CHEMICAL CARCINOGENS

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Recogniton of the causative role that chemicals in the workplace play in carcinogenesis dates back to 1775 when Percival Pott, a London surgeon, linked a high prevalence of scrotal cancer in young chimney sweepers to their occupational exposure to soot produced by the coal burned in the chimneys they cleaned. Today, over 200 years after Dr. Pott's discovery, workers in the United States and other industrialized countries are exposed to a multitude of chemicals, many of which are recognized as, or suspected to be, carcinogens.

Carcinogenic effects of chemicals in man are difficult to document because 1) cancers are generally not clinically evident until a lapse of up to 20 to 30 years after the first exposure has occurred and 2) chemical exposures in many workplaces are so complex that it is difficult to pinpoint the specific causal agent or agents and the concentrations of the agents primarily responsible for the ultimate carcinogenic effect manifested decades later.

For example, workers occupationally exposed to coke oven emissions are at increased risk of developing lung and kidney cancer. Yet, in spite of lengthy research and the evidence as related to cancer, all the specific carcinogens in the chemically complex coke oven exposures responsible for the increased carcinogenic risks have not been determined.

LEVEL OF EXPOSURE

There is considerable debate among scientists regarding the level of exposure to a given carcinogen required to cause cancer. It is beyond the scope of this chapter to review all of the arguments offered as to whether or not a threshold exists for chemical carcinogenesis.

We have currently no established scientific method to determine threshold levels for chemical carcinogens, if indeed such thresholds do exist. Moreover, if a threshold for a given chemical carcinogen were to exist, it would not necessarily be determinative of a safe exposure since in the industrial environment workers may be exposed to multiple carcinogenic agents which may compete for the same target site.

Multiple exposures can occur on the job, in the diet, and in the ambient and home environments. Under these circumstances, some people may have already received doses from multiple exposures in excess of any presumed threshold for any single carcinogenic chemical. Consequently, any incremental increased exposure to chemical carcinogens could then result in an increased risk of cancer, especially if this incremental exposure may already be in the area where the slope of the

dose-response curve has steepened (1). As a result, the National Institute for Occupational Safety and Health (NIOSH) has taken the position that it is not currently possible to demonstrate safe levels of exposure to all chemical carcinogens (2).

RECOGNITION OF HAZARDS

Carcinogenic hazards may be identified by epidemiologic studies of people who have been exposed to suspect chemical agents and by experiments in animals exposed to controlled amounts of chemical agents. In the workplace, the primary route of exposure is through inhalation although concomitant ingestion and skin contact can also be important. Consequently, inhalation exposure experiments in animals constitute the most relevant toxicologic approach for simulating the most prevalent exposure conditions in the workplace.

In assessing the evidence for cancer, be it from animal or epidemiologic data, one must consider the strengths and weaknesses of the individual studies as well as the consistency of evidence between studies. There are, however, no universally accepted criteria for the quality or the consistency of the data that are required before considering that a given chemical represents a carcinogenic hazard to man.

EPIDEMIOLOGIC STUDIES

Identification of carcinogenic hazards from epidemiologic data generally involves the use of cohort studies; that is, tracing the present and future mortality experience of groups of individuals exposed to a common chemical agent at or during a specific time period and comparing their mortality experience with a matched group not so exposed during the same time period.

Most frequently chosen as a control group in these studies is a group from the general population matched for age, sex, and race. By comparing the mortality experiences among the exposed and nonexposed control populations, it is possible to ascertain if exposure has increased the risk of a given cause of death. In this type of study, the calculation of a standardized mortality ratio (SMR) in order to compare the frequency of death from a given cause or causes in the exposed population with that in the control populations is extremely informative. An index of more than 1.0 indicates that an excess risk may exist in the exposed population. In such comparisons, however, because the working population may in general be healthier than the general population, an apparently less risky SMR of 0.90 to 1.0 on a specific cause of death may actually indicate an increased risk among those who have been exposed — the so-called "healthy worker effect."

As noted, the usual latent period or lapse time for development of chemically-induced cancer is about 20 years. Consequently, a mortality study which does not include an adequate proportion of workers with

long latent or lapse times following onset of exposure may yield erroneous conclusions as to the lack of health effects of those chemicals in the work environment that are being studied.

ANIMAL STUDIES

In epidemiologic studies, once a chemical or exposure condition has been shown to cause cancer, preventive measures may not be adequate to protect those who have had previous exposures, but who have not lived long enough for effects to be expressed in terms of clinical illness. A major advantage of experimental animal studies is the possibility of detecting a chemical cancer hazard earlier than if one waited for epidemiologic evidence of cancer in man to become available. Under such circumstances, preventive action can be taken much sooner.

