, seven were based on at least some evidence of human carcinogenicity. The other carcinogen, 1,2-dibromo-3-chloropropane (DBCP), was regulated primarily because it caused infertility in men. The evidence of its carcinogenicity consists of animal data. Regulation of three carcinogens under the "14-carcinogen standard" was based on human evidence, that of nine on animal evidence. The remaining two substances were regulated because of their chemical relationship to other carcinogens. Most OSHA regulations of carcinogens based only on animal evidence occurred with the regulation of the 14 carcinogens in 1974. Standards since then have been based mostly on human data, although for OSHA's 1984 regulation of ethylene oxide the primary evidence for its carcinogenicity is animal data. The primary evidence for several chemicals now being considered for regulation, including formaldehyde and methylene chloride, is animal evidence.

For the five substances regulated primarily as carcinogens under the Clean Air Act, EPA has relied on human evidence of carcinogenicity. EPA's intent-to-list decisions for eight of ten substances have relied on animal bioassays for evidence of carcinogenicity; the other two substances show both animal and human evidence of carcinogenicity.

The National Toxicology Program (NTP)

Since 1961, the Federal Government has been developing a testing program for determining the carcinogenicity of chemicals, first at NCI, and since 1978, at NTP. The program encompasses long-term animal studies and other tests to determine carcinogenic activity. NTP is probably the largest such testing program in the world, and is thus important in advancing knowledge of carcinogenic chemicals.

Early testing at NCI focused primarily on understanding the etiology and biological mechanisms of cancer. In the late 1960s, the Federal Government expanded carcinogenicity testing. Today, NTP bioassays and other tests provide important information for developing risk assessments and issuing regulations.

NTP was created to coordinate the toxicity testing of the then Department of Health, Education, and Welfare and to provide a mechanism for regulatory agencies (and others) to request bioassays on chemicals of regulatory interest. The NTP budget consists of contributions from several different agencies in the Department of Health and Human Services (FDA/National Center for Toxicological Research (NCTR), CDC/NIOSH, and the National Institute of Environmental Health Sciences (NIEHS)), although the lion's share of funds derive from NIEHS. The Director of NIEHS is also the Director of NTP. Activities of the contributing agencies are coordinated by the NTP Steering Committee, which consists of the heads of these agencies and the NTP Director. Formal authority to approve and monitor the general plan of NTP activities is vested in an Executive Committee that consists of the heads of the four major health and environmental regulatory agencies (CPSC, EPA, FDA, and OSHA), the heads of four research agencies (National Institutes of Health (NIH), NCI, NIEHS, and NIOSH) and the Assistant Secretary for Health of the Department of Health and Human Services (DHHS). This structure allows both the regulatory agencies and research agencies a voice in planning and operating NTP.

The nomination of chemicals for NTP testing is invited from any source, including the regulatory and research agencies. NTP's established procedures to evaluate nominations include review by the interagency Chemical Evaluation Committee, solicitation of public comments, review by NTP's Board of Scientific Counselors, and final decision by the NTP Executive Committee.

After selection, a protocol is prepared and testing begins. Testing consists of various preliminary studies, a long-term dosing regimen (which by it-

self takes 2 years), sacrifice, and pathologic examination, including microscope studies of tissues and tumor diagnoses. NTP has established procedures for ensuring the quality of these diagnoses, which are crucial to determining the final bioassay results. The resulting data are analyzed and the draft technical report is submitted to a peer review committee. Peer reviewers have the training and experience appropriate to judge the quality of the bioassay and to interpret bioassay results. NTP has chosen to include on its peer review committees people of different perspectives, including academics and representatives of industry, environmental organizations, and labor unions.

