When Science Isn’t Enough: Wilhelm Hueper, Robert A. M. Case, and the Limits of Scientific Evidence in Preventing Occupational Bladder Cancer

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A recent outbreak of occupational bladder cancer in a Buffalo, New York, factory confirmed the carcinogenicity of ortho-toluidine, an aromatic amine that had first been implicated in human bladder cancer cases decades earlier. Events leading to this outbreak replicated the history of numerous earlier bladder cancer outbreaks among workers exposed to beta-naphthylamine and benzidine, two other aromatic amines that were widely used in the dye and rubber industries and that have been responsible for bladder cancer outbreaks in the United States, Germany, Switzerland, England, France, Italy, Austria, Czechoslovakia, the former Soviet Union, Poland, and China. The historic development of scientific knowledge of occupational bladder cancer prefigured many debates that later occurred around other environmental carcinogens; two of the giants of occupational medicine, Wilhelm Hueper and Robert A. M. Case, played seminal roles in the study of these chemicals.

Examination of the history of worker exposure to aromatic amines and the subsequent development of bladder cancer at Du Pont, Allied Chemical, and other U.S. manufacturers demonstrates that these carcinogens were regulated only after cancer epidemics were recognized. Production and use of aromatic amines continues in developing countries; these nations will inevitably experience similar outbreaks unless steps are taken to eliminate exposure to these deadly chemicals. This paper chronicles the history of occupational bladder cancer in the United States, highlighting the roles of Hueper and Case in occupational cancer investigation and prevention.

Key words: bladder cancer; occupational cancer; dyes; aromatic amines; benzidine; beta-naphthylamine; ortho-toluidine; history of occupational health; rubber industry.

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In February 1988, the union representing workers at a Goodyear Tire and Rubber Company plant in Buffalo, New York, requested that the U.S. National Institute for Occupational Safety and Health (NIOSH) investigate what it believed to be an outbreak of bladder cancer among its members. Since 1957, Goodyear had been using the chemical ortho-toluidine (o-T) in the production of Wingstay 100, an antioxidant added to rubber products. Union officers, with the assistance of Dr. Steven Markowitz of the Mount Sinai School of Medicine, had identified eight cases of bladder cancer between 1973 and 1988 among workers exposed to o-T. They feared additional cases would be discovered once a more comprehensive search was made.

NIOSH epidemiologists determined that 13 Goodyear workers, among the 1,749 workers employed at the plant, had developed bladder cancer during those years. Six of these workers were among the 73 who had been employed for ten years or more in the department in which Wingstay was produced. The expected number of bladder cancer cases among the 73 was 0.22; NIOSH calculated that the exposure increased their risk of disease by more than 2,000%.1

Goodyear purchased o-T from two of the leading chemical manufacturers in the United States: Du Pont and Allied Chemical. The outbreak occurred 60 years after the first cases attributable to similar chemicals had been recognized at Du Pont and Allied’s dye production factories, almost 40 years since the first appearance of cases in which o-T was implicated, and a decade after definitive studies had been published documenting o-T’s carcinogenicity. Hundreds of workers at Du Pont and Allied’s own factories had already developed bladder cancer following exposure to these chemicals.

For many years, o-T had been a mainstay of the dye industry, having been used to make magenta and several other important colors. The chemical is an aromatic amine, similar in structure to benzidine, alpha-naphthylamine (ANA), beta-naphthylamine (BNA), and
other chemicals used in the dye and rubber industries that had been widely recognized to cause bladder cancer in humans.

In the century since aromatic amines were first used to create dyes, these chemicals have been responsible for bladder cancer outbreaks involving thousands of cases in the United States, Germany, Switzerland, England, France, Italy, Austria, Czechoslovakia, the former Soviet Union, and Poland. Recounted here are episodes in the history of occupational bladder cancer in the United States; similar chronologies exist for each of these countries, in which use of the carcinogens was regulated or banned, but only after the epidemics had occurred. Most of the cases have been associated with exposure to benzidine, ANA, or BNA, although other aromatic amines have been implicated as well.

