INSIGHTS
CHEMICAL CARCINOGENS AND CANCER IN PERSPECTIVE

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CHEMICAL CARCINOGENS AND CANCER IN PERSPECTIVE

Advancement of chemical technology is the primary mission of the Texas Institute for Advancement of Chemical Technology. The purpose of this report is to advance technology through an informed public.

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CHEMICAL CARCINOGENS AND CANCER IN PERSPECTIVE

Our inability to find cures for all of the dreaded diseases called cancer makes cancer an emotional issue. Out of confusion, the general public has become an easy prey for those who claim to know all of the answers. Exaggerated claims in the 1970's by a number of people, including some with scientific training, that almost all cancer was caused by industrial pollution have been discredited by the careful studies of Doll and Peto[1]†, Higginson[2], Higginson and Muir[3], Cole[4], and Wynder and Gori.[5]

Many have heard only the exaggerated claims and formed opinions on that basis. There are, however, real risks which must not be confused with exaggerated claims. The purpose of this paper is to "set the record straight," present facts provided by scientists, and give an assessment of just where we are.

There follows an abbreviated summary of some of the findings and conclusions of this report. A more detailed treatment of this subject is presented in the "Special Report: A Brief Review of Chemical Carcinogenesis." Personal copies may be obtained upon request from the author.

Summary of Findings and Conclusions

- Cancer is a prevalent disease, but there is no evidence to support the allegation that an epidemic exists.
- The allegation that 60% to 90% of the cancer mortality is caused by "man-made" chemicals is not supported by experimental evidence. The most reliable estimate to date attributes 4% to occupational hazards and 2% to pollution for a total of 6% or 9% if alcoholic beverages are included.
- The leading causes of cancer according to the most reliable estimates are: tobacco use (30%) and diet or lifestyle (35%), which includes factors such as lack of dietary fiber, caloric intake, excess fat and possible hormone carcinogenesis.
- A comparison of the mortality for each type of cancer experienced by the countries throughout the world with those of the United States shows that there is the possibility of avoiding over 70% of the cancers in the United States. The avoidance

† The study of Doll and Peto[1] is the most thorough and massive of those made to date, and it is drawn upon heavily throughout the present analysis. At the time this study was published, Sir. Richard Doll was Honorary Director, Imperial Cancer Research Fund, Cancer Epidemiology and Clinical Trials Unit and Warden of Green College, Oxford, United Kingdom, and Mr. Richard Peto was Imperial Cancer Research Fund Reader in Cancer Studies, Nuffield Department of Clinical Medicine, University of Oxford, Radcliffe Infirmary, Oxford, United Kingdom.

This study by Doll and Peto is a report commissioned by the Office of Technology Assessment, U.S. Congress, to provide background material for their assessment of "Technologies for Determining Cancer Risks From the Environment" (OTA, 1981).

of the full 70% is an unrealistic possibility because of the many conflicting factors involved in the comparison. For example, the prevention for one type of cancer could be the cause for another.

- It has been alleged that the United States ranks first of all nations in cancer mortality. The fact is the United States is ranked between 18th and 22nd in the numerous studies which have been made.
- Cancer research has contributed to a better understanding of body functions such as cell division in terms of the chemical reactions. This improved understanding has led to new theories of cancer formation which hold the promise of more effective treatments and cures, more accurate methods of risk assessment, and more effective preventions within the foreseeable future.
- Cancer research has also resulted in discoveries of the body's involvement in the cancer formation and prevention process. It is now generally recognized that cancer causing agents either introduced into the body or produced within the body have been heavily counterbalanced by an abundance of repair mechanisms, anticarcinogens, and inhibitors provided by nature.
- A cheap reliable test for chemical carcinogens remains to be discovered. The presently used animal tests are both expensive and fraught with difficulties of interpretation and use in risk assessment.
- We now know that we are exposed to a "sea" of natural carcinogens whose levels far exceed those of man-made carcinogens in most instances. However, this knowledge should not be used as a license to make significant additions of carcinogens to our surroundings.
- No health hazards have been found by the experimental studies of the Texas Air Control Board and the Houston Regional Monitoring Program. The range of all substances detected were within the range of levels considered typical of heavily urbanized areas across the United States.
- In an extensive five year experimental study by EPA, called the TEAM study, the scientists concluded, contrary to popular belief, that people living in heavily industrialized areas containing petrochemical, paint, and plastic processing plants are not subjected to greater exposures to the commonly identified toxic chemicals, than are people living in less industrial areas, or even rural areas. A further finding was that people are exposed to far greater concentrations of toxic chemicals indoors than outdoors. Ironically, people spend most of their time indoors, while regulations on toxic materials largely pertain to outdoor levels.
- Industry has made tremendous strides in reducing emissions at ever increasing costs. This effort has been directed toward the reduction of cancers caused by occupational hazards (4%) and environmental pollution (2%). Should we not consider spending more on cancer research directed toward the prevention, treatment, and cures of the remaining 90+%?

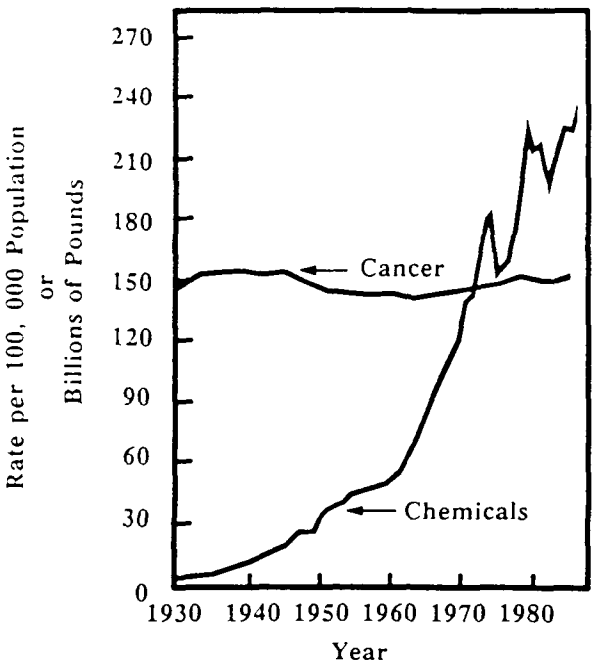


Figure 1. The overall cancer rate has remained essentially constant while the production rate of organic chemicals has increased over two hundred fold during the past 50 years. [Age-adjusted to the 1970 U. S. Census; United States Trade Commission,[6] and U. S. National Center for Health Statistics and U. S. Bureau of the Census.[7]]

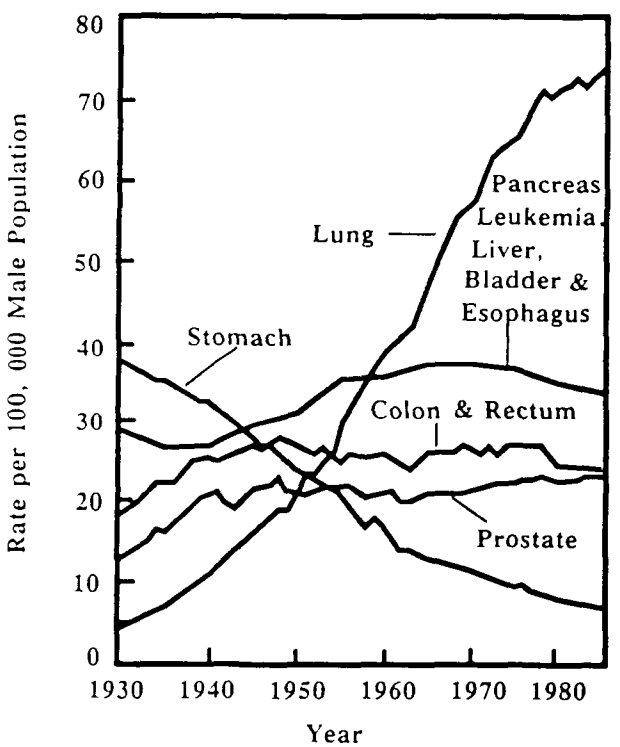


Figure 2. Age-adjusted cancer death rates for selected sites, males, United States. [Age-adjusted to the U. S. 1970 Census. Source of data: U. S. National Center for Health Statistics[6] and U. S. Bureau of the Census.[7]]

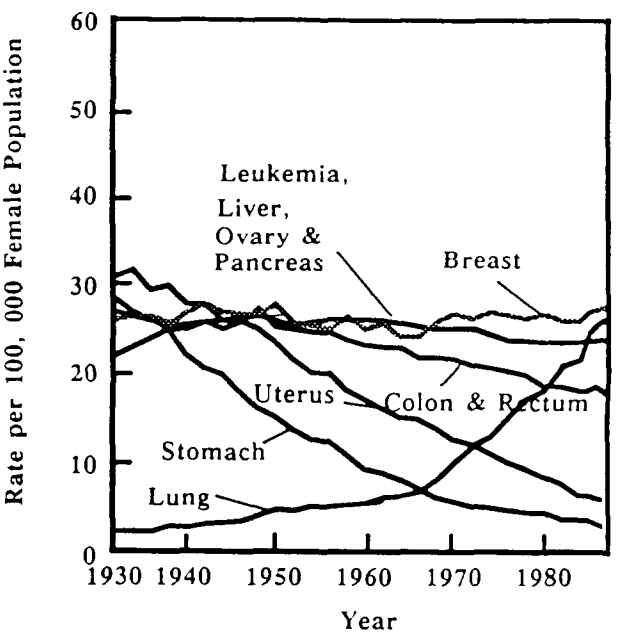


Figure 3. Age-adjusted cancer death rates for selected sites, females, United States. [Age-adjusted to the U. S. 1970 Census. Source of data: U. S. National Center for Health Statistics[6] and U. S Bureau of the Census.[7]]

Comparison of Cancer Mortality with the Production of Chemicals

A cancer epidemic has been alleged and attributed to man-made chemicals. As shown in Figure 1, the facts do not support this allegation.[6,7,8] The total cancer mortality rate has remained essentially constant from 1930–1985. [To correct for yearly changes in population, it is customary to age-adjust all rates relative to the population for a particular year.] Over this period of time (1930–1985), the production rate of synthetic chemicals has increased over two hundred fold. Likewise, emissions from automobiles and diesel-powered vehicles (which contain some carcinogenic materials) have increased enormously, but total cancer mortality rate has not.