The number of chemicals tested depends primarily on the resources available. The NTP budget increased approximately 40 percent between 1979 and 1981. From fiscal year 1981 to 1987 the total NTP budget rose from \$70.5 to \$77.9 million, which, after adjustment for inflation, represents a small decline. Budget reductions necessitated by the Gramm-Rudman-Hollings Act have affected NTP. Recently, NCTR discontinued long-term NTP animal tests on one antihistamine and continued two other tests only because NIEHS agreed to pay 75 percent of the costs to complete the 2-year exposure phase. NTP has now agreed to fund completion of these two studies. Given current resources, more chemicals are nominated than can be tested.

The entire process—nomination, selection, preliminary testing, chronic testing, necropsy, data analysis, review, and publication—is a long one. OTA examined the process for a group of chemicals reviewed by NTP's Chemical Evaluation Committee in fiscal year 1981 and 1982. None of these chemicals has passed through the entire testing process. Of the 30 chemicals approved for testing in those 2 years, 4 have reached the stage of chronic testing.

The time from nomination to selection is more than 2 years for most chemicals. Some shortening of this period should be possible. But much of the remaining time required (between selection and beginning chronic exposures) is difficult to

shorten because it is used to develop information important for the design, conduct, and interpretation of the bioassay.

The nomination process raises at least two issues. First, nominations and selections are important because they may set the regulatory agenda for the following decade. Today, several agencies are working on regulations for such chemicals as methylene chloride, 1,3-butadiene, 4,4'-methylene dianiline, and benzene, which NTP tests showed to be carcinogenic. These test results and the resulting regulatory action proceed in part from selection decisions of a number of years ago.

Second, NTP's recent decisions on testing the benzodiazepines (which include Valium and Librium) raise the issue of who should pay for carcinogenicity testing—government manufacturers, drug sponsors, pesticide registrants, or others. There are advantages to testing through common protocols and in the Federal Government's program. There is also reason to argue that the manufacturers and sponsors of chemicals have a responsibility to pay for the toxicity tests of their products.

Regulatory Responses to NCI/NTP Test Results and the *Annual Report*

NCI/NTP Bioassay Results

As of June 1987, the NCI/NTP bioassay program has completed testing of 308 chemicals in a total of 327 studies. Chemicals are typically tested in both sexes of rats and mice, for a total of four "experiments." At the end of the study, the results of each experiment are classified as clear evidence, some evidence, equivocal evidence, or no evidence for carcinogenicity, or as an inadequate test.

OTA has analyzed the regulatory uses of the NCI and NTP test results subject to peer review and audit approval by September 1986. These results represent 284 chemicals studied in 295 tests. For the analysis, "clear evidence" and "some evidence" for carcinogenicity were grouped as "positive" results. The chemicals tested were grouped based on the number of the four experiments for each that showed positive results. Of the 284 chemicals, 36 yielded four positive results, 25

three positives, 51 two positives, and 32 one positive result, for a total of 144 chemicals testing positive in at least one experiment.

OTA did not incorporate any additional data on the affected animal tumor sites, on whether both high and low doses (or all three doses in a three-dose experiment) produced a response, or on chemicals' estimated potencies. The grouping of substances for this analysis is also based only on the results of NCI/NTP testing. OTA has not used the bioassay results of others or the results of human epidemiologic studies.

Annual Report on Carcinogens

In 1978, Congress mandated that the DHHS publish an annual report listing all known carcinogenic substances and substances reasonably thought to be carcinogenic to which a significant number of people in the United States are exposed. Furthermore, the report is to describe regulatory actions on these substances, and estimate how much those actions have reduced risk. The legislation's first sponsors thought this discussion would help focus on chemical exposures that still present risks, and thus on areas for regulatory activity.

The substances discussed in the report are chosen by an interagency committee, including representatives of CPSC, EPA, FDA, NCI, NIEHS, NIOSH, the National Library of Medicine, and OSHA. The committee bases its decisions on the previous *Annual Report*, lists of chemicals judged to be supported by sufficient evidence for carcinogenicity by the International Agency for Research on Cancer (IARC), and animal testing results from NTP and other peer-reviewed studies. They publish the list of possible additions for comments and then make their final selections. The latest *Annual Report*, the fourth, lists a total of 148 substances, groups of substances, and exposures. For this analysis, OTA eliminated double-counted chemicals in this list for a total of 145 chemicals.