While production and use of many of the carcinogenic aromatic amines no longer occur in the industrialized countries, they continue throughout the developing world. Developing countries involved in the manufacture of dyes or rubber products using aromatic amines now face outbreaks of bladder cancer, the virtually unavoidable toll associated with these chemicals.

Benzidine manufacture did not begin in China until 1956, although benzidine had been imported for at least a decade earlier. Until its production was ended in 1977, more than 100,000 tons were produced in the cities of Tianjin and Jilin. Recent studies of manufacturing workers in those cities, and of workers employed in dye production factories in Shanghai and Tianjin, where benzidine was used to produce dyes, have reported bladder cancer risks as high as 7,500% of that of unexposed workers.

Similarly, researchers have reported that workers in chemical and dye manufacturing facilities in India have extensive unprotected exposure to cancer-causing chemicals. It is virtually inevitable that bladder cancer cases will follow these exposures; indeed, a recent case-control study found a fivefold excess risk of bladder cancer among workers in chemical/pharmaceutical/rubber plant workers in Bombay.

**OCCUPATIONAL BLADDER CANCER IN THE SYNTHETIC DYE INDUSTRY**

Since its inception, the synthetic dye industry has been dominated by the largest multinational chemical manufacturers. While the technology developed for dye production has resulted in important advances in chemical, munitions, and pharmaceutical manufacturing (Ehrlich’s treatment for syphilis, for example, was an aromatic amine dye that killed spirochetes by infiltrating them in a manner similar to the way indigo blue dye penetrates textiles), the intermediate chemicals used in producing dyes have been responsible for a series of epidemics of bladder cancer in virtually every region of the world where the industry has located.

The synthetic dye industry can be traced to the 1856 discovery by William Henry Perkin, an 18-year old British chemistry student, that coal tar could be transformed into a synthetic dye. Perkin had been attempting to prepare artificial quinine from coal tar, until then a useless byproduct of the distillation of coal to produce gas for lighting. Instead of quinine, he synthesized a delicate mauve solution, which he named mauvine. Perkins’ discovery was the first in a rapid series of scientific advances related to dyes that occurred throughout Europe in the second half of the nineteenth century. While not as colorfast as natural dyes, these artificial dyes were the beginning of an important new industry that provided textile dyers with bright and inexpensive colors.

Armed with the first patents, the English chemical industry initially dominated the global dye market. The German industry, however, grew very rapidly, with substantial public and private-sector investment in the construction of research facilities and the education and employment of organic chemists. Seeing the opportunity for sustained industrial development, the German government built formidable university laboratories to train scientists and provide the basic research needed by the organic chemical industry. As a result, German scientists obtained hundreds of patents, which they then used to dominate the world dye market for decades.

While the dye industry was notable for its size and financial return, its importance in economic history stems primarily from its relationship to the development of the synthetic organic chemical industry. The patents and production processes of the dye industry became the basis for the global expansion of organic chemical production, including pharmaceuticals (most notably sulfa drugs and aspirin), explosives, synthetic resins, petroleum additives, and numerous other materials.

The first bladder cancer cases among dye workers were seen by Rehn, a surgeon in Frankfurt-am-Main, a center of the German chemical industry. In 1895, Rehn reported that three of the 45 workers employed in the production of fuchsine had developed bladder cancer. By 1906, he had identified 38 workers with bladder cancer; other physicians in Germany and Switzerland reported dozens of additional cases among dye workers during the subsequent decade.

