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HAZARDOUS SUBSTANCES AND CANCER INCIDENCE: INTRODUCTION TO THE SPECIAL ISSUE ON RISK ASSESSMENT AND RISK MANAGEMENT*

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Summary

This paper is the introduction to a special issue that focuses on analyzing risks. It presents general background information on epidemiology and animal research for helping us learn more about the causes of cancer. It describes the positions of different groups on the question of a link between increased synthetic chemical production and an increased incidence of cancer. Finally, it heralds the new analytic approach and puts each paper of the series in perspective in terms of determining the current and future impacts of hazardous substances.

I. Introduction

All of the papers in this special issue focus on various aspects of hazardous substances. Indeed, as the evidence increasingly underscores, such substances are accumulating in our homes, workplaces, air, water, and land at an alarming rate. The acute or immediate implications on the environment, the affected species, and human health are more easily recognized and are beginning to be well understood. The chronic or long-term implications of exposure are still largely unknown, and may remain so for many years to come.

The chronic health effect that receives the most attention is cancer, one of the leading causes of death in all age groups. One in four of us will ultimately get cancer, and about one in five of us will die from it. There are many different types of cancer. Some are readily cured, whereas others are nearly always fatal. The various cancer types carry different symptoms, and widely different courses of treatment must be employed to deal with them. In practice, cancers of different organs are different diseases and it is unlikely that a single cure will prove effective against all cancer types.

In the last few decades, we have made notable progress in treating certain

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cancer types. These efforts can prolong the lives of cancer patients and lead to a decrease in deaths from certain cancers. On the other hand, although we have focused much on reducing the cancer death rate, we have been less successful in reducing the incidence rate, or preventing cancer. Basic cancer research may eventually help us to better understand the nature of cancer, but in the meantime, since it is unlikely that cancer will ever be cured, we must do more to address cancer prevention.

What follows is a discussion of what is currently known of the causes of cancer. In Section II, I summarize some of the difficulties in establishing the causes of cancer. In Section III, I review the positions of those involved in the contentious debate on whether or not the cancer incidence rate is increasing. This debate is ultimately tied to the question of what causes cancer. In Section IV, I describe the difficulties in determining the risks from hazardous substances spread throughout our environment given the uncertainties in the causes of cancer. I then link the papers of this special issue to this research.

II. Human cancer links

In the decades since World War II, our use of hazardous chemicals has increased significantly. The question of whether or not this has resulted in a corresponding increase in cancer incidence is inextricably tied to our ability to link exposure to disease. Epidemiology, the examination of common characteristics of people developing a disease, is used to shed light on the causes of cancers that have already occurred. Animal studies are also somewhat useful for establishing causation, and for examining the mechanisms of cancer. The most important function of such studies, however, is their use as predictors for human carcinogenesis and therefore as a tool for prevention. Short-term tests for mutagens are best used as a screen for potential carcinogens. Below we discuss each of these study types in turn and establish their utility in determining cancer causation.

Epidemiological studies

The epidemiology of cancer is fraught with uncertainty. In prospective cohort studies, for example, which follow a huge number of healthy individuals for years, the study must begin with an assumption of cause and effect so that the proper data are obtained. Historical cohort studies and retrospective case-control studies are designed to study people who have already developed cancer and, in many cases, have already died from it.

Even in well-designed epidemiological studies, it is difficult to include enough cancers of one type to determine its potential cause. Although cancer registries can help in the statistical respect, they cannot shed light on causation. Other problems with such studies are that cancer latencies may result in disease ten to fifty years after exposure; cases of cancer caused by a

particular carcinogen may not be significant in the background of cancers contracted for other reasons; it may not be easy to draw conclusions from unknown conditions, specifically dose related, that existed decades earlier; and it may be difficult to identify a unique cause for an effect, given the possibility of other confounding factors that may be contributing [1].