Even after allowing for a latency period of 15 to 25 years for cancer to develop after exposure, the data do not demonstrate any detectable cancers from the above exposures. Cancer is a highly prevalent disease, but this fact alone does not make it an epidemic. Only if a disease is growing rapidly throughout a population at a rate clearly in excess of that normally expected is it classified as an epidemic, and obviously it is not as shown in Figure 1.

A more detailed analysis of cancer death rates from 1930–1985 is presented for men and women in Figures 2 and 3, respectively. Observe that the decrease in stomach, colon, uterus, and ovarian cancer rates is approximately equal to the increase in the lung cancer rates. If it were not for lung cancer, the total mortality rate would have declined.

These figures further demonstrate that there is no cancer epidemic in the United States, except possibly for lung cancer which is known to be caused primarily from the past uses of tobacco. The perception that there is a significantly higher cancer rate today than there was in the past exists because of the following reasons. First, because of the discovery of preventions and cures for the once fatal infectious diseases which have been almost eradicated, cancer has become a more prevalent cause of death. Also, as illustrated by Figure 4, great strides have been made in the treatment of the major cardiovascular diseases. Since everyone must die of something, the prolonging of life allows time for tumors and cancers to develop with the result that cancer will become even more prevalent than it is today as a "disease of old age." Thus, our success in the treatment and cure of other diseases has contributed to cancer's becoming more and more a disease of the elderly; 60% of all cancer deaths occur in persons 65 or older, 34% in persons 45 to 64, and 6% in persons under 45 years of age as shown by Schottenfeld[9] in Figure 5. Second, many cancers were not diagnosed in the past, particularly in the elderly, whose deaths were frequently attributed to "natural causes" and "old age." Diagnostic methods have improved and are continuing to do so, leading to the identification and treatment of cancers which would have been missed in the past. The advent of new medical knowledge, better nutrition and improved lifestyles, all supported by industrial development has led to longer, healthier lives. This does not mean that cancer should not be prevented; it means we must find ways to abate it where we can, and not lose benefits that we now enjoy, but enhance them. Third, people are more open today about diagnosis of cancer and the subsequent treatments than they were in the past. There was a tendency to keep the diagnosis a secret and in many instances, it was even withheld from the patient.

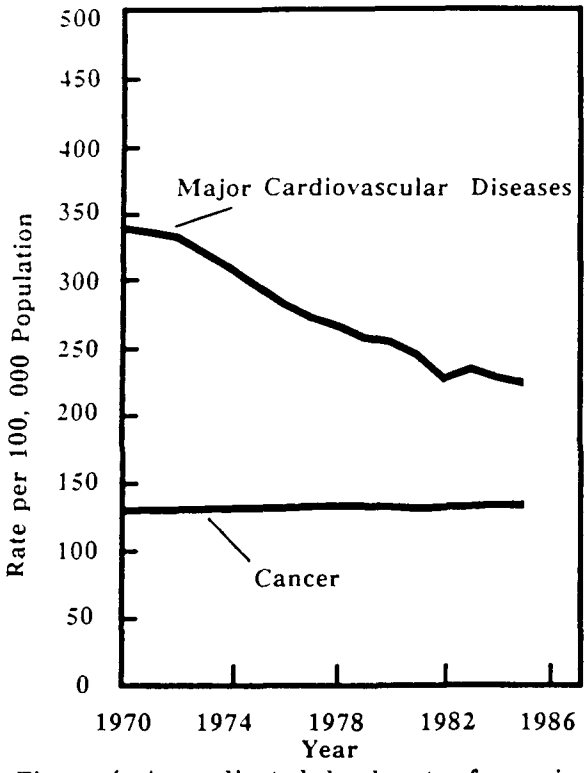


Figure 4. Age-adjusted death rates for major cardiovascular diseases and malignant neoplasms. [Source: Vital Statistics of U. S. Department of Health and Human Services: age-adjusted to the 1940 U. S. Census.[7]]

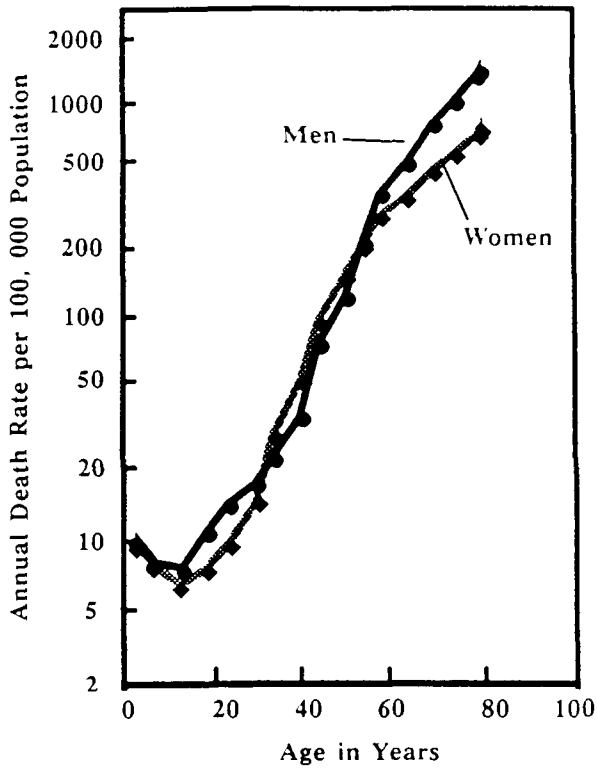


Figure 5. Cancer death rates by age and sex. Source: Vital Statistics of the United States, 1977. [From Schottenfeld, D., *Cancer*, 47(5), 1095 (1981).]

Leading Causes of Cancer

On the basis of an analysis of a vast volume of data on the various types of mortality up until 1980, Doll and Peto[1] deduced the distribution of the causes of cancer mortality shown in Figure 6 with the range of acceptable estimates shown in Table 1. These results discredit the claims of those who claimed that 60% to 90% of all cancer mortality resulted from "man-made" chemicals. As shown in Figure 6, diet is the leading cause of cancer with 35%, and use of tobacco is second with 30%.

Doll and Peto point out that although the figure of 35% is a plausible total for diet, the parts that contribute to it are uncertain in the extreme as indicated by the range of acceptable estimates from 10 to 70% shown in Table 1. Also, as indicated in Table 1, the firmest estimates in Figure 6 are those for tobacco, alcohol, and geophysical factors. Observe that the range of acceptable estimates of -5 to 2% for food additives in Table 1 reflects the fact that food additives contain antioxidants and other preservatives which may behave as anticarcinogens; that is, they may counteract the effect of chemical carcinogens.

To estimate the cancer mortality attributable to occupational hazards, Doll and Peto divided all cancer mortality into three groups and on the basis of the latest scientific evidence in the literature estimated the number in each group that could have been caused by occupational exposure. The results of this analysis are shown in Figures 6 and 7.

From the distribution of cancer mortality caused by occupational hazards, shown in Figure

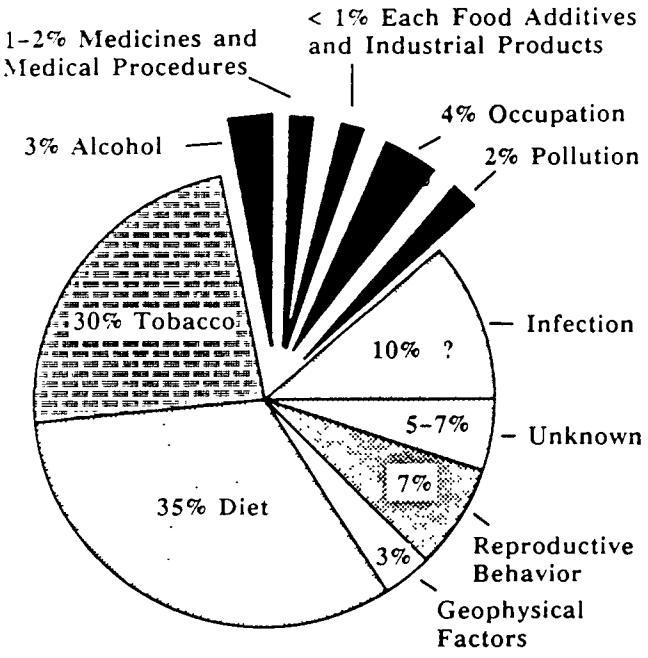


Figure 6. Distribution of cancer proposed by Doll and Peto.[1] [Age-adjusted to the 1970 U. S. Census.]

Table 1. Range of Best Estimate for the Cause of Cancer Shown in Figure 6. [Taken from Doll and Peto.[1]]

Cause of Cancer	Percent of All Cancer Deaths: Best Estimate	Range of Acceptable Estimates
Tobacco	30	26 to 40
Alcohol	3	2 to 4
Diet	35	10 to 70
Food Additives	< 1	< -5 to 2
Reproductive and Sexual Behavior	7	1 to 13
Occupation	4	2 to 8
Pollution	2	< 1 to 5
Industrial Products	< 1	< 1 to 2
Medicines and Medical Procedures	1	0.5 to 3
Geophysical Factors	3	2 to 4
Infection	10 ?	1 to ?
Unknown	5 to 7*	?

*The "?" used by Doll and Peto to denote their uncertainty has been replaced by 5 to 7 so that the best estimates have a sum of approximately 100.