OTA Analysis

OTA examined regulatory responses to three groups of chemicals: all NCI/NTP-tested chemicals with at least one positive experiment, the

NCI/NTP chemicals with three or four positive experiments, and the chemicals listed in the fourth *Annual Report on Carcinogens*. While OTA analyzed the three separately, in fact there is some overlap of the three lists. All the chemicals testing positive in three or four experiments of course also tested positive in at least one experiment. In addition, many of the chemicals with three or four positive results have been listed in the *Annual Report*.

OTA focused on the chemicals of potential regulatory interest for each agency or program: the chemicals found in specific environmental media, such as air or drinking water, occupational settings, consumer products, pesticides, food, and drugs. Information on exposures is, unfortunately, often simply unavailable. Quantitative information is particularly difficult to obtain. So OTA relied on information on estimated production levels, estimated number of workers exposed, and qualitative data on the presence of particular chemicals in given situations. Even using this information on regulatory jurisdictions, OTA found apparent gaps in regulatory coverage. Figure 1-2 summarizes OTA's analysis of agency actions and nonactions on chemicals in their jurisdictions.

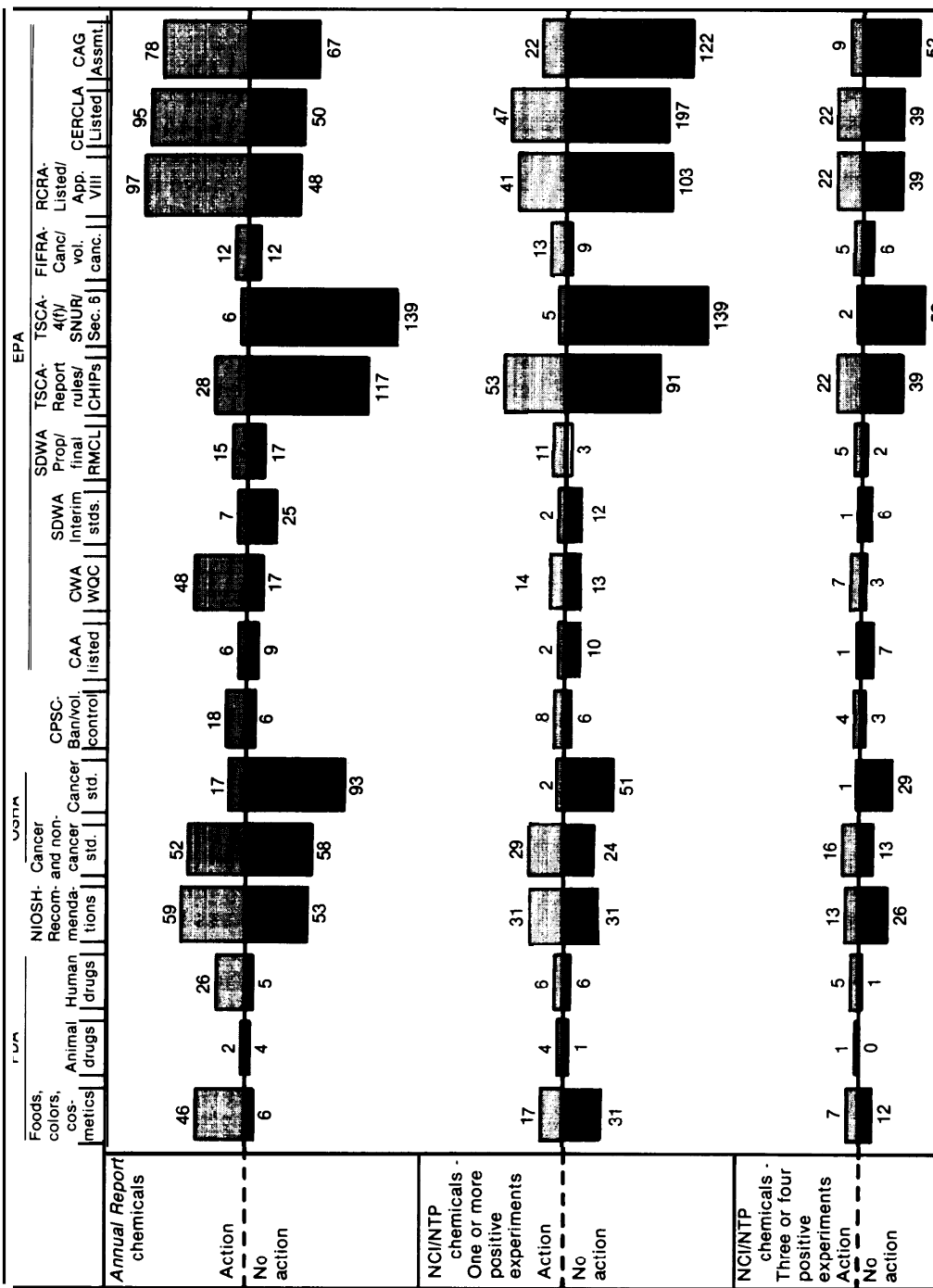
The impact of these regulatory gaps on human health depends on factors not analyzed by OTA, including the extent and magnitude of exposures, the potency of the chemicals, and other potentially synergistic or antagonistic exposures and risk factors. Many agency analyses conducted to develop information prior to regulation on information hazards, risks, control technologies, costs, and other factors—have not been included in the actions discussed here.

