33 / Compounds Associated with Carcinogenesis

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OF ALL THE occupational health aspects of particular concern to professional workers in the disciplines involved with occupational medicine, industrial hygiene and safety, the role of carcinogenic agents is the most vexing and perhaps the most poorly understood. A vast body of scientific evidence has been accumulated demonstrating relationships between occupational exposures and the development of cancers. Hazards range from actinic or solar ultraviolet effects of exposure outdoors to those workers engaged in deep underground mining. The "mixed dusts," consisting of iron oxide and silica in various ratios or quantities, also have been suspected and are discussed in Chapter 10. Other suspected or implicated agents are arsenic, asbestos, beryllium, cadmium, chromium, cobalt, iron, nickel, radioactive substances, certain aromatic amines and their derivatives and, most recently, vinyl chloride, discussed in depth elsewhere in this book.

Relationships between concomitant exposures from multiple exposures have yet to be systematically explored. Detailed discussions of some of the metals and their compounds and certain other substances believed to be carcinogenic are found in corresponding chapters.

A remarkably detailed contribution on environmental cancer hazards presenting the many variable factors regarding the elucidation of the problems of occupational carcinogenesis was published by Hueper[46] in 1972 and is a noteworthy introduction to the most complex of all occupational health problems. The prominent British investigator, Doll,[30] reported his concepts on established risks relating to occupational lung cancer. He began with those cancer risks that were with radiation exposure, mentioning mines that had been worked successfully for silver, nickel, cobalt, bismuth, arsenic, radium and uranium, and referred to the well-known suggestion that lung cancer might be due to the radioactivity. This suggestion appeared in the medical literature for the first time in 1921 (the Schneeberg mines). He continued with a discussion of chromates, asbestos, combustion and distillation products of coal for gas production, suspected risks in the absence of radiation, such as arsenic, iron, "isopropyl oil" and beryllium. He also included views on site specificity, emphasizing in his conclusion that "in recent years the mortality from lung cancer due to non-industrial causes has increased enormously; now in Britain lung cancer accounts for more than 10% of all deaths among men aged from 45 to 64 years, the ages at which a risk of industrial cancer may most readily be detected. In these circumstances, the discovery of a new risk by simple clinical observation is difficult and if any additional risks remain to be discovered, it is probable that they will be revealed by planned prospective studies, undertaken with the special object of finding out whether any

risks exist. That all the existing risks have been discovered seems most unlikely. Moreover, new materials and new processes are being introduced into industry almost daily and there is no reason to suppose that they will necessarily all be free from risk. It may be expected that industrial studies will continue, as in the past, to make important advances in our knowledge of all aspects of carcinogenesis. In this respect, detailed studies of the relationship between exposure, incidence, and duration of latent period may be of particular value."

Animal studies have demonstrated clues of great importance for estimating future risk to exposed workers. Especially noteworthy in this regard is the toxicologic study of animals exposed to vinyl chloride by Torkelson *et al.*[90] In 1954[42] and in 1956[43] Heath reported his studies of the production of malignant tumors by cobalt in the rat. "The results obtained show that cobalt metal is capable of producing malignant tumors in the muscles of a high proportion of the rats treated, owing to neoplastic changes both in connective tissue and striated muscle. When it became evident that cobalt was a strong carcinogen, a search of the literature revealed that as early as 1942, there was a German report of malignant tumors in two out of a number of rabbits injected intrafemorally with cobalt metal (although at the time this was unknown to Heath). One of these tumors was a spindle cell sarcoma at the injection site arising six years after injection, and the other at a site remote from the injection site was a multiple adenocarcinoma of the lung with peritoneal metastases.

"The results described in this paper must inevitably raise the question of what is the causative agent of the high incidence of pulmonary cancer in the Schneeberg miners. The radioactive as well as the arsenic content of the Schneeberg ores have both been incriminated as carcinogenic factors. Because a typical analysis of the Schneeberg mine dust shows 0.19 per cent of cobalt arsenide and 0.08 per cent of nickel cobalt, it seems likely that the cobalt might also be held suspect as believed long ago by Osler and others.[20] It also seems desirable to reinvestigate the possible carcinogenic hazards of inhalation of cobalt-bearing dusts by workers in industry. Some work on these lines with negative results in relation to the cemented tungsten carbide industry where cobalt is used as a cement has already been reported."[73]

A study of cancer mortality among uranium mill workers by Archer *et al.*[6] was concerned with mortality (from all causes) for a small group of uranium mill workers. The only specific cause of death that was significantly excessive was malignant disease of the lymphatic and hematopoietic tissue, referring to data from animal experiments that suggested that this excess may have resulted from irradiation of lymph nodes by thorium-230. Earlier studies by Archer and associates[3] describing health hazards of uranium mining and milling documented an increased incidence of lung cancer in uranium miners in the United States. Subsequently, they reported the correlation between radon exposure and the incidence of lung cancer.[65]

In Sweden, measurements of radon were carried out by the Radiological Protection Service in all mines during 1969 and 1970. These showed that 22 of 82 mines had a radon daughter level of more than 30 picocuries (pCi)/liter. Following these major reports, Jorgensen[52] reported his investigation of the mortality from lung cancer among miners of the LKAB Company (Luossavaara-Kirunavaara), in Kiruna, Sweden between 1950 and 1970. The iron ore mine in Kiruna (about 150 kilometers north of the Arctic Circle) began as an open pit mine (the ore being mainly hematite), but in the late 1950s,

underground mining was started. This mine, said to be the largest of its type in the world, employs about 4400 miners. These miners generally do not migrate from their birthplace, so available reports of deaths of miners represent nearly all deceased miners from the Kiruna mine.

From the medical and hygienic points of view, important environmental factors are brought out by Jörgensen. Diesel-powered vehicles were introduced in 1958 for subterranean transportation and were increased in numbers until today there are 75 trucks and 35 front loaders that are continually in use underground. Exhaust fumes are controlled by scrubbers and/or catalytic afterburners and by an extensive ventilation system forcing air throughout the mine. Dust measurements in the mine revealed concentrations of between 3 and 9 mg/m^3, with about 40% of the particles being less than 5 μm in diameter. Dust concentration around the loading operation at times has been between 10 and 15 mg/m^3 but has decreased recently because water spraying has been introduced. "Wet drilling" has been used since the early 1930s and has practically eliminated the risk of pneumoconiosis.

Jörgensen reported, "No one realized that there could be radioactivity in the mine in Kiruna until 1970 when radon concentrations were measured." In most places, there were found concentrations of radon daughters of between 10 and 30 pCi/liter. However, in some unventilated galleries, very high concentrations were found. This was attributed to the fact that the radon had not had time to evaporate in the running water. The levels of radon measured in the mine today probably are representative of the earlier conditions. On some occasions, however, and at some places near water inlets in the LKAB mine, the radon concentration previously had been considerably higher for short periods of time.

In this retrospective study, mortality among the workers revealed 13 cases of lung cancer, whereas only 4.5 were expected among the rest of the male population in this community. The lung cancer mortality rate among non-mine workers was equal to that of Sweden in general. Because the study was done at a time when concurrent exposure investigations of workers to radon daughters and diesel exhaust fumes were not possible and because there is a possibility of noxious interaction, this study should be followed up in 5–10 years.

S:t Clair Renard[81] reported extremely high rates of mortality from carcinoma of the lung among underground miners at the Malmberget (also LKAB) iron ore mine in northern Sweden. Among the potentially causative factors were the relatively high radon levels found at various plateaus of the mine until recently, when the ventilation system was improved. The report by Boyd *et al.*[17] that radon-222 in a hematite mine in England had caused carcinoma of the lung (1968–1970) moved the Swedish Mine Association to collaborate with the National Institute of Radiation Protection in the examination of the content of radon-222 in the air in all Swedish mines.

The results of both these studies showed a definite tendency toward a high mortality from lung cancer among Swedish miners (underground miners: 6 expected, 26 observed). There also appeared to be a correlation between respiratory cancer in the mines and a high radon concentration in the air.