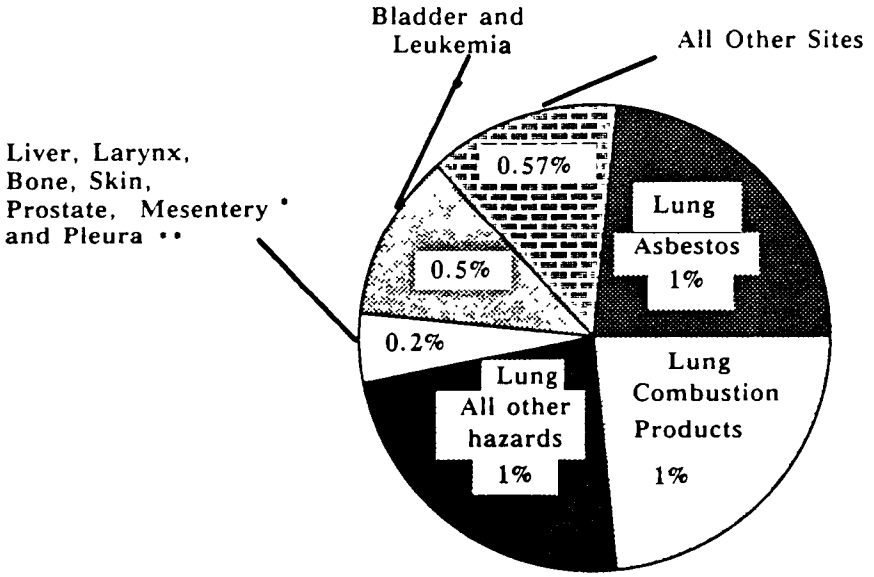


Figure 7. Distribution and types of the 4% occupational cancer mortality estimated by Doll and Peto[1] [Total number of cancer deaths was 401, 955, age-adjusted to the 1970 U. S. Census. Of these, 17,069 were attributed to occupational hazards.]

* Membranes that attach organs to body walls.

** Membranes that facilitate movement of lungs.

7, it is evident that lung cancers caused by asbestos, combustion products, and all other hazards makes up three-fourths of all cancer resulting from occupational hazards (3% out of 4%). Although tobacco has affected large segments of the population, workers and others, as shown in Figure 6, it is not classified as an occupational hazard; whereas, asbestos is so classified because of its overwhelming contribution to hazards of the work place relative to those of the general public.

The results of Doll and Peto[1] given in Figures 6, 7, and Table 1 are supported by the studies performed by others such as Higginson and Muir[3] and Wynder and Gori.[5] Higginson and Muir refer to "life-style" rather than diet, meaning factors such as lack of dietary fiber, caloric intake, excess fat, and possibly hormone carcinogenesis. Thus, these estimates are seen to be in general agreement, although not exact, with those of Doll and Peto.

Avoidance of Cancer

The estimate that over 70% of all cancers are avoidable was deduced by Doll and Peto[1] by identifying those countries, or areas of countries, having the lowest mortality rate for each type of cancer and comparing them with the corresponding rates for the United States. As a basis for the United States, the mortality rates from the Connecticut registry were used. These studies suggest that our higher cancer rate for each type of cancer can be attributed to some aspect of our lifestyle, general environment or genetic constitution which differs from those of the country having the lowest cancer incidence. While some of these cancers may be individually avoidable, it should not be inferred that the full 70% are avoidable because of the many conflicting factors unaccounted for by Doll and Peto's simple comparison. For example, the prevention for one type of cancer could be the cause for another.

The Environmental Movement

During the 1960's, the environmental movement was born because of pollution problems, many of which were severe at that time. The movement was strongly fueled by scientists such as Rachel Carson,[10] a biologist with the Fish and Wildlife Service. Her book, *Silent Spring* focused mainly on pesticides of which DDT was her greatest concern. Her dramatic approach led to a needed tightening up of the regulations on the manufacture and use of pesticides.

She was followed by others who predicted a catastrophic end to our way of life by as early as the 1980's and certainly by the early 2000's. Their remedy was "zero growth" and a "redistribution of Western wealth to Third World nations." Barry Commoner, also called for a change in our constitution and system of government. Recently, he gave a full exposition of his views along the same lines in the *New Yorker* magazine (June 15, 1987).

An "uncontrollable decline" was predicted by a group from the Massachusetts Institute of Technology in which industrial resources, industrial output, food supply, and population would crash somewhere near the year 2005. This report was prepared at the request of the Club of Rome and it was published by Meadows and Meadows.[11] The authors of the

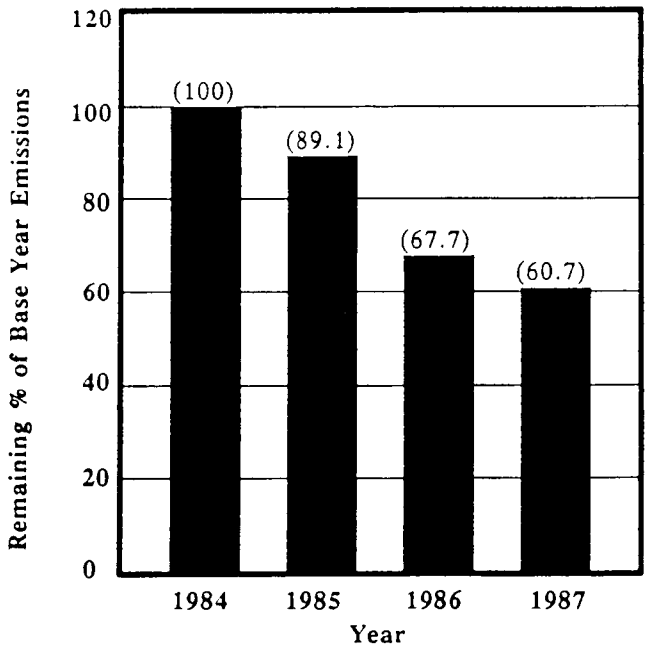


Figure 8. Air emissions by Dow Chemical U. S. A. were reduced 40% from 1984 to 1987, and from 1974 to 1984, they were reduced by 70%. [Taken from *The Point is ...* , No. 117, June 30, 1988.]

report admitted their lack of data as discussed by Edith Efron.[12]

Obviously, our way of life hasn't come to a catastrophic end. More people are employed today than ever before. Industry has made tremendous strides in the handling of its waste problems. Typical of the reduction of emissions throughout the chemical industry is that shown in Figure 8 for the air emissions by Dow Chemical Company from 1984 through 1987. From 1974 to 1984, Dow's air emissions were reduced by 70%, and from 1984 to 1987 they were further reduced by 40%.

There are, however, some areas in obvious need of improvement. For example, waste disposal in many cities, particularly those in the Northeast, has become a serious problem. Air pollution caused by automobiles continues to be a problem in our cities, regardless of whether they are located in industrial or non-industrial areas.

In conclusion, there are no signs pointing to a collapse of our society by the early 2000's, but to improve our quality of life, we must continue to discover and allocate resources for the prevention and abatement of pollution posing true risks.

Ranking of the Various Countries in Cancer Mortality

In the middle 1970's, those who had led the environmental movement in the 1960's joined by others and with widespread publicity in the press, turned to cancer (which they attributed to "man-made chemicals") as their rallying cry. The same solutions of zero growth and redistribution of the wealth offered for the pending environmental disaster were offered as the solution to the cancer problem.

Dan Rather opened his documentary entitled "The American Way to Death" on October 15, 1975 with this statement: "The news tonight is that the United States is number one in cancer. The National Cancer Institute estimates that if you're living in America, your chances of getting cancer are higher than anywhere else in the world."[13] The truth is that the United States ranked 8th for Blacks and 25th for Whites out of a total of 36 countries as determined and published by Mitsui Segi[14] two years prior to the broadcast. Segi's analysis was based on the death rates of the nine most common cancers: buccal, esophagus, colon and rectum, lung, stomach, breast, uterus, and leukemia. In an independent study by the World Health Organization, the United States was ranked 19th for men and 18th for women out of 44 nations.[15] Unfortunately, the public has probably never learned of the actual ranking of the United States by Segi at the time of Rather's statement nor of the ranking by the World Health Organization in 1977. According to the most recent study [*Facts and Figures*, 1988, American Cancer Society and World Health Statistics Annual 1983–1986], the United States ranks 22nd for men and 21st for women, out of 50 nations.

Exaggerated estimates of cancer mortality caused by "man-made chemicals" began to appear in the middle 1970's prior to the publication of Doll and Peto's[1] careful study in 1981 in which they attributed 4% of the cancer mortality to occupational hazards and 2% to pollution, for a total of approximately 6% or 9% if alcoholic beverages are included, recognizing that exposure to alcohol is largely a matter of lifestyle. [This estimate is based on the assumption that the net contribution of food additives and industrial products and medicines (shown in Figure 6) is zero because of the possible anticarcinogenic effect of food additives and the fact that medicines save more lives than they take.] It appears that Commoner, Epstein[16] and others managed to equate "environmental factors" with "man-made chemicals" and industrial pollution. The term "environmental factors" includes not only chemical carcinogens, but also lifestyles such as diet (35%; see Figure 6) and smoking (30%). As early as 1969, Higginson[17] had published the estimate that all cancers (exclusive of those related to skin pigmentation) were influenced by the environmental factors such as diet and tobacco. Under no stretch of the imagination can these environmental factors be equated to man-made chemicals.

The claims of 60% to 90% cancer mortality from man-made chemicals are also easily refuted by simply comparing the cancer rates in industrial and non-industrial areas. For example, the incidence of cancer (exclusive of tobacco-related lung cancer) in non-industrial Geneva, Switzerland is higher than industrial England. Also, non-industrial San Francisco has a higher cancer incidence than nearby industrial Pittsburgh, California (American Industrial Health Council.[18])

Research Developments — Discovery of Metabolism of Chemicals to Carcinogens, Inhibitors, Anticarcinogens, Cocarcinogens, and Promoters

A chemical **carcinogen** may be defined as any substance which causes cancer. From a practical point of view, this simple definition is subject to many ambiguities as indicated by the discussion which follows. There are two major classes of chemicals that induce cancer,

direct acting and indirect acting carcinogens. During the years 1970-74, the Millers[19] demonstrated that indirect carcinogens (or precarcinogens) enter the body of animals as noncarcinogens and are then metabolized to carcinogens as shown in Figure 9. On the other hand, direct acting carcinogens are in their carcinogenic form prior to entering the body. Other chemicals known as **inhibitors** and **anticarcinogens** have been discovered. When applied or taken simultaneously with a known animal carcinogen, anticarcinogens can delay the appearance of tumors, diminish the number of tumors, prevent tumors from occurring, or reverse the early phases of the carcinogenic process as illustrated in Figure 10. Inhibitors are generally regarded as those substances which inhibit or delay cancer formation by decreasing the rate of cell division.