Apart from these difficulties inherent in epidemiological studies, there are other errors in methodology that can arise. The first is the "too few" problem where even a much increased cancer risk can be masked by the small sample size. The second is the "short follow-up" problem where including people with very short exposure times will significantly lower the cancer risk [2].

The limitations of epidemiology for cancer prevention are obvious. The results of such studies can indeed help to establish a substance as a carcinogen; they cannot, on the other hand, prevent those who have already been exposed to a carcinogen from developing cancer.

Animal studies

Animal studies are obviously more easily conducted than epidemiological studies. Their primary advantage is that other so-called lifestyle factors can be controlled, and the results are perhaps slightly more definitive than those of epidemiological studies. Another advantage is that animals have shorter lifespans, and the data can be obtained more quickly and more cheaply.

In spite of these advantages, animal tests have severe drawbacks. First, two-year tests on two animal species are expensive, ranging in cost from $500,000 to $1,000,000. Second, because of wide differences in species sensitivity, animal data cannot be directly translated to humans. Third, and perhaps most important, a substance that is carcinogenic in animals may not be carcinogenic in humans; conversely, a substance that is not carcinogenic in animals may be carcinogenic in humans. This shortcoming can have serious consequences.

How good are animal tests in predicting what will be carcinogenic in humans? There are some 39 established human carcinogenic agents and circumstances [3]. In addition to circumstances like reproductive history, this includes 26 agents or industrial processes that are known to induce cancer in humans [2]. These identified human carcinogens include aflatoxin, a natural carcinogen; asbestos, a fibrous industrial material; diethylstilbestrol (DES), a drug; and soot, tars, and oils that are present during various manufacturing processes. For all of the human carcinogens, there is good evidence that the substances induce cancer in animals as well [3].

The sample of substances for which there is general agreement on human carcinogenicity is very small. We can therefore say very little about the correlation between animal and human carcinogens. Because of the small sample size, there is no assurance that animal testing will identify all human carcinogens. Such substances, if they are marketed, could ultimately cause many deaths. Furthermore, there may be substances that do cause cancer

in laboratory animals and do not induce the disease in humans. If we prevent such substances from being marketed, we will forego their potential benefits. Nevertheless, animals studies may be the best predictive tool we have.

Short-term tests

In the last few decades, several short-term testing procedures have been developed. Perhaps the most notable, the Ames assay, was developed in 1975 [4]. Original results indicated that ninety percent of a set of carcinogens showed positive in the Ames test (ten percent were false negatives); thirteen percent of a set of non-carcinogens gave a positive Ames test result (false positives) [2].

Although short-term assays are useful for screening chemicals for further testing, they are not especially reliable for predictive purposes. For instance, the Ames assay can have much less than ninety percent success in identifying carcinogens in certain chemical classes. DDT is an example of a carcinogen not identified in the Ames assay. Furthermore, it can miss whole classes of chemicals altogether. For instance, the test misses most heavy metals, some of which are carcinogens.

Cancer causation

Of the three types of studies described above, only epidemiological studies can definitely establish a substance or process as a human carcinogen. It is ironic and tragic that such "proof" requires the illness or death of human beings. As a result, epidemiology has its main use in verifying that substances are carcinogens; its utility does not lie in prevention. On the other hand, animal tests cannot unequivocally identify human carcinogens. Nevertheless, they are the only studies that can be employed as predictors. Short-term assays can provide supporting data for the animal tests. In the final analysis, we face a dichotomy: to obtain certain proof, we must have deaths; to act on uncertain predictions, we must forego proof.

III. Cancer in an industrial society

The theory of cancer development that is most widely accepted introduces the concepts of the initiator and promoter [5]. Initiators begin the process by transforming a normal cell into a neoplasm; promoters exacerbate the process by causing proliferation of the transformed cell into a tumor, bringing it to the disease stage [6]. The process of developing overt clinical disease is potentiated by the immune system. We know little about initiators and promoters but are beginning to recognize that cancer development is probably a multistage event, and that interaction of several different exposures to different agents may lead to an increase in cancer risk. Indeed, synergistic interactions among multiple agents may be necessary before the disease manifests itself. In spite of these theories, we still tend to think of cancer as a series of diseases, each of which has a single cause.