Regulation of Chemicals Tested by NCI/NTP

While a number of regulatory actions appear to have been based directly on positive NCI/NTP test results, there also appear to be substantial gaps in *regulatory* activity. In the NCI/NTP bioassay program, 144 chemicals tested positive in at least one experiment. Considering each agency and program individually reveals that no agency has regulated more than a third of the chemicals

with positive test results. More typically, an individual agency will have acted out of concern for carcinogenicity on 5 to 30 of the 144 chemicals.

FDA has taken action on 17 of the 48 positive NCI/NTP chemicals associated with food additives, color additives, or cosmetics. The balance have been evaluated, but have not been subject to further action. FDA has acted on 4 of the 5 positive NCI/NTP chemicals associated with animal drugs, and 6 of the 12 positive NCI/NTP chemicals that are human drugs bear labeling that warns of carcinogenicity. OSHA has set exposure standards for 29 of the 53 positive NCI/NTP chemicals that are of interest in the workplace, although 27 of these 29 are regulated by standards based on concern for noncarcinogenic toxicity, which were adopted by OSHA in 1971. NIOSH has provided OSHA with recommendations on 31 of the 62 positive NCI/NTP chemicals in its OTA-defined jurisdiction. Regulatory action or voluntary exposure reductions have occurred for 8 of the 14 positive NCI/NTP chemicals in CPSC's jurisdiction. EPA has listed under the Clean Air Act 2 of 12 positive NCI/NTP chemicals within the act's jurisdiction. Water quality criteria have been prepared for 14 of the 27 positive NCI/NTP chemicals in the jurisdiction of the Clean Water Act. Of the 14 positive NCI/NTP chemicals in the jurisdiction of the Safe Drinking Water Act, 12 have been addressed by some regulatory attention, although for many of these, the regulatory process is not yet finished. EPA has developed information on 53 of the 144 positive NCI/NTP chemicals in the TSCA's jurisdiction. For 5 of the 144 chemicals, EPA has issued SNURs, begun accelerated reviews, or taken action under section 6 of the act. Under FIFRA, there have been EPA-ordered or voluntary cancellations for 13 of the 22 positive NCI/NTP chemicals used as active pesticide ingredients. Of the 144 positive NCI/NTP chemicals, 41 have been included in RCRA's list of hazardous wastes or its Appendix VIII list, while 47 of the 144 positive NCI/NTP chemicals are listed under CERCLA. CAG has prepared health assessments for 22 of the 144 positive NCI/NTP chemicals. No actions have occurred for 43 of the 144 positive NCI/NTP chemicals.

