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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL
NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH
CINCINNATI, OHIO 45226

INTERIM REPORT NO. 2
HETA 88-159

GOODYEAR TIRE AND RUBBER COMPANY
NIAGARA FALLS, N.Y.

MARCH, 1992

I. SUMMARY

In December 1989, NIOSH released Interim Report No. 1 regarding HETA 88-159 at the Goodyear Tire and Rubber Company in Niagara Falls, New York. In that report, NIOSH investigators concluded that there was an elevated risk of bladder cancer (Standardized Incidence Ratio 6.48, $p<0.0001$) in workers employed in Department 245, which has used *o*-toluidine and aniline since 1957. Based on this initial investigation, and a subsequent review of the human and animal data in the scientific literature, NIOSH concluded in a Hazard Alert (NIOSH 1990) that *o*-toluidine and aniline are potential occupational carcinogens as defined in the OSHA carcinogen policy [29 CFR 1990]. Therefore, NIOSH recommended reducing occupational exposure to these two chemicals to the lowest feasible concentration.

To further characterize worker exposure to *o*-toluidine and aniline at the Goodyear Niagara Falls facility, NIOSH investigators conducted a follow-up exposure survey in Department 245 from February 27 through March 9, 1990. Because both *o*-toluidine and aniline have potential for absorption through the skin, a sampling strategy was developed to measure exposure through the air and indicate potential exposure from liquid chemical to the skin. Personal air, skin liquid contact indicator (dermal) badges, and glove samples were collected on workers to measure airborne exposure and indicate potential dermal contact with liquid chemical. Area air and dermal badge samples were collected from representative locations throughout Department 245 to measure worst case exposure potential. Wipe samples were collected from several representative work surfaces to indicate the presence of residual liquid chemical, and bulk samples were obtained at various stages of the process to determine the presence of *o*-toluidine, aniline and 4-aminobiphenyl in the process reactant. Concurrently with the environmental sampling, urine samples were collected from both exposed and unexposed workers before and after the workshift to

determine whether Department 245 workers had higher levels of *o*-toluidine and aniline in their urine than unexposed workers, thereby indicating occupational exposure from all possible routes to these chemicals. Also, blood samples were collected from exposed and unexposed workers to analyze for hemoglobin and albumin adducts of *o*-toluidine.

The personal air results for *o*-toluidine and aniline ranged from 87.4 to 1630 micrograms per cubic meter ($\mu g/M^3$) and 53.9 to 726 $\mu g/M^3$, respectively, as an 8-hour time-weighted average (TWA). These results are less than the Occupational Safety and Health Administration (OSHA) permissible exposure limits (PELs) of 22,000 and 8,000 $\mu g/M^3$, and the American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit values (TLVs) of 9,000 and 8,000 $\mu g/M^3$, for *o*-toluidine and aniline respectively. The area air sample results for *o*-toluidine and aniline ranged from 36.8 to 2,460 $\mu g/M^3$ and 3.90 to 1,440 $\mu g/M^3$ respectively, as an 8-hour TWA. The personal dermal sample results for *o*-toluidine and aniline for two Department 245 workers may have indicated actual contact with liquid chemical. The personal glove sample results for *o*-toluidine and aniline ranged from not detected (ND) to 180 μg/set, and ND to 230 μg/set respectively. The surface wipe sample results for *o*-toluidine ranged from ND to 50 μg/sample; no aniline was detected. There were seven process bulk samples analyzed for the presence of *o*-toluidine and aniline; four had detectable levels *o*-toluidine, while aniline was detected in all seven. Trace amounts of 4-aminobiphenyl were detected in three of the nine bulk samples analyzed.

Postshift urine samples from unexposed control workers averaged 2.7 $\mu g/L$ *o*-toluidine and 3.7 $\mu g/L$ aniline (preshift samples averaged 2.6 and 1.1 $\mu g/L$ for *o*-toluidine and aniline respectively). Postshift urine samples from Department 245 workers averaged 104 $\mu g/L$ *o*-toluidine and 32.3 $\mu g/L$ aniline (preshift averages were 17.4 and 18.5 $\mu g/L$ respectively, for *o*-toluidine and aniline). *o*-Toluidine and aniline concentrations in preshift urine samples from Department 245 workers were also significantly elevated compared to concentrations in workers from another department. This provides conclusive evidence that Department 245 workers were absorbing *o*-toluidine and aniline into their bodies during the workshift. However, since the rate of absorption through the lungs and skin is unknown, the environmental data collected during this exposure characterization survey does not permit a definitive assessment of the relative contribution of either air or dermal exposure to the bodily absorption of *o*-toluidine and aniline, as reflected in the concentrations of these substances (and their metabolites).