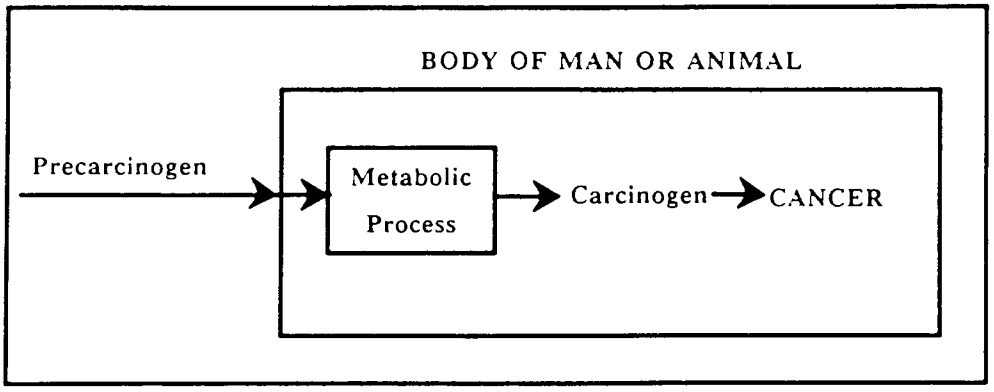


Figure 9. The metabolic processes of the body may convert a precarcinogen into a carcinogen.

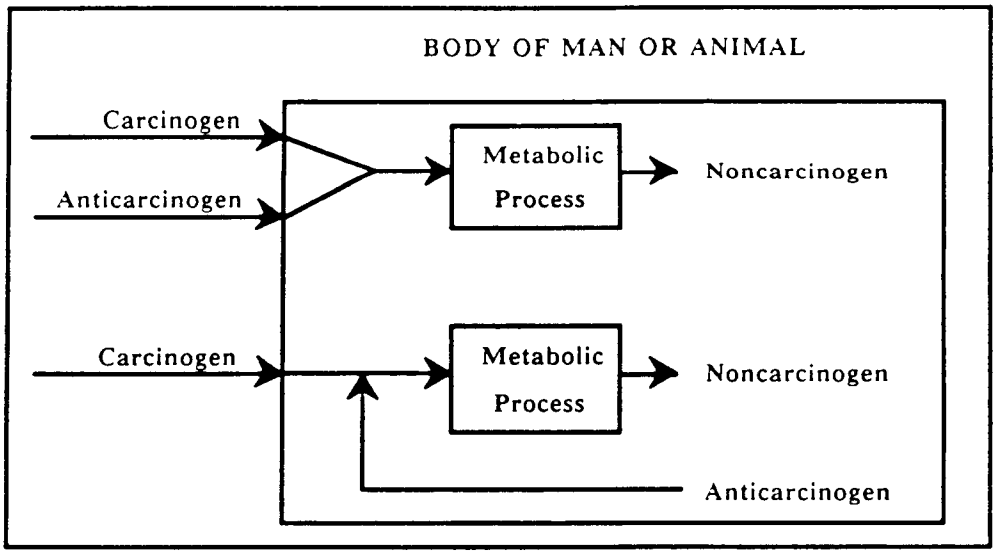


Figure 10. Carcinogens may be converted to noncarcinogens by anticarcinogens from either internal or external sources.

Other chemicals called **cocarcinogens** and **promoters** have somewhat overlapping meanings. The name "cocarcinogens" is usually reserved for those chemicals which enhance the action of carcinogens, particularly in the initiation phase of the cancer process as illustrated in Figure 11. On the other hand, the term "promoter" is generally used to mean any chemical which promotes the cancer process by increasing the rate of cell division of the initiated cells. In addition to substances which are carcinogenic, it is well known that radiations such as ultraviolet, x-rays and gamma rays can cause cancer through the formation of free radicals from chemicals in the near neighborhood of the DNA or from the DNA itself.

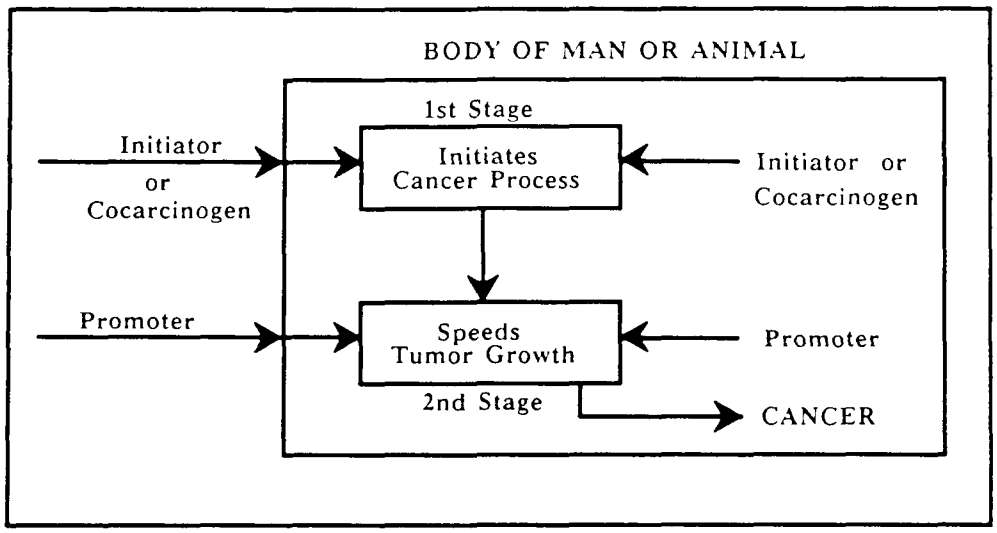


Figure 11. Graphic illustration of the "Two-Stage" or "Initiator-Promoter" theory of cancer formation.

Research Developments — The Two-Stage Theory of Cancer Formation

The discoveries of initiators and promoters led to the **two-stage** or **initiator-promoter** theory of cancer which is illustrated in Figure 11. The initiation step is thought to consist of a mutation of the DNA molecule by an initiator molecule (or activated metabolite) which becomes chemically bound to or reacts with the DNA or other macromolecules. Consequently an initiator is also frequently referred to as a **mutagen**. [Ames et al.[20], developed a simple, inexpensive test for the identification of mutagens. Unfortunately, it was subsequently demonstrated that this test was incapable of identifying all mutagens and carcinogens.] Although only two possible major mechanistic steps have been outlined, the cancer mechanism has for decades been thought to consist of many steps; perhaps as many as six or seven. The two-stage mechanism properly defined may be the most prevalent of the DNA based mechanisms. Although they are not substances, radiations can be included in this mechanism by virtue of the fact that they act like mutagens by damaging the DNA directly, or indirectly by damaging macromolecules such as enzymes that are involved in its formation or functions. Molecules damaged by radiation are highly reactive and tend to react with body chemicals in their immediate vicinity.

To further complicate the picture of the cancer mechanism, it is now known that initiators, cocarcinogens, promoters, inhibitors, and anticarcinogens are also produced internally in the body. However, all of the cancer causing agents either introduced to or produced within the body have been heavily counterbalanced by an abundance of repair mechanisms, anticarcinogens, and inhibitors provided by nature, as illustrated in Figure 12.

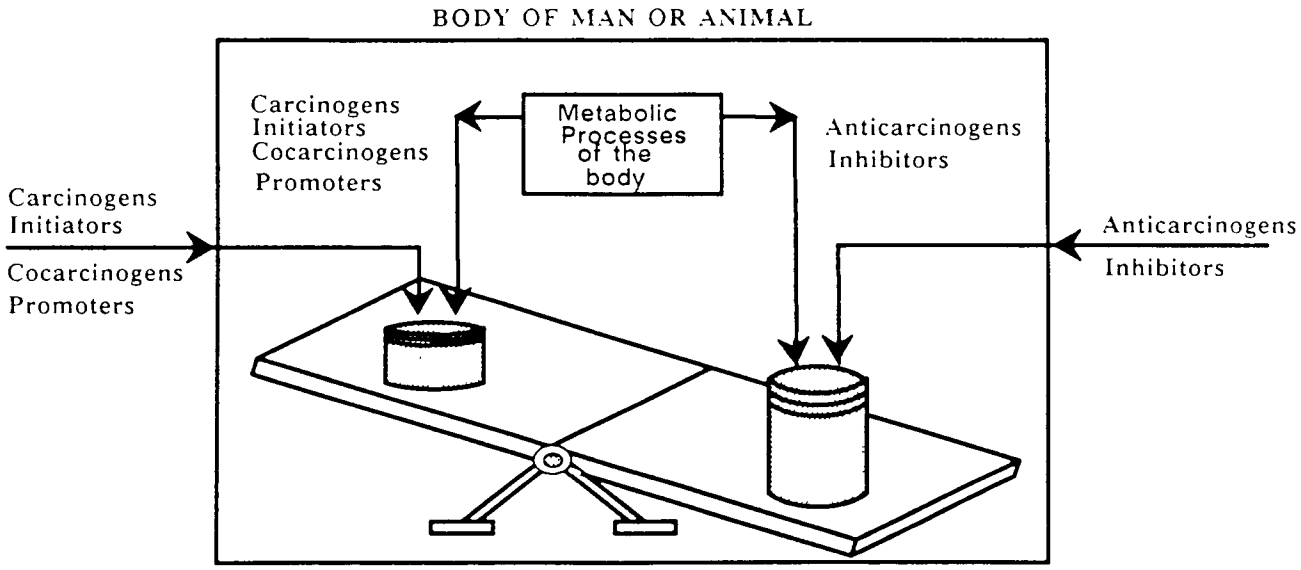


Figure 12. Nature has heavily counterbalanced the body defenses against the development of cancer.

