DU PONT
management bulletin

APRIL 1976 VOL 5/NO 1

DU PONT MOBILIZES AGAINST THE RISK OF OCCUPATIONAL CANCER

The company's experience puts it in good position to meet the challenge posed by new findings on the dangers of long-term, low-level exposure to chemicals.

The news media recently have given a great deal of attention to the search for causes of cancer, with special focus on the problem of cancer resulting from on-the-job exposure to carcinogens (substances that cause cancer). Chemical company employees understandably may be concerned by this public discussion.

This *Management Bulletin* attempts to place the problem in perspective. It discusses the reaction of Du Pont and the rest of industry to the new facts being uncovered, and it describes the company's efforts to insure a safe working environment.

Du Pont is involved in the issue because it makes or uses a few of the materials that have been identified as potentially carcinogenic in human beings. The company's long-standing commitment to the safety of its employees extends to the carcinogen problem. As described later, determining what is safe in handling carcinogens is more difficult than with other kinds of hazards. Nevertheless, Du Pont believes these substances can be handled safely, but the company is committed to closing down any operation where they cannot be.

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Du Pont and other chemical producers are supporting legislation that would provide added public protection by giving the Federal government additional power to require testing and screening of new compounds and regulate the use of substances that are toxic. The industry is concerned, however, that some of the proposed laws grant too broad authority to screen and test chemicals.

The Long-Term Exposure Hazard

Much of the present concern over occupationally related cancer arose as a result of two incidents at other chemical companies in which it was discovered that employees had developed cancer after long-term exposure to carcinogens. In one case, vinyl chloride monomer caused a rare liver cancer in exposed workers, and in the other, the chemical bis-chloromethyl ether was found to cause lung cancer. During the long period over which those chemicals were produced, neither had been considered carcinogenic. Substances such as asbestos, beta-naphthylamine and benzidine were known to be cancer hazards on the job, but the number of occupational carcinogens was thought to be limited. Today 17 substances are currently subject to workplace control through government regulation because of carcinogenicity.

"Our understanding of the potential effects of long-term low-level exposure to certain chemical substances is clearer than it was just a few years ago," says William R. Galloway, Jr., Du Pont's director of environmental affairs. "We've learned that some previously unsuspected materials are more dangerous than was thought to be the case. But, at Du Pont we have several things in our favor. For example, our concern for

safety has led us to tightly control exposure to products that have toxic effects, such as damage to body organs. Chemicals that are carcinogenic are also likely to have other toxic effects. Thus, some chemicals that may turn out to be carcinogens are already under tight controls because of their toxicity.

"In 1935 we established one of the first industrial toxicology laboratories in the country, the Haskell Laboratory for Toxicology and Industrial Medicine. It has done outstanding work in identifying hazards and helping establish safe practices. A major expansion of the laboratory is under way. We have been monitoring the health of our employees through periodic physical exams since 1915. These preventive measures stand us in good stead as we tackle the current problem."

The Cancer Problem

"The attention that has been given to the cancer problem in the media may make it seem that we are in a cancer epidemic," says Galloway, "and that the disease is increasing due to exposure to the products of industry, and especially to chemicals. But the facts give a different picture."

It is true that cancer now causes about one-fifth of all deaths in the U.S., and that makes it the second leading cause of death, after heart disease. Roughly half of all cancer deaths are caused by the three most common forms of the disease—cancer of the lung, the large intestine and the breast.

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The incidence of cancer has gone up, but that statistic by itself can be misleading. The death rate from cancer has increased in recent decades for men but *not* for women. According to the latest analysis of trends by the American Cancer Society, the death rate from all types of cancer per 100,000 population (age adjusted) *declined* 9 per cent among women between the periods 1951-53 and 1971-73. The rate increased 19 per cent among men, mainly due to a large increase (135 per cent) in lung cancer. Thus, increases in the overall cancer death rate have resulted largely from a higher rate of lung cancer. Most experts now attribute the increase in lung cancer to cigarette smoking.

The U.S., incidentally, is not the world leader in cancer deaths. In a World Health Organization list of 44 countries it ranks 19th in deaths from cancer in men, and 18th for women. Many West European countries rank ahead of the U.S. Furthermore, some less industrialized nations have higher cancer rates than more industrialized countries.