Based on these findings, the NIOSH investigators recommend that the Goodyear Tire and Rubber Company undertake a detailed evaluation of this manufacturing process to determine where engineering controls may be installed to eliminate, or further reduce, the occupational exposure to *o*-toluidine and aniline in

Department 245. They also recommend that Goodyear develop and implement a comprehensive personal protection program for use in Department 245 when adequate engineering exposure control is not possible. Finally, a voluntary program of urine monitoring should be established for workers in Department 245, including managers and maintenance personnel. The goal of these recommendations is to implement an environmental control program that is effective in maintaining urine *o*-toluidine and aniline concentrations among exposed workers in Department 245 within the range of urine *o*-toluidine and aniline concentrations among controls.

DISCLAIMER

Mention of company names or products in this report does not constitute endorsement by the National Institute for Occupational Safety and Health.

II. INTRODUCTION

On February 9, 1988, NIOSH received a request from the Oil, Chemical and Atomic Workers International Union (OCAW) to conduct a Health Hazard Evaluation of the Goodyear Tire and Rubber Company facility in Niagara Falls, New York. The OCAW request stated that eight cases of bladder cancer had occurred in the workforce at that facility from 1973 to 1986, and that all of the cancer victims were exposed to *o*-toluidine while working in Department 245 of the Niagara Falls facility. In response, three NIOSH investigators conducted a survey of the facility on May 2 and 3, 1988 to initiate an epidemiologic study.

Department 245 manufactures an anti-oxidant (Wingstay®) used in chemical manufacturing at other Goodyear facilities and an accelerator (Morfax®) used in the manufacture of rubber. NIOSH investigators conducted a toxicological review of all of the human and animal data in the scientific literature for all of the chemicals used in Department 245. This review found that two of the chemicals used in Department 245, *o*-toluidine and aniline, are aromatic amines for which there is some evidence of bladder carcinogenicity (IARC, 1982).

Interim Report No. 1, issued in December 1989 reported an elevated risk of bladder cancer (Standardized Incidence Ratio 6.48, $p<0.0001$) in Department 245 of the Niagara Falls facility. The increased risk of bladder cancer was hypothesized to be related to *o*-toluidine and aniline exposure, on the basis that (1) primary aromatic amines have been the major class of compounds associated with large occupational bladder cancer risks, (2) *o*-toluidine is the only chemical present in large quantities in the department for which the IARC considers there to be sufficient evidence of carcinogenicity, (3) there is limited evidence for the carcinogenicity of aniline in experimental animals, (4) *o*-toluidine produces bladder tumors in female rats, a species relatively resistant to bladder tumors, (5) *o*-toluidine and aniline are major starting chemicals used in Department 245 (both are starting chemicals in the Wingstay® process, and aniline is a major starting chemical for the Morfax® process), and (6) it did not appear that other known human bladder carcinogens, such as 2-napthylamine, had ever been used or produced at the facility, and the only other known or potential human carcinogen potentially present in Department 245, 4-aminobiphenyl, a potential contaminant of the aniline starting chemical and of diphenylamine, which is an intermediate of the Wingstay® process, was present in only trace amounts, if at all, in bulk samples of aniline and intermediate process liquids.

Diphenylamine was an additive (25% by volume) to a finished Wingstay® product (200) to produce the product RWC4396, from 1972 through 1985 only. This addition took place outside the Wingstay® production area directly by hose from a tank truck of molten chemical to the finished Wingstay® 200 holding tank. The

product was then pumped through a hose directly into a rail tank car. Therefore, exposure to diphenylamine would have only been to one operator conducting the transfer, and would most likely have been very low due to the enclosed transfer system. RWC4396 was a very small percentage of the total Department 245 production. During the 1970's and 1980's contamination of commercial diphenylamine with 4-aminobiphenyl was not detected in six of ten different brands tested, and was found only in trace levels (94 ppm highest) in the other four. (Safe, et. al. 1977). This evidence does not support a view that diphenylamine contaminated with 4-aminobiphenyl might be the major etiologic agent in the bladder cancer excess.