In the last few years, the question of what causes cancer has become extremely controversial. The controversy surrounds the use of the term "environmental" carcinogens, which is taken to mean synthetic chemicals by some, and all non-genetic factors by others [7]. The focus of the debate is the fraction of cancer that is caused by environmental agents.

It is indeed important to establish how much of cancer has a non-genetic origin because such cancers are preventable. Some, like cancers induced through smoking or other lifestyle habits, can be prevented by an individual's decision; others, like asbestos-induced cancers, can only be prevented through changes in governmental policies. The higher the fraction of cancers caused by agents in the workplace and general environment, the more responsibility we, as an industrial society, have to prevent it. The argument over the causes of cancer is therefore highly political.

In what follows, I first present time series data on synthetic chemical production. I then discuss the information and disagreements on the causes of cancer, and try to sort out the relationship between synthetic substances and cancer.

Synthetic chemicals

There is no question that synthetic chemical manufacture has burgeoned since World War II, particularly in the last few decades. Many of these chemicals and chemical products are hazardous in one way or another. There are some 60,000 chemicals of industrial importance in commerce today, and about 1,000 new substances are introduced into the market each year [8]. Workers are exposed to them during the production stage; users are exposed to them while they are used; the public at large is exposed to them in the air, water and at disposal sites.

In 1960, total production of synthetic organic chemicals amounted to 53,925 million pounds*; in 1970, the total was 138,322 million pounds; in 1980, it reached 215,125 million pounds. According to these data, between 1960 and 1970, synthetic organic chemical production grew by an astounding two and one-half times. For the entire period 1960 to 1980, the increase was slightly less than four-fold [9, 10]. Certain families of chemicals grew somewhat faster; the persistent halogenated hydrocarbons, for example, increased more than four times [9,10]. Members of this class include the established human carcinogen vinyl chloride, and the animal carcinogens trichloroethylene and perchloroethylene.

Since some synthetic organic chemicals are animal carcinogens, their rapid growth would be expected to ultimately lead to a corresponding increase in cancer rates. Such an increase would tell us something about the fraction of cancers caused by exposure to toxic chemicals.

*Totals exclude tar, tar cruds, and primary products from petroleum and natural gas.

The causes of cancer

The landmark attempt to assign the causes of fatal cancers was made by Doll and Peto in 1981 [3]. As part of the research the two epidemiologists also examined whether or not total cancers or cancers of specific types had increased over time. Non-melanoma skin cancers were excluded from the analysis because they are easily curable and rarely fatal. Doll and Peto found that cancers in three organs, the lung, the breast, and the large intestine, accounted for nearly half of all cancer deaths in 1978. Deaths from breast and colon cancer have largely remained constant, with a few fluctuations, since 1930. There has been a decrease in cancers of the stomach and uterine cervix. There has been a large increase in cancer of the lung, which Doll and Peto attribute to tobacco use. They conclude that there have been no large changes in the incidence of non-respiratory cancers.

In assigning the causes of cancer, Doll and Peto attributed around 30 percent of all cancer deaths to smoking; approximately three percent to alcohol; about 35 percent to dietary factors, like excess fats, lack of fiber, and naturally occurring carcinogens in food; approximately ten percent to infection; about seven percent to reproductive and sexual behavior; and four percent to other factors. They further estimated that exposure to carcinogens in the workplace, from pollution, food additives, and industrial products together caused less than eight percent of all cancer deaths [3].

