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GOODYEAR TIRE AND RUBBER COMPANY
NIAGARA FALLS, NEW YORK

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I. SUMMARY

In February 1988 a representative of the Oil, Chemical and Atomic Workers (OCAW) International Union requested that the National Institute for Occupational Safety and Health (NIOSH) conduct a health hazard evaluation of a chemical manufacturing plant operated by The Goodyear Tire and Rubber Company in Niagara Falls, New York. The union requested this evaluation because eight cases of bladder cancer had been reported between 1973 and 1988 among current and former employees of the plant. The union believed that these workers had been exposed to ortho-toluidine, a suspect bladder carcinogen.

In response to the request, NIOSH investigators visited the plant on May 2-4, 1988. We discussed the history of the problem, conducted a walk-through survey of the plant, and reviewed personnel and medical records. We returned to the plant on August 1, 1988, to collect personnel records for the purpose of a bladder cancer incidence study.

Cases of bladder cancer were identified from records of the company and union and from the New York State Cancer Registry. The number of bladder cancers observed among Goodyear workers was compared to the number expected based on New York State incidence rates. The study was restricted to the time period 1973 through 1988 because New York State Cancer Registry records were thought to be relatively complete during that time period.

There were 14 cases of bladder cancer observed and 3.54 expected based on New York State incidence rates among the 1749 individuals ever employed at the plant. The ratio of observed to expected cases (also known as the Standardized Risk Ratio or SIR) of 3.95 was found to be highly statistically significant (p=0.00002) indicating that this risk was very unlikely to have occurred by chance. There were 8 cases observed and 1.20 (SIR=6.64; p=0.00004) expected among 795 workers ever employed in an area of the plant

where workers were definitely exposed to o-toluidine and aniline. There were 4 cases observed and 1.05 expected (SIR=3.81; p=.02) among workers considered to have possible exposure to o-toluidine and aniline because they worked in maintenance, janitorial/yard and shipping departments. The SIR among 681 workers considered "probably unexposed" was not significantly different from 1.00. Therefore, the excess risk of bladder cancer is associated with exposure to o-toluidine and aniline.

The association of the excess risk of bladder cancer with exposure to o-toluidine and aniline is further supported by (1) toxicologic evidence that o-toluidine, and aniline to a lesser extent, are aromatic amines which are carcinogenic in rodents and (2) epidemiologic evidence that bladder cancer risk increases with increasing duration of employment and time since first employment in the area of the plant with exposure to o-toluidine and aniline. The results of this investigation provide evidence to support the I.A.R.C's conclusion that "o-toluidine should be regarded, for practical purposes, as if it presented a carcinogenic risk to humans." Although NIOSH has not made specific recommendations regarding occupational exposure to o-toluidine, it is our general policy that exposure to carcinogens be reduced to the lowest feasible level. Since exposure to o-toluidine and aniline within this cohort cannot be separated, and since aniline also shows some evidence of carcinogenicity in animals, it would be prudent to reduce exposure to aniline as well.

Given the high bladder cancer risks observed in this investigation, we believe that it is important to (A) assess current exposures to o-toluidine and aniline (B) notify current and former workers about the risk (C) establish a bladder cancer screening program for current and former workers and (D) continue to monitor bladder cancer incidence in the cohort.

II. INTRODUCTION

In February 1988 a representative of the Oil, Chemical and Atomic Workers (OCAW) International Union requested that the National Institute for Occupational Safety and Health (NIOSH) conduct a health hazard evaluation of a chemical manufacturing plant operated by The Goodyear Tire and Rubber Company in Niagara Falls, New York. The union requested this evaluation because eight cases of bladder cancer had been reported between 1973 and 1988 among current and former employees of the plant. The union believed that these workers had been exposed to ortho-toluidine, a suspect bladder carcinogen.

In response to the request, NIOSH investigators visited the plant on May 2-4, 1988. We discussed the history of the problem, conducted a walk-through survey of the plant, and reviewed personnel and medical records. An investigator from the Mt. Sinai School of Medicine participated in the visit as a consultant to the OCAW. We returned to the plant on August 1, 1988, to collect personnel records for the purpose of a bladder cancer incidence study. An investigator from the Mt. Sinai School of Medicine assisted in this study by requesting medical records for known bladder cancer cases.

The union was concerned about a possible increase in the number of heart disease deaths among these workers. We plan to conduct a standardized mortality ratio (SMR) analysis to assess the risk of heart disease among this cohort. This report pertains only to the results of bladder cancer investigation, because we have not completed collecting the data for the mortality study.

III. BACKGROUND

A. Description of the Plant, Processes, and Substances

The plant opened in 1946 for the production of polyvinylchloride (PVC) in Department 145. Workers in this area of the plant are known to have an excess risk of liver cancer related to vinyl chloride exposure (Nicholson, 1975). In 1954 construction of Department 245 was begun for the manufacture of chemical products. Production of Wingstay 100 began in 1957. In 1970 an expansion of Department 245 was completed and the manufacture of Morfax began.

Wingstay 100 Process

Wingstay 100 is an antioxidant that is used mainly by Goodyear plants. All chemical raw materials are received at the tank farm and pumped to storage tanks. The raw materials are fed by a computer weight control system to a premix tank. The premix chemicals are ortho-toluidine (o-toluidine), aniline, hydroquinone and toluene.

This premix solution is pumped to a chemical reactor where a catalyst is added to drive the reaction. The solution is heated to reaction temperature and held there until complete. Steam pressure moves the reactor product to a degasser where the excess reactants are removed. Steam pressure is then used to transport the material through the final filtering system and on to the holding tank where it is held heated as a liquid until ready to flake.

The molten material is gravity fed to the flaker pan where it is picked-up by the flaker drum. As the flaker drum turns, it cools the product into a film and brings the film into contact with a conditioning roll which conditions (partially crystallizes) the film to make it flakable. The flaker drum continues to cool and crystallize the material until it reaches the flaking knife. The flaked product is transported by bucket elevator to a vibration conveyor that moves the product to the bagging units where it is sealed in 50 pound bags.