Because of the significant excess of bladder cancer in Department 245, NIOSH investigators determined that a detailed environmental and biological characterization of worker exposure to *o*-toluidine and aniline at the Goodyear Niagara Falls facility was necessary. Pursuant to this, NIOSH investigators conducted a pre-survey site visit on January 23, 1990, to inspect Department 245 and collect the necessary information to prepare for the detailed exposure characterization. Based on observations of the working conditions in Department 245 during this pre-survey visit, NIOSH investigators provided a letter (January 30, 1990) recommending that Goodyear tighten process integrity, clean up spills, improve housekeeping, investigate installation of engineering exposure controls, and implement a personal protective program as necessary to reduce the *o*-toluidine and aniline exposure potential to workers in Department 245.

The detailed environmental and biological exposure survey characterization of current exposures in Department 245 was conducted from February 27 through March 9, 1990. Because both *o*-toluidine and aniline exposure potentially can occur by absorption through the skin, as well as by inhalation, a personal breathing zone and area sampling strategy was developed to detect exposure of the skin to liquid chemical, as well as to measure airborne exposure. Personal air samples were collected to measure inhalation exposure, and dermal and glove samples were collected on workers to detect potential contact with liquid chemical. Area air samples were collected from representative locations throughout Department 245 to determine the worst case air concentrations, and area dermal badge samplers were placed next to the area air samplers to indicate the amount of passive absorption of *o*-toluidine and aniline by this type of sampler from the air. Wipe samples were collected from several representative work surfaces to indicate potential dermal exposure to residual *o*-toluidine and aniline of workers not wearing gloves in the process areas. Bulk samples of process starting chemicals, process reactant at various stages of the process, and finished products were collected to determine the presence of *o*-toluidine, aniline, and the potential process contaminant 4-aminobiphenyl (a known human bladder carcinogen). During the detailed survey, NIOSH investigators observed that the

potential for dermal exposure may have been reduced by additional protective measures that had been implemented since the May, 1988 NIOSH initial visit. These measures included: the wearing of gloves by most workers during at least a portion of the workshift; the wearing of Tyvek® suits during sparkler filter cleaning and *o*-toluidine and aniline rail tank car unloading operations; and the use of top loading/unloading rail cars. A letter reporting the results of the environmental monitoring was sent to Goodyear on July 17, 1990.

Concurrent with the air samples, urine samples were collected from both exposed and unexposed workers before and after the workshift to analyze for concentrations of *o*-toluidine and aniline. Blood samples were collected from exposed and unexposed workers to analyze for hemoglobin and albumin adducts of *o*-toluidine. Since a proprietary chemical present in the department is metabolized to aniline, and therefore could confound measurement of aniline in the workers' urine samples, air and dermal exposures to this chemical were evaluated as well. This report presents all of the results of the environmental sampling and the urine results of the biological sampling. The laboratory analysis for the blood samples has not been completed. The results will be sent to the individual participants and, in aggregate form without personal identifiers, to Goodyear and OCAW.

III. BACKGROUND

A. Description of the Facility and Process

The Pathfinder Chemical Corporation opened the Niagara Falls facility in 1946 with the production of polyvinyl chloride (PVC). Workers in this area of the plant (Goodyear Department 145) are known to have an excess risk of liver cancer related to vinyl chloride exposure (Nicholson, 1975). In 1954, construction for expansion of the facility was completed, and a new Department (245) began the manufacture of 2-mercaptobenzothiazole (Captax®). The Goodyear Tire and Rubber Company purchased the Niagara Falls facility in 1956. Production of the anti-oxidant Wingstay 100® (known internally at Goodyear as Nailax) began in 1957 (in Department 245). In 1970, an expansion of Department 245 was completed and the manufacture of the rubber accelerator Morfax® (known internally at Goodyear as Kagarax) began. Process chemicals, flow diagrams, a description of the designed chemical reactions for each of these two processes, and a diagram of the facility layout are provided in Section XII (Tables and Figures) of this report.