The Doll/Peto assertion that there has been no increase in cancer in the United States apart from that caused by smoking is notable because it suggests that there has not been an increase in cancer from the strong industrialization that occurred in the last few decades. They do reach the conclusion, however, that most cancer is avoidable. Indeed, if some 65 percent of cancer deaths are attributable to the combined effects of tobacco and diet as estimated, then, in principle, 65 percent of cancers are avoidable through abstention from tobacco and eating the proper foods. These cancers can be avoided as a matter of personal choice, since the same person who takes the risk (contracting lung cancer) derives the benefit (pleasure from smoking). In contrast to the large fraction of cancers avoidable through personal choice, Doll and Peto conclude that only a small fraction of cancers could be prevented by regulating workplace and general environmental exposure.

A team composed of members from the National Cancer Institute, the National Institute of Environmental Health Sciences, and the National Institute for Occupational Safety and Health had earlier reached a very different conclusion from the Doll/Peto analysis. Their results, called the Bridbord et al. Study, suggested that occupationally related cancer should be responsible for twenty percent or more of all cancer deaths [11]. The work focused on cancer deaths from asbestos, nickel ores, arsenic, chromium, benzene, and petroleum fractions. It concluded that asbestos alone could contribute as much as thirteen to eighteen percent to the cancer death rate, and that the other five carcinogens could account for ten to twenty percent more.

Another group, the Toxic Substances Strategy Committee (TSSC) in a

1980 report to the President, also disagreed with the Doll/Peto conclusions. The Committee found that real cancer rates are increasing significantly, at a rate of two percent per year for females and 1.3 percent annually for males [12]. The report states that with adjustments for age, both the incidence and mortality of cancer are increasing, even after taking account of cigarette smoking.

Epstein and Swartz support the conclusions of Bridbord et al. and disagree with those of Doll and Peto [13]. They argue that the Bridbord et al. report probably underestimates the fraction of cancer deaths caused by occupational and environmental carcinogens. They contend, furthermore, that cancer deaths have increased and that the increases cannot be explained by smoking alone. They suggest that relying on overall age-adjusted incidence or mortality rates (as did Doll and Peto) will mask large increases in various kinds of cancer that are occupationally related.

Davis et al. agree with Doll and Peto that there has been no generalized increase in cancer mortality, apart from that caused by smoking [14]. This research does show, however, that mortality rates for some cancers that are strongly associated with occupational exposure have increased in males between the ages of 45 and 84. Specifically, it notes significant increases in cancers of the brain and lung, and in multiple myeloma in men aged 55 to 84. These cancers are strongly correlated with workplace carcinogens, and men in older age groups would be expected to have longer sustained exposure to some chemicals.

The Davis et al. group has also focused on past and current chemical production trends. Production of synthetic chemicals that are recently documented carcinogens, including benzene, chloroform, vinyl chloride, and ethylene oxide, approximately doubled during the 1970s in comparison with the 1960s. Workers in vinyl chloride plants in the 1930s and 1940s did not develop angiosarcoma, a rare liver cancer, and brain cancer until decades later, in the 1960s and 1970s. If these latencies or time periods between exposure and onset of cancer hold for the more recently marketed chemicals, then we would not expect the cancer rate increases reflecting the growth in the 1970s to appear until the end of the century. Furthermore, any changes that did occur would probably be small because they would affect limited subgroups of the population. This group emphasized that past cancer rates may not primarily reflect occupational and general environmental chemical exposure, but that future rates unequivocally will [4].

Davis et al. criticize the Doll/Peto work for excluding those over 65. They emphasize the importance of including males older than 45 because they would be more likely to have developed cancers after 20 year or more latency periods. In addition, people under 45 have shown a significant decrease in incidence and mortality for many forms of cancer, and combining the younger and older age groups obscures any increase the older group alone might show. Indeed, approximately half of all cancers develop in people 65 or over. The research also stresses that we simply do not know to

what extent the large lung cancer increase reflects tobacco use alone. It may, in fact, be a result of synergies or enhancing interactions between cigarette smoking and exposure to environmental carcinogens, rather than to tobacco alone [14].