History of the Wingstay 100 Process

Wingstay 100 production began in 1957 with one reactor on line. A second reactor, with an additional holding tank, was operational in 1969, and in 1970 a new hydroquinone air-transfer system was installed. An improved recycle recovery system was completed in 1972. In 1978 the installation of a premix charge reactor feed system was completed and in 1980 a liquid catalyst system was installed. According to the operators, the only change that significantly affected chemical exposure was the installation of the premix charge system. This is an automatic mixing system which, due to design changes such as improved ventilation and lower temperatures, produces less fumes . In 1984 a 3300-lb. semi-bulk bag system was installed for hydroquinone to replace the use of 300-lb. fiber drums.

Morfax Process

Morfax is a rubber accelerator that is manufactured and commercially marketed by Goodyear. The chemical raw materials are received at the Tank Farm and pumped to the Charge Room. The chemicals are premixed as they are received and held in two storage tanks as mixtures. One tank holds a mixture of carbon disulfide and flaked sulfur, and the other tank holds a mixture of a proprietary chemical, aniline and benzothiazole (recycled by-product from process). The mixtures are pumped to a charge header and then enter the first in a series of autoclaves or reactors.

A reaction occurs in the first autoclave, which generates heat. The heat and reaction speed is controlled by a cold "dowtherm" system. From this point the reaction continues as the reactant flows from the bottom to the top of the autoclave. The reactant then flows from the top of the first to the bottom of No. 2 autoclave and continues in a like manner through the remaining autoclaves.

The product that leaves the last autoclave is mercaptobenzothiazole (MBT). The MBT leaves the last autoclave and proceeds to the Steam Stripper where hydrogen sulfide (H_2S) is driven off with super heated steam and sent to the Sulfur Removal Unit (SRU). Also, the benzothiazole by-product, which is added in the charge room, is separated here. The stripped MBT is fed to one of two storage tanks and held for further processing.

MBT from the storage tanks is fed to a centrifuge dewatering system and then to the feed make-up tank. Morpholine, isopropanol, water, and sulfur are added to the feed make-up tank, which is steam heated and mixed by agitation. The reactant is transferred to a second tank, which serves as the feed tank for the Morfax reactor and is heated. The material is continuously pumped from the feed tank to the Morfax reactor, and bleach is added during the reaction. The reactant flows from the reactor and into a holding tank, where it is quenched with water. The quenched product is sent through a dewatering centrifuge and then to a fluid bed dryer. After drying, the finished Morfax is transported by gravity to a vacuum bagger.

The SRU unit previously mentioned reclaims sulfur from the stripped H_2S. This is accomplished by heating the incoming gas and passing the vapors and gas over two catalytic reactor beds to remove the sulfur. The sulfur flows into a collection tank at the end of each pass. The trace remaining gases are burned and then vented to the atmosphere via an emission stack.

History of the Morfax Process

Morfax production began in Department 245 in 1970. The SRU unit was installed in 1971 in order to reduce sulfur based air pollutant emissions. The fluid bed dryer was completed in 1978.

B. Personnel, Medical, and Industrial Hygiene Programs

The company maintains personnel records for current employees in the personnel office, and records for former employees in a storage room in the plant. These records are thought to be complete for workers who were employed as far back as 1946. Employment history, including all changes in departments and job titles, and dates of these changes is recorded in the personnel folder. The personnel folder also has social security number and date of birth. The company provides a death benefit; hence, the corporate office has copies of death certificates for deceased workers who were eligible for this benefit. The company employs a full-time nurse on-site. Medical records for current workers are kept in the Nurse's office in the plant, while the medical records for former workers are stored in the storage room along with the personnel records. A medical surveillance program for current employees has been in effect at the plant since 1980, and although it is a voluntary program, about 90 percent of current employees participate in it. All employees are offered a physical examination at least once a year. The exam includes urine cytology and urinalysis. A questionnaire, which includes questions about smoking habits, is also completed as part of the physical examination.

The industrial hygiene and safety programs at the plant are administered by the corporate industrial hygiene department, and the programs are carried out by the plant industrial hygiene and safety specialist. Industrial hygiene monitoring of all process chemicals is conducted annually at a minimum. The annual monitoring results are evaluated according to a four point classification system, which is used to determine the frequency of monitoring. In this system exposure levels above the TLV require quarterly monitoring. At the time of the

NIOSH survey (May 1988) a contractor was conducting an extensive evaluation of the ventilation system. Personal and area monitoring for various chemical exposures in department 245 began in 1982.

Respiratory protection is provided and required in certain areas such as enclosed vessels. A respirator program is conducted which includes pulmonary function and fit testing of new employees, annual fit testing of current employees, and weekly repair, cleaning, and disinfection of respirators.

C. Potential Health Effects of Chemicals Present

Table 1 summarizes the chemicals present in Department 245. Two of the chemicals used in this department, o-toluidine and aniline, are aromatic amines for which there is some evidence of carcinogenicity. The IARC reviewed data on the carcinogenicity of aniline and o-toluidine in 1982 (IARC, 1982). Regarding aniline, the IARC concluded that "there is limited evidence for the carcinogenicity of aniline hydrochloride in experimental animals. The available epidemiologic data are insufficient to allow a conclusion as to the carcinogenicity of aniline." Regarding o-toluidine, the IARC 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 responsible agent. O-toluidine should be regarded, for practical purposes, as if it presented a carcinogenic risk to humans." The IARC classification of these chemicals remained the same in 1987 (IARC, 1987).

It is possible to compare the carcinogenicity of aniline and o-toluidine in experimental animals because they have been tested in similar experiments, which are summarized in Table 2 (NCI, 1978, NCI, 1979). In the assays of aniline HCl in mice, no statistically significant increases were noted between exposed and control animals for any tumor site, while o-toluidine HCl, in lower doses, produced a significant increase of "hepatocellular carcinomas and adenomas" in females and "hemangiosarcomas, all sites," in males. In rats, aniline HCl produced an excess of "fibromas or sarcomas" in both male and female animals and an excess of hemangiosarcomas in males. O-toluidine HCl, given at the same doses as aniline HCl, produced several different types of tumors, including transitional cell carcinomas and papillomas of the bladder in females. Two other bioassays for o-toluidine in rats have reported bladder tumors among exposed but not control animals, but the differences were not statistically significant (Weisburger, 1978, Hecht, 1982).