To date, there are a number of instances in which data on cancer in experimental animals have been used to establish occupational health regulations in the United States. It is increasingly evident that experiments in animals can be important indicators of cancer risk for man. Almost all chemicals shown to be carcinogenic in man by epidemiologic studies have also been shown to be carcinogenic in appropriate animal models. Although this does not necessarily mean that a positive test for cancer in animals provides incontrovertible evidence of cancer risk for man, it does indicate that the chemical should be considered at least as a potential carcinogen for man.

Experts frequently recommend testing chemicals in more than one animal species, primarily to avoid false negative results. Nevertheless, this should not be interpreted to mean that, before a chemical can be called a carcinogen, it must be positive in two or more species tested. Naturally, however, the greater the number of studies that show that certain chemicals produce cancer in different species of laboratory animals, the greater the confidence in the conclusion that those substances pose a carcinogenic threat to man.

POTENTIAL OCCUPATIONAL EXPOSURES

The boundaries of potential occupational exposures to chemical carcinogens are ever expanding. The following occupations are some of those subject to recent investigations.

Asbestos workers
Auto repairmen
Bakery workers
Clothing pressers
Coke oven workers
Dairy industry workers
Dental laboratory technicians
Electricians
Leather workers
Photoengravers
Roofers
Rubber workers
Vinyl chloride workers

Table 4 presents a list of occupational chemicals and substances which cause, or are suspected of causing, cancer and the target organ or tissue. It should be emphasized that this list is substantially incomplete in that many, if not most, chemicals in the workplace have not been adequately tested for their carcinogenic potential. As such, however, the format of Table 4 attempts to organize a growing body of data in a manner that may be useful for physicians in making a differential diagnosis of the possible occupational etiology of cancer cases in individuals. Additionally, this list may lead physicians and other health professionals to become more aware of the magnitude of the growing problem of chemical carcinogens in the workplace. Since occupational carcinogens may effect virtually all organ systems, physicians should be alert to investigate situations where clinically evident cancer could be associated with on-the-job chemical exposures.

One helpful data source for physicians is the registry of suspected carcinogens maintained by NIOSH as a subfile of the Registry of Toxic Effects of Chemical Substances (3). This Registry contains approximately 1,500 suspect carcinogens, most of which have not been adequately tested. Their inclusion on this list does not represent a process of substantive evaluation with respect to the adequacy of scientific data related to carcinogenicity. Rather, this list is a useful starting point to ascertain the extent of data regarding carcinogenic responses for a given compound. Even with these caveats, it should be evident that a number of compounds in this list may be shown to be carcinogenic in man following more detailed evaluation.

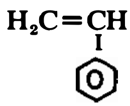
Observations by alert physicians and alert workers have frequently helped to identify problems of carcinogenic risk in the workplace long before they might otherwise be realized. Examples of this are hepatic angiosarcoma, a rare liver cancer caused by occupational exposure to vinyl chloride, and leukemia among workers in the manufacture of styrene-butadiene rubber. A number of other occupational chemicals have been shown to produce "marker" or unusual forms of cancer, such as the pleural and peritoneal mesotheliomas due to asbestos, and hepatic angiosarcoma due to inorganic arsenic. It is likely that careful follow-up of rare cancers or unusually high incidences of common cancers may help to uncover unsuspected chemical cancer hazards among other worker populations.

Unsuspected occupational cancer problems might also be predicted on the basis of structural similarity with certain chemicals and substances already shown to cause cancer in humans or animals. For example, Table 5 lists compounds that by virtue of their structural similarity to vinyl chloride would be suspected of posing possible carcinogenic risks to man. Surveillance by alert physicians of workers exposed to these substances might help to early identify potential future problems. Similarly, it is most important for clinicians to be aware of newer data on carcinogenesis emerging from experimental studies on animals. For example, preliminary data have indicated that trichloroethylene produces liver cancer in experimental animals (4), and data from Russia have suggested a human carcinogenic lung and skin response to chloroprene (5).

Table 4. Confirmed and suspected occupational carcinogens by target organ.

Target Organ/Tissue	Occupational Carcinogen	
	Confirmed	Suspected
Bone		Beryllium
Brain	Vinyl Chloride	
Gastroenteric Tract	Asbestos	
Hematopoietic Tissue (leukemia)	Benzene Styrene Butadiene and other Rubber Manufacture Substances	
Kidney	Coke Oven Emissions	Lead
Larynx	Asbestos, Chromium	
Liver	Vinyl Chloride	Aldrin Carbon Tetrachloride Chloroform DDT Dieldrin Heptachlor PCB's Trichloroethylene
Lung	Arsenic Asbestos Bis (chloromethyl) ether Chloromethyl methyl ether Chromates Coke Oven Emissions Mustard Gas Nickel Soots and Tars Uranium Vinyl Chloride	Beryllium Cadmium Chloroprene Lead
Lymphatic Tissue		Arsenic Benzene
Nasal Cavity	Chromium, Isopropyl Oil, Nickel, Wood Dusts	
Pancreas		Benzidine PCB's
Pleural Cavity	Asbestos	
Prostate		Cadmium
Scrotum	Soots and Tars	
Skin	Arsenic Coke Oven Emissions Cutting Oils Soots and Tars	Chloroprene
Urinary Bladder	4-Aminobiphenyl Benzidine B-Naphthylamine	Auramine 4-Nitrodiphenyl Magenta

Table 5. Suspected carcinogens based upon structural similarity to vinyl chloride.