1. Wingstay® Processes

There are four Wingstay® products that have been produced in Department 245. These are Wingstay® 100, Wingstay® 200, Wingstay® 100AZ and RWC4396. Wingstay® 100 is the primary

antioxidant manufacturing process, and the other three are variations of that. The process for three of the four products is exactly the same until the final product reaches the holding tanks, at which point the specific additives for the particular product are introduced. For Wingstay® 200, the starting raw materials are varied slightly from Wingstay® 100.

a. Wingstay 100® Process

Wingstay 100® is used primarily by Goodyear in tire manufacturing as an anti-oxidant. The liquid chemical raw materials (shown in Figure 1) are received by rail car and are pumped to storage tanks in the tank farm. Hydroquinone is received in bulk as a powder at Building 33. The liquid raw materials are fed as needed by a computer weight control system to a premix tank. The liquid premix chemicals are *o*-toluidine, aniline, mixed xylidines, phenol, and toluene. Hydroquinone powder is transported by an air transfer system to a bulk bagging unit, which then loads the hydroquinone through an opening at the top of the Premix tank. An automixer then blends the premix chemicals into solution. The designed chemical reactions for the Wingstay® process are shown in Figure 2.

This premix batch solution is pumped to a chemical reactor where a catalyst is added to drive the reaction. The batch solution is heated to reaction temperature and held there until complete, and excess reactants are removed under vacuum to the continuous recycle recovery system. The batch reactant is transferred to a degasser via steam pressure where it is neutralized by the addition of sodium carbonate and water. Steam pressure is then used to transport the material through the final filtering system and onto the holding tank where it is held as a heated 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 partially crystallizes (conditions) the film to make it flakable. The flaker drum continues to cool and crystallize the material until it reaches the flaking knife which removes the solid product. The flaked product drops onto a bucket elevator which transports it to an open vibration conveyor belt. The belt moves the product to the bagging units where it is sealed in 50-pound bags in preparation for shipment. This open conveyor system is a continuous source of fugitive dust emission into the process area.

b. Wingstay® 200 Process

The Wingstay 200® manufacturing process flow is exactly the same as 100. The only difference from 100 is that mixed toluidine isomers are used instead of *o*-toluidine, and mixed xylidine isomers are added to the starting chemicals.

c. Wingstay® 100AZ Process

Wingstay® 100AZ is produced by first processing a batch of Wingstay® 200 through to the holding tanks, and then adding a small amount of solid magnesium carbonate. The material is then sent through the flaker and on to the bagger.

d. RWC4396 Process

RWC4396 was produced by first running a batch of Wingstay® 200 through to the final holding tank, at which point molten diphenylamine was pumped to the holding tank from a heated tank truck. The diphenylamine handling took place in the holding tank area, which is outside of the Wingstay® production area. The final product was 25% diphenylamine, and was pumped while molten from the holding tank directly into a heated rail tank car for transport.

2. History of the Wingstay® Processes

Wingstay® production began in 1957 with one reactor. A second reactor, with an additional holding tank, was made 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 reactor charge feed system was completed, and in 1980, a liquid catalyst feed system was installed. In 1984, a 3300-pound semi-bulk bag system was installed for hydroquinone transfer to the premix tank to replace the use of 300-pound fiber drums.

According to Goodyear process operators, the only change since production began in 1957 that they feel has significantly reduced chemical exposure was the installation of the premix reactor charge system, which was designed to reduce exposure to the premix chemicals. The premix reactor charge system is an automatic mixing system which, due to design features such as improved ventilation and lower temperatures, produces less premix chemical vapors.

The amount of Wingstay® 100 production gradually increased from about four to six million pounds per year in 1957 to about eleven to thirteen million pounds per year in the mid to early sixties, and has gradually increased to sixteen to eighteen and a half million pounds per year currently. Wingstay® 200 production started in 1959 and has remained at ten to twenty percent of the total Wingstay® production. Wingstay® 100AZ production has ranged from about seventy thousand to three hundred thousand pounds per year, with production starting about 1978. RWC4396 production totaled approximately eight million pounds over the time period of its production life (1972 through 1985), with an average rate of two hundred to one million pounds per year. RWC4396 production was terminated in 1985. The exact production start-up date is unknown due to incomplete records.