In the initial reports, the substance or substances responsible for the cancers were the subject of speculation. Published reports consisted primarily of case series, listing the exposures of each worker who had been diagnosed as having bladder cancer. In 1921, the International Labour Office (ILO) issued a monograph entitled “Cancer of the Bladder among Workers in Aniline Factories” that reviewed the exposure histories of all cases reported through 1920. Examining the accumulated evidence, the ILO asserted that the chemicals most likely to have caused these cases were benzidine and BNA, and that “the most rigorous application of hygienic precautions” was necessary to prevent further cases from developing.
DU PONT AND THE DEVELOPMENT OF THE U.S. DYE INDUSTRY

While the United States synthetic dye industry began on a small scale in the late 1800s, it was soon dominated by the local output of European-owned plants. U.S. manufacturers were not able to compete successfully, because German and Swiss dye producers controlled virtually all important patents in the field. With the first World War, the U.S. government seized enemy-owned plants and patents and distributed them at low cost to U.S. chemical companies.12 As a result, two New Jersey manufacturers, E. I. du Pont de Nemours & Co. and American Cyanamid, along with Allied Chemical and Dye Corporation (later Allied Chemical, subsequently the Allied Corporation, and now Allied-Signal), became the three largest synthetic dye producers in the United States.

Du Pont constructed the Chambers Works, its first factory for the production of organic chemicals, in Deepwater, New Jersey, across the Delaware River from Wilmington, the center of the Du Pont industrial empire.15,16 Among the chemicals produced there were BNA and benzidine, two products that were soon to be identified as powerful carcinogens.

The Chambers Works, which opened during World War I, was soon the site of a major occupational disease outbreak, unrelated to dye production, accompanied by a national scandal. In the early 1920s, Du Pont and General Motors, which at the time was partly owned by Du Pont, agreed to manufacture and distribute leaded gasoline, a product designed to reduce automobile engine “knock.” Du Pont chose the Chambers Works for its production facility. The neurologic effects of the organic lead exposure were so severe and widespread there that workers labelled the plant the “House of Butterflies,” because of the hallucinations experienced by so many of the lead-poisoned workers. A New York Times reporter who investigated the situation reported that over 300 workers had been poisoned, and eight had been killed by the lead, during the first two years of production.17 The national notoriety Du Pont earned through the “House of Butterflies” scandal may have convinced the company that public disclosure of further outbreaks of occupational disease would most profitably be managed differently.

The first bladder cancer cases among workers at the Chambers Works were apparently recognized by Du Pont physicians in 1931, although they may have started appearing some years earlier. For the next several years, these physicians documented the rapidly growing epidemic both at national conferences and in the scientific literature; at least 83 cases had been recognized by 1936.18-20 This chronology is displayed graphically in Figure 1, comparing the accumulation of scientific information with exposure levels and bladder cancer cases at the Chambers Works.

An internal Du Pont document records that BNA production began at the Chambers Works in 1919: “It was cast in open pans, broken with a pick, and transferred by hand into barrels, ground in an open mill, and shoveled by hand into operating equipment. There was no ventilation provided. Gross exposures occurred.” While some improvements were introduced in 1934, following the cancer outbreak, significant levels of exposure nevertheless continued throughout the 1930s and 1940s. The manufacturer considered additional improvements in 1940 but moved slowly and eventually decided to delay any changes because of World War II. No further improvement in the BNA production process was implemented until 1948; total enclosure of the production process was completed in 1951, more than 35 years after BNA production began and 20 years after the epidemic was recognized. The new process was used for only four years; Du Pont terminated BNA production in 1955.21
After its initial flurry of publications, Du Pont stopped reporting additional cases in the scientific literature for the next several decades; the number of bladder cancer cases, however, continued to rise. A 1947 letter from Dr. E. E. Evans, medical director of the Chambers Works, to Dr. Arthur Mangelsdorff, of the Calco Chemical Company (predecessor to American Cyanamid) in Bound Brook, New Jersey, revealed that less than two decades after the first cancer cases appeared, every member of the original group engaged in the production of BNA had developed bladder cancer. By the 1990s, more than 400 cases of bladder cancer had been identified among Chambers Works employees exposed to aromatic amines.