In 1968, S:t Clair Renard began a study of lung cancer in the Malmberget mine, reviewing all cases of respiratory cancer in all men 20–74 years of age in his community dying between 1950 and 1972. Of the 41 cases found, many once had worked in the mine. The Gällivare-Malmberget communities are north of the Arctic Circle near the LKAB Kiruna

mine (the same company reported by Jörgensen), yielding essentially magnetite ore with some hematite. The mine was opened in 1809 and has conducted operations completely underground since 1930. The quartz content of the rock is 10–20%.

Among the many potential causative factors of lung cancer listed by the author are smoking habits, quartz dust, exhaust from diesel motors, radon and its decay products and poor ventilation. The interrelationships were too complicated to have been analyzed as part of his timely reporting.[82]

Another vital consequence from the ever-deeper mining activities was the increased need for greater volumes of artificial ventilation. To warm the air going into the mines, air was forced through great masses of crushed rocks. Thus, air exposed to rocks with low uranium content but large surface areas could be enriched with radon as it was pumped down to the depths of the mines. When the problems were identified and a possible explanation given, the ventilation system was changed and augmented. At present, the Malmberget mine is aerated with 50 million tons of air yearly (for comparison, 10 million tons of ore and rock are brought up every year).

S:t Clair Renard indicated that the results from the ventilation have been encouraging, remodeling measurements during recent months having showed decreasing radon levels, lower than 0.1 WL* (10 pCi/liter decay products of radon) in all parts of the mine. He concluded, "The results of this study should be of interest in mining areas all over the world where uranium occurs as a trace element, either occurring directly in the mines or as fission products exposed through cracks in the surrounding rock or brought into the mines with water from outside sources."[83]

*300 pCi/liter = 1 Working Level (see Chap. 22).

Recently, Dinman[28] proposed a classification of biologic evidence for occupational carcinogenesis, identifying three major groups: group 1, *definitely* carcinogenic; group 2, *probably* carcinogenic; and group 3, *presumably* carcinogenic. Group 1 requires epidemiologic and experimental evidence of carcinogenesis. Representatives of this group are beta-naphthylamine, chromium, nickel, 4-aminodiphenyl and benzidine. Others were "uncharacterized or contaminated mixtures," such as mineral-derived tars, pitches, oil and asbestos. In addition, arsenic, mustard gas and hematite as an "uncharacterized mixture" were included.

The second group, probably carcinogenic based on experimental findings, included 4-nitrophenyl and alpha-naphthylamine as epidemiologically associated with experimental findings and the "uncharacterized or contaminated" substances auramine and magenta. Group 2 "experimental cases" also included beryllium. Group 3, presumably carcinogenic based on animal experiments only, included the following compounds: nitrosoamines (*N*-nitrosodimethylamine, alkylating agents [with the exception of mustard gas], dichlorobenzidine, *o*-toluidine and dianisidine).

According to Dinman, "there are some cautions to be applied to indicate relative levels of carcinogenic ordering even within grades of this classification. For example, where experimentation presents design problems for benzidine induction of bladder tumors in animals, the strength of the epidemiological evidence for that compound's cancer potential in man leaves no more room for doubt of its potency than in the case, for example, of beta-naphthylamine (BNA). Conversely, as regards the chromates, epidemiological plus a single report of experimental induction[57] place chromates at the same level as benzidine in this evidentiary classification, even though it appears that

the various salts and oxides of this element are less carcinogenic than benzidine."

At the Symposium on Chemical Carcinogens held in Pittsburgh in June of 1973, Weisburger[100] presented his viewpoints on the environment and cancer on the mechanism of carcinogenesis. Among the several major carcinogenesis problems pointed out by him was the carcinogenic hazard due to mixtures of agents. Often there are pronounced synergistic effects. He outlined the steps of carcinogenesis in relation to man, stating that "there is an essential difference between carcinogens and other toxicants and, by and large, bona fide real carcinogens do combine with DNA. Once that combination is formed, it is not reversible except by so-called repair enzymes, which, in turn, may lead to miscoding. Carcinogens are toxic, of course, kill cells, and the dead cell does not cancerize. When carcinogens react with DNA to yield a viable cell, it is an abnormal, latent tumor cell and the action is not reversible—most toxic effects are reversible. Primary carcinogens do not require metabolic activation. Others are the ethylene amines, sulfur, mustard, lactones, epoxides or bis(chloromethyl)ether. Those do not require metabolism. Thus, with such chemicals, I would predict, although extensive studies have not really been done, age may play a lesser role in the relative hazard to agents of this type.

"The other major class of agents requires biochemical activation. Thus, with these, one would predict that the major effects would hinge on the ratio of activation to detoxification. If a young person has a higher ratio of activation to detoxification, he would be at a higher risk than an older person. Some of these chemicals are synthetic, some are natural products like cycasin, a plant carcinogen, or like mycotoxins. The environment contains naturally occurring as well as synthetic carcinogens. I am much more concerned about naturally occurring carcinogens that we are exposed to, eat or consume unknowingly than about synthetics. It was shown very clearly that something can be done about the synthetics. You know they are hazardous; you should and can control them. The people producing such chemicals know it is dangerous and control them, but their customers do not always appreciate the potential risk. I think this is an area where education and information are very important.

"Also, we now understand that primary carcinogens, like certain alkylating agents as beta-propiolactone or bis(chloromethyl)ether, or active intermediaries obtained by host-controlled reactions, are carcinogenic because they interact with DNA structure or function. Changes in DNA may mean mutation. We know that direct alkylating agents are mutagenic as was demonstrated beautifully back in the 40s. But other experts in the field of mutagenesis, who tested not alkylating agents but procarcinogens 25 years ago, found them not mutagenic. The chemicals tested, such as polycyclic aromatic hydrocarbons or aromatic amines, were not mutagenic because they tested the procarcinogens, and they had no way of activating them in their system. Today, we know that if we activate such materials biochemically, they can be mutagenic. This gives us new tools which we are currently exploring to assess potential risks in the environment. Methods are available to resolve the question whether a product is mutagenic in two weeks, whereas it takes up to two years to find out whether a chemical is carcinogenic in an animal model. Thus, it is possible to get an inkling or a feeling for such risks in two weeks rather than two years. We need to be careful about the interpretation of the results obtained in such systems. I would not necessarily ban or recommend that a product be abolished because it is mutagenic in one system. One of you showed me a reprint

where a widely used chemical expressed mutagenic properties under some conditions. If a chemical is mutagenic, I would like to recommend caution. It is a blinking yellow light. Depending on additional information, such a product might warrant testing for carcinogenicity in the conventional animal systems. At the same time, one would wish to minimize human exposure. Quick mutagenicity tests provide tools to select from the hundreds of thousands of chemicals, natural and synthetic, we concern ourselves about, as to whether they require assays in animal systems. Also, under extensive exploration is the problem of using transformation of cell cultures to develop a quick preview of possible hazards. An advantage is the possibility of using human cell systems. Again, I wish to emphasize the problem of converting into vitro the chemicals to be tested which need biochemical activation in order to detect a possibly carcinogenic material without false negatives by such abbreviated procedures."

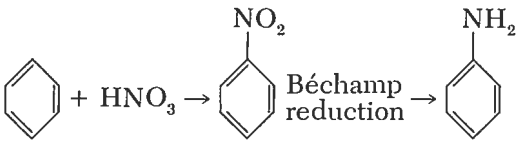
Among occupational groups, those workers engaged in the preparation of coke and its by-products have long been recognized as being at risk for the development of skin and lung cancers. These occupational and environmental observations have been comprehensively reported in the NIOSH Criteria Document for a Recommended Standard . . . Occupational Exposure to Coke Oven Emissions.[92] That there is much controversy is an understatement. Highlighted in an editorial by Nelson[75] in May, 1973 in the *New England Journal of Medicine* were several new and practical applications of chemical carcinogens. He stated that "evidence has been accumulating in occupational settings for many years that external factors, both chemical and physical, are identifiable causes of occupational cancer. It has been estimated that possibly as much as 80% of all cancer is of environmental origin."[39] A variety of clues provide the basis for such speculation; perhaps the most persuasive stem from studies of migrant populations that clearly show that geographic differences in certain cancer rates tend to disappear in migrant populations in which the cancer rates move toward those of the native populations, clearly implying an important role in external factors in determining cancer rates.[40]

"Where occupational causes of cancer have been identified, it has been possible to intervene and prevent the disease. The implications of this simple and indeed obvious message concerning the wide role of external factors in cancer causation have been surprisingly neglected. Fortunately, however, the promise of cancer prevention is now receiving more attention. It is of interest that of the seven stated objectives of the new National Cancer Plan, the first four are aimed primarily at prevention. Of these objectives, number one is to 'Develop the means to reduce the effectiveness of external agents in increasing the probabilities of development of cancers in existing individuals or in individuals of subsequent generations.' "[91]

AZO DYES

The "azo" dyes form the largest class of synthetic dyes. Having been developed for coloring every fiber, both natural and synthetic, their use has been extended to the coloration of solvents and many other nontextile substances. These chemicals are derived from "aromatic hydrocarbons" typified by benzene, toluene and xylene and have a distinctive "aromatic" odor. Originally, most were made from coal tar as by-products from coke manufacturing, but now they are obtained primarily from petroleum sources. The hydrocarbons mentioned, including naphthalene and anthracene, are basic

compounds in the synthesis of most aromatic amines (see Otterson, Chapter 31). Amines contain nitrogen as NH_2; of these, aniline is the best known.