3. Morfax® Process

Morfax® is a rubber accelerator that is manufactured by Goodyear and commercially marketed. The liquid chemical raw materials (shown in Figure 1) are received by rail car and are pumped to storage tanks in the tank farm. The chemicals are pumped to the premix tanks in the Charge Room as needed. The process chemicals are blended in the Charge Room premix tanks, and then pumped to and held as mixtures in two storage tanks until needed. A carbon disulfide and flaked sulfur mixture is held in one tank. The carbon disulfide is pumped as needed from the tank farm, and the sulfur is added as needed from a make-up tank in the Charge Room. The make-up tank is kept manually filled as necessary by the Charge Room Operator using 50-pound bags of sulfur. The other tank holds a mixture of a liquid proprietary chemical, aniline, (pumped as needed from the tank farm) and benzothiazole (recycled by-product from the Morfax® process). The two mixtures are then pumped to a charge header which feeds the starting chemical solution to the first in a series of five autoclaves or reactors. The designed chemical reactions for the Morfax® process are shown in Figure 3.

A reaction occurs in the first autoclave, which generates heat. The heat and, therefore, 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 the second autoclave and continues in a like manner through the three remaining autoclaves.

The product that leaves the last autoclave is 2-mercaptobenzothiazole (MBT). The MBT then proceeds to the steam stripper where hydrogen sulfide is driven off with super-heated steam and sent to the sulfur removal unit. Benzothiazole is a by-product that is separated here and transferred to the charge room premix chemical storage tank previously described. The stripped MBT is then pumped into one of two storage tanks and held for further processing.

MBT is then fed from the storage tanks to a centrifuge dewatering system and on 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 to initiate a chemical reaction. The initial reactant is then transferred to the Morfax® main reactor feed tank, which is heated. The initial reactant is continuously pumped from the feed tank to the Morfax® main reactor, with bleach being added as needed during the reaction. The finished 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 to a granular solid, the finished Morfax® is transported by gravity to a vacuum bagger where it is sealed in 50-pound bags in preparation for shipment.

The sulfur removal unit previously mentioned reclaims sulfur from the hydrogen sulfide gas. This is accomplished by heating the incoming gas and passing it over two catalytic reactor beds to remove the sulfur. The reclaimed 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.

4. History of the Morfax® Process

Morfax® production began in Department 245 in 1970. The sulfur removal unit was installed in 1971 in order to reduce sulfur-based air pollutant emissions, and a fluid bed dryer was added to the unit in 1978 which further reduced sulfur emissions.

In 1970, 390,000 pounds of Morfax were produced in Department 245. Production gradually increased over the years and is currently about 6,000,000 pounds per year.

B. Description and History of the Workforce

As of August 1, 1988, the date on which NIOSH staff microfilmed all personnel records at the Goodyear, Niagara Falls Facility, there were 1748 individuals identified as ever having worked at the plant. Of these, 1642 were male and 106 female. As of the date of personnel record examination there were 293 active employees, of which 66 were assigned to Department 245. The current worker population is relatively young, with 71% 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.

Based on the work histories in the personnel records, 795 individuals had ever worked in Department 245, and were therefore considered to have definite exposure to *o*-toluidine and aniline. There were 273 of these employees who did not work exclusively in Department 245, but had worked in maintenance, janitorial or shipping departments, and were considered possibly exposed. Of the total workforce, 680 had never worked in departments considered to have probable or possible exposure to *o*-toluidine and aniline.

IV. STUDY DESIGN AND METHODS

Due to the large excess of bladder cancer occurrences among employees of Department 245, and the fact that air monitoring has always shown levels of *o*-toluidine and aniline to be well below all applicable exposure standards, NIOSH investigators determined that to adequately evaluate whole body personal exposure, biomonitoring must be conducted to account for other routes of exposure in addition to inhalation. Environmental monitoring was performed to determine whether exposures met current environmental exposure criteria, to document potential routes of dermal exposure, and to identify possible ways to reduce worker

exposure.

Because of the severity of the cancer risk, it was obvious to NIOSH investigators that the maximum number of workers possible should be evaluated. Since the total current Department 245 workforce consisted of about 50 workers (with two or three additional maintenance personnel working in the area), or about 18 per shift, it was determined that it was logistically possible to monitor the entire Department 245 workforce on a given workshift. It was also determined that three different work shifts should be monitored in order to evaluate the exposure to as many different workers as possible.