The medical research community is now gradually shifting more of its effort toward identifying the causes of cancer in an effort to prevent it (but the main emphasis is still on finding a cure). In the past, research on causes tended to focus on two areas —viruses and the genetic makeup we inherit from our parents. So far, viruses have been linked with cancer in animals, but not in man. Heredity may turn out to be implicated in cancer, but more as a factor that makes a person susceptible than as a cause in itself.

Lately, the attention of scientists has turned to so-called "environmental" causes. The term refers to cancer caused by exposure to all materials in our environment—not just materials in the air and water, but substances we come in contact with because of diet, our lifestyles, our occupations. Cigarette smoking is an environmental factor. Recent estimates by government agencies and private researchers variously attribute 50 to 90 per cent of all cancer to environmental causes, but there are big gaps in the knowledge on which these estimates are based.

The Occupational Risk

How serious a problem is occupationally related cancer? In one sense, of course, any incidence of cancer resulting from on-the-job hazards is very serious because it involves human suffering and probable loss of life. Insofar as it might have been prevented if knowledge of the hazard were greater, any single incidence of cancer is tragic.

But the question must be asked, how serious is occupationally related cancer in the context of the total cancer problem? That question is nearly impossible to answer because research in epidemiology—the study of the distribution of disease in human populations—has lacked data to separate the occupational causes from other causes of cancer. John Higginson, director of the International Agency for Research on Cancer, of the World Health Organization, estimates that less than 1 per cent of all cancers have been shown to be related to occupational factors. But he also says that the causes of most cancers are still unknown. John Weisburger, a widely known cancer specialist with the Naylor Dane Institute, recently said that occupationally related cancer was probably in the range of 1.5 to 3 per cent of all cancer deaths. But he noted that estimates in this area must be largely a matter of guesswork.

The Past Is Not Always a Happy Story

The risks do exist, and they are risks that something can be done about. But it's not simple.

Du Pont's experience bears that out. In the 1930s, the company realized that an unusually high incidence of bladder tumors was becoming evident among employees who worked with dyes at the Chambers Works in New Jersey. Largely to investigate the problem, the company established Haskell Laboratory near Wilmington. It was one of the first industry installations devoted solely to studying potential hazards posed by products.

The bladder tumor cause was identified as beta-naphthylamine, a dye intermediate. Tight controls were established, exposure to the product was greatly reduced, and medical

monitoring of employees was begun. Process redesign was undertaken. In the end, Du Pont stopped manufacturing the chemical largely because it was felt exposure could not be reliably limited to a safe level when the product reached customers' plants. Nevertheless, 276 cases of bladder tumor among Chambers Works employees exposed to the chemicals have been recorded over the years—mainly resulting from exposure during a period of 30 years ago, or earlier. (In addition, 63 cases have been recorded among employees who worked at another plant which Du Pont acquired and owned during the 1930s in Wisconsin.)

Significantly, in scientific, medical and industrial circles, this incident at the time was considered something of a rarity, as explained by Dr. John A. Zapp, director of Haskell Laboratory for the past 23 years.

"The idea that many substances might be carcinogenic was not given a great deal of consideration in the scientific community," Dr. Zapp says. "As late as 1952, a leading pharmacologist of the Yale University School of Medicine wrote a textbook in which he said that only three pure agents were known to cause cancer in man — beta-naphthylamine, arsenic and radiation."

In fact, other materials had been found to be carcinogenic, but this reference indicates something of the state of scientific knowledge in this field at the time.

In studies of new chemicals, emphasis traditionally was on determining acute toxicity, the level of short-term exposure that caused adverse reactions in experimental animals. Less attention was given to chronic toxicity, the effect of low-dose exposure over the lifetime of experimental animals.

The Problems of Testing

Haskell and other laboratories now do increasing numbers of chronic toxicity studies. The trend, in part, is due to Federal legislation requiring long-term tests on all drugs, food additives and agricultural chemicals before they are marketed. It's also due to the recent upsurge of concern over carcinogens, and Du Pont's determination to identify and control this hazard.

Chronic toxicity tests are quite expensive. They call for large numbers of animals and can last two or three years, or more.