Figure 1-2.—Agency Actions on Annual Report and Positive NC/NTP Chemicals^a

^aFor each agency or program, OTA included only chemicals in the OTA-defined jurisdiction for that agency or program. Agency decisions that regulation is not necessary or appropriate were included in the no action groups. Because of overlap between the three lists of chemicals, it is not appropriate to add them together. All actions through July 1987 are represented in this figure.

Key to acronyms: CAA—Clean Air Act; CAG—Carcinogen Assessment Group; CERCLA—Comprehensive Environmental Response, Compensation, and Liability Act; CHIPs—Chemical Hazard Information Profiles; CPSC—Consumer Product Safety Commission; EPA—Environmental Protection Agency; FDA—Food and Drug Administration; FIFRA—Federal Insecticide, Fungicide, and Rodenticide Act; NCI—National Cancer Institute; NIOSH—National Institute for Occupational Safety and Health; NTP—National Toxicology Program; OSHA—Occupational Safety and Health Administration; RCRA—Resource Conservation and Recovery Act; RMCL—recommended maximum contaminant level; SDWA—Safe Drinking Water Act; SNUR—Significant New Use Rule; TSCA—Toxic Substance Control Act; WQC—Water Quality Criteria.

SOURCE: Office of Technology Assessment, 1987.

Limiting attention to those chemicals with three or four positive experiments reveals that agencies and programs have each acted on 1 to 22 of the 61 NCI/NTP chemicals with these results. Chemicals with three or four positive experiments will generate greater concern because in these cases there are positive results from both rats and mice. FDA has taken some regulatory action on 7 of the 19 chemicals with three or four positive experiments associated with food or color additives or cosmetics. The one animal drug with three or four positive results has been revoked while 5 of the 6 chemicals with three or four positive experiments have been removed from human drugs or have been labeled for carcinogenicity. OSHA has regulated 16 of the 30 chemicals with three or four positive experiments that are in its jurisdiction. One of these standards is based on carcinogenicity. NIOSH has made recommendations on 13 of the 39 chemicals in its jurisdiction with three or four positive results. In CPSC's jurisdiction, 4 of 7 chemicals have been subject to regulatory or voluntary action. Under the Clean Air Act, EPA has listed one of eight chemicals with three or four positive results. Water quality criteria have been issued for 7 of 10 chemicals in the Clean Water Act jurisdiction, and some regulatory action has occurred for 6 of the 7 chemicals under the jurisdiction of the Safe Drinking Water Act. Information has been developed under TSCA for 22 of the 61 chemicals with three or four positive experiments and SNURs, accelerated reviews, and section 6 actions have addressed 2 of the 61. EPA-ordered and voluntary cancellations have occurred for 5 of the 11 active pesticide ingredients with three or four positive experiments. RCRA lists include 22 of the 61 chemicals with three or four positive experiments, and the CERCLA list covers 22 of the 61. CAG assessments address 9 of the 61. No actions have addressed 23 of the 61 chemicals with three or four positive experiments.

Regulation of Chemicals Listed in the *Annual Report on Carcinogens*

All the *Annual Report* chemicals have been addressed by at least one agency, although a large number of these chemicals have not been acted on by all the agencies and programs that might

have an interest in them. Except for chemicals on the lists adopted under RCRA and CERCLA, no agency has regulated as many as half the chemicals included in the *Annual Report*. Generally, agencies have acted on 5 to 60 of these 145 *Annual Report* chemicals.