**WHEN SHOULD DU PONT HAVE KNOWN?**

Could the Du Pont physicians have been unaware before 1930 of the extensive scientific literature on occupational bladder cancer? The pathogenesis, treatment, and prevention of the disease had been discussed at length in the medical journals of Britain, Germany, Switzerland, and Austria in numerous epidemiologic studies and review articles. Germany and Switzerland had made bladder cancer among dye workers a compensable occupational disease in 1925.2

Most importantly, the International Labour Office had published its monograph on occupational bladder cancer in February 1921, only a few years after Du Pont began dye production at the Chambers Works. The explicit purpose of this report was to inform dye manufacturers in countries where the industry was young, such as the United States, of the dangers of dye production.12

Further, Du Pont (and other American chemical companies) were in regular, direct contact with the dye producers of Central Europe and England. In the aftermath of World War I, six German chemical manufacturers, including three that are still of paramount im-
portance in the global economy (Hoechst, BASF, and Bayer) formed the cartel, Interessen Gemeinschaft Farbenindustrie, in an attempt to dominate the world chemical industry. Dyes and dye-related chemicals were its most important products; I. G. Farben translated is the Community of Interest of the Color Industry. During the third and fourth decades of the century, Du Pont collaborated with Farben; Imperial Chemical Industries (ICI), the British chemicals giant that held monopolistic control of dye production and sales throughout the British Commonwealth; and the leading Swiss, French, and Italian chemical and dye producers, building joint business ventures and monopolistically dividing the world's chemical markets. Du Pont and Farben actively negotiated from 1927 through 1929 to form a joint dye-producing venture, tentatively called the American Dyes Company. When the companies realized they would not be able to reach a successful agreement, they both accepted a state of "amicable cooperation," which was maintained virtually until fighting between the United States and Germany began.11,12

Farben played a vital role in the Nazi war effort, producing the synthetic rubber and petroleum that enabled Hitler's tanks to storm Europe. Using production techniques perfected in manufacturing dyes, Farben's factories also produced pharmaceuticals and munitions, as well as Zyklon B, the poison gas used in extermination-camp gas chambers throughout the Reich. Farben built its own synthetic rubber and oil factory at Auschwitz (known as I. G. Auschwitz). An estimated 25,000 prisoners were worked to death there, sometimes dying at a rate greater than 1% per day.25

WILHELM HUEPER: FROM DU PONT EMPLOYEE TO ADVERSARY

The rapid evolution of Du Pont policy on the role of scientific investigation into the prevention of occupational cancer is illuminated by the meteoric rise and fall within the company of a German immigrant toxicologist, Dr. Wilhelm Hueper, who went on to become one of the United States' leading experts in environmental carcinogenesis. In addition to his ground-breaking work on occupational bladder cancer, Hueper made important scientific contributions in the study of air and water pollution, synthetic hydrocarbons, and fuel additives. His work provided much of the scientific basis for the Delaney Amendment, banning carcinogens from food. Although he served as chief of the U.S. National Cancer Institute's Environmental Cancer Section from 1948 until 1964, Hueper's refusal to separate his scientific work from his crusade for a non-carcinogenic environment brought him much controversy.26

In 1934, some months after writing an unsolicited memorandum to Mr. Irenee DuPont suggesting that employees at the Chambers Works were being exposed to bladder carcinogens and were likely to develop bladder cancer, Hueper was hired by Du Pont to join in its newly formed Haskell Laboratory of Industrial Toxicology.27 Working for Du Pont, he was able to perfect the first animal model for bladder carcinogenesis.28 In his capacity as a Du Pont toxicologist, he requested permission to visit the Chambers Works. The experience shocked him:

When the betanaphthylamine experiment had been well under way for several months, I requested that I should be shown the incriminated operation in the Chambers Works, so that I could form an enlightened judgment of the occupational hazard. Several associates and I crossed the river a short time later to fulfill this task. The manager and some of his associates brought us first to the building housing this operation, which was located in a part of a much larger building. It was separated from other operations in the building by a large sliding-door allowing the ready spread of vapors, fumes and dust from the betanaphthylamine operation into the adjacent workrooms. Being impressed during this visit by the surprising cleanliness of the naphthylamine operation, which at that occasion was not actively working, I dropped back in the procession of visitors, until I caught up with the foreman at its end. When I told him "Your place is surprisingly clean," he looked at me and commented, "Doctor, you should have seen it last night; we worked all night to clean it up for you." The purpose of my visit was thereby almost completely destroyed. What I had been shown was a well-staged performance. I, therefore, approached the manager with the request to see the benzidine operation. After telling him what I just had been told, his initial reluctance to grant my request vanished and we were led a short distance up the road where the benzidine operation was housed in a separate small building. With one...
look at the place, it became immediately obvious how the workers became exposed. There was the white powdery benzidine on the road, the loading platform, the window sills, on the floor, etc. This revelation ended the visit. After coming back to Wilmington, I wrote a brief memorandum to Mr. Irenee DuPont describing to him my experience and my disappointment with the attempted deception. There was no answer but I was never allowed again to visit the two operations.27

Hueper’s disagreements with Du Pont intensified and he was told that he would not be able to publish his findings. He was later dismissed in 1937. Du Pont refused him permission to publish or present data on his work on experimental induction of bladder cancer with aromatic amines, which was conducted while at Du Pont.27,29

Nevertheless, Hueper’s seminal text *Occupational Tumors and Allied Diseases* was published in 1942. It contained the most thorough review of world literature on occupational carcinogenesis to date.30 Recognizing Du Pont’s role in the bladder cancer epidemic at the Chambers Works, Hueper initially wanted the book’s dedication to read “To the victims of cancer who made things for better living through chemistry.” This was a caustic allusion to Du Pont’s well-known advertising slogan “Better things for better living from chemistry.” In the end, probably fearful of the company’s retribution, he dedicated the book “to the memory of those of our fellow men who have died from occupational disease contracted while making better things for an improved living for others.” Hueper wrote later, with great bitterness, that he believed that the Du Pont Company had attempted to undermine his scientific credibility, as well as to threaten his ability to work, by denouncing him as first a Nazi and later a communist sympathizer.27,31
While Hueper pioneered the laboratory study of aromatic amines, the most important epidemiologic work was performed by Robert A. M. Case, whose groundbreaking investigation of bladder cancer mortality among British dye workers identified almost accidentally an entirely new industry where aromatic amines were causing bladder cancer. As Case recounts the history, by 1938 the British government and chemical industry were "totally convinced" that both BNA and benzidine were bladder carcinogens. While Hueper's animal studies in the 1930s made it impossible to deny that BNA was a carcinogen, the initial animal study of the carcinogenicity of benzidine, the other important dye intermediate implicated in many of the bladder cancer outbreaks, was negative. Du Pont toxicologists had tried to induce bladder cancer in four dogs, none of which developed the disease. Through the 1940s the human evidence of the carcinogenicity of benzidine was limited, primarily because there were few workers who were exposed to benzidine alone and not to BNA. While the ILO and numerous scientists had already been convinced of benzidine's ability to cause bladder cancer, Gehrmann, Du Pont's Medical Director, declared in a 1948 international occupational medicine conference:

We feel that it cannot be concluded that Benzidine is a cause of bladder tumours until conclusive proof that Benzidine workers who have developed tumours have never been exposed even in the slightest degree to Beta Naphthylamine (even an old Beta contaminated building constitutes exposure) and that the incidence of bladder tumours in workers exposed to Benzidine is greater than the incidence of idiopathic bladder tumours in such a group.38