Benzene Nitrobenzene Aniline

Unfortunately, "analine" and "aniline dyes" have become known as dangerous substances, thought capable of producing serious disturbances, such as aplastic anemia, first observed with benzene exposures (benzene was one of the first solvents isolated from the coal tar aniline compounds) and bladder tumors.

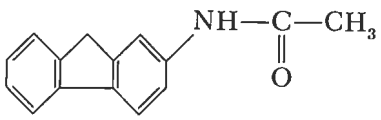
Occupational exposure to aromatic amines has long been associated with the development of bladder cancer. Historically, the population at risk has been limited to individuals employed in the "aniline" dye industry. The term "aniline cancer" was used in earlier days to denote cancer of the urinary bladder in workers engaged in the production of "aniline" dyes. Hueper[45] published a paper in 1934 in which he reviewed the history, significance and epidemiologic evidence of "aniline cancer" in the dye industry. Hueper credited Rehn with reporting the first cases of occupational bladder tumors in 1895 in 3 workers in a German dye factory. In his review article, Hueper mentioned the beginning of what was to become a growing controversy concerning the etiology of occupational bladder cancer. He stated that aniline, benzidine and naphthylamine were the principal etiologic candidates, but emphasized major epidemiologic "pitfalls," including:

1. Worker exposure to more than one suspect compound, further complicated by shifting of workers between departments.
2. Different degrees of exposure hazard between processes.
3. Unsuspected impurities in trace amounts possibly more harmful than the parent compound.
4. Different composition of dyes and production methodology in different factories complicating statistical comparison.

Colors used in textile dyeing processes are considered to be generally nontoxic or of a low order of toxicity and no evidence has been shown that chronic occupational health problems have resulted from their use. The "intermediate process" or "indirect dyeing" of fibers applied by successive stages in order to attain good fixation required a number of "intermediates." Some of these intermediates are the naphthalenes and several aromatic amines that have been suspected or known to be carcinogenic. Of great concern are benzidine, some of its related compounds and alpha-naphthylamine. (These will be discussed further.)

In January, 1974, the U. S. Secretary of Labor of the Occupational Safety and Health Administration announced a standard for 14 carcinogens.[31] Because of this significant action, these substances are presented here in summary form. The OSHA work practices are found in this standard.

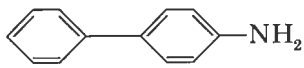
2-Acetylaminofluorene (2-AAF)



In 1941, Wilson *et al.*,[102] during a study of the toxicity in animals of a promising new pesticide, 2-acetylaminofluorene, discovered that it was a potent carcinogen. By 1961, there were more than 500 reports of studies of the carcinogenic effects of this substance or its related compounds. Although most of these

studies resulted in carcinoma in rats, carcinogenic effects have been demonstrated in other laboratory animals as well. Liver and bladder tumors were produced in most animals on a dietary regimen of this substance. Weisburger *et al.*[101] noted from 5 patients treated with a single oral tracer dose of radioactive 2-AAF that man may convert 2-AAF, in part, to the potent carcinogenic metabolite, *N*-hydroxy-2-AAF. From this observation, it seems reasonable to conclude that 2-AAF, which has been shown to be carcinogenic in many animal species, probably is carcinogenic in man.

4-Aminodiphenyl



4-Aminodiphenyl, also known as xenylamine, has been used in rubber manufacturing as an antioxidant. Scott[85] recommended that its manufacture be terminated because its carcinogenic potency is at least equal to that of beta-naphthylamine and the prospect of safe processing is remote. In 1954, Walpole *et al.*[99] first reported 4-aminodiphenyl to be carcinogenic in the urinary bladder of dogs. These investigators found multiple epithelial tumors in the urinary bladder of each animal. Concerning occupational exposure to 4-aminodiphenyl, they stated, "We, therefore, conclude that its manufacture and handling today would carry with it grave risks to the working population involved unless adequate precautions were taken to avoid skin contact or the inhalation of vapour or dust by the use of totally enclosed plant and daily changes of clothing for the operators."

In 1956[25] and in 1958,[26] Deichmann *et al.* published reports concerning their experiments with dogs dosed orally. Carcinomas were diagnosed in the bladders of all animals, with death occurring from 4 to 18 months following the initial appearance of tumors.

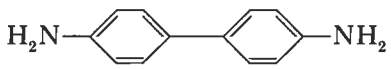
As with other aromatic amines, attention has focused on the importance of *N*-hydroxylated metabolites of 4-ADP as proximate carcinogens. Fefer, Brill and Radomski[32] consistently recovered "substantial" amounts of *N*-hydroxy-4-aminodiphenyl (*N*-OH-4-ADP) in animal studies. These investigators also obtained evidence of the presence of the nitroso derivative.

In 1955, Melick *et al.*[71] presented the results of their epidemiologic investigation of the incidence of bladder cancer in workers engaged in the production of 4-ADP. Production of this aromatic amine was from 1935 to 1955 in the United States. Of 171 workers examined in several plants, 11.1% developed bladder tumors in 5 to 19 years following initiation of exposure. Exposure duration ranged from 1 to 19 years. In a later report,[72] this range increased from 133 days to 35 years. The incidence of bladder tumors increased with time in the study group. In Plant 1, the number of workers exhibiting tumors of those examined was 12/71 in 1953 (16.9%), 23/186 in 1958 (12.4%) and 42/261 in 1970 (16.1%). In Plant 2, these statistics were 1/44 in 1953 (2.3%), 2/45 in 1958 (4.4%) and 10/54 in 1970 (18.5%). The 315 workers examined in this later report were included in a study by Koss *et al.*[56] of 503 workers examined who had been exposed to 4-ADP. Of the 503 workers examined, 435 had no cytologic evidence of bladder cancer, 16 had "suspicious cytology" for carcinoma, 8 had conclusive cytologic diagnosis of carcinoma, 9 had doubtful cytology and 35 had histologically confirmed carcinoma of the bladder. Of the 24 workers with either suspicious or conclusive cytologic diagnosis of carcinoma, 7 died of unrelated disease prior to histologic proof of bladder carcinoma, 10 were lost to follow-up and the remaining 7 had no histologic proof of carcinoma. Hence, it is conceivable that at the time of the report the 35 workers with histologically con-

firmed carcinoma of the bladder could be expanded to 52, if those workers with positive cytologic examinations were to be found histologically positive. As stated by the investigators, "as evidence from the data previously presented, many years may be required until the clinical proof of cancer is available."

From the work of Melick and Koss it is evident that more cases of bladder carcinoma will be diagnosed in this particular population. Of greater importance is its clear implication in the induction of bladder tumors in workers engaged in its production. Deichmann and Radomski[24] considered 4-ADP to possess a relative carcinogenic potential for the dog 6 times greater than that of beta-naphthylamine, 17 times greater than that of 4-nitrobiphenyl and 27 times greater than that of benzidine. The accumulated experimental and epidemiologic evidence thus demonstrates that 4-ADP may be the most hazardous aromatic amine carcinogen.