The epidemiologic data available for both chemicals are extremely limited. Case (1954), in a large study of bladder cancer in British dyestuff workers, found no evidence that workers exposed to aniline alone had an increased risk of bladder tumor. No other epidemiologic studies on aniline are available. The IARC cites several reports regarding o-toluidine and aniline. None are adequate epidemiologic studies from which the risk of bladder cancer in workers exposed to o-toluidine, but not also exposed to other aromatic amine carcinogens, can be calculated. One recent study reported a 72-fold increase (8 cases observed vs. 0.11 expected) of bladder cancer among 116 workers involved in the manufacture of 4-chloro-o-toluidine between 1929 and 1970 (Stasik, 1988). O-toluidine was also present at this plant, although exposure to 4-chloro-o-toluidine was thought to be more extensive.

Based on this review, we believe that o-toluidine is more highly carcinogenic in experimental animals than aniline, and is therefore more likely to be a human bladder carcinogen than aniline. However, because aniline did produce tumors in one rat bioassay study, the possibility that aniline might also be carcinogenic cannot be excluded.

IV. Study Design and Methods

In order to evaluate whether workers in Department 245 have an increased risk of bladder cancer in relation to their exposure to o-toluidine and aniline, we conducted both an evaluation of exposures in Department 245 and a bladder cancer incidence study.

A. Exposure Assessment

The objectives of the industrial hygiene portion of this HHE were to provide a description of the processes and the chemicals present, review any industrial hygiene sampling data collected by the company, and collect area air samples at appropriate process locations as a qualitative indication of worker exposure to process chemicals. During the site visit on May 2-4, 1988, information was recorded regarding the specific chemicals and steps of the processes, pictures of the process equipment were taken, and ten process operations/areas were monitored for eight different chemical agents (o-toluidine and aniline, morpholine, a proprietary chemical, carbon disulfide, chlorine, hydrogen sulfide, and toluene).

The area air sampling was conducted according to the recommended NIOSH methods when possible. Long-term detector tubes were used to sample for hydrogen sulfide and chlorine. Personal monitoring pumps were used to sample at the maximum flow rate allowable for each method since the objective for this study was to collect bulk area air samples for qualitative measurements. The sampling and analytical methods, flow rates and media used are listed in Table 3.

In addition to evaluating the potential for exposure among current workers during the environmental survey, information was collected to determine: 1) who in the workforce was potentially exposed to o-toluidine and aniline; 2) whether it was possible to separate workers exposed to both o-toluidine and aniline in the Wingstay process from those exposed to aniline alone in the Morfax process; and 3) whether historical exposure levels could be estimated for these chemicals, either in Department 245 in general, or in specific jobs/areas within Department 245.

B. Epidemiologic Investigation

The goal of the epidemiologic investigation was to compare the number of bladder cancers observed among Goodyear workers, particularly those with potential exposure to o-toluidine and aniline, with the number of bladder cancers expected based on New York State incidence rates. This section will describe the methods used in the epidemiologic investigation:

1. Personnel records were microfilmed for all workers employed at the plant since 1946. A computer file was created which contains identifying information, such as name, social security number and date of birth. In addition, the computer file contains information about department, job title, and dates, for every job a person worked at Goodyear.

2. An attempt was made to determine whether each person is living or dead, and the dates of death. To make this determination, the following sources were used: information from company personnel records, death certificates from the company pension program, deaths reported to the Social Security Administration from 1962 to 1988 and current addresses from the Internal Revenue Service and the Post Office.

3. Bladder cancer cases which were identified from the company and the union were confirmed by requesting medical records. Additional cases were identified by matching the computer file of Goodyear workers with the New York State Cancer Registry. Medical records were not sought for individuals identified only from the Registry.

4. A computer program was used to calculate the numbers of bladder cancers expected among Goodyear workers (Waxweiler et al, 1983). This program adds up, for all workers under study, the years of observation (i.e., the time from starting employment until diagnosis of bladder cancer, death, or the end of the study period) and divides them into 5-year intervals based on age and calendar time. The program uses a unit called "person-years at risk." Five person-years at risk may be equivalent to five persons contributing one year of observation within the interval, or one person contributing five years.

5. To obtain the expected number of bladder cancers, the number of person-years within each interval is multiplied by the rate of bladder cancer in the comparison group during the same age and calendar time specific interval. The comparison group in this study is the New York State population (excluding New York City). Bladder cancer incidence rates have been obtained from the New York State Cancer Registry.

6. The computer program adds the observed and expected numbers of bladder cancers in all the 5 year age and time intervals to provide a summary number of bladder cancers observed versus number expected. The observed and expected numbers were calculated separately for males and females, and then combined, because the rates of bladder cancer in the comparison population differ for males and females. Although rates of bladder cancer differ for U.S. whites and non-whites, we have combined whites and non-whites in our analysis because the New York State registry rates are not stratified by race. Of the 670 individuals in the cohort whose race is known, 91% are white, which is comparable to the proportion of whites in New York State, excluding New York City, which is approximately 94%.

7. Since the New York State Cancer Registry did not code the social security number of cases prior to 1973, and did not have incidence rates before 1973, person years at risk in the analysis did not begin until January 1, 1973, or date of starting employment, whichever occurred later. Bladder cancer cases occurring prior to that date were excluded from the analysis. Person years at risk were accumulated either to the date of diagnosis, date of death, or the the end date of the study (January 1, 1989). This end date was chosen because the New York State Cancer Registry had searched their files for cases through December 1988. Although the registry was able to provide incidence rates only through 1985, we found that bladder cancer incidence rates were not changing markedly over the preceding several years. We applied the 1980-1985 New York State incidence rates to the years 1986-1988.

V. Evaluation Criteria

A. Environmental Standards and Recommended Levels

The Occupational Safety and Health Administration (OSHA) standard for occupational exposure to o-toluidine requires that its concentration in air not exceed 5 ppm (22 mg/m^3) for an 8-hour Time Weighted Average (TWA). The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a Threshold Limit Value (TLV) of 2 ppm (9 mg/m^3) for an 8-hour TWA , and indicates a possibility of cutaneous absorption [ACGIH, 1986]. NIOSH has no recommended exposure limit for o-toluidine. ACGIH has classified o-toluidine as a suspect carcinogen for humans [ACGIH, 1986].