Thus, Du Pont continued to permit exposure to benzidine, although Gehrmann himself, after a 1933 visit to Germany, recommended to his employer that it should "take immediate steps to construct all operations so that there shall be absolutely no dust, no fumes nor any skin contacts (with benzidine)."39

What had caused Gehrmann's change in heart? Research by Barry Castleman provides the answer:

In the early months of 1949 the medical officer to the Imperial Chemical Industries Dyestuffs Division visited the Du Pont Chambers Works dye plant. This man, the late Dr. Michael Williams, was accompanied by another British researcher, and they were shown around by the corporate medical director who had given the paper at the London medical congress. After the plant tour, he drove Dr. Williams and his colleague to their next destination, quite a long drive. Dr. Williams, who often recounted the story, noticed that his companion in the back of the car had his eyes closed, and said to the DuPont doctor, "Look, you are a company man, and Dr. So-and-So is asleep. Can you explain to me why, after the records and so on that you have shown to us today, you are so certain that benzidine is not causing any of the trouble?"

He got the reply, witnessed by the other Briton, who was in fact not asleep but thinking, "We here know very well that benzidine is causing bladder cancer, but it is company policy to incriminate only the one substance, Beta-naphthylamine."40

Case later confirmed the story, admitting that he was the "dozy Brit" in the back of the car. The next year, 1950, animal studies supported by Allied Chemical provided the indisputable evidence that benzidine was a carcinogen. Corporate policy changed slowly. The 1954 edition of the textbook Modern Occupational Medicine, written and edited by Du Pont staff, stated that while...
BNA caused cancer, benzidine was only a “suspected cause of tumors.” It was not until 1967—17 years after the publication of Allied Chemical’s animal studies—that Du Pont’s production of benzidine ended.

Du Pont continued to use benzidine purchased from other manufacturers until 1972. The following year, in response to a petition from the Oil, Chemical and Atomic Workers Union, OSHA issued an emergency temporary standard for benzidine, BNA, and 12 other carcinogens. Federal regulation made benzidine production no longer feasible in the United States; the last two manufacturers of the chemical ceased operations by 1976. Benzidine-based dye manufacture, in which worker exposure to benzidine is virtually unavoidable, was also curtailed. Eight of the nine U.S. producers of these chemicals discontinued operations between 1974 and 1979. As a result, much of production of benzidine-based dyes moved to developing countries, including Mexico, India, Egypt, and Poland, countries where labor and environmental regulation were weak or nonexistent. U.S. importation of these dyes soared from 21,730 pounds in 1974 to 266,915 pounds in 1978.66

DENOUEMENT AT DU PONT: ORTHO-TOLUIDINE “DISCOVERED” TO CAUSE BLADDER CANCER

While each subsequent year saw additional bladder cancers appearing among men working at the Chambers Works, they were always ascribed to exposure to BNA or benzidine, two substances no longer used at the plant. In 1990, the same year the ortho-toluidine-related outbreak at Goodyear’s Buffalo plant was recognized, Du Pont physicians identified the first case of bladder cancer at the Chambers Works in which o-T was a prime suspect. The cancer occurred in a 34-year-old who had worked for eight years in o-T production and who had begun work at the plant after the date Du Pont reported that the use of benzidine had been discontinued.

Ortho-toluidine had been widely used in the dye industry for many decades, especially in the production of magenta, one of the early important commercially manufactured dyes. Subsequently, it was adopted by the rubber industry as an antioxidant, used to improve rubber’s resistance to oxidation and the effects of aging and exposure to the sun. o-Toluidine had been incriminated in earlier bladder cancer outbreaks, although most workers in these cases had also been exposed to other powerful carcinogens. The first reports of bladder cancers among workers exposed only to o-T were published in the early 1950s; there were five cases at one factory where magenta was produced, and no other suspect carcinogen was present. Over the next three decades, several reports and studies were published in the international literature implicating o-T in outbreaks of bladder cancer.