Benzidine



Benzidine, also called 4,4′-diaminobiphenyl and *p*-diaminodiphenyl, occurs as white or slightly reddish crystals, leaflets or as a crystalline powder and is used in the manufacture of azo dyestuffs. It is manufactured by reduction of nitrobenzene to hydrazobenzene with subsequent conversion to benzidine or its salts and coupled with other intermediates to form dyes. Benzidine base possesses a significant vapor pressure and is readily absorbed through the skin. Although its salts, such as the mono- and dihydrochloride and the sulfate, exert no significant vapor pressure, skin absorption can occur. Derivatives, such as 3,3′-dichlorobenzidine (DCB) (discussed later), are also important intermediates in the dyestuff industry.[51]

The prevalence of bladder cancer among workers in the aniline dye industry was known for many years, although the etiology of the disease was not clearly understood.[10, 13, 33, 36, 45] In 1937, Berenblum and Bonser,[14] based on their observations and review of the published literature, drew several conclusions:

1. Aniline cancer is associated with the handling of certain "intermediate products" used in the manufacture of dyes.

2. Of these intermediate products, aniline, benzidine and alpha- and beta-naphthylamine appear to be implicated most frequently, probably the most important being benzidine and beta-naphthylamine.

3. Although these substances may themselves be the responsible agents, there is the alternative possibility that the disease is due to traces of unsuspected substances that are present.

4. The bladder tumors develop only after a long latent period (usually 10–25 years in man), and sometimes not until many years after the men have ceased work.

A confusing factor in determining whether or not benzidine, or beta-naphthylamine, is a human carcinogen is that of multiple exposure, a problem that Berenblum and Bonser recognized as early as 1937. Workers in aniline dye plants usually were exposed to many aromatic amines, thereby complicating any investigation of cause-and-effect relationships. Increased incidence of bladder cancer in such plants was known but the specific causative agent was not known.

Scott[85] stated that it had been held that all stages of the manufacturing process were considered to be hazardous. Men engaged in the reduction to hydrazobenzene apparently were affected equally with those doing the conversion to benzidine and its separation. Other men engaged on other processes in the same building were affected also, and the whole operation was regarded as dangerous until Barsotti and Vigliani[10] described a factory in which hydrazobenzene was made in one building and conveyed to another factory for conversion to benzidine. No tumors had oc-

curred among the men making hydrazobenzene, but tumors had arisen in some of the benzidine workers. So far, no tumors have been induced in experimental animals with hydrazobenzene. Scott and Williams[86] believe that the hazard exists after the conversion of hydrazobenzene to benzidine. It must be remembered that if hydrazobenzene dust or vapor is swallowed, it will be converted to benzidine by the action of the hydrochloric acid in the normal stomach.

In later years, populations of workers exposed to only benzidine were studied.[37, 68, 103] From observation of these groups, the role of benzidine as a human carcinogen became clear.

In 1954, Case *et al.*[18] published the results of their study of workmen engaged in the manufacture and use of the dyestuff intermediates aniline, benzidine, alpha-naphthylamine and beta-naphthylamine in the British chemical industry. They determined the incidence of tumors of the urinary bladder among such workers during a 5-year field survey. Only 0.72 would have been expected from the whole male population of England and Wales ($p < 0.001$). The tumors appeared after an average induction period of 16 years. From the evidence of Case *et al.*, bladder cancer is a fatal disease—only 20% of all patients having survived more than 10 years from the first recognition of the disease. Processmen, pressmen, filtermen and laborers engaged in the manufacture and use of benzidine experienced the greatest risk. The data conclusively indicated that the risk of dying of bladder cancer from benzidine exposure greatly exceeded that of the general population.

Goldwater *et al.*[37] studied workers in a coal tar dye plant in an effort to ascertain the association between bladder cancer induction and exposure to certain aromatic amines. The incidence of urinary bladder tumors in workers exposed to alphanaphthylamine, beta-naphthylamine (BNA) and benzidine, the average incubation period, the average survival time and the incidence of malignant tumors other than those of the bladder were determined. The population studied included all male workers in the factory in question from 1912 to 1962, thus spanning a period of 50 years. The total number of workers exposed to all three compounds was 366, of whom 96 (26.2%) developed malignancies of the bladder. Of 76 workers exposed to benzidine alone, 17 (21.3%) developed bladder cancer. The incidence of bladder cancer in workers exposed to BNA plus benzidine was significantly greater than for those exposed to benzidine alone, 45.5% versus 21.3%, respectively. For the induction of bladder cancer from benzidine, the average time was 18.7 years, calculated to the first diagnosis of malignancy. Following diagnosis of bladder malignancy from benzidine, the mean survival time was approximately 3 years.

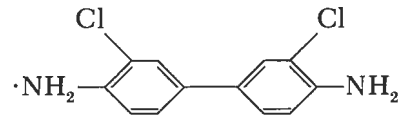
A cohort study of workers exposed to beta-naphthylamine and benzidine was published by Mancuso and El-Attar in 1967.[68] Their primary purposes were to investigate (1) whether the previously reported[67] epidemiologic evidence of cancer of the pancreas could be substantiated over a long period, (2) the comparative carcinogenicity of beta-naphthylamine and benzidine and (3) the possibility of additive or synergistic effects. A cohort study was performed on 639 males employed during the period 1938–1939 in a company manufacturing beta-naphthylamine and benzidine and who were followed in 1965 in order to determine the mortality pattern. The company cohort was characterized as containing three groups of workers: (1) exposed, (2) not exposed and (3) exposure not known. Malignancies of the bladder and kidney constituted 35% (20/57) of all malignant neoplasms. The observed mortality rate

for cancer of the bladder for white males in the company cohort, 25–64 years of age, was 78/100,000 as compared with 4.4/100,000 for white Ohio males of those ages. All cancers of the bladder for white males in the cohort occurred in the exposed group; the average annual mortality rates were 335/100,000 and 971/100,000 for the age groups 45–64 and 65 and over, respectively. Cancer of the pancreas (6 cases) constituted 32% of the malignant neoplasms of the digestive system. The comparative cohort mortality rate for cancer of the pancreas was 39/100,000 whereas the rate for white males (Ohio residents) in the general population 25–64 years of age was 7.5/100,000. The incidence of cancer in workers exposed to beta-naphthylamine was almost 4 times that in those exposed to benzidine alone. Likewise, exposure to both compounds was more hazardous than exposure to either carcinogen alone. As reported previously, benzidine was firmly implicated as a cause of human bladder cancer.

The recently published findings by Zavon *et al.*[103] also demonstrate that benzidine is a human carcinogen. They observed a group of 25 workers engaged in the manufacture of benzidine for an average of 10.6 years. Workers who developed tumors had an average exposure to benzidine in excess of 13 years whereas the nontumor group averaged less than 9 years of exposure. Of the 25 benzidine-exposed workers, 13 (52%) developed bladder tumors and 11 of these were malignant. The exposure time began as early as 1929, when production began, and as late as 1958, when it was discontinued. Determinations of the benzidine content of air samples from various locations in the plant were performed in 1958; the highest benzidine concentration, 17.6 mg/m^3, was obtained in the area where the final product was shoveled into steel drums. From 1929 to 1945, the final product was benzidine *sulfate;* from 1945 to 1958, the *hydrochloride* salt was prepared. The results of this study thus implicate both the hydrochloride and the sulfate salts of benzidine as human carcinogens. It should be mentioned that 3 of the 25 men involved in the study had approximately 1 year of exposure to beta-naphthylamine, 3 had exposure to *o*-toluidine and 7 had been engaged in dichlorobenzidine (DCB) production at some time. However, compared to their exposure to benzidine, their exposures to other compounds, including BNA, which also is a human carcinogen, appear insignificant. Of the workers in whom bladder cancer developed, 6/11 (55%) had no known exposure to either BNA or DCB. The authors concluded that the manufacture of benzidine was associated with a high risk of developing bladder cancer.

Epidemiologic studies[18, 37, 68, 103] of worker populations exposed to benzidine demonstrate that the compound and its salts are also human carcinogens. The incidence of bladder cancer in benzidine workers greatly exceeds the incidence of the disease in the normal population. Workers involved in the manufacture, handling or use of this demonstrated human bladder carcinogen now are protected by current regulations promulgated by OSHA.