The OSHA standard for aniline is 5 ppm (19 mg/m^3) for an 8-hour TWA. ACGIH has proposed a TLV of 2 ppm (10 mg/m^3) for an 8-hour TWA, and indicates a possibility of cutaneous exposure [ACGIH, 1986]. NIOSH has no recommended exposure limit for aniline.

The OSHA standards and ACGIH recommended levels for chemicals NIOSH sampled for during the survey are given in Table 3.

B. Evaluation of the Epidemiologic Study Results

The results of the bladder cancer incidence study were evaluated by testing the statistical significance of the ratio of observed to expected numbers of bladder cancer cases. This ratio, which is called the standardized incidence ratio (SIR), was calculated for several subgroups of the Goodyear population. These subgroups, which were defined by the industrial hygiene evaluation, included (1) workers ever employed in Department 245, who are presumed to have had exposure to o-toluidine and aniline; (2) workers in maintenance, janitorial/yard and shipping departments, who are presumed to have possible exposure to o-toluidine and aniline; and (3) all other workers, who are thought to have a low probability of exposure to o-toluidine and aniline. The statistical significance of the SIR (i.e., the probability that an SIR as great or greater would have occurred by chance) was tested using the simple continuity corrected chi-square statistic [Armitage, 1971; Monson, 1980]. In addition, the 90% confidence interval (the range of numbers in which we are 90% confident the true risk falls) was calculated (Fisher, 1956).

For workers ever employed in Department 245, we also calculated the SIR for bladder cancer by length of employment and by latency (time from first exposure to date of diagnosis of bladder cancer, death, or end of the study, which is January 1, 1989). Duration of employment and latency intervals were selected prior to conducting the analysis. Duration of employment intervals were under 1 year, 1 to 4.99 years, 5 to 9.99 years, 10 to 14.99 years, 15 to 19.99 years and over 20 years. Latency intervals were under 5 years, 5 to 9.99 years, 10 to 14.99 years, 15 to 19.99 years, 20-24.99 years, 25 to 29.99 years and 30 or more years. Duration was accumulated only for time in Department 245 and latency began on the date first employed in Department 245.

Cigarette smoking is the major non-occupational risk factor for bladder cancer (Howe, 1980). In planning this study we thought it might be important to evaluate the possible contribution of differences in smoking habits between the cohort and the referent population, particularly if relatively small increased risks (on the order of 1.5 to 2.5) for bladder cancer were observed. Medical records at GNF contain information about smoking habits, which has been collected systematically as part of the yearly physical since the early 1980's. We, therefore, visited the plant in June 1989 and microfilmed a 5% sample of the most recent smoking history of current and former workers.

VI. Results

A. Exposure Assessment

Review of Company Data:

The Goodyear Industrial Hygiene program to monitor workers for process chemical exposures began in 1982. Goodyear management said that no monitoring data exist prior to that. Therefore, it is not possible to determine what employee exposures were before 1982. However, process workers have stated that they believe the installation of the premix chemical charging system in 1978 significantly reduced the exposure to those chemicals (see process discussion).

The worker exposure monitoring data that Goodyear industrial hygiene staff have collected since 1982 show that air concentrations of all chemicals present in Department 245 have been consistently less than one part per million (ppm).

Walk Through Survey Results:

One potentially hazardous exposure situation was observed during the survey in Building B32 where the neutralized catalyst is filtered from the liquid Wingstay 100. The Wingstay 100 filters were manually cleaned by utility operators. During the cleaning procedure there were visible vapors coming off the filters and the workers wore no respiratory protection.

The filter cleaning operation takes about an hour and is typically performed 2 to 3 times per shift. Chemical vapors potentially present during cleaning are o-toluidine, aniline, and toluene, although the concentration of these chemicals in the Wingstay 100 product is very low (sub-ppm range) at the time it reaches the filters.

The air samples collected during the survey showed only sub-ppm levels of process chemicals at the filter location (Table 4). However, there was an obvious potential for inhalation, as well as skin exposure at the neck and face of the operators. Rubber gloves and cotton coveralls were worn by the operators. Biomonitoring or skin exposure assessment of these workers has not been conducted by Goodyear.

As shown in Table 4 the results for all the area air samples collected were less than 1 ppm. The sample with the highest concentration of o-toluidine, 0.93 ppm, was collected in the Wingstay Flaker area. The highest aniline concentration, 0.17 ppm, was also found in the Wingstay Flaker area. The highest toluene concentration of 0.33 ppm was in the Wingstay Flaker area as well. An air sample collected in the Tank Farm had a carbon disulfide concentration of 0.17 ppm. Morpholine was measured at 0.03 ppm in the Morfax Charge Room. Hydrogen sulfide was not indicated on detector tube samples collected in the Morfax Stripper and SRU area. A detector tube sample in the Morfax Reactor area indicated a chlorine concentration of 0.1 ppm. The dust samples that were collected in the Wingstay and Morfax Bagging and Packaging areas had nondetectable (<0.03 ppm) levels of o-toluidine and aniline.

Identification of Workers Potentially Exposed to O-toluidine and Aniline

Both o-toluidine and aniline are used in the Wingstay 100 process and aniline is also used in the Morfax process. According to the company and the union representatives, employees in department 245 often rotate within the two processes doing similar jobs. The personnel record includes the department and general job title in which a worker has been employed, but does not specify the process. Hence, we are not able to determine weather a worker was employed in the Wingstay 100 or Morfax process. Moreover, since the Wingstay 100 process utilizes both chemicals, i.e., aniline and o-toluidine, it would be difficult to separate exposures even if the work histories were more specific.

Department 245 employs chemical process operators, utility workers, maintenance personnel, and supervisors. All chemical process operators are exposed to mixtures of chemicals, and the mixture is dependent on the process location. However, the personnel records do not include process specific job titles. Utility workers are employed in general process areas to assist the operators; hence, they incur similar exposures. Maintenance personnel work in all areas of the process, and thereby have a potential for exposure to all chemicals in the process. Thus, we can conclude that a potential for exposure to both o-toluidine and aniline has been present in department 245. We cannot, however, quantify the levels of exposure to employees for years prior to 1982, nor can we identify employees who were exposed to only one of the two chemicals.