A. Study Population

Participation in the study was requested of all individuals working in the Wingstay® and Morfax® processes in Department 245, as well as Maintenance operators (not permanently assigned there) who would be working in the Department. In addition, workers in Department 145, which manufactures vinyl chloride, were asked to participate in the study as a comparison group since they had minimal opportunity for occupational exposure to *o*-toluidine and aniline. They worked in a separate building and did not share locker or break room facilities with Department 245 workers (they did, however share a common lunch room). The environmental and biological monitoring survey was conducted on the days and times listed in Table I below (the Wingstay® process operates 7 days a week, with 4 shifts of workers rotating, while the Morfax®

process operates 3 days a week, with 3 shifts of workers rotating):

TABLE I
Shifts, Dates and Times for
Environmental and Biological Monitoring

Date	Time	Wingstay®	Morfax® and Vinyl Chloride
Tues 3/6/90	7AM to 3PM	D shift	D shift
Wed 3/7/90	3PM to 11PM	A shift	C shift
Thurs 3/8/90	11PM to 7AM	B shift	B shift

Department 245 workers on these shifts were asked to participate in both the environmental and the biological portions of the survey, while Department 145 workers were asked to provide biological samples only. Biological samples were also collected from Wingstay® workers on the 3PM to 11PM shift (C) Tuesday, but environmental monitoring was not conducted for that shift since the 7AM to 3PM shift was monitored that day, and there was

insufficient personnel and equipment to conduct environmental monitoring over consecutive shifts. Maintenance workers currently assigned to Department 245 were included in the survey along with Maintenance workers who had recently transferred from Department 245 but wished to participate in the biological monitoring. The latter were not included in the statistical analysis, however.

Although we encouraged all workers in Department 245 to participate in both the environmental and biological sampling phases of the study, some individuals elected to participate in only one or the other, or none.

B. Strategy for Environmental and Biological Exposure Study

A sampling approach was developed to measure worker exposure, or indicate potential exposure when actual exposure measurement techniques did not exist, for all worker exposure routes from all potential *o*-toluidine and aniline exposure sources identified within Department 245. Based on observation and inspection of process operations, the potential environmental routes of exposure were airborne vapor/mists (inhalation) and skin contact with process liquid chemical spills and residuals (dermal, there is an American Conference of Governmental Industrial Hygienists skin notation for both chemicals.)

Personal air samples were collected to measure inhalation exposure, and dermal and glove samples were collected on workers to detect potential contact with liquid chemical. Area air samples were collected from representative locations throughout Department 245 to determine the worst case air exposure levels, and area dermal badge samplers were placed next to the area air samplers to indicate the amount of passive absorption of *o*-toluidine and aniline by this type of sampler from the air. Wipe samples were collected from several representative work surfaces to indicate potential dermal exposure to residual *o*-toluidine and aniline of workers not wearing gloves in the process areas. Bulk samples of process starting chemicals, process reactant at various stages of the process, and finished products were collected to determine the presence of *o*-toluidine, aniline, and the potential process contaminant 4-aminobiphenyl (a known human bladder carcinogen).

Concurrently, urine samples were collected from both exposed and unexposed workers before and after the workshift to analyze for concentrations of *o*-toluidine and aniline. Blood samples were collected from exposed and unexposed workers to analyze for hemoglobin and albumin adducts of *o*-toluidine. Since a proprietary chemical present in the department is metabolized to aniline, and therefore, could confound the measurement of aniline in the workers' urine samples, air and dermal exposures to this chemical were evaluated as well.