3,3′-Dichlorobenzidine (DCB)



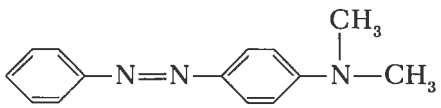
The potential of benzidine to induce cancer of the urinary bladder has precipitated inquiry into its chlorinated derivative, 3,3′-dichlorobenzidine. Today, DCB is a widely used intermediate in the organic pigment industry and is considered indispensable in the production of certain pigments. Akiyama[1] related in-

dustrial experience in Japan with finding DCB in the urine of not only the charging operators but also in the urine of dryers and crackers.

The Russian industrial experience with DCB was summarized by Lipkin[62] in a 1962 article. Lipkin stated that a 1958 hygienic study revealed ". . .very unfavorable working conditions and the presence of considerable contact of workers with dichlorobenzidine in industry." He noted that, in the following year, DCB production was halted in Russia.

The case for the carcinogenicity of DCB has rested on the validity of controlled experimental studies with several animal species because of the absence of a clearly defined worker population exposed only to DCB for any significant length of time. Where a worker population may exist, the period of actual exposure to DCB often is short and on the order of only a few years. Workers who have developed bladder tumors while working with DCB have been exposed concomitantly to such generally accepted occupational carcinogens as beta-naphthylamine and benzidine. Because no significant worker population exposed exclusively to DCB has been found to exist,[85] a safe occupational exposure to DCB cannot be demonstrated. Therefore, the case for the human carcinogenicity of DCB must rely on extrapolation to humans of the most pertinent experimental animal studies of oncogenesis.

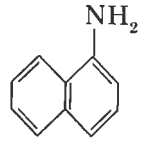
4-Dimethylaminoazobenzene (DAB)
"Butter Yellow"



The events leading up to the demonstration by Kinosita[53] that 4-dimethylaminoazobenzene (DAB) produced cancer of the liver when added to the food of rats are well summarized by Badger and Lewis.[7] Since the initial report by Kinosita, numerous reports have confirmed the fact that DAB, also referred to as *p*-dimethylaminoazobenzene and "butter yellow," produces liver tumors in the rat. For example, 23 articles, all published in the year 1954, reported positive results in tests on the carcinogenicity of DAB in rats.[93]

In summary, DAB has been demonstrated to be carcinogenic in rats, dogs, neonatal mice and trout. The results reported in dogs, even though quite limited, must be accorded considerable weight. In the absence of adequate epidemiologic data to the contrary, DAB must be regarded as a potential carcinogen for man.

Alpha-naphthylamine (1-NA)



Alpha-naphthylamine (1-NA) is primarily used in the manufacture of azo dyes and for certain rubber processing. Scott[85] noted that under contemporary industrial practices (1962), the beta-naphthylamine (2-NA) content of 1-NA was approximately 4%. It is understood that in current industrial practices, this level of contamination by 2-NA can be kept below 0.5%.[54] In his evaluation of the literature and state of the art concerned with occupational exposure to 1-NA, Scott stated, "It is, therefore, difficult to escape the conclusion that alpha-naphthylamine is carcinogenic to man. . . . The standard of precautionary measures in its manufacture and use should be as high as that recommended for benzidine." It should be noted that, as concerns industrial exposure, Scott believed that 1-NA should not be considered in terms of purity but ". . . as it is found in industry, and there can be no doubt epidemiologically

and theoretically of the risk attached to it."

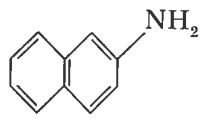
In 1952, Barsotti and Vigliani[9] published results of an epidemiologic survey conducted among workers exposed to aromatic amines. Of the 902 workers surveyed, 30 had been exposed to 1-NA and 23 of these had been examined cystoscopically; 14 were normal, 7 had bladder congestion and 2 had sessile papillomas. One of the papillomas appeared following 4 years' exposure and a 20-year latency period and the other following 25 years' exposure and 1 year of latency. All workers had additional exposure to toluidines, anisidines, xylidines, chloroanilines and phenetidines.

An interesting conclusion was reached by Case *et al.*[18]: "The average induction time is not appreciably influenced by the severity or duration of the exposure. It, therefore, appears to be a characteristic of the causal agent. This suggests that it is possible that the beta-naphthylamine content of alpha-naphthylamine is not the sole causative agent in the latter substance unless it is assumed that alpha-naphthylamine could retard the production of beta-naphthylamine tumors."

The main direction of research efforts to determine causation of bladder tumors induced by the naphthylamines has been the identification of those metabolites that possess this potentiality.

As yet, however, the ultimate carcinogenic metabolite(s) has not been clearly identified. Although the final resolution of this situation may be only academic to the occupational environment, the fact that an ultimate, active, hazardous substance has not been identified for even 2-NA precludes the dismissal of 1-NA as noncarcinogenic until it is clearly demonstrated that its metabolites are not carcinogenic for man. The demonstration that one such metabolite, *N*-OH-1-NA, was carcinogenic for rats and mice and was found to possess a greater carcinogenic potential than does its 2-NA counterpart[12] underscores this particular point. In addition, the extensive epidemiologic study in the dye industry by Case *et al.*[18] failed to eliminate an active role for 1-NA as a bladder carcinogen.

Beta-naphthylamine (2-NA)



In the past, 2-NA has been used in the dye industry as an intermediate and in the rubber industry as an antioxidant. Its current commercial usage is considered minimal and its manufacture by the only known source in the United States supposedly ceased in 1972.

The induction of bladder tumors in workers exposed to 2-NA is one of the most well-established cause-and-effect relationships in occupational medicine. As mentioned earlier, Rehn is credited by Hueper as reporting the first cases of occupational bladder tumors in 1895 in 3 workers in a German dye factory. Many of the early epidemiologic studies were of limited usefulness as concerns specific etiologic roles, as Hueper[45] stated in 1934: "While aniline, benzidine and naphthylamine are the substances at the present time mainly accused of responsibility for the production of bladder tumors (International Labour Office), the exact chemical nature of the causative agent is not known." Thus, for some time, the term "aniline cancer" was used to describe occupational bladder cancer in dyestuff workers.

Numerous epidemiologic investigations have proceeded from these earlier reports, including limited surveys in the United States. However, the industry-wide epidemiologic survey by Case *et al.*[18] in 1954 is the only in-depth, comprehensive epidemiologic survey undertaken of workers exposed to 2-NA. This

survey included 4622 men who had been employed for 6 months or more in the dyestuffs industry. Case *et al.* estimated that the expected number of death certificates mentioning tumor of the bladder for this population should be 3–5 but actually found that of the 262 known cases of bladder tumors in this population, 127 of 144 death certificates mentioned tumor of the bladder. The over-all risk of death due to bladder tumor was estimated at 30 times the general population. Of 55 workers of the 262 total with bladder tumors who had received exposure to 2-NA only (excluding any exposure to benzidine or 1-NA), 26 or 27 death certificates mentioned the presence of bladder tumors. It was verified that risk of bladder tumors was present in both the manufacture and use of 2-NA. Case *et al.* estimated the latency period from initiation of exposure to 2-NA to development of tumors to be 16±6 years. In this regard, it was also determined that the induction period was constant with respect to age at entry and age at onset, although tumors were observed in workers exposed for fewer than 5 years or for more than 45 years. Based on the observation that the risk of bladder tumor development increased to a maximum and then decreased, Case *et al.* suggested that for a given level of risk there are both hypersusceptibles and hyposusceptibles present in the worker population and that selection might be possible by altering the level of risk. However, they considered reduction in employment time to be impractical in eliminating this risk, since tumors had been observed in workers exposed for less than 1 year. Case *et al.* considered that 2-NA was a more potent cause of bladder tumor than benzidine by a factor of 3 and 1-NA by a factor of 5.

Earlier, Barsotti and Vigliani[9] had observed in an epidemiologic study published in 1952 that 2-NA and benzidine carried the highest carcinogenic potential in the dyestuff industry.