The animal evidence on o-T’s carcinogenicity developed in a similar progression. The results of early animal studies suggested this chemical might be carcinogenic, although the utility of animal models in this period was limited. By the early 1970s, however, several studies had demonstrated increased incidences of tumors in laboratory animals exposed to o-T. This prompted the National Cancer Institute (NCI) to conduct its own bioassay, which showed definitively, in 1979, that o-T was an animal carcinogen.

In 1982, the International Agency for Research on Cancer concluded that “there is sufficient evidence for the carcinogenicity of o-toluidine hydrochloride in experimental animals. An increased incidence of bladder cancer has been observed in workers exposed to o-toluidine, but as all were exposed to other possible carcinogenic chemicals, o-toluidine cannot be identified specifically as the carcinogenic agent. O-toluidine should be regarded, for practical purposes, as if it presented a carcinogenic risk to humans.” While Allied stopped manufacturing o-T in the late 1970s, Du Pont’s production continued in the face of mounting evidence that there was no safe level of exposure. Exposures continued at other plants around the country as well. In the period 1981-1983, NIOSH estimates that almost thirty thousand U.S. workers were exposed to o-T. Only after NIOSH’s publication of the Goodyear study did Du Pont begin to collect the data necessary to determine whether there was an increased incidence of bladder cancer among its workers exposed to o-T.

Similarly, there is no evidence that Goodyear attempted to eliminate exposure to o-T in light of the accumulating evidence of the chemical’s carcinogenicity. While the earlier studies should have, at minimum, raised serious concerns on the part of o-T users, the 1979 NCI bioassay, followed by the 1982 IARC report, should have effectively ended any possible debate about the importance of eliminating exposure to the chemical. Yet more than a decade later, workers at Goodyear were still being exposed to o-T.

ALLIED CHEMICAL

The Allied Chemical and Dye Corporation began production of benzidine at its Buffalo, New York, plant in 1915, and of BNA the following year. Like Du Pont, Allied did nothing to protect its employees from these materials until 1935, when the first workers with bladder cancer were discovered at the plant. During the next 15 years, Allied continued to accumulate cases while sponsoring important toxicological experiments that demonstrated in 1950 that benzidine was an animal carcinogen. In contrast to Du Pont, Allied managers admitted that benzidine was a human carcinogen on the basis of human data alone, before their animal studies were concluded. However, the benzidine manufacturing process was not fully enclosed until 1957, and production continued until 1976.
Allied decided to eliminate the open distillation and flaking of the chemical. Allied finally ceased production of BNA in 1955, but continued to purchase it from other U.S. production facilities through 1962 for use in dye production. Allied did not initially publish information about bladder cancer among its workers, although in 1965, the New York State Health Department identified 96 workers at the plant who had developed bladder cancer, 46 of them dying from it. Allied eventually made a public count of the number of bladder cancer victims of the plant in 1974; by that point, at least 151 workers at the plant were known to have developed the disease, although, as with Du Pont, the actual number of cases is likely to have been substantially higher.

CINCINNATI CHEMICAL WORKS: IGNORING THE EVIDENCE FROM HOME

The three largest Swiss chemical firms, Ciba, Geigy, and Sandoz (the first two eventually merging to form Ciba-Geigy) were among the first important dye manufacturers. Dye production formed the primary basis for the Swiss national chemical industry, just as it had in Germany. From dyes, the firms expanded to pharmaceuticals, pesticides, and other chemicals, and they remain among the world's leading chemical manufacturers. Following the German model of I. G. Farben, the Swiss dye manufacturers formed an Interessen Gemeinschaft (I.G.), or Community of Interest, to control the production and marketing of dyes.