"The cost of doing such a study in 1958 was more than $100,000," Dr. Zapp recalls. "Today, the cost can run five times that amount."

Testing for carcinogenicity is a complex matter

Testing for carcinogenicity is a complex matter. One problem is simply the lack of an exact correlation between animal carcinogens and human carcinogens. There is, however, high probability that a substance which causes cancer in appropriate species of laboratory animals may also be a human carcinogen at sufficient dose levels.

There are enormous technical problems in doing studies that pinpoint the effects of very low concentrations—fractions of one part per million, for example.

But the biggest puzzle now is, what substances should be tested for carcinogenicity? Many thousands of compounds are produced by modern industry, and all cannot be subjected to lengthy, costly testing. There are, however, some indicators as to which materials are likely to be hazardous.

For example, if a substance has a chemical structure similar to that of a known carcinogen, it immediately attracts suspicion. But "guilt by association" has its limitations. A notorious instance in which it did not apply was vinyl chloride monomer. This substance is not chemically related to other carcinogens and was, in fact, long regarded as relatively nonhazardous. Now, toxicologists are looking closely at similar chlorinated hydrocarbons.

Recent interest has focused on development of relatively short "screening" tests to determine which chemicals should be tested further. One widely used screening test is for mutagenicity, the ability of a substance to cause mutations in a cell. Rapidly multiplying bacteria or yeast cells are used, and mutagenicity can be established fairly quickly. It appears that about 85 per cent of all carcinogens are also mutagens.

On the other hand, not every chemical that proves mutagenic will prove carcinogenic as well. Very little is known, in fact, about what percentage of mutagens might be expected to cause cancer in animals. Thus, the screen could lead to wide testing of noncarcinogenic substances.

These are some of the difficulties in tracking down potential cancer-causing agents. A great deal of scientific expertise is now being brought to bear on the problem, and it seems reasonable to assume that testing methods will become more reliable in the years ahead.

Lists and More Lists

In the meantime, lists are being compiled of substances that, to some degree or another, have been linked with cancer.

One such list contains 1,500 substances. It was published by the National Institute of Occupational Safety and Health, a Federal agency that does research but has no regulatory power. To be on the list a substance must have been associated in some way with cancer in the scientific literature. Du Pont's view is that many of the items should not be included because the evidence cited is in error, is inadequate, or is contradicted by other evidence.

Undoubtedly, research will continue to identify more carcinogens. At present, however, when definite proof of carcinogenicity is required, the lists are relatively short. The American Conference of Governmental Industrial Hygienists, for example, lists 23 carcinogenic agents for which it has recommended limits of exposure.

The list that is perhaps best known is the Occupational Safety and Health

Administration's list of 17 carcinogens for which that agency has issued regulations. (Many of the regulations are based on information originally developed by industry.) The regulations aim at limiting employee exposure and require monitoring of concentration levels in regulated plant areas.

Du Pont makes two and uses one of the chemicals on the list, and formerly made or used certain others. The two are produced at Chambers Works in relatively small units. On the basis of its experience and on published studies, Du Pont believes that one of these, alpha-naphthylamine, is not a carcinogen. The other chemical identified by OSHA as a carcinogen is "Moca" curing agent, a rubber curing agent. The chemical ethylenimine, also on the list, is purchased for use at Ft. Madison, Iowa, in producing intermediates for coatings, but does not appear in the products as sold. The company adheres closely to all OSHA requirements in handling these substances. Du Pont's medical surveillance programs have revealed no health problems among employees working with these substances.

(A fourth item on the OSHA list, beta-propiolactone, has been detected in less than toxic levels in a closed waste stream at Parkersburg, W.Va. The chemical is destroyed in waste treatment.)

The OSHA list of regulated substances undoubtedly will be expanded. Meanwhile, NIOSH and the National Cancer Institute intermittently release to the news media information on other substances that some researchers have linked with cancer.

Du Pont's Decision

"The safety of our products and of the people who make and use them has always been of the highest priority to us," says Galloway. "As a consequence, we have developed our own system for managing the carcinogen problems."