FDA has acted on 46 of the 52 *Annual Report* chemicals in its jurisdiction for food and color additives and cosmetics, and on 2 of the 6 *Annual Report* chemicals used as animal drugs. Of the 31 *Annual Report* chemicals with human drug uses, 26 have been removed from the market or have carcinogenicity warning labels. OSHA has exposure standards for 52 of 110 *Annual Report* chemicals in its jurisdiction; 17 of these standards are based on carcinogenicity. All *Annual Report* chemicals are covered by OSHA's hazard communication standard. NIOSH has made recommendations on 59 of the 112 *Annual Report* chemicals in its jurisdiction. Voluntary and regulatory actions have been taken on 18 of the 23 *Annual Report* chemicals in CPSC's jurisdiction. EPA listings under the Clean Air Act address 6 of 15 *Annual Report* chemicals in the act's jurisdiction. For 48 of 65 *Annual Report* chemicals in the jurisdiction of the Clean Water Act, water quality criteria have been prepared. Interim standards under the Safe Drinking Water Act, and the current RMCL/MCL process address 21 of 32 *Annual Report* chemicals within the act's jurisdiction. EPA has developed information on 28 of the 145 *Annual Report* chemicals in the TSCA jurisdiction and issued SNURs, started accelerated reviews, or section 6 actions on 6 of the 145. EPA-ordered and voluntary cancellations have affected 12 of the 24 *Annual Report* chemicals used as active ingredients in pesticides. The RCRA lists address 97, and the CERCLA lists 95 of the 145 *Annual Report* chemicals. CAG assessments cover 78 of the 145.

Comments on the OTA Analysis

In comments on a draft of this background paper, officials of Federal regulatory agencies emphasized their belief that they have acted appropriately in regulating the chemicals tested by NCI/NTP and the chemicals in the *Annual Report*. They pointed out that statutes require they

assess the risks and benefits of using chemicals, and the technical feasibility and costs of regulatory action. Because of these considerations, as well as their judgments about the weight of evidence for carcinogenicity, in some cases they have decided not to regulate substances. In other cases, the chemicals are being considered as subjects of regulatory action.

Future Improvements

Today the hope for a more complete understanding of cancer causation rests on research into biochemical markers, pharmacokinetics, and molecular mechanisms. Nevertheless, science cannot now answer all the questions that are raised in this field. Even in the face of such uncertainty, however, it is important to take action to protect public health.

Ever since the development of carcinogenicity bioassays, there has been skepticism about the reliability of animal results for estimating human risk. The Federal agencies have usually assumed the usefulness of animal test results. However, regulated industries have often disputed these results in particular cases and express concern that society not impose unnecessary regulations. These disputes are not likely to go away.

To force regulatory action, Congress has legislated a variety of statutory mechanisms. The most common of these have been statutory deadlines, which have sometimes led to regulatory action, but are also frequently missed by the agencies. In the 1984 RCRA amendments, Congress in-

cluded “hammers”-statutory provisions that go into effect if EPA misses particular deadlines. Congress has also mandated requirements, such as TSCA’S ban of PCBs, and agency adoption or consideration of designated lists of chemicals. In one case (that of saccharin regulation), Congress prohibited an agency from acting. A final congressional mechanism is requiring agencies to consider or respond to recommendations of another agency or organization. For example, OSHA must consider the recommendations of NIOSH, EPA must respond to nominations of chemicals by the ITC, and, in the original Safe Drinking Water Act, EPA was to respond to National Academy of Sciences recommendations.

In light of the regulatory gaps revealed by OTA’s analysis of agency responses to positive NCI/NTP bioassay results and the list of chemicals in the *Annual Report on Carcinogens*, Congress may wish to consider a statutory requirement mandating that agencies regulate these chemicals or at least publicly respond to these sources of information, even if, for various reasons, they choose not to regulate. On the other hand, such a requirement might make developing the *Annual Report* or selecting chemicals for NTP testing more difficult. In addition, regulatory action may not always be necessary and, if taken, may impose costs on regulated industries. Finally, in light of the importance exposures play in determining the need for regulation, it might be appropriate to develop additional information on the extent of human exposures to these chemicals.