What can we say about cancer and the increase in production of synthetic chemicals and their introduction into the general environment from this discussion? Although the data are inadequate for analysis and very little agreement exists among the experts, it is probably safe to conclude that there has been no obvious generalized increase in cancer deaths except those related to smoking in the last fifty years. Deaths from certain types of cancer that are linked to chemical exposure have probably increased, and total cancer deaths over the period may have increased for certain segments of the population.

It is uncertain how much of the current cancer death rate is related to exposure to toxic chemicals. Some of the deaths from tobacco may actually have been caused by interactions between smoking and chemicals. Estimates of current cancer deaths attributable to toxic chemicals range from eight to about thirty percent. This implies that of about 450,000 cancer deaths that are expected to occur in 1984, between 36,000 and 135,000 will be caused by synthetic chemicals. Even if the lower number is accurate, it still represents a huge number of deaths that could have been prevented by controlling exposure to hazardous chemicals.

There is little doubt that the increased production of synthetic organic chemicals and their widespread incorporation into our food, water, air, and land will eventually have consequences. No one really knows yet how serious these consequences will be. In the next section, I discuss the methods that are now being used to learn more about toxic substances in the environment and what the future may hold.

IV. Hazardous materials assessment

The method by which we seek to examine if there have been increases in cancer is epidemiology. Most of the evidence linking the disease to toxic chemicals has been determined from the workplace where a small group has been heavily exposed. A new and different approach is necessary for two reasons. First, we need to determine what the future cancer incidence might be as a result of the more generalized environmental exposures that began occurring in the last decade. Second, we need a method for predicting the health consequences of chemicals and chemical products that firms propose to market in the future.

In response to these needs, methods for estimating the impacts of hazardous substances on our society and identifying techniques for reducing or preventing deleterious outcomes are emerging. Other efforts in the last decade have focused on modeling transport of toxic substances as they move through the environment, exposure of various population groups, and the

response of a population. There is much uncertainty in the results of environmental transport models because of the chemical and physical transformations that a substance can undergo as it passes through the air, water, or soil. Because epidemiological data are available for only a few substances, we must commonly use the results of animal tests and dose—response models to estimate the human health risks. There is uncertainty in the dose—response models, which are designed to extrapolate the high doses used in animals for statistical reasons, to the low doses likely to be encountered in the general environment.

Davis and Gusman defined the term "exposure assessment," which encompasses the assessment, mitigation, transport, exposure, and health effects studies. They maintain that such assessments belong to an orphaned professional field which relies on input from a host of disciplines including toxicology, epidemiology, pharmacology, pharmacokinetics, medicine, biochemistry, chemistry, environmental engineering, and science [15]. A more common term for the emerging field may be "risk analysis." It is composed of both risk assessment, which is equivalent to exposure assessment defined above, and risk management or the implementation of policies to reduce the risk. The papers in this issue are at the forefront of this emerging field. Below I discuss each in turn.

Technical assessment

The first set of three papers is concerned with assessing certain practices and evaluating the methods for reducing a particular threat posed by specific hazardous substances. The first paper, entitled *The Interaction of Flammability and Toxicity in an Aerosol Product*, explores and compares the characteristics of liquid hydrocarbon and carbon dioxide propellants used in aerosol cans by manufacturers of a nondestructive test material. When chlorofluorocarbon (CFC) propellants were banned, some manufacturers chose hydrocarbon propellants, which offer a superior performance and the disadvantage of flammability; others chose CO_2 propellant, which is cheaper but offers an inferior performance.

The second paper in this set is called *Substitution Analysis: A Case Study of Solvents.* This work seeks to identify alternatives to CFC solvents, which are suspected of depleting the ozone layer. The research concludes that few alternatives are as good technically as CFC-based solvents given current equipment and procedures.