Based on the evaluation of exposure, we divided the study population into three groups for epidemiologic analysis: (1) workers ever employed in Department 245, who are presumed to have had exposure to o-toluidine and aniline, (2) workers in maintenance, janitorial/yard and shipping departments, who are presumed to have possible exposure to o-toluidine and aniline, and (3) all other workers, who are thought to have a low probability of exposure to o-toluidine and aniline. The "probably unexposed" group includes individuals who worked solely in the polyvinyl chloride production department (Department 145). No attempt was made to analyze bladder cancer risk by job within Department 245 because we are unable to associate these jobs with degree of exposure to specific chemicals.

B. Epidemiologic Assessment

There were 1749 individuals identified from personnel records at the plant, of whom 1643 were male and 106 were female. The distribution of year of birth of the cohort is shown in Table 5. The cohort is currently quite young, with 71.0% being born after 1940 and thus not having reached the age groups (50 and beyond) in which bladder cancer incidence rises in the general population (SEER, 1985). As of August 1, 1988, the date on which we microfilmed personnel records at the plant, 293 of the 1749 workers were still actively employed at Goodyear.

Based on the work histories present in the personnel records, 795 individuals worked in Department 245 and were, therefore, considered to have definite exposure to o-toluidine and aniline; 273 had never worked in Department 245 but had worked in maintenance, janitorial/yard or shipping departments, and were considered possibly exposed, and 681 had never worked in departments considered to have probable or possible exposure to o-toluidine or aniline.

A total of 15 individuals in the cohort have been identified as having had bladder cancer. One has been excluded from the statistical analysis because the date of diagnosis of his bladder tumor was prior to 1/1/73, the date when we begin counting cases and "person-years-at-risk." Of the fourteen cases included in the statistical analysis, eight had worked in Department 245, four had worked in departments considered to have possible exposure, and two had worked only in other areas. The individual who was excluded from the analysis had worked in a department considered to have possible exposure. A summary of the characteristics of the fifteen cases is provided in Table 6.

Table 7 presents the number of observed and expected bladder cancer cases for the total cohort and for the groups of workers considered definitely exposed, possibly exposed, and unlikely to be exposed to o-toluidine and aniline. The risk of bladder cancer is statistically increased in the cohort as a whole, but the highest risk is observed among workers who had ever been employed in Department 245. Workers in this Department had an SIR of 6.64, which implies that they were 6.64 times more likely than New York State residents of similar age and sex to develop bladder cancer. Workers considered to be possibly exposed also had a significantly increased SIR for bladder cancer of 3.81. Among individuals who were considered non-exposed, there were 2 observed and 1.29 expected bladder cancer cases (SIR=1.55; 90% CI=0.28-6.18).

Tables 8-11 examine the trends in bladder cancer risk among workers in Department 245 by duration of employment in the department, time since first employment in the department (latency), age and calendar time. The SIR's for duration of employment categories of 10 or more years are generally over 20 (except in the last two categories in which no cases were observed). The SIR's are greatest in latency categories of over 20 years, which is consistent with the latency period for occupational bladder carcinogens (Matanoski, 1981). There is no discernable trend in bladder cancer risk with age or time period.

We did not analyze the data collected on smoking habits of recent Goodyear workers because the SIR's found in this study were so high that smoking could not possibly explain them. Even if 100% of the population were smokers, we estimate (using a method described by Axelson and Steenland, 1988) that this would account for only an SIR of 1.7.

VII. DISCUSSION AND CONCLUSIONS

This investigation found an elevated risk of bladder cancer among workers "ever-employed" at the Goodyear plant in Niagara Falls. The risk was highest (SIR=6.64) among workers in an area of the plant with definite exposure to o-toluidine and aniline, intermediate (SIR=3.81) among workers considered to have possible exposure, and lowest (SIR=1.55) among workers considered unexposed. Therefore, the excess risk is associated with exposure to o-toluidine and aniline. The association of this excess risk with exposure to o-toluidine and aniline is further supported by (1) the toxicologic evidence that o-toluidine, and aniline to a lesser extent, are aromatic amines which are carcinogenic in rodents, and (2) the epidemiologic evidence that bladder cancer risk increases with increasing duration of employment and time since first employment in Department 245. Bladder cancer risk among workers with over 10 years employment in Department 245 is particularly high, approximately 20 times greater than the risk in the general population.

It is important to be cautious in interpreting the results of this study on the relative bladder cancer risks in subgroups of the Goodyear population, and in applying these results to characterize risk for individual workers. Subgroups of workers found to have relatively low risks now (such as the group with under 5 years duration of employment in Department 245) may be found to have higher risks in the future, since the cohort is still quite young and many workers have not had 20 years since they began exposure. In addition, our classification of workers into exposure categories may be imperfect. For example, it is possible that some maintenance workers in the "possibly exposed" group had extensive exposure to o-toluidine and aniline, or that some laboratory workers in the "probably unexposed" group did routinely handle o-toluidine.

There are several methodologic reasons why our study would tend to underestimate the risk of bladder cancer. Firstly, we may have missed cases that occurred among former workers who have moved out of New York State. Currently, about 28% of cohort members have addresses outside New York State. Secondly, we assumed that all cohort members not known to have died or developed bladder cancer were alive and free of disease until the end of the study.

Because occupational bladder cancer is thought to have a mean or median latency period of 20 years, bladder cancers occurring now are probably related to exposures at least 10-20 years ago (Matanoski, 1981). Since there is no exposure data prior to 1982, and there were changes in the process prior to that time which may have influenced exposure levels, we believe it is impossible to estimate levels of exposure associated with the increased bladder cancer risk.