Suspected Carcinogen	Structure
Vinyl Chloride	$H_2C=CH$ Cl
Bromoprene	$H_2C=CHCH_2Br$
Chloroprene	$H_2C=CHCH_2Cl$
Epibromohydrin	$H_2C-CH-CH_2Br$ \ / 0
Epichlorohydrin	$H_2C-CH-CH_2Cl$ \ / 0
Perbromoethylene	$Br_2C=CBr_2$
Perchloroethylene	$Cl_2C=CCl_2$
Tribromoethylene	$Br_2C=CH$ Br
Trichloroethylene	$Cl_2C=CH$ Cl
Styrene (Vinyl Benzene)	
Vinyl Bromide	$H_2C=CH$ Br
Vinylidene Bromide	$H_2C=C Br$ Br
Vinylidene Chloride	$H_2C=C Cl$ Cl

IN VITRO SCREENING TESTS

In vitro screening techniques have been developed which have promise for identifying chemicals with potential for causing cancer (6). These techniques are based upon a number of end points such as mutations and inhibition of DNA repair mechanisms. Such tests are done on a number of cell systems, including human cell cultures and bacteria.

Preliminary evidence reveals that nearly 90 percent of chemicals established to be carcinogens by animal or human data give positive test results in one or more of these in vitro test systems(7) It is not known what proportion of chemicals selected at random without prior knowledge as to their carcinogenic activity will give a positive result in these tests. Strictly speaking these tests *per se* do not indicate carcinogenic activity. Nevertheless, they offer considerable promise in the identification of those chemical agents which should be tested for carcinogenicity. Thus, the practicing physician needs to know about these test procedures and results, because they may give important clues as to the existence of potentially carcinogenic chemicals.

INFORMATION SOURCES

Well over one thousand chemicals have shown at least one positive test result for carcinogenicity. These chemicals are in Suspected Carcinogens, A Subfile of the Toxic Substances List (3), published in 1975 by NIOSH and updated periodically. The International Agency on Research on Cancer has also published a series of monographs which review the carcinogenicity of a large number of chemicals (8). The National Cancer Institute (NCI) currently has approximately 300 chemicals on long-term test for cancer in animals and much new information will become available over the next several years.

Both NIOSH and NCI maintain systems which issue bulletins giving summarized, recent information on the carcinogenicity of chemicals. Copies of the bulletins may be obtained from these agencies. They are intended to make more people aware of new research information on chemicals and cancer so that appropriate medical and other precautions and action can be taken to monitor and prevent undue exposure. Additionally, such bulletins will likely lead to new research studies to clarify the existence and magnitude of suspected carcinogenic risks.

Occupational health physicians must be aware of these data sources. The information they provide on cancer risk may provide the clues which would facilitate the physicians' recognition of corroborative evidence based upon their own clinical experience. Such evidence would in turn help to stimulate adequate control actions to minimize future occupational and environmental exposure to these chemicals.

REFERENCES

1. Rall, D. P. 1975. Extrapolating Environmental Toxicology: Cost and Benefits of Being Right and Wrong. Presented at the meeting of the American Association for the Advancement of Science, Jan. 30, 1975, New York City.
2. Fairchild, E. J. 1976. Guidelines for a NIOSH policy on occupational carcinogenesis. Ann. N.Y. Acad. Sci. 271:200.
3. Christensen, H. E., and T. T. Luginbyhl, eds. June, 1975. Suspected Carcinogens — A Subfile of the NIOSH Toxic Substances List. U.S. Department of Health, Education, and Welfare, Washington, D.C.
4. Lloyd, J. W., R. M. Moore, and P. P. Breslin. 1975. Background information on trichloroethylene. J. Occup. Med. 17:603.
5. Lloyd, J. W., P. Decoufle, and R. M. Moore. 1975. Background information on chloroprene. J. Occup. Med. 17:263.
6. U.S. Department of Health, Education, and Welfare, Test Procedures Working Group of the Committee to Coordinate Toxicology and Related Programs. 1977. Draft Document: Methods for Determining the Mutagenic Properties of Chemicals. Department of Health, Education, and Welfare, Washington, D.C.
7. McCann, J., and B. N. Ames. 1976. A simple method for detecting environmental carcinogens as mutagens. Ann. N.Y. Acad. Sci. 271:5.
8. International Agency for Research on Cancer. 1972-1976. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Volumes 1-11. World Health Organization, Lyon, France.

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