Kleinfeld[54] published the results in 1965 and 1967 of an epidemiologic study of workers exposed to 2-NA and other aromatic amines in a dyestuffs plant. Of 376 employees examined, 109 (29%) were discovered to have bladder malignancies. Of 54 workers exposed to 2-NA only, 17 (31.5%) were discovered to have bladder malignancies. The mean latency period for workers exposed to 2-NA only was 20 years, with a range of 6–38 years. Mixed exposure to 2-NA and benzidine resulted in an incidence of bladder malignancies of 50%.

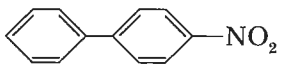
The carcinogenicity of 2-NA is well established by both animal data and human experience. Although an ultimate carcinogenic metabolite has yet to be identified, this aromatic amine is clearly implicated as a highly hazardous substance in any occupational environment.

Case *et al.*[18] considered the risk of bladder cancer in workers exposed to 2-NA to be 61 times greater than that in the general population. Scott[85] reported: "There is undoubtedly overwhelming evidence that beta-naphthylamine is a highly active carcinogen not only to laboratory animals but also to man in industrial conditions of manufacture and use, so much so that its manufacture has been given up in Britain and some other countries solely because of the danger associated with it." Scott considered the manufacture of 2-NA ". . . to be by far the most hazardous occupation in the dyestuffs industry."

The American Conference of Governmental Industrial Hygienists (ACGIH) in their Documentation of the Threshold Limit Values,[2] noted that authorities who have studied the problem appear to be in general agreement that banning the use of this material is justifiable in view of

the disastrous consequences to workers who have been engaged in its manufacture and use.

4-Nitrobiphenyl (4-NBP)

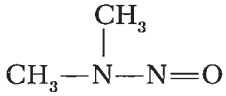


The industrial importance of 4-nitrobiphenyl (4-NBP) was intimately associated with the production of its reduced derivative, 4-aminodiphenyl (4-ADP). With the discontinuance of production of 4-ADP in 1955, due principally to the demonstration by Walpole *et al.*[99] in 1954 that 4-ADP produced carcinoma of the urinary bladder of dogs, the production of 4-NBP was discontinued also.

The carcinogenicity of 4-NBP is strongly supported by the induction of bladder carcinoma in dogs. The evidence that 4-NBP is metabolized in vivo to 4-ADP, which is a highly carcinogenic aromatic amine, and the possible evidence that human cases of bladder cancer attributed by Melick *et al.* to the exposure of 4-ADP only suggest that the carcinoma may have been induced by exposure to 4-NBP.

The carcinogenicity of 4-NBP was announced in 1958 by Deichmann at the 7th International Cancer Congress, London, July, 1958,[26] which was based on the studies by Deichmann *et al.*,[25] initiated in 1955.

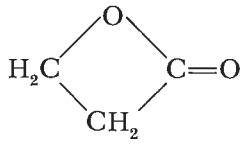
N-*Nitrosodimethylamine (DMN)*



Barnes and Magee[8] undertook the first extensive study of the toxicity of *N*-nitrosodimethylamine, also called dimethylnitrosamine (DMN), in response to the request of the medical officer of a firm that had been using it in the laboratory as a solvent. Two of 3 men working in that laboratory had developed cirrhosis of the liver. In their acute toxicity experiments with rats, rabbits, mice, guinea pigs and dogs, the lethal dose was found to be in the range of 10–50 mg/kg. In chronic exposure experiments with rats, 200 ppm DMN in the diet proved lethal in approximately 1 month, 100 ppm required 2–3 months and 50 ppm was tolerated for at least 110 days, at which time the study was terminated. The principal pathologic changes observed in the acute and in the higher-dose chronic exposure studies were hemorrhage and necrosis of the liver. In those rats surviving the longest, fibrosis and bile duct proliferation were observed also. Little change was observed in other organs.

DMN has produced cancer in a variety of sites and by several methods of administration in the rat, mouse, hamster, guinea pig, rabbit, trout, guppy and newt. In view of this broad spectrum of carcinogenic activity in experimental animals, DMN must be regarded as potentially carcinogenic for man.

Beta-Propiolactone (2-oxetanone)



Beta-propiolactone (BPL), also called 2-oxetanone, beta-propionolactone and Betaprone, is a colorless liquid with a pungent odor. It is soluble in water and miscible with ethanol, acetone, ether and chloroform. It is formed by a reaction of ketene and formaldehyde.[41] Celanese Corporation, the only known producer, manufactures it at Pampa, Texas, primarily as an intermediate for the manufacture of acrylates.

Although its primary industrial use is in the synthesis of acrylic acid and acry-

lates, BPL has been shown to be an effective vapor-phase decontaminant for the treatment of enclosed spaces. Medically, BPL has also been used successfully to sterilize collagen sutures, human plasma and homotransplants, bone and heterografts. Its value as a toxoiding agent and in preparing sterile vaccines has been reported.[70]

Celanese Corporation is constructing a new acrylate manufacturing facility not based on the BPL process, and in 1973 announced its intention to discontinue production of BPL.[15]

Compounds such as BPL are highly reactive because of the strong tendency of the strained four-membered ring structure to open. BPL is an extremely corrosive chemical, the vapor being irritating to the eyes, nose, throat and respiratory tract in general, and to other mucous membranes. In man, it is reported to be a skin vesicant, producing irritation and blister formation. Adequate protective clothing and equipment are recommended for workers likely to have dermal contact.

Demonstrated carcinogenicity. Results of pertinent animal experiments relating to the carcinogenicity of BPL were made available to the National Institute for Occupational Safety and Health.[27, 76, 99] Although epidemiologic evidence implicating BPL as a human carcinogen is not available, experimental animal data suggest that BPL should be a carcinogen for humans. Every precaution should be taken to prevent worker exposure.

Bis(chloromethyl)ether (BCME)

$$ClCH_2—O—CH_2Cl$$

The first accounting of a carcinogenic potential for bis(chloromethyl)ether (BCME) was made by Van Duuren *et al.*[94] in 1968. In this report, the authors compared the toxicity of BCME with its monofunctional analog, chloromethyl methyl ether (CMME), and discovered the former to possess much greater potential for inducing skin tumors in mice and rats than the latter. They classed BCME with such other biologically active alkylating agents as nitrogen mustards, epoxides and beta-lactones.

In light of the startling incidence of lung carcinomas among rats following chronic inhalation of 0.1 ppm BCME, the National Institute for Occupational Safety and Health promptly undertook an investigation of plants producing ion exchange resins, a manufacturing process in which BCME may be found as a contaminant in the chloromethylation of polystyrene beads.[5]

Selected for study was a chemical facility that developed and had used an anion exchange production system since about 1955. An industrial hygiene survey was made of this facility in early 1972.[74] As sputum cytology was considered a sensitive method for assessing early injury to the bronchial epithelium by carcinogenic agents long before lung malignancy appears radiographically, sputum samples were obtained by standard techniques on 115 current employees at this facility. Survey results indicated that the incidence of moderate and marked atypical cytology was significantly higher. Although no malignancies were detected during this sputum survey, the results were consistent with a carcinogenic stimulus of BCME.

Further substantiation of the human carcinogenicity of BCME is provided by provisional results of a NIOSH retrospective cohort study of lung cancer incidence among all former and current employees of this plant. A significantly increased risk of lung cancer (4 observed vs 0.54 expected, $p<0.01$) was demonstrated within 15 years since onset of exposure among those individuals employed for 5 or more years in production-maintenance operations involving BCME. In

addition to the 7-fold increase in lung cancer among this group, a preponderance of undifferentiated oat cell carcinomas was found. This pattern of risk and histology is similar to that recently reported by Figueroa *et al.*[34] from a study of another ion exchange facility. They reported on lung cancer found in chloromethyl methyl ether workers and suggested another occupational hazard that increases the risk of lung cancer. They surveyed and studied a chemical manufacturing plant with approximately 2000 employees where periodic chest x-ray surveys had been carried out for many years. In 1962, the management became aware that an excessive number of workers suspected of having lung cancer were reported in one area of the plant, and promptly engaged consulting services to identify and resolve what appeared to be a serious problem. A group of 125 men were studied for the next 5 years. Fourteen were lost at various intervals during the investigation because of job termination, but 4 of the remaining 111 men developed lung cancer during the 5-year period of observation. These 4 were from a group of 88 men in the age group from 35 to 54, giving a 5-year cancer incidence of 4.54%. The best estimate of the expected number of cases must be derived from the youngest age group under investigation in the Pulmonary Neoplasm Research Project.[16] In this study, there were 2804 men 45–54 years of age. Sixteen (0.57%) of these developed lung cancer in the first 5 years of observation. Smoking habits were very similar to those of the plant workers. The proportions of cigarette smokers were 78% and 74%, respectively, and the proportions of cigarette smokers using one or more packages per day were 24% and 20%, respectively. The slightly higher age of the Pulmonary Neoplasm Research Project groups makes the incidence of 0.57% an overestimate of the expected number. However, if we accept it as the best available rate, the 5-year incidence was 8 times higher in the plant workers. Using the binomial theorem, this difference is statistically significant at a probability of 0.0017.