The third paper in this set is *A Survey of Monitoring Technologies for Subseabed Disposal of Radioactive Waste.* It assesses the advances in monitoring that would be required in the event that the subseabed is considered for disposal of radioactive waste. It includes a summary of physical, chemical, biological, and ecological monitoring techniques that might be appropriate.

General risk analysis

The second set of four papers in this issue deals generally with risk analysis. The first paper, *Quantitative Risk Analysis for Toxic Chemicals in the Environment*, is an introduction to risk analysis for managers. It summarizes the steps in determining the human health risks from toxic chemicals in the environment that can cause chronic effects.

The second paper in this set, called *The Management and Assessment of Risks from Recombinant Organisms*, focuses on the nontraditional path used to develop policies for recombinant DNA. Instead of the more common stages of research, risk assessment, and risk management through which most hazardous materials questions evolve, recombinant DNA deviated significantly. Almost directly after the laboratory technique was developed, restrictions were instituted. This step preceded the research and risk assessment phases.

The third and fourth papers in this set deal with risk management, or questions about implementing policies for reducing risks. One, entitled *On the Use of Confidence Levels in Risk Management*, describes a method for using uncertainty as a component of management decisions. It illustrates the utility of such a method by applying it to situations where safety goals must be met and where cost—benefit criteria are evaluated. The other, called *On the Usefulness of Quantitative Safety Goals for State Regulation of Energy Systems*, assesses the importance of quantitative risk assessment to management. Five case studies are analyzed and compared in terms of the risk they pose, and the decisions to mitigate them. The research draws some general conclusions on the utility of quantifying risk.

Applied risk assessment

Each of the three papers in the third set illustrates the application of risk assessment. From them, we get a flavor of the complexity of such assessments. The first, *Risk Analysis of Hazardous Materials in Oil Shale*, determines the occupational, public, and ecosystem risks for a one million barrel per day shale complex. Lung disease for miners was found to be a significant problem — public health risks were less serious; the most important effect on the ecosystem was the risk to aquatic organisms.

The second, entitled *Estimating the Chronic Health Risk From Coal-Fired Power Plant Toxic Emissions*, presents a risk assessment of two case studies, arsenic and selenium. A series of models is used to describe the environmental transport, exposure, and the chronic human health effects of each pollutant. The research also presents an analysis which illustrates that dose—response models are the source of greatest uncertainty.

The third paper, *Computer-Based Environmental Exposure and Risk Assessment Methodology for Hazardous Materials*, presents a method for modeling overland and surface water transport of toxic substances. The research describes two case studies where the pesticides Alachlor and toxaphene were applied to farmland, one in Iowa and the other in Mississippi. The results showed that four species of fish were damaged by toxaphene, but that Alachlor had no discernible impact.

Human health implications

The fourth and final set of three papers focuses on the human response. The first two address dose—response models, the models that are used to extrapolate the results of high doses of toxic substances used in animal experiments to low doses more likely to be encountered by humans. The third reviews theories of biological interaction. The first paper is entitled *Improved Confidence Limits for Low-Dose Carcinogenic Risk Assessment From Animal Data*. It presents a generalized extrapolation method that is based on the multistage cancer model. The procedure is linear and utilizes all of the available data. Its utility is illustrated by application to two hazardous substances, ethylene thiourea (ETU) and hexachlorobenzene (HCB).

The second paper in this set, *Uncertainty in Health Risk Analysis*, addresses the quantitative nature of the analysis of health risks. Its main focus is on the probabilistic nature of risks, and it emphasizes that analyses of carcinogenic risks differentiate between uncertainty and inability to know. A case study on arsenic illustrates that uncertainty in dose—response models is high.

The third paper of the group, *Elementary Models For Biological Interaction*, is a discussion of the Hewlett—Plackett theory with a basis in bioassay, and the sufficient-component cause theory with a basis in epidemilogy. Both are theories that describe biological response to hazardous exposure. The results show that the theories correspond in their description of disease rates and biological interaction.