When there is suspicion that a chemical is carcinogenic, an immediate effort is made to assess the potential hazard and determine what action is required. The manufacturing department, in cooperation with Haskell, may determine that the substance is probably linked to cancer, and that further steps are necessary. The first concern is to safeguard the health of employees, with a program which may include revision of work practices, requirements for additional protective equipment, process changes, or other improved engineering controls. Employees are informed why such steps are necessary.

When there is suspicion that a chemical is carcinogenic, an immediate effort is made to assess the potential hazard

A program for monitoring and measuring exposure levels may already be in effect. If not, the program is instituted along with an examination of employee medical histories to determine possible adverse effects on health. Medical surveillance procedures, as well as the recording of employee exposures, are undertaken.

Depending on the circumstances, a variety of groups—employees, customers, appropriate governmental agencies, other producers, the media—may be notified of the actions taken. And if safe handling cannot be assured, production is to be shut down and sales halted until adequate safeguards are developed.

Carrying Out the Intent

As William Galloway has pointed out, Du Pont has the capacity to carry out the program described above.

The process of determining whether a substance may be linked with cancer begins with Haskell Laboratory's review of chemicals made or used at Du Pont plants. The laboratory has been assessing the degree of hazard these substances might present.

The assessment may be based on references to the chemical in scientific studies, the chemical's similarity

to known carcinogens, or the results of screening tests.

Long-term testing requiring lifetime animal tests may be indicated. The growing demand for such studies is the main reason for the current expansion of Haskell. Laboratory space is being increased by 70 per cent.

When all available evidence on a chemical has been accumulated and evaluated, the decision may be made to describe it either as causing cancer in human beings; as causing cancer in animals; or as a suspected animal carcinogen, the evidence being moderate but inconclusive. This identification by Du Pont is in addition to the OSHA list of regulated substances.

At this time, nine chemicals have been identified by Du Pont as causing cancer in animals, or as suspected of doing so:

1. m-Toluenediamine (MTD), a dye intermediate made at Chambers Works.

2., 3. Zinc and lead chromates, used in making pigments frequently found in paints—but not in Du Pont's major lines of consumer paints. Made at Newark, N.J.

4. Ethylenethiourea, primarily a neoprene curing agent made at Chambers Works.

5. Dioxane, purchased for use as a solvent in making adhesive products at Parlin, N.J., and South San Francisco, Calif., and precious metal compositions at Niagara Falls, N.Y.

6. Beta-propiolactone (see above).

7. Hexamethylphosphoramide (HMPA), a solvent used in making "Kevlar" aramid fiber, made at Chambers Works and used at the Spruance plant, Richmond, Va.

8. Carbon tetrachloride, made at Corpus Christi, Texas, used at several other plants as an intermediate for fluorocarbons and "Hypalon" synthetic rubber.

9. 1,-4 Dichloro-butene-2 (DCB), intermediate for nylon and neoprene, made at Pontchartrain, La., and Victoria, Texas.

The steps taken to reduce exposure may range from setting up restricted areas where no one is allowed without protective clothing, to installing new vent and scrubber systems, to redesigning the process, to special maintenance procedures.

Galloway points out that measures such as these are nothing new to Du Pont.

"We have a tremendous amount of experience in handling hazardous products safely," he says. "Just to take two examples, we've been producing tetraethyl lead and chlorine for many years, in large quantities. We've learned to control the risk and make these products safely."

Du Pont's carcinogen analysis may include studies of the incidence of health problems among employees exposed to the chemical. Dr. Sidney Pell, epidemiologist in Du Pont's Medical Division, describes this work:

"In 1956 we established a cancer registry. It essentially is a record of all employees who develop cancer, except for nonfatal types of skin cancer. When company employees as a group are compared to large populations outside the company that have been studied, there is no significant difference between the employees and comparison groups."

Studies are also done of employees exposed to a specific chemical. In this type of study, employees who have been exposed at some time in the past are followed to the present to determine whether they have experienced an excessive incidence of some form of cancer.

Dr. Pell has done one study, of Du Pont employees working with zinc and lead chromates, in which there was some suggestion of a higher than normal incidence of lung cancer. The data were too limited to support definite conclusions. A multi-company study sponsored by members of the industry is nearly complete, and it may provide conclusive evidence as to whether there is a problem.