While this study was in progress, plant management made a careful investigation of the work histories of several men whose lung cancers developed while they were working in the area under study. They concluded that the only common denominator was the exposure to chloromethyl methyl ether. Management is yet unable to provide exact information on the exposure of the employees to CMME.

Further evidence that CMME could be a carcinogen was stimulated by a 44-year-old man admitted to Germantown (Pa.) Dispensary and Hospital in December of 1971 because of cough and hemoptysis. A detailed occupational history revealed that he was a chemical operator who had been exposed to CMME for 12 years. The patient stated that 13 of his fellow workers had lung cancer, and he suspected that this was his diagnosis. All had worked as chemical operators in the same building of a local chemical plant where they mixed formalin, methanol and hydrochloric acid in two 3800-liter kettles to produce CMME. During the process, fumes often were visible. To check for losses, the lids on the kettles were raised several times during each shift. The employees considered it a good day if the entire building had to be evacuated only 3 or 4 times per 8-hour shift because of noxious fumes.

Recently, these agents have been found to be highly carcinogenic for mice and rats.[58, 60, 94, 95] Indeed, the inhalation of as little as 0.1 ppm of BCME (bis[chloromethyl]ether) has produced squamous cell carcinoma in the lungs of rats.[58] A recent report of 6 cases of lung cancer suspected of being due to occupa-

tional exposure to CMME in California[19] is a rare reference to a possible carcinogenic effect of this chemical for man.

The finding that all but 1 of the 13 histologically confirmed cases involved oat cell carcinoma of the lung, a particularly rare type of lung carcinoma in the general population, implicated an alkylating agent as the etiologic factor. Wagoner *et al.*[98] found in their epidemiologic study of uranium miners published in 1965 that oat cell carcinoma was the predominant type of lung cancer observed in uranium miners. In a Japanese study,[97] workers exposed to mustard gas, also an alkylating agent, were found with oat cell carcinoma. In a report, Archer, Saccomanno and Jones[4] presented evidence that the number of cases of oat cell carcinoma of the lung among uranium miners was 24 times greater than that "expected." Therefore, alkylating agents are considered to be radiometric in their biologic activity.

Figueroa *et al.*[34] stated in their paper that commercial-grade CMME contains 1–8% BCME. On the basis of previous animal investigations, which demonstrated that BCME is a more potent carcinogen than CMME, it could be supposed that the BCME content of the CMME may have been responsible for the observed carcinogenic effects in humans in this study. However, the fact that substantial exposure to CMME (and, it must be presumed, to BCME also) did occur in each of the 14 cases implies that a carcinogenic role for this halo ether cannot be eliminated.

In 1973, Thiess *et al.*[89] reported that of 18 individuals employed in a technical research center, 6 died from carcinoma of the lung. In addition, 2 of 50 production facility employees died from lung cancer within the same 6-year exposure period (1956–1962). The average latency period to the appearance of lung tumors was 8–16 years. Of the 8 cases of lung carcinoma found, 5 were diagnosed as "small-cell carcinoma" ("oat cell carcinoma"). No environmental measurements were made for BCME concentration in the work place during the period under study (1956–1962). However, the concentrations were considered minimal because of the readiness with which BCME can be detected by its strong irritant action at very low concentrations.

It is of interest that the production facility, where 2 of the cases of lung cancer occurred, was a "closed unit" equipped with an exhaust apparatus within which workers were required to wear air-supplied masks.

The investigators[89] concluded that "On the basis of information now available, we believe that the lung cancer cases reported by us are, with definite probability, caused by many years of breathing unknown amounts of dichlorodimethyl ether (BCME). This assertion is supported by animal tests available in the meantime and also by the known observations made in California."

Van Duuren, Laskin and Nelson[96] summarized the potential hazard associated with exposure to CMME and BCME in a letter to the Editor of *Chemical and Engineering News* on March 27, 1972. "Chemical carcinogens can be either direct-acting or indirect-acting. The latter type have to be metabolized in vivo to proximal carcinogens, and, hence, these indirect-acting agents are highly organ- and species-specific since the metabolic patterns vary by organ and species. The direct-acting agents, which include alkylating carcinogens such as CMME and BCME, act normally at the site of exposure and they are carcinogenic in several species and organs but usually only at the site of exposure. Since these direct-acting alkylating agents are carcinogenic in several animal species, they must be regarded as potentially carcinogenic in man. The alpha-chloro ethers should, there-

fore, be regarded as potentially serious occupational hazards in the chemical industry and in research laboratories where they may not always be handled with proper precautions."

An announcement[77] recently has been made that hydrogen chloride (HCl) and formaldehyde (HCHO) combine under ordinary ambient conditions, or in aqueous solutions, to form BCME. The importance of this discovery as concerns the ubiquitous availability of BCME is readily apparent. It must not be overlooked in this respect, however, that CMME rapidly decomposes both in air and in aqueous solutions to yield the above reactants.

$$ClCH_2—O—CH_3 + HOH \rightleftharpoons CH_3OH + HCHO + HCl$$

Hence, pure CMME, even under the most rigid experimental conditions, is practically impossible to obtain or, once produced, to maintain without the subsequent formation of small amounts of BCME. Therefore, the practicability of exposure to CMME in the work place without concomitant exposure to BCME is highly questionable.

It is very possible, based on available animal studies and epidemiologic investigations of exposed workers, that BCME may be one of the most hazardous carcinogens found in the work place. The fact that, under ordinary conditions, BCME is formed whenever formaldehyde and hydrogen chloride are present requires continuous surveillance of work places where these two compounds may be present simultaneously. The hazard of lung cancer from occupational exposure to BCME requires strict measures to ensure that employees are not exposed to this substance by any route.

Chloromethyl methyl ether (CMME)

$$CH_3—O—CH_2Cl$$

Chloromethyl methyl ether (CMME) is used commercially in organic synthesis as a chloromethylating agent in the manufacture of ion exchange resins, in the treatment of textiles, in the manufacture of polymers and as a solvent for polymerization reactions. Because of its reactivity, CMME is highly irritating to the skin, eyes and mucous membranes.[94] With the exception of one less —Cl atom, CMME is structurally identical to its highly carcinogenic bifunctional analog, bis(chloromethyl)ether (BCME). It is, therefore, of utmost importance in any consideration of the health consequences of occupational exposure to CMME that cognizance be given to concomitant exposure to BCME, which is normally present in commercial-grade CMME in quantities of 1–7%.[34, 96] Likewise, in evaluating experimental evidence implicating CMME as a carcinogen, it is important also to know the BCME content of the CMME.

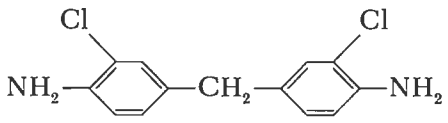
A field survey conducted by NIOSH personnel in 1972[74] revealed 6 cases of lung cancer in a West Coast facility that formed both BCME and CMME in the manufacture of ion exchange resins and employed approximately 75 "blue collar" workers. At least 4 of the 6 employees with lung cancer had worked in operations involving exposure to BCME and CMME. It was concluded from the field survey that an excess lung cancer risk was suspect in the worker population, and the results of a recent sputum cytologic survey among workers has demonstrated a greater than normal proportion with atypical sputum cells. Although BCME was suspected as the etiologic agent in this survey, the contributory influence of CMME was not known.