V. Conclusions

In the last few decades, we have become increasingly reliant on chemical and industrial processes and products. Prior to 1970, there was little control on releases of hazardous materials into the workplace, air, water, and land. Today, although we have government agencies to monitor and check dangerous exposure, the task they face is formidable. Indeed, we are only now finding that many of the hazardous substances in place in society can cause severe health problems, including birth defects and, most notably, cancer.

Some researchers have found increases in the incidences and deaths of workers from various types of cancers associated with workplace exposure. It is not yet clear whether the widespread use of toxic materials has led to a generalized increase in the cancer incidence. Because the production of such substances increased markedly only in the last decade, we may not know the full influence of their ubiquity until the turn of the century.

Epidemiological studies will play the major role in ultimately linking the substances to the disease. Although it is unequivocally useful for such retrospective conclusions, epidemiology must not be used for prospective policy-making. Animal studies, on the other hand, are useful for deciding which chemicals pose a potential threat to humans. Decisions on whether to introduce substances into commerce must be based on the results of such laboratory studies and on research efforts like those described here.

We can learn more about the processes of toxic species in the air, land, and water through assessment studies and environmental modeling. We can get more information on the problems we face in using hazardous substances by performing risk analyses. We can explore the impacts of such substances on human health by using animal data and dose—response modeling techniques. How to best perform these studies, including those of this issue, is still evolving; how to wisely interpret their results to save lives is the challenge of our decade.

References

1 S. Epstein, The Politics of Cancer, Anchor Books, Anchor Press, Doubleday, Garden City, New York, 1979.
2 L. Tomatis, C. Agthe, H. Bartsch, J. Huff, R. Montesano, R. Saracci, E. Walker and J. Wilbourn, Evaluation of the carcinogenicity of chemicals: A review of the monographs program of the international agency for research on cancer, Cancer Res., 38 (1978) 877.
3 R. Doll and R. Peto, The causes of cancer: Quantitative estimates of avoidable risks of cancer in the United States today, JNCI, 66 (1981) 1191.
4 B.N. Ames, J. McCann and E. Yamasaki, Methods for detecting carcinogens and mutagens with the Salmonella mammalian microsome mutagenicity test, Mutat. Res., 31 (1975) 347.
5 P. Armitage and R. Doll, Stochastic models for carcinogenesis, in: L. LeCam and J. Neyman (Eds.), Proceedings of the Fourth Berkeley Symposium on Mathematical Statistics and Probability, Vol. IV, Berkeley, University of California Press, 1961, p. 19.
6 E. Farber and R. Carneron, The sequential analysis of cancer development, Adv. Cancer Res., 31 (1980) 125.
7 A.M. Lilienfeld, Some aspects of cancer epidemiology, Biometrics Supplement: Current Topics in Biostatistics and Epidemiology, 1982, p. 155.
8 Assessment of new chemical regulation under the Toxic Substances Control Act, General Accounting Office, June 15, 1984.
9 United States International Trade Commission Reports, Synthetic organic chemicals, United States sales and production, 1980.
10 United States Tariff Commission, Synthetic organic chemicals, United States production and sales, 1960 and 1970.
11 K. Bridbord et al., Estimates of the fraction of cancer in the United States related to occupational factors, National Institute of Environmental Health Sciences and National Institute of Occupational Safety and Health, September 15, 1975.
12 Toxic chemicals and public protection, Council on Environmental Quality, Washington, D.C., United States Government Printing Office, 1980.
13 S. Epstein and J.B. Swartz, Fallacies of lifestyle cancer theories, Nature, 289 (January 15, 1981).
14 D.L. Davis, K. Bridbord and M. Schneiderman. Cancer prevention: Assessing causes, exposures, and recent trends in mortality for U.S. males, Int. J. Health Serv., 13 (1983) 337.
15 D.L. Davis and S. Gusman, Exposure assessment: New frontier, old problems, Toxic Subst. J., (summer 1982).