In conclusion, the results of this investigation provide evidence to support the I.A.R.C's conclusion that "o-toluidine should be regarded, for practical purposes, as if it presented a carcinogenic risk to humans." (I.A.R.C., 1982) Although NIOSH has not made specific recommendations regarding occupational exposure to o-toluidine, it is our general policy that exposure to carcinogens be reduced to the lowest feasible level. Since exposure to o-toluidine and aniline in this cohort cannot be separated, and since aniline also shows some evidence of carcinogenicity in animals, it would be prudent to reduce exposure to aniline as well.

VIII. FUTURE PLANS AND RECOMMENDATIONS

Given the high bladder cancer risks observed in this investigation, we believe that it is important to (A) assess current exposures to o-toluidine and aniline, (B) notify current and former workers about the risk, (C) establish a bladder cancer screening program for current and former workers, and (D) continue to monitor bladder cancer incidence in the cohort. NIOSH's plans and recommendations on each of these issues are discussed below.

A. Assessing Currrent Exposure Levels to O-toluidine and Aniline

Thus far, the exposure data collected by NIOSH and the company for o-toluidine and aniline is limited to air sampling. Since both o-toluidine and aniline have the potential for absorption through the skin (ACGIH, 1986), it is important to assess whether workers are adequately protected from exposure via this route. Methods are available to measure both o-toluidine and aniline in human urine (El-Bayoumy et al, 1981). Both o-toluidine and aniline are measurable in urine of adults who are not occupationally exposed to these compounds (El-Bayoumy et al, 1981). One possible source of o-toluidine and aniline in the urine is cigarette smoke (Patrianakes and Hoffman, 1981), but El-Bayoumy (1981) reported that there was no difference between levels of o-toluidine and aniline in urine of smokers and non-smokers. Since the bladder cancer risks observed among Department 245 workers are so high, we believe that the potential for exposure to o-toluidine and aniline among current workers should be minimized as much as possible. We, therefore, plan to conduct an exposure survey in Department 245 which might identify work areas where exposures to o-toluidine and aniline are not adequately controlled. We are currently drafting a protocol for an exposure survey which will include monitoring for o-toluidine and aniline contamination on surfaces, monitoring for potential dermal absorption, and collecting urine samples from workers to measure o-toluidine and aniline concentrations.

B. Notifying Current and Former Workers About the Findings of the Investigation

Among the 794 individuals who ever worked in Department 245, only 161 were current employees of the Goodyear plant as of August, 1988 when we microfilmed personnel records. In the group that currently appears to have the highest risk of bladder cancer, that is workers who were employed in Department 245 for over 10 years, 112 of 204 were current employees as of August 1988. It is, therefore, important to notify former, as well as current workers, about the findings of this study. As part of our worker notification program, we are developing a letter and fact sheet which we propose to send to all current and former workers. This material will be shared with the company and union prior to its distribution. In addition, we believe that it might be useful to hold meetings at the plant to answer questions about the study and about bladder cancer. We will solicit the cooperation of the company and the union in planning notification activities.

C. Planning a Bladder Cancer Screening Program

There is considerable controversy over the value of screening in preventing disability and death from bladder cancer. In addition, there are new techniques available for bladder cancer screening, such as quantitative fluorescence image analysis (QFIA) (Hemstreet et al, 1988) and home dipstick testing for microhematuria (Messing et al, 1987). Because bladder cancer screening is a complex and evolving area, we believe that it is very important that a screening program be well-designed and that the data be collected in a systematic way. This will allow the results to be evaluated to ensure that the program is of benefit and is designed to offer the best possible screening approach.

The Goodyear Company has offered currently employed workers screening examinations (annual urine cytology and urinalysis) for bladder cancer since the late 1970's. In addition, in the past year the company has offered cystoscopy to current workers. Both of these approaches have limitations. Urine cytology and urinalysis, particularly if conducted on only one urine sample annually, may miss the earlier, low grade tumors. Four of the thirteen bladder cancer cases at Goodyear who were included in the analysis had at least one urine screening test performed as part of their company physical in the three years prior to diagnosis, and all of the results were normal. A limitation of cystoscopy is that without concurrent urine cytology and where indicated, random biopsy, it may miss carcinoma-in-situ, a flat lesion which has a higher potential to develop into an invasive tumor than do low grade papillary tumors. In addition, cystoscopy is an invasive procedure with potential complications, which many individuals are reluctant to undergo. A major limitation of both programs offered by the company is that they include only current workers. We recommend that a screening program be established that would include both current and former workers. NIOSH is willing to assist the company and union in designing the program and in identifying experts on bladder cancer screening. We would also recommend that, at least for workers still residing in the local area, this program be conducted at a single facility in order to ensure the application of recommended screening methods and uniform collection of specimens.

D. Monitoring Bladder Cancer Incidence in the Cohort:

We believe that it would be valuable to continue to monitor the occurrence of bladder cancer in the cohort, both by analyzing the results of the medical screening program and by collecting data from the New York State Cancer Registry and from death certificates. This would enable NIOSH to monitor changes in risk among various subgroups within the cohort.

The walk-through survey of the plant identified one area, where Wingstay 100 filters are cleaned, in which immediate remedial action is needed. It is recommended that during the cleaning of the Wingstay catalyst filters, workers be provided with, and required to wear, appropriate respiratory and skin protection. In addition to coveralls and gloves impervious to process chemicals, the use of both respiratory and skin protection for the face, such as an air supplied hood, should be considered. Further recommendations on current conditions in Department 245 await the completion of the proposed exposure survey.