Van Duuren *et al.*[94] presented the first evidence for the carcinogenicity of the alpha-haloethers in 1968 and classified them with such other biologically active alkylating agents as nitrogen mustards,

epoxides and beta-lactones. The study, which involved skin application of BCME or CMME to mice (2.0 mg/0.1 ml benzene 3 times weekly for 47 weeks), provided no evidence for CMME of "complete" carcinogenicity, although a slight irritating activity was elicited in mice when croton resin (0.025 mg/0.1 ml acetone) was used as a promoting agent. Of 20 rats injected subcutaneously with CMME (1–3 mg/injection 3–4 times monthly), 13 developed sizable palpable lesions in the treatment area. The purity of the CMME used in the study was verified by infrared spectrophotometry and gas-liquid chromatography with no BCME detected.

Although contaminating exposures to BCME have precluded conclusive evidence for the carcinogenic activity of CMME, the industrial experience with this halo ether is sufficient reason to consider CMME as a carcinogen.

4,4'-Methylene-bis(2-chloroaniline) (MOCA)[*]



A preliminary report concerning the carcinogenicity of orally introduced 4,4'-methylene-bis(2-chloroaniline) in rats was made by Grundmann and Steinhoff[38] in 1970. In 1971, these two investigators published a more extensive paper[87] of their completed findings. In the later paper, the toxicity and carcinogenicity of 4,4'-methylene-bis(2-chloroaniline) was compared with that of 4,4'-diaminodiphenylmethane (DDM). Both of these compounds are used as hardeners or curing agents for epoxy resin systems and isocyanate-containing polymers.[84, 88] Although commercial production of 4,4'-methylene-bis(2-chloroaniline) began in 1962,[61] DDM has been in production for more than 25 years.[84] The investigators quote previous work to document the strong toxic effect of DDM on both rat and human liver as well as the carcinogenic effect on rat liver. Schoental[84] has also demonstrated the carcinogenicity of DDM on the rat liver. An accidental acute poisoning episode occurred in 1965 in Great Britain in which 84 persons became ill, some seriously, with jaundice following the consumption of bread accidentally contaminated with DDM.[55]

In general, Grundmann and Steinhoff considered 4,4'-methylene-bis(2-chloroaniline) to be less toxic but more carcinogenic than the nonchlorinated compound, DDM.

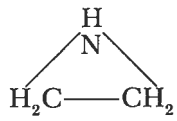
Another industrial study involved the finding by Mastromatteo[69] in 1965 that 2 of 6 employees, both in their thirties, who had a mixed exposure to 4,4'-methylene-bis(2-chloroaniline), TDI and several isocyanate-containing resins developed urinary frequency with hematuria, eye irritation and respiratory irritation with cough and tightness in the chest. The hematuria can best be related to the 4,4'-methylene-bis(2-chloroaniline) than to the other substances. The author considered the conditions to be mild, but also considered that exposure to this substance, primarily by dust inhalation, was the cause of the observed cystitis.

The results of the experimental animal studies reported by several independent groups of investigators[59] clearly demonstrated an active oncogenic role for 4,4'-methylene-bis(2-chloroaniline).

Although industrial experience from reported studies is minimal,[61, 69] the positive findings in two animal studies by three independent investigators[59] firmly implicate 4,4'-methylene-bis(2-chloroaniline) as a human carcinogen.

[*]4,4'-Methylene-bis(2-chloroaniline) or 3,3'-dichloro-4,4'-diaminodiphenylmethane has been given the registered trademark MOCA by E. I. du Pont de Nemours & Co., Inc.

Ethyleneimine (EI)



Ethyleneimine (EI), (also known as aziridine), is an extremely reactive, small-ring heterocyclic alkylating agent. The dual functionality and high degree of reactivity of EI are responsible for the synthesis of many derivatives in an increasing list of applications,[35] including textile treatment chemicals, adhesives and binders, rocket and jet fuels, chemosterilant chemicals and chemotherapeutic agents to name a few.

Early interest in EI centered on its possible application as an antineoplastic agent. Because of the general type of cytotoxic activity associated with EI in this role, subsequent investigators were led to question its possible role as a chemical mutagen and carcinogen.

Its high chemical activity causes it to be very irritating to the skin and mucous membranes. The renal toxicity of EI in the rat and rabbit has been described by Davies *et al.*,[21-23] who also found that as little as 0.01 ml/kg body weight caused the death of rabbits from neurotoxic effects within a few hours.

A study sponsored by the National Cancer Institute in 1969 concerning the bioassay of industrial chemicals for tumorigenicity in mice was published by Innes *et al.*[50] The investigators' comments on their classification of liver tumors as "hepatomas" stated ". . . the term 'hepatoma' as used in this manuscript should not be considered as implying that these tumors are benign. Indeed, it seems more reasonable to conclude that the great majority had malignant potentiality." They concluded by stating that "the dose received by the mice was far above that likely to be received by humans, but there was no way to predict whether man would be more or less susceptible to tumor induction by the compound."

The case for the carcinogenicity of EI, then, rests on the possible extrapolation to humans of the findings in two separate, controlled animal studies, one involving rats[99] and the other mice.[50]

This position is compatible with that of NIOSH concerning the prior demonstration of carcinogenicity in at least two animal species.

OSHA Work Practices

This section applies to any activity in which a carcinogen is manufactured, processed, used, repackaged, released, handled or otherwise present in any manner.

Definitions

The 14 substances defined as "carcinogens" by OSHA means the substances or compositions containing such substances, but does not include substances containing less than 1% by weight of the listed carcinogens,[31] except 4-aminodiphenyl, benzidine (and its salts), 4-nitrobiphenyl, beta-naphthylamine, bis(chloromethyl)ether and methyl chloromethyl ether. These latter OSHA-defined carcinogens must be found in less than one-tenth per cent by weight of the substance weight.

After the emergency standard was published on May 3, 1973 in Volume 38 of the Federal Register on page 10929, it became apparent that a single standard for the 14 substances would not be adequate. Therefore, 14 different standards were promulgated to enable accommodation of the physical properties, physical state, biologic properties and use of each of the chemicals. Thus, provisions were made for the immediately corrosive activ-

ity of beta-propiolactone and ethyleneimine for deluge showers and eye wash fountains near places where exposures might be expected. Principally, volatile materials will not be present long enough for routine washing or showering to have effect as a protective measure. Thus, a requirement to wash on each exit and shower at the end of the day would not offer any significant protection to employees working in areas where the volatile materials, methyl chloromethyl ether, bis(chloromethyl)ether, ethyleneimine and beta-propiolactone, are present in a closed system or closed system transfer operation. Wash requirements are retained for those materials in isolated system operations because the closed confinement of glovebox gloves would inhibit vaporization if a leak should occur. Special provisions are made for premix operations involving 4,4'-methylene-bis(2-chloroaniline) and liquid prepolymer. These premix solutions, frozen or otherwise, are packaged in such a way and used only after the 4,4'-methylene-bis(2-chloroaniline) and the prepolymer have started to react. No dust hazard exists and a vapor hazard is unlikely. For this reason, the standard requires only protective clothing such as smocks, coveralls or long-sleeved shirts and pants and gloves.

"Present" includes manufactured, processed, used, prepackaged, released, handled or otherwise present. For details about engineering, hygienic and medical controls, refer to Chapter 15—Industrial Hygiene and Chapter 26—Creation of a Safe Working Environment in Plants Handling Highly Toxic Chemicals.

As has been stressed repeatedly throughout this book, sound occupational health practice is based on two major concepts—control at the work site by primary engineering and hygienic measures (including environmental *monitoring), followed or paralleled by medical surveillance as a secondary phase.*

We gratefully acknowledge the assistance given by Drs. E. M. Dixon and Keith H. Jacobson in the preparation of this chapter.

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Occupational Medicine

PRINCIPLES AND PRACTICAL APPLICATIONS

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YEAR BOOK MEDICAL PUBLISHERS, INC.
CHICAGO • LONDON

Reprinted, July 1977

Library of Congress Catalog Card Number: 74-15405

International Standard Book Number: 0-8151-9864-7