Research Developments — The Two–Mutation Theory of Cancer Formation

This model, recently investigated by Moolgavkar and Knudson[21] and Wilson,[22] was also called a "two-stage" model. However, to avoid confusion with the two-stage model described above, the Knudson-Moolgavkar model is referred to herein as the "Two-Mutation" model as suggested by Wilson[22] because the two stages shown in Figure 11 have in effect been replaced by two critical mutations.

These two mutations on the critical path for the transformation of a normal cell to a cancerous one are assumed to be irreversible. An important feature of the newer model which enables it to account for a greater variety of cancers is the recognition of the role of increased cell division rates throughout the cancer formation process. Since cocarcinogens are known to increase normal cell division rates, a cocarcinogen (both external and internal) may be one of the inputs to the first mutation in the same manner as shown for Stage 1 in Figure 11 for the two-stage model.

By increasing the rate of cell division, the probability that damaged DNA will undergo division before it can be repaired is increased. Thus, the mutation becomes fixed

irreversibly in all future cells. Increased rates of cell division also increase the probability of the occurrence of mutations resulting from uncontrollable events such as errors in DNA gene transcription, cosmic radiation, and natural mutagens. Normally, all or nearly all damaged DNA macromolecules are repaired. However, any damaged DNA which is not repaired before cell division leads to a genetic change or mutation becoming fixed in future cells.

Chemicals (and other agents) can contribute to cancer incidence in two ways. First, the agent may react directly with DNA, increasing the number of damaged DNA molecules thereby increasing the probability that a damaged DNA molecule will escape repair before cell division. Second, the agent may react with some other component in the cell which causes an increase in cell division or the agent may kill the cell. If it kills the cell, there follows a temporary increase in the rate of cell division such as is observed in the formation of scar tissue, which in turn contributes to cancer formation by increasing the probability of occurrence of mutations resulting from uncontrollable events such as those enumerated above. Thus, the concept of accelerated cell division provides an explanation for the causation of cancer by agents such as viruses which may not react directly with DNA but which do cause cell damage and chronic irritation.

Research Developments — Inhibited Gap Junction Communications: A Nongenetic Based Model

This report deals primarily with mechanisms based on genetically caused cancers because most of the work, beginning with Armitage and Doll,[23] has been done in this area. However, there are significant cancers which cannot be directly attributed to genetic changes in the sense that the carcinogens causing these cancers are not mutagens. For example, potent carcinogens such as polybrominated biphenols (PBB) do not exhibit mutagenic behavior according to all of the short-term tests.

The Gap Junction Intercellular Communication (GJIC) model proposed by Trosko[24] provides an explanation for carcinogens whether they are either mutagenic or nonmutagenic. This model was the first to recognize intercellular communication and its importance in inhibition of cell division of initiated or mutated cells. In this model it is supposed that the process is initiated by the mutation of a cell by any means (some mutagenic or uncontrollable event independent of the carcinogen in question). Once formed, these initiated cells are held in check by surrounding normal cells through intercellular communication. This process functions through the transfer of negative growth factors in the form of calcium ions, pH changes, free radicals, and small molecules which are transferred across a membrane-protein interface (called a Gap Junction) from one cell to another.

Any substance such as a carcinogen or an event (a cosmic ray or a cell death) can inhibit or block the intercellular communication which releases the initiated (mutated) cells from the restraining effects of surrounding normal cells. Once the gap junctions have been blocked, the cell division process of the mutated cells is no longer restricted, and uncontrolled cell division occurs with the progression to the formation of malignant cells.

As recognized by Trosko, the Gap Junction Intercellular Communication model possesses

the same complications associated with all models of cancinogenicity such as species, tissue and cell type specificity. Also, many chemicals (PCB, DDT, TCDD, phenobarbital) under one set of biological conditions act as carcinogens and under some other set, act as anticarcinogens.

Research Developments — Identification of Human Carcinogens by Epidemiologists

From the standpoint of the public, the definition of a carcinogen given above is taken to mean "any substance which causes cancer in humans." Since substances which cause cancer in humans do not necessarily cause cancer in animals, and conversely, carcinogens should be classified into two subgroups: **human carcinogens** and **animal carcinogens** (and further subdivided into mouse, rat, etc.). However, confusion in the general public exists because the single designation "carcinogens" is used for both human and animals.

Identification of human carcinogens has been through the use of epidemiological studies rather than experimental investigations of potential cancer causing substances. Epidemiologists begin with all of the deaths that have occurred in a given location over a specified period of time. By use of an analysis of death certificates, case histories, personal interviews, they attempt to establish the major cause of each death and the exposure and lifestyle of the decedent. On the basis of information of this type, epidemiologists have discovered most if not all of our presently known carcinogens as illustrated in Figure 13. Of the more than 600 chemicals and chemical mixtures considered by the International Agency for Research on Cancer (IARC), 23 chemicals and 7 processes have been associated with cancer in humans. According to Wilkinson, no new human carcinogens have been identified by IARC within the past 10 years.[25]

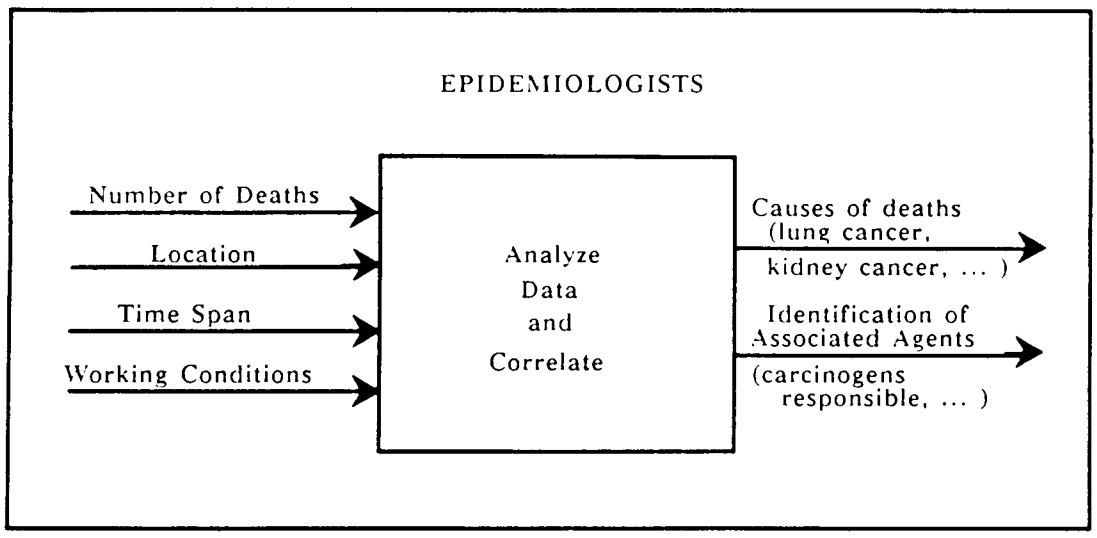


Figure 13. Most if not all human carcinogens have been identified by epidemiological studies.

Research Developments — Animal Tests and Associated Problems

In order to avoid the possibility of introducing chemicals into the environment which would cause cancer in humans, an extensive effort has been under way to develop laboratory tests which would predict the carcinogenicity of a substance in humans. However, animal tests are very expensive.

Although animals are used for testing substances for their carcinogenicity, this approach is fraught with difficulties because of the different responses exhibited by different animal species to chemicals. Responses may differ not only from one species to another, but from male to female of the same species, and also from animals to humans. For example, rats and humans develop cancer from the natural occurring carcinogen aflatoxin B_1, but mice and monkeys are relatively resistant[26] as shown in Figure 14. To further complicate the picture and add to the confusion is the fact that a given carcinogen can affect entirely different organs in different mammalian species. For example, benzidine is said to cause bladder tumors in man, liver tumors in the hamster, and acoustic tumors in the rat while estrogens are reported to cause breast tumors in mice, uterine and abdominal tumors in the guinea pig, and kidney tumors in the hamster.[12] Thus, the extrapolation of the results of animal tests to humans always invites uncertainties.

Research Developments — Problems in Extrapolation from High-Dose Animal Tests to Low-Level Environmental Exposure to Humans

Human exposure to chemicals ordinarily occurs at low-dose levels. For animal tests at these correspondingly low levels of exposure to be meaningful, a prohibitively large number of animals (millions) would be required. The alternative of obtaining a significant number of tumors in a relatively small population by use of high doses has become standard procedure in animal tests. However, this approach leads to further difficulties because many chemicals are carcinogenic at high doses but not at low doses. Thus, the extrapolation from high-dose animal tests to low-dose human exposure becomes even more difficult as depicted in Figure 15.