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XI. DISTRIBUTION AND AVAILABILITY OF REPORT

Copies of this report have been sent to:

1. Goodyear Tire and Rubber Company
2. Oil Chemical and Atomic Workers International Union
3. Director, DSHEFS
4. R. Lemen, NIOSH/W
5. OSHA Regional Administrator
6. New York Department of Health

TABLE 1

LIST OF CHEMICALS USED OR PRODUCED IN WINGSTAY 100 AND MORFAX PROCESSES IN DEPARTMENT 245

HETA 88-159
GOODYEAR TIRE AND RUBBER COMPANY
NIAGARA FALLS, NEW YORK

Wingstay 100 (Diaryl-p-phenylenediamine)	Morfax (4-morpholinyl-2-benzothiazole disulfide)
o-Toluidine	Morpholine
Aniline	Aniline
Hydroquinone	Carbon disulfide
Toluene	Proprietary chemical A
Phenol	Sulfur
Ferric Chloride	Sodium Hydroxide
Diphenylamine	Mercaptobenzothiazole
	Isopropyl Alcohol
	Sodium Sulfide
	Chlorine
	Benzothiazole

TABLE 2
Comparison of the Carcinogenicity of Aniline-HCl and O-toluidine in Bioassays Conducted With Similar Methodology

Chemical	Animal	Dose (mg/kg feed)	# of Animals M	# of Animals F	Sites/Sexes In Which Statistically Significant Dose-related Trends Were Observed			References
Aniline HCL	$B6C3F_1$ mice	0	50	50				NCI, 1978
		6000	50	50	NONE			
		12000	50	50				
					Hepatocellular Carcinomas-Adenomas Female		Hemangiosarcomas All Sites Male	
O-Toluidine HCL	$B6C3F_1$ hybrid Mice	0	20	20	0/20		1/19	NCI, 1979
		1000	50	50	4/49		1/50	
		3000	50	50	13/50		10/50	
					Fibrosarcomas or sarcomas Male	Fibrosarcomas or sarcomas Female	Hemangiosarcomas Male	
Aniline HCL	Fischer 344 rats	0	25	25	0/25	0/24	0/25	NCI, 1978
		3000	50	50	5/50	1/50	19/50	
		6000	50	50	18/48	7/50	21/48	
					Sarcomas, fibrosarcomas angiosarcomas & osteosarcomas of multiple organs Male	Sarcomas, fibrosarcomas angiosarcomas & osteosarcomas of multiple organs Female	Sarcomas, angiosarcomas, osteosarcomas of the spleen Female	
O-toluidine HCL	Fischer 344 rats	0	20	20	0/20	0/20	0/20	NCI, 1979
		3000	50	50	15/50	3/50	9/49	
		6000	50	50	37/49	21/49	12/49	
					Transitional-cell sarcomas and papillomas of the urinary bladder Female		Fibromas of the subcutaneous tissue in the integumentary system Male	
		0			0/20		0/20	
		3000			10/45		28/50	
		6000			22/47		27/49	
					Fibroadenomas of the mammary gland Female		Mesotheliomas of multiple organs or of the tunica vaginalis Male	
		0			6/20		0/20	
		3000			20/50		17/50	
		6000			35/49		9/49	

TABLE 3
SAMPLING AND ANALYTICAL INFORMATION FOR AIR MONITORING
CONDUCTED AT THE GOODYEAR TIRE AND RUBBER COMPANY
NIAGARA FALLS, NEW YORK
HETA 88-159
5/8/88

Chemical Name	NIOSH Method #	Sampling Media	Flow Rate	OSHA PEL*	REL's (ppm)+ NIOSH	REL's (ppm)+ ACGIH
o-toluidine	2002	Silica Gel Tube	200 cc/min	5 ppm	NA	2
Aniline	2002	Silica Gel Tube	200 cc/min	5 ppm	NA	2
Toluene	1501	Charcoal Tube	200 cc/min	200 ppm	100	100
Morpholine	S-150	Silica Gel Tube	200 cc/min	20 ppm	NA	20
Carbon Disulfide	1600	Charcoal Tube	200 cc/min	20 ppm	1	10
Hydrogen Sulfide	NA	Detector Tube	20 cc/min	20 ppm	10	10
Chlorine	NA	Detector Tube	20 cc/min	1 ppm	0.5	0.5

* = Occupational Safety and Health Administration Permissible Exposure Limit based on an eight hour time weighted average sample.

\+ = National Institute for Occupational Safety and Health and the American Conference of Governmental Industrial Hygienists Recommended Exposure Limit in parts per million based on an eight or ten hour time weighted average sample, depending on the chemical.

NA = No Standard has been adopted at this time.

TABLE 4
RESULTS FOR AREA MONITORING CONDUCTED IN DEPARTMENT 245 AT THE GOODYEAR TIRE AND RUBBER COMPANY NIAGARA FALLS, NEW YORK HETA 88-159 5/8/88

Area Monitored	Analyte	Associated Job	Sample Time*	Sample Result+
Tank-Farm	o-Toluidine	Tank-Farm Operator	454	0.07
" "	Aniline	" "	454	0.07
" "	Carbon Disulfide	" "	453	0.17
Wingstay Premix	o-Toluidine	Premix Operator	458	0.10
" "	Aniline	" "	458	0.02
Wingstay Flaker	o-Toluidine	Reactor Operator	469	0.93
" "	Aniline	" "	469	0.17
" "	Toluene	" "	468	0.33
Wingstay Recycle	o-Toluidine	Reactor Operator	469	0.10
" "	Aniline	" "	469	0.02
" "	Toluene	" "	469	0.17
Wingstay Filters	o-Toluidine	Filter Operator	473	0.13
" "	Aniline	" "	473	0.03
" "	Toluene	" "	473	0.27
Wingstay Bagging & Packaging	o-Toluidine	Bagging/Packaging Operator	478	N.D.#
	Aniline		478	N.D.
Morfax Charge Room	o-Toluidine	ChargeRoom/Autoclave Operator	458	0.02
" " "	Aniline		458	0.02
" " "	Morpholine	"	458	0.03
Morfax Stripper & SRU Operations	Hydrogen Sulfide	Stripper/SRU Operator	456	N.D.
Morfax Reactors	Chlorine	Reactor Operator	451	0.10
Morfax Bagging & Packaging	o-Toluidine	Bagging/Packaging Operator	460	N.D.
	Aniline		460	N.D.

* = Times reported are in minutes.
\+ = Results reported are in parts per million.
\# = N.D. - The chemical was not detected in the analysis.