In 1929, the Swiss I. G. began manufacturing benzidine at the Cincinnati Chemical Works in Cincinnati, Ohio. As early producers of dyes, the cartel's original manufacturing facilities in Switzerland had experienced numerous bladder cancer cases in the pre-World War I era; by 1925, the Swiss government had recognized bladder cancer in dye workers as an occupational disease. R. A. M. Case reported that in 1938, the three Swiss manufacturers recognized benzidine as an occupational bladder carcinogen in England, the year the first cases of benzidine-related bladder cancer appeared at its British subsidiary, the Clayton Aniline Company, Ltd. Clayton's medical officer reported that 66 workers, including 23 exposed only to benzidine, had developed bladder cancer by 1951.

Ignoring the extensive epidemiologic evidence and the control measures in effect in their own European factories, the Swiss managers operated the benzidine production process in Cincinnati with little concern about worker exposure. Laborers at the plant shoveled benzidine by hand, with no controls provided (Dr. Eula Bingham, personal communication). When the first cases of occupational bladder cancer were recognized at the Cincinnati Chemical Works in 1958, the company management expressed surprise, and subsequently contracted with a group of scientists from the University of Cincinnati to undertake a bladder cancer screening program. Among this group was Dr. Eula Bingham, who went on to become the head of U.S. OSHA during the Carter Administration. Of the 25 men screened (all but two of whom were working in benzidine production in 1958), 13, or 52%, had developed bladder cancer by 1972. Excess rates of bladder cancer were also detected by Dr. Thomas Mancuso, a colleague of Hueper and another pioneer in occupational epidemiology, in a second Ohio benzidine-manufacturing plant owned by the Cincinnati Chemical Works.

ADDITIONAL BLADDER CANCER OUTBREAKS IN THE UNITED STATES

Similar outbreaks of bladder cancer attributable to BNA, benzidine, and related chemicals have been documented in Connecticut, New York, New Jersey, and Pennsylvania. The last BNA manufacturing facility in the United States, located in Augusta, Georgia, ceased production in 1972; by 1982, 36% of the workers who had had more than 20 years' exposure had developed bladder cancer. Field studies conducted by NIOSH in the early 1970s identified at least five other plants where uncontrolled exposure to these chemicals had been permitted to occur for many years.

CONCLUSION

The German dye industry discovered in 1895 that two of its most important (and profitable) chemicals were bladder carcinogens. With the publication and dissemination of the 1921 ILO report, the uncontrolled exposure of dye workers to these carcinogens should have been eliminated. While the body count continued to mount, the dissemination of scientific information about bladder cancer outbreaks to chemical manufacturers had little impact on the decision-making processes of corporate managers. Instead, each manufacturer went through its own discovery process, ignoring well-publicized warnings and allowing uncontrolled exposure to occur until the human cost became so obvious that it was no longer acceptable.

This chronology underscores the limitation of voluntary compliance with workplace health regulation. Acknowledging that it could not be manufactured safely, Switzerland banned BNA production in 1938, and Great Britain followed in 1952. In the absence of regulation in the United States, Du Pont did not stop producing this carcinogen until 1955 and Allied continued to manufacture BNA-containing chemicals through 1960, and to purchase it for two additional years. Smaller companies maintained production, often with virtually no protection for their workers, until federal intervention finally began a decade later.

This same tragic sequence was replicated for benzidine, although with a slower chronology. And then the
sequence was repeated once again, decades later, with o-T, a chemical for which substantial evidence as to its carcinogenicity existed. The presence of a national workplace safety and health regulatory apparatus in the 1970s and 1980s, combined with powerful scientific evidence of the carcinogenicity of o-T, did little to prevent the bladder cancer outbreak at Goodyear. The findings of this historical analysis demonstrate the weakness of current federal regulation of workplace exposures, as well as the need for greatly strengthened government and worker-controlled workplace safety and health regulatory mechanisms.

Production and use of aromatic amines continue in developing countries. Given years of uncontrolled production, these nations will inevitably experience similar outbreaks of bladder cancer. Reduction of exposure levels will limit the number of cases in the future; only the elimination of exposure to these deadly chemicals will completely protect workers from future bladder cancer risks.

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