In another current study being done by Dr. Pell, there will be enough data to support reliable conclusions. Dr Pell is studying the medical histories of employees exposed to chloroprene, a neoprene intermediate once made at Chambers Works and now made at Victoria, Texas, and Pontchartrain, La., and used at Pontchartrain and

Louisville, Ky. Recent reports in Soviet technical literature claimed a higher incidence of cancer among workers in a neoprene plant, and these reports prompted the Du Pont study. So far, Dr. Pell says, the data do not indicate a statistically significant excess mortality from any form of cancer among employees as a result of exposure to chloroprene. The study is continuing.

What is "Safe?"

But the question still persists, what is a "safe" level of exposure to a carcinogen? It is a very difficult question to answer. The problem is not the same as with acute toxicity, where safe levels can usually be fully demonstrated in the laboratory.

"If you want me to give you an absolutely guaranteed level of safe exposure to a carcinogen, I can do it. The level is zero," says Dr. Zapp. "But that's because it's logically impossible to prove that just one molecule of the substance would never have a harmful effect on anyone who might come in contact with it.

> "What we consider ourselves obliged to do is to operate responsibly in the light of the best knowledge we can obtain."

"On the other hand, we know that the carcinogenic effect is dose-related." Dr. Zapp says. "That is, the incidence of cancer and the time it takes for a cancer to develop are directly related to the level of exposure. This means that we can reduce exposure to a point where cancer will not occur in a person's lifetime. There is evidence that we have done just that, with certain industrial chemicals that we now know cause cancer in animals and could expect to cause cancer in man. But there is no indication they have caused cancer in exposed employees."

Another perspective is offered by Galloway: "What we consider ourselves obliged to do is to operate responsibly in the light of the best knowledge of hazards that we can obtain. Fortunately, our employees are very cooperative in the process of establishing safety procedures and they understand the importance of following them. They are accustomed to changes in procedures as hazards are constantly redefined. All this works in our favor."

Toxic Substances Act

The Toxic Substances Act now being considered in committees of Congress may eventually give the government a strong hand in requiring manufacturers to detect and manage the carcinogen risk.

When passed, the legislation would give the Environmental Protection Agency the power to require testing of substances, including tests for carcinogenicity. It would permit the EPA to require testing and screening of new chemicals before they are marketed.

Richard E. Heckert, Du Pont senior vice president, recently outlined the company's response to proposed legislation, a position shared by many other chemical firms.

"The chemical industry supports additional Federal legislation on toxic substances that will close the gaps in present laws and offer greater protection to workers, consumers and the general public," Heckert said. "We support Federal authority to require testing of selected chemicals, and premarket notification or screening of new chemicals and significant new uses of established chemicals. We also support the authority to restrict or limit uses, or ban production of chemical substances."

There are two proposed bills which give the EPA broad power to require testing and screening of a wide range of substances. Du Pont and others would prefer to focus efforts on substances that appear to present significant risks. The industry is also concerned that excessively broad premarket testing and screening requirements could inhibit the industry's traditional emphasis on innovation and development of new products. In the development stages, new chemicals are already routinely handled with great care until their degree of toxicity is established.

Du Pont favors, in general, a bill sponsored by John Y. McCollister (R.-Neb.), according to Heckert. The McCollister bill limits testing and screening to significant risk areas. It also requires that the least burdensome controls be imposed to prevent or sufficiently reduce the risk. Banning would take place only if necessary. Consideration of the economic impact would be required when a substance is controlled. The Ford Administration has endorsed the McCollister bill, with certain amendments which Du Pont finds acceptable. A new bill containing these amendments has been introduced as H.R. 12336.

The Industry Initiative

The chemical industry is initiating its own positive action. Du Pont and 17 other chemical companies have joined to establish the Chemical Industry Institute of Toxicology. The companies have pledged about $15 million for initial costs, and a headquarters site has been selected near Raleigh, N.C.

CIIT will first concentrate on the carcinogenic potential of nonproprietary, widely used chemicals. The first two to be investigated will be ethylene and toluene. Emphasis will be on both testing chemicals and on developing new test methods for studying toxicity. Results of the studies will be made public.

The new institute is evidence of the industry's belief that the hazards can be identified and precautions can be taken to establish safe working conditions.