TABLE 5

DISTRIBUTION OF YEAR OF BIRTH OF STUDY COHORT

HETA 88-159
GOODYEAR TIRE AND RUBBER COMPANY
NIAGARA FALLS, NEW YORK

DECADE	NUMBER	PERCENT
Before 1920	102	5.8
1920-1929	142	8.1
1930-1939	258	14.8
1940-1949	591	33.9
1950-1959	563	32.3
After 1960	88	5.0
Unknown	5	-
Total	1749	100.0

TABLE 6
LISTING OF BLADDER CANCER CASES
HETA 88-159
GOODYEAR TIRE AND RUBBER COMPANY
NIAGARA FALLS, NEW YORK

Exposure Group	Case #	Yr. 1st Exp.	Duration of Exp.# (Yrs.)	Latency (Yrs.)	Yr. Dx.	Age Dx.	Stage	Source of case##	Pathology	Vital Stat
Worked in 245 - "Definite exp."	1	70	11	16	86	71	1	R	Unknown	Alive/89
	2	57	18	23	80	61	1	P,R	Gr 1 Papillary Tumor	Alive/89
	3	69	4	9	78	64	1	R	Unknown	Alive/86
	4	57	25	25	82	57	3	P,R	Adenocarcinoma	Dec'd/83
	5	57	21	21	78	43	1	P,R	Gr 2 Papillary trans. cell. ca.	Dec'd/82
	6	61	10	25	86	53	1	P,R	Gr 2 Papillary trans. cell. ca.	Alive/89
	7	57	13	23	80	56	2	P,R	Gr 2 Papillary trans. cell ca.	Alive/89
	8	57	7	31	88	64	-	P	Mult. Gr 2-3 papill. trans. cell carcinomas	Alive/89
Worked in maintenance, janit./yard, shipping - "possibly exposed"	9	57	11	25	86	60	3	R	Unknown	Alive/89
	10	63	9	10	73	56	1	P,R	Unknown	Alive/88
	11	79	5	5	84	52	1	P,R	Gr 1-2 Papill. trans. cell ca.	Alive/89
	12	79	8	9	88	60	1	P	Gr 2 Papillary trans. cell ca.	Alive/89
Probably not exposed	13	-	-	-	75	46	-	R	Unknown	Alive/89
	14	-	-	-	83	64	3	R	Unknown	Alive/88
Not included in analysis	15	57	15	15	72	44	-	P,R	Gr 3 Trans. cell ca.	Dec'd/86

Duration of exposure includes only the time period prior to diagnosis. For individuals who worked in Department 245, duration of exposure includes only time in 245. For workers in "possibly exposed" jobs, duration of exposure includes only time spent in those jobs.

P= Case reported by company or union, R=case identified from N.Y.S. Cancer Registry.

TABLE 7

OBSERVED AND EXPECTED NUMBERS OF BLADDER
CANCERS AMONG GOODYEAR WORKERS, BY EXPOSURE GROUP

HETA 88-159
GOODYEAR TIRE AND RUBBER COMPANY
NIAGARA FALLS, NEW YORK

Probability of exposure to o-toluidine & aniline	Number of persons	Bladder cancers observed	Bladder cancers expected	SIR	p-value	90% Confidence Interval
Definitely exposed	795	8	1.20	6.64	.00004	3.30-12.0
Possibly exposed	273	4	1.05	3.81	.022	1.30-8.72
Probably unexposed	681	2	1.29	1.55	.37	0.28-4.89
Total	1749	14	3.54	3.95	.00002	2.39-6.18

TABLE 8

TRENDS IN BLADDER CANCER RISK BY DURATION OF EMPLOYMENT IN DEPARTMENT 245

HETA 88-159
GOODYEAR TIRE AND RUBBER COMPANY
NIAGARA FALLS, NEW YORK

Duration of exposure in 245(years)	Bladder cancers observed	Bladder cancers expected	SIR	p-value	90% Confidence Interval
Under 5	1	0.86	1.16	.58	0.06-5.51
5-9.99	1	0.10	9.62	.10	0.49-45.7
10-14.99	3	0.11	28.9	.0002	7.88-74.7
15-19.99	1	0.04	27.2	.036	1.39-129
20-24.99	1	0.07	13.3	.073	0.68-63.0
25-29.99	1	0.02	46.1	.022	2.33-216
Over 30	-	-	-	-	-

TABLE 9

TRENDS IN BLADDER CANCER RISK BY TIME SINCE FIRST EMPLOYMENT IN DEPARTMENT 245

HETA 88-159
GOODYEAR TIRE AND RUBBER COMPANY
NIAGARA FALLS, NEW YORK

Time since 1st employment in 245(years)	Bladder cancers observed	Bladder cancers expected	SIR	p-value	90% Confidence Interval
Under 5	-	0.08	-	-	-
5-9.99	1	0.17	5.8	.16	0.30-27.5
10-14.99	0	0.26	-	-	-
15-19.99	1	0.32	3.1	.28	0.16-14.6
20-24.99	4	0.17	22.8	.00003	7.79-52.2
25-29.99	1	0.15	6.8	.15	0.35-32.4
Over 30	1	0.04	24.3	.04	1.24-115

TABLE 10

TRENDS IN BLADDER CANCER RISK AMONG WORKERS IN DEPARTMENT 245 BY AGE

HETA 88-159
GOODYEAR TIRE AND RUBBER COMPANY
NIAGARA FALLS, NEW YORK

Age	Bladder cancers observed	Bladder cancers expected	SIR	p-value	90% Confidence Interval
Under 40	0	-	-	-	-
40-44	1	0.09	11.3	.09	0.58-53.7
45-49	0	0.12	-	-	-
50-54	1	0.16	6.1	.15	0.32-29.6
55-59	2	0.19	10.3	.02	1.87-33.1
60-64	3	0.20	14.7	.001	4.09-38.8
65-69	0	0.19	-	-	-
70-74	1	0.06	17.1	.06	0.85-79.1
75-79	0	0.06	-	-	-

TABLE 11

TRENDS IN BLADDER CANCER RISK AMONG WORKERS IN DEPARTMENT 245 BY TIME PERIOD

HETA 88-159
GOODYEAR TIRE AND RUBBER COMPANY
NIAGARA FALLS, NEW YORK

Time Period	Bladder cancers observed	Bladder cancers expected	SIR	p-value	90% Confidence Interval
1973-74	0	0.07	-	-	-
1975-79	2	0.25	8.02	.03	1.42-25.1
1980-84	3	0.41	7.36	.008	1.99-18.9
1985-89	3	0.48	6.30	.01	1.70-16.2