Research Developments — The Theory that Cancer is Formed by a System of Competing Chemical Reactions within the Body is Gaining General Acceptance

The bodies of all animals are composed of chemicals, and a vast number of chemical reactions take place continuously in order to effect the various body functions. A generalization and vast simplification of the sequence of chemical reactions which a potential chemical carcinogen may undergo upon entering the body is pictured in Figure 16 [based on the ideas of Gehring and Blau.[27]] When a chemical is introduced into the body by any means [inhalation, oral, injection], it is first absorbed in body tissue [State I]. Next it may react with any one of several types of body tissue to form a new compound,

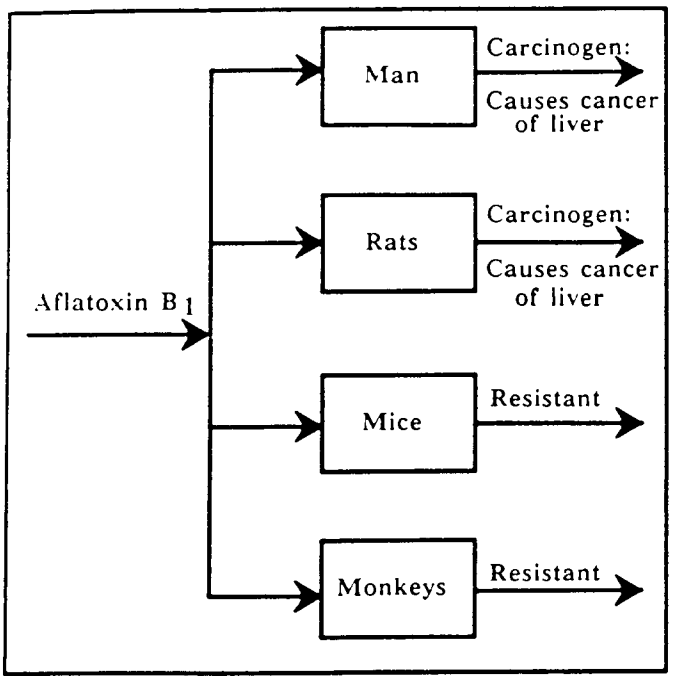


Figure 14. Aflatoxin B_1, a natural carcinogen found in grains and peanuts, has a different effect on different animal species.

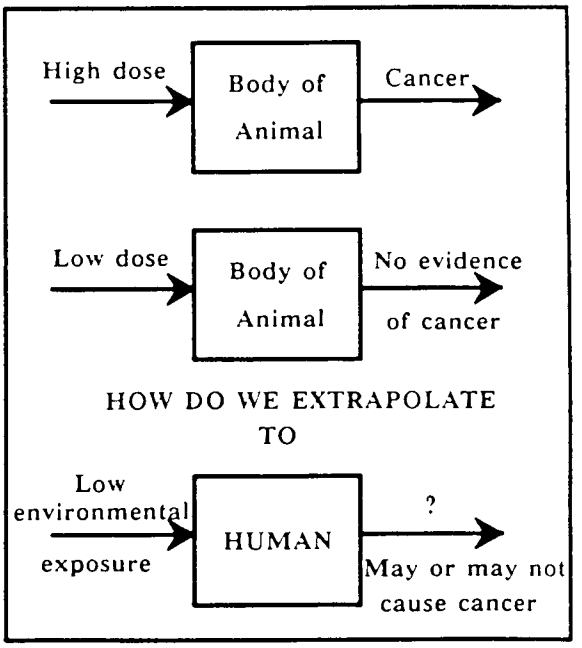


Figure 15. How do we extrapolate from high dose rates for animal tests to low exposure rates for humans?

called a "metabolite" [State II].

Finally the new chemical compound may react with DNA to give damaged DNA [State III]. The body possesses other chemicals [called the repair mechanism] which are capable of reacting with the damaged DNA and returning it to its original form. If the concentration of these DNA repair chemicals is too low, relative to the amount of chemical carcinogen introduced into the system, then some of the damaged DNA can no longer be repaired and begins to replicate itself which may result in cancer. The replication of damaged DNA is the crucial event in the initiation of carcinogenesis. Replication of the damaged DNA produces new cells whose DNA no longer appears to be in need of repair by the repair system of the body.

The reaction mechanism implied by Figure 16 and the mathematical equations describing it may be formulated in a manner analogous to that used in the description of a system of chemical reactions occurring in an industrial chemical reactor.

This set of simultaneous equations is called a **Pharmacokinetic** model. "Pharmacokinetics" is derived from the Greek word "*pharmakon*" meaning drug or poison and the word "kinetics" which refers to the speed of a chemical reaction. When the transport of a chemical from its point of entry into the body to the reaction site within the body is included in the model, the combined model is called a **Physiologically-Based Pharmacokinetic** model. Both *in vivo* and *in vitro* data are generally needed in the

evaluation of the parameters in this model as demonstrated by Clewell and Andersen[28] for methylene chloride. After the rate constants and other parameters appearing in the equations have been so determined, the resulting set of equations may be solved simultaneously on a computer. The results obtained by the computer simulation were in good agreement with experimental data or tests in mice, rats, and humans.

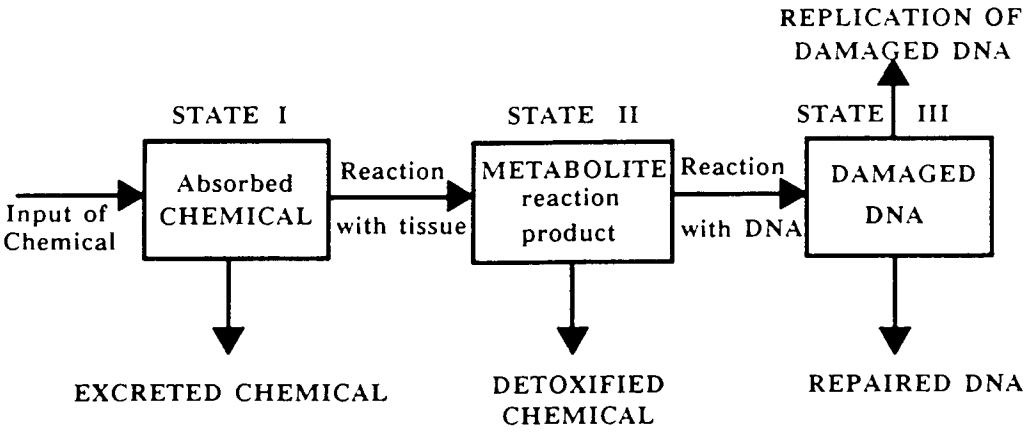


Figure 16. Model of the system of competing reactions of a chemical in a mammal that can lead to the formation of cancer. [Based on Gehring, P. J., and G. E. Blau, *J. Environ. Pathol. Toxicol.*, *1*, 163 (1977).]

Research Developments — At High Doses of a Chemical Carcinogen, the DNA Repair Mechanism is Overwhelmed and Cancer Formation Results

To illustrate the overwhelming of the DNA repair system, the hydraulic analogy shown in Figure 17 was used by Gehring and Blau.[27] This analogy illustrates that at low doses of the chemical carcinogen [low flow rates in Figure 17], the body's repair system is able to repair all of the damaged DNA, but as the dose level [flow rate] is increased, the repair system is eventually overwhelmed, and replicas of damaged DNA are produced.

The overwhelming of the repair system was also demonstrated by Gehring and Blau[27] through the use of a numerical example based on the model shown in Figure 16. A typical computer output for a simulated example by Gehring and Blau[27] is shown in Figure 18. To simplify the presentation, only the two final products produced by the sequence of reactions [shown in Figure 16] are presented; namely, repaired DNA and the replicas of damaged DNA. The amounts of these compounds formed for different dose levels of the chemical carcinogen are plotted in this figure. Observe that at low-dose levels, the formation of replicated damaged DNA molecules is relatively small. However, for initial doses greater than 10^{-4}, replicas of the damaged DNA begin to form faster than the other products. Also, the ability of the system to repair damaged DNA relative to the dose of carcinogen

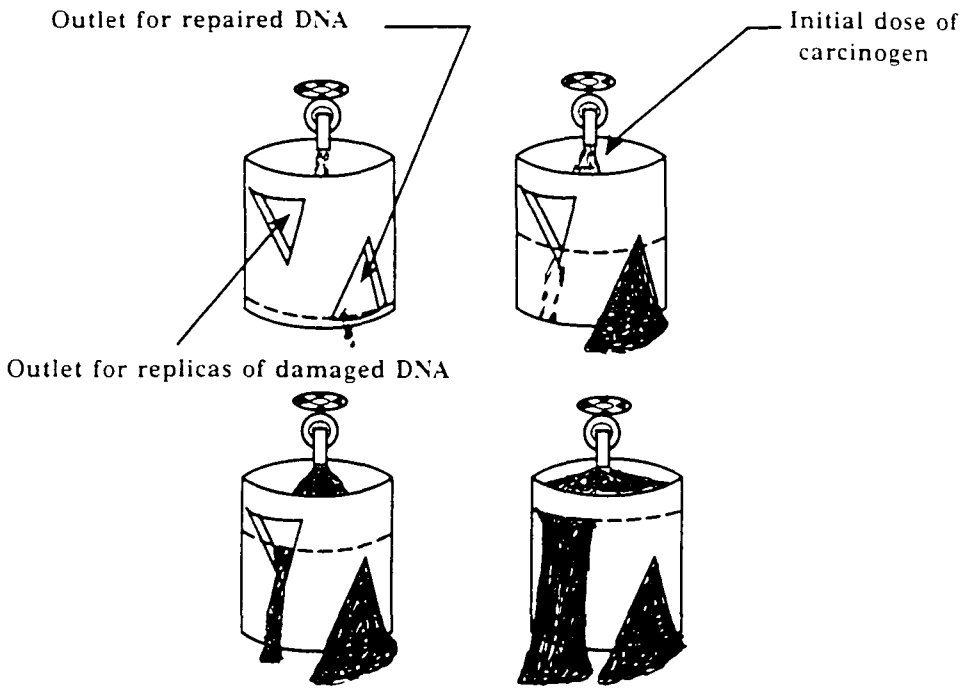


Figure 17. Hydraulic analogy of the overwhelming of the repair system for damaged DNA. [From Gehring, P. J., and G. E. Blau, *J. Environ. Pathol. Toxicol.*, 1, 163 (1977).]

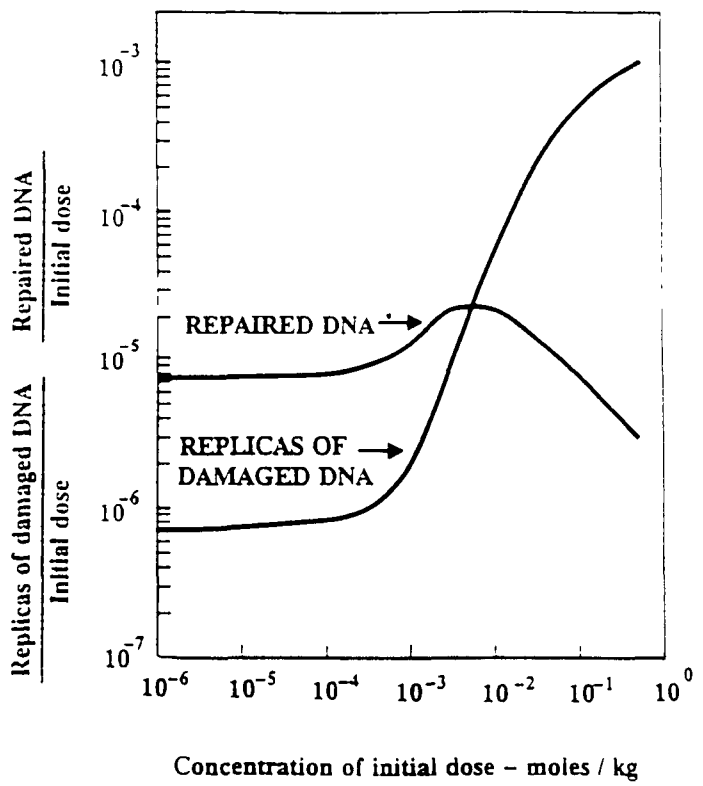


Figure 18. As the concentration of the initial dose of the chemical carcinogen is increased, the repair system for the damaged DNA becomes overwhelmed and the formation of replicas of the damaged DNA increases dramatically . [From Gehring, P. J., and G. E. Blau, *J. Environ. Pathol. Toxicol.*, 1, 163(1977).]

begins to decrease at dose concentrations above 10^{-2} (or one-hundredth), which implies that the repair system is becoming overwhelmed; damaged DNA is being produced faster than it can be repaired. For example, a 100-fold increase in the initial concentration of the carcinogen from 10^{-4} (or one-ten-thousandth) to 10^{-2} increases the damaged DNA produced by 10,000-fold for the system shown in Figure 18. Note, however, that this multiplication factor does not apply at low initial concentrations near the origin of the graph in Figure 18.

Research Developments — Some Advances in the Techniques of Risk Assessment

In order to reduce some of the uncertainty in the estimation of human hazards by extrapolation from animal studies, Clewell and Andersen[28] propose the use of PB-PK (Physiologically-Based Pharmacokinetic) models because they take in account actual physiological properties of the various species, the specific partitioning of different chemicals between tissues and blood, and the concentration dependent rates of metabolism. Because of the fundamentals on which PB-PK models are based, they are particularly useful for high dose–low dose extrapolations. As an example of the use of PB-PK models to improve risk assessments, Andersen et al.[29] cite the estimations of Singh et al.[30] and Blancato et al.[31] By following the conventional default procedure for methylene chloride, Singh et al.[30] estimated the risk for continuous exposure. Subsequently, a lower risk was estimated by Blancato et al.[31] through the use of PB-PK modeling. Although, a lower risk was obtained in this instance by PB-PK modeling than by classical methods, this is not always the case.

Other advanced techniques have been introduced by Sielken[32] which aid in more accurate extrapolations from high to low doses and from one species to another. Sielken developed an Individual Response Model based on the biological effective dose which took several factors into account including individual susceptibilities, background exposures, genetic traits, pre-existing diseases, and behavioral traits. In addition, the Individual Response Model is a dynamic model in that it may be used to predict the probability that a randomly selected individual from the population will have a carcinogenic response at a specified time in the future from an administered dose of a chemical carcinogen having a given concentration or following a given concentration pattern over time.

Research Developments — Measures of Potency and Possible Hazards of Chemical Carcinogens Relative to Natural Carcinogens

As a basis for comparing the relative carcinogenic potency of chemicals in chronic-exposure animal experiments, Peto et al.[33] proposed the use of an index called the "TD_{50}" (the tumorgenic dose rate 50). The TD_{50} is defined as the chronic dose rate in milligrams of the dose of chemical per kilogram of body weight of the animal weight per day, which would be required to give half of the animals tumors within the standard lifespan for the species (with appropriate adjustments being made for background and experimental procedures as described by Peto et al.[33]). Ames et al.[34] have computed and tabulated the TD_{50}'s for

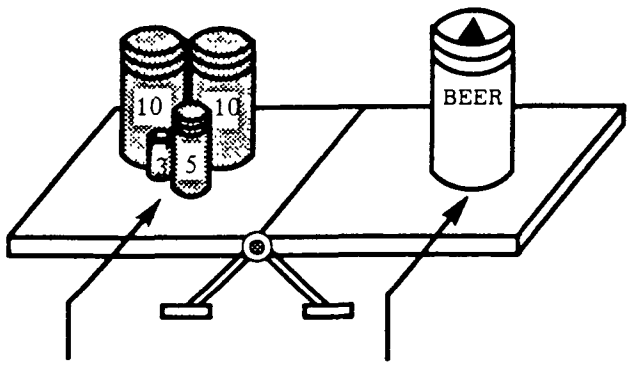
975 chemicals and natural carcinogens in rodents.

Since the animal experiments for the determination of the TD_{50}'s are carried out at high-dose rates where many metabolic processes and other defense mechanisms are normally overwhelmed, this index may be a poor measure of the carcinogenicity of the chemicals at low dose rates at which humans are usually exposed. Because of the nonlinearity of the relationship of tumors produced versus dose rate, the linear extrapolation of TD_{50}'s to low dose rates at which human exposures customarily occur is generally highly inaccurate.

Ames et al.[34] ranked the possible carcinogenic hazards of chemicals and natural carcinogens in terms of the ratio of the human exposure to these substances to the rodent exposure (as measured by the TD_{50} index). The ranking so obtained may be stated relative to any of the others. If, for example, the possible hazard of consuming one raw mushroom daily, or one basil leaf daily, or three and one third peanut butter sandwiches daily is assigned the ranking of 1, and the possible hazards of other substances may be ranked relative to these as illustrated in Figures 19 and 20.

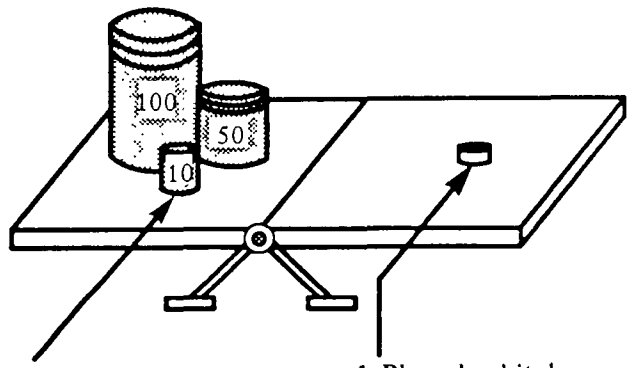
Because of the nonlinearity of the tumor frequency versus dose and all of the other problems (enumerated above) involved in the extrapolation from animals to human, these rankings in terms of relative possible hazards cannot be regarded by any measure as a risk assessment; nor was it proposed as one. Instead it may be used, as suggested by Ames et al.[34], to raise the question of further consideration and possible experimental investigations.

RELATIVE RANKING OF POSSIBLE HAZARDS



Relative Ranking = 28 1 Beer (12 oz)

Figure 19. One twelve ounce beer has the Relative Ranking of 28. [3 1/3 peanut butter sandwiches have a Relative Ranking of unity.]



Relative Ranking = 160 1 Phenobarbitol sleeping pill

Figure 20. One phenobarbitol pill has the Relative Ranking of 160.

In this same article, Ames et al.[34] called attention to the fact that nature is a far greater producer of chemical carcinogens than is man. Although we are exposed to a "sea" of natural carcinogens, this should not be taken as a license to make significant additions to our surroundings. On the other hand we cannot, in fact, technically or otherwise, reduce the exposure to all chemical carcinogens to zero. Thus the level of reduction becomes a

risk management problem which has been dealt with by Deisler in a series of papers.[35–39] The approach recommended by Deisler for dealing with this problem is to first select a set of very desirable but realistically achievable, quantitative goals, which broadly applied would achieve the following:

"(1) cause the deployment of our resources and information so as to protect the most people from the risk of cancer as soon as effectively possible;

(2) lay a foundation for continuing risk reduction and control; and

(3) as a desired, long-term end point, to reduce the contribution of the incidence of cancer related to industrially derived agents to a total cancer level as near to insignificance as possible when compared with the total incidence of cancer from all causes regardless of what the contribution is today."[36]

Cancer Mortality along the Upper Texas Gulf Coast

The determination of cancer mortality resulting from environmental exposure is difficult because of the many "confounding factors" such as occupational exposure, smoking, and migrating populations.

The "Ill Winds Study" by Molinari[40] attributed the higher cancer rates (than the U.S. average) in the Texas Gulf Coast Counties of Chambers, Jefferson, Galveston, and Harris to the fact that each contained or was downwind of one or more petrochemical plants.

While this study was faulted by its methodology and strongly criticized by epidemiologists, there is no question about the higher cancer death rate along the Upper Gulf Coast, but there is a question as to what is the cause. Smith et al.[41] cited one major epidemiological study for Harris County which showed that air pollution caused 3% of the cancer mortality in white males during the study period, 1981–1983. However, the principal investigator of this study stated that neither of the "confounding factors," smoking and occupational hazards, was adequately controlled, and if they had been, it is likely that the contribution of air pollution would have dropped to less than 1%. This is consistent with an EPA study, called the "Six Month Study,"[42] which estimated the potential of air pollution for causing cancer in the U. S. population at 1,700 to 2,000 cases per year or roughly 0.2%.

Because of the continued concern of the citizens over the health consequences of exposure to ambient air contaminants, the Texas Air Control Board (TACB) commissioned the "Gulf Coast Community Exposure Study" (GCCES). The Final Report of this study by Rogers et al.[43], released in 1988, presents the results of a quantitative study of the environmental contaminants detected at 6 Texas monitoring locations: Austin, Beaumont, West Orange, Cloverleaf (Harris County), Cloverleaf Q.A. (Harris County), and Texas City from October 9, 1985 through September 26, 1986.

The air samples collected at the monitoring stations were analyzed for 15 chemicals of which only the six shown in Table 2 were detected at more than one site. The conclusion of the report was that the data showed no indication of a health risk. "The levels of all substances which were detected were within the range of levels considered typical of heavily urbanized areas across the United States,"[43] as shown in Table 2.

The highest concentration measured for any pollutant was benzene, and at the measured upper bound of 18 micrograms per cubic meter which corresponds to a Ranking of 0.0839, which is 12 times smaller than the Relative Ranking of 1 for the human exposure to the natural carcinogens in a diet containing one basil leaf or three and one-third peanut butter sandwiches, daily.

Table 2. Comparison of Emissions of Study-Site Cities with Those of Other U. S. Cities. [From Rogers et al.,[43] "Final Report: Gulf Coast Community Exposure Study," Texas Air Control Board, March (1988).]

Substance	Annual Average at Study Sites	Annual Average in U. S. Cities
Benzene	6 - 18	2 - 20
Formaldehyde	1.5 - 6.9	4 - 6
Pyrene	0.01 - 0.02	0.0001 - 0.036
Chrysene	0.006 - 0.01	0.0006 - 0.01
Benzo(a)pyrene	0.005 - 0.014	0.0001 - 0.03
Benzo(ghi)perylene	0.005 - 0.007	0.003 - 0.01
Lead	0.22 - 0.24	0.05 - 3.4

Data are in micrograms per cubic meter.

This section is concluded by a brief description of the most recently published (October, 1988) epidemiological study of Harris County. In this ecological analysis, Buffler et al.[45] took several confounding factors into consideration which were not considered in earlier studies. Elevated lung cancer rates in Harris County compared with the other U.S. counties led to the initiation of this study which examined the air pollution-lung cancer mortality relation for white males in Harris County, Texas, 1979–1981. Factors taken into account were : median age, two social and demographic factors (family life cycle and migration), an age-dependent smoking index, and air pollution as measured by total suspended particulates. Air pollution was not demonstrated to be a strong determinant of lung cancer in that the presence of air pollution accounted for less than 5% of the total variation in intraurban lung cancer mortality. The relation between air pollution and lung cancer was highly dependent on which social and demographic factors were selected for inclusion in the analysis. Their final conclusion was that the hypothesis that air pollution is contributory to lung cancer cannot be tested until other stronger individual risk factors for lung cancer can be better measured and controlled in the studies.

The Houston Regional Monitoring Program

This is a continuing program which is supported by 35 companies. Samples are collected at 6 locations and analyzed for 173 chemical compounds. The results obtained thus far mirror those reported by the Texas Air Control Board in the Gulf Coast Community Exposure Study.[43]

Results of a Study of Liver Cancer Rates in Brazoria County

As a consequence of a study by Hoover and Fraumeni[46] in which a 10% excess mortality rate above the U.S. average was found for chemical-industry counties, a study by Buffler et al.[47] was sponsored by the National Cancer Institute. Thirty-nine cases of liver cancer cases were identified for the period 1960 to 1975. The actual number of cases observed was too small to establish an association with occupational chemical exposure, although the liver cancer mortality rates were slightly higher for Brazoria County than they were for the U.S. A deficit of liver cancers were observed in white males, the group in which the carcinogenic effect of occupational exposure to chemicals would be expected to be observed.

The TEAM Study (the Total Exposure Assessment Monitoring Study[44])

The results from an extensive five year study by EPA (reported in 1985) in which scientists concluded that, contrary to popular belief, people living in heavily industrialized areas containing petrochemical, paint, and plastic processing plants are not subjected to greater exposures to the commonly identified toxic chemicals than are people living in less industrialized, or even rural areas.

A further significant finding was that people are exposed to far greater concentrations of toxic chemicals indoors than they are outdoors, even in those cities where plants that manufacture or use these chemicals are located. This finding has also been confirmed by European studies. By use of both indoor and outdoor monitoring systems, the EPA investigators found indoor levels to be two to five times greater than outdoor levels for the commonly identified toxic chemicals. At highest exposures the indoor levels were up to 10 times greater than the outdoor levels.

Industrial Epidemiological Studies

Industrial epidemiological studies are characterized by the "healthy worker effect" which can be attributed to several factors. The conditions for employment require that people entering the work force be in good health. The nature of the employment requires that people establish a healthier life style (regular routine for work, rest, meals) than is followed by the general public. Workers also receive better medical care than does the general public.

Typical of the results of industrial epidemiological studies are those published by Dow Chemicals' Epidemiological Department. These extensive studies numbering over 60 involved many highly publicized chemicals, and except for those workers exposed in the past to arsenic, asbestos, and vinyl chloride, total mortality rates as well as cancer mortality rates were less than those for the surrounding neighborhood. Extensive studies published by Union Carbide Department of Epidemiology found an excessive cancer mortality for only one subcohort of workers, and these had worked in vinyl chloride plants no longer in existence.

In a series of studies conducted by the Medical Department of Phillips Petroleum Company, no job associated cancers were detected in the carbon black production workers and no job associated leukemia was found in the refinery workers.

Typical of industry's efforts in the area of epidemiological studies is the following report from Exxon's Department of Medicine and Environmental Health : "Based upon 137,702 person-years of observation, the mortality experience of workers at Exxon's refineries and chemical plants in three areas of the United States was found to be generally lower than that of the U.S. population."

Du Pont established an epidemiological section in its Medical Division in 1956. Since that time, the company has conducted more than 80 special studies and published over 65 scientific papers. In addition, Du Pont maintains company wide registries for mortality, cancer incidence, coronary heart disease, cerebrovascular accidents.

Shell Oil Company has performed several epidemiology studies of its work force. Overall, all cause and cancer mortality has been well below that for the U.S. population. Isolated specific cause of death elevations have been found at some locations; however no work related cause has yet been identified. Investigations of these mortality subgroups continue. Shell encourages publication of studies and routinely notifies employees as well as state and federal authorities of all study results. Shell also supports and participates in larger industry studies involving more than one company.

Although the lower mortality rates from all causes other than cancer can be attributed to the factors listed above (pre-employment screening, lifestyle, and better medical care), the lower cancer mortality rates cannot (yet) be so explained. General forms of cancer cannot (yet) be screened for, and various comparisons for lifestyles have not (yet) turned up a reason why cancer, too, cannot exhibit the healthy worker effect.

Prioritizing Our Efforts and Expenditures

Our problem is one of putting the reduction of cancer mortality caused by occupational hazards (4%) and environmental pollution (2%) in perspective. Our present rate of increase in industrial environmental costs is depicted in Figure 21. We are all in favor of a clean, livable environment; this may not be a uniquely risk-free or unaltered environment. Where do we stop — how much is enough? Even if we closed all chemical plants, eliminated all automobiles, alcohol, and all other possible sources of occupational hazards and environmental pollution, we would still be left with an estimated 90+% of the cancer mortality.

Instead of spending more and more of our national resources on the impossible goal of totally eliminating environmental risks, should we not move faster on a broad front in an assault on the 90+% cancer mortality? If we can take measures to reduce risks and mortality 10-fold should we wait to begin acting? Should we not spend more on cancer research?

Our future is brighter than many would have us believe. Although there is a 20 to 30 year latency period for cancers caused by asbestos and tobacco, a decline in cancer can be expected because of the decreased exposure to these substances. Also, new developments

and progress are being made in cancer research. For example, an Associated Press release of December 16, 1988 described a study by Wen-Hwa Lee, Professor of Pathology at the University of California, Davis, which suggests that a genetically engineered virus carrying a cancer suppressing gene is able to prevent the formation of malignant cells. Lee said the results suggest that this technique could be used to genetically convert malignant tumor cells, which are fast growing, to cells that grow normally. He said this technique holds promise for development within five years. Furthermore, the quantification of the cancer process through the use of pharmacokinetics is a rapidly advancing field. In 1937, Teorell[48] applied the well-known principles of chemical kinetics to the effect of drugs on animals and humans. Recent advances in this area by numerous authors including Gehring and Blau[27] and Andersen et al.[29] give renewed hope for a better understanding and quantification of the cancer process in the not too distant future.

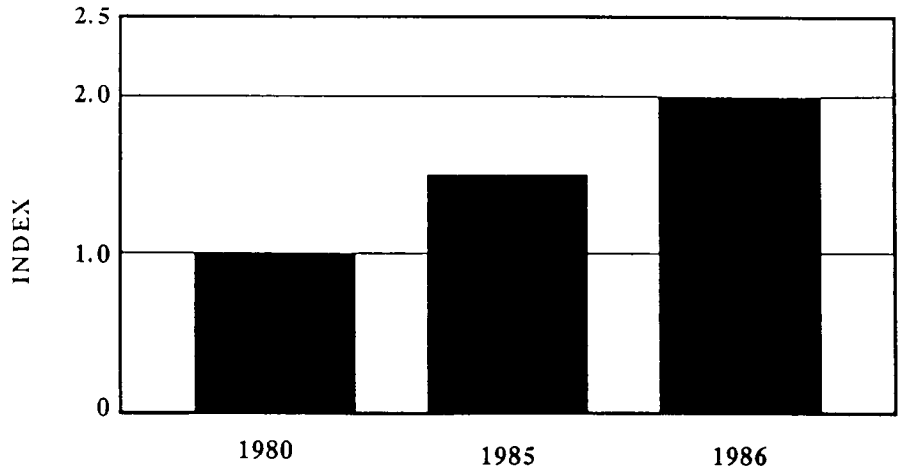


Figure 21. Environmental costs for Texas industries are 100 % above those of 1980. [Courtesy of Dow Chemical Company.]

We must find a way to strike the proper balance between a clean, livable environment and an unaltered environment. The balance is between achieving and maintaining a livable, viable environment and the existence of an industry of the magnitude required to provide the necessary benefits for a populated world. Neither supersafety nor environmental carelessness is the answer. To solve these problems will require the sincere cooperation of the general public, industry, and government.

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