1. Air Sampling Rationale and Methods

The fact that the relative humidity in the Niagara Falls region is known to be high at times, and the observation of condensation on surfaces within Department 245 during the preliminary site visit on January 23, 1990, prompted NIOSH investigators to consider the effect of humidity when selecting the air sampling and analytical method. The validated techniques available for *o*-toluidine, aniline and the proprietary chemical were NIOSH method 2005, using silica gel tubes, and OSHA method 73, using sulfuric acid-treated glass fiber filters. A laboratory study was performed at the NIOSH Hamilton facility to evaluate the effect of humidity on these two methods for the three specific analytes. The collection efficiency of the silica gel was significantly reduced as humidity increased, while the filters were affected very little. The filters were also tested for stability and recovery when sampling for both *o*-toluidine and aniline, and were found to have excellent collection and storage stability at all humidity levels tested. Therefore, to evaluate personal and area airborne exposure to *o*-toluidine and aniline, a modified OSHA method 73 was used (see Appendix A). For the proprietary chemical, similar laboratory humidity tests of monitoring methods were performed, and it was determined that a large (520/260 milligram) silica gel tube was the best collection method available under humid conditions. Also, the laboratory study showed that the proprietary chemical was not trapped by the acid-treated filters, and did not interfere with the collection of *o*-toluidine and aniline while passing through the filters. Therefore, the filter cassette and silica gel tube were arranged in-line, so that the worker would only be required to wear one monitoring pump for the personal monitoring.

The OSHA 73 method used two stacked sulfuric acid treated 37 millimeter (mm) diameter 0.8 micrometer (μm) pore size glass fiber filters (GFF) in a closed-face cassette. The filters were separated by a spacer using no support pads for either filter. The filter cassette was followed in line by a 520/260 milligram (mg) silica gel tube. This media assembly was connected by tubing to an SKC Model 224-PCXR7 personal air sampling pump set in low-flow mode. Each pump was pre-calibrated to operate at 400 cubic centimeters per minute (cc/minute) with a variable limiting orifice. A total sample air volume not exceeding 100 liters was collected in accordance with the OSHA 73 method for TWA exposure monitoring. Several of the same type of sampling pumps were also calibrated in high flow mode at 1000 cc/minute with the same sampling train to evaluate short-term peak exposure when workers performed tasks with higher potential for airborne exposure. The higher flow rate was utilized for the peak sampling to improve the probability of collecting enough chemical to be above the limit of detection of the analytical method.

The filter tube and pump sampling trains were placed on the workers at the beginning of the work shift for the TWA sampling

such that the air inlet was fastened in the breathing zone. The air sampling media was changed at mid-shift after about 100 liters of air flow. For peak exposure sampling of job tasks with higher airborne exposure potential, an additional sampling pump and media train, pre-calibrated at 1000 cc/minute, were placed on the worker (in the same way as the personal sample) prior to performance of the particular task, and the pump was turned on when the worker was ready to begin. The peak sampling train was promptly removed at completion of the work task. At the end of the shift, or peak sampling period, the sampling train was removed, the cassettes plugged, the tubes capped, and both were stored in refrigeration until laboratory analysis. The sampling pump calibration was checked and logged in at this time as well.

At the analytical laboratory the samples were prepared for analysis by placing the two filters in separate 20 milliliter (ml) scintillation flasks designated as the A and B sections of each sample. Quality control (QC) spikes were received on dry acid treated filters in 20 ml scintillation flasks and were treated the same as the samples. To each sample and QC, 3 ml of deionized (DI) water, 1 ml .5 N NaOH, and 2 ml of toluene were added. They were then shaken for 10 minutes and the phases allowed to separate prior to transferring at least 1 ml of the toluene layer into 4 ml wisp vials.

All standards, samples, and QC spikes were derivitized by the addition of 24 ml of heptafluorobutyric acid anhydride (HFAA). They were then shaken for 10 seconds and the reaction allowed to process for 10 minutes, after which, 1 ml of pH 7.0 phosphate buffer was used to wash away the excess HFAA by shaking vigorously for 10 seconds and allowing phases to separate. The toluene layer was then transferred to a gas chromatograph (GC) vial for analysis.

The analysis was performed on a HP5890 GC equipped with an electron capture detector. A 6' x 2 mm internal diameter (ID) glass column packed with 3% OV-101 on 100/120 mesh Suplcoport was used for separation of the analyte, at an isothermal temperature of 100 degrees centigrade (°C). The NIOSH calculated limit of detection (LOD) for the acid treated filters was 0.3 μg/sample for *o*-toluidine and 0.4 μg/sample for aniline. The calculated limit of quantitation (LOQ) was 1 μg/sample for *o*-toluidine and 2 μg/sample for aniline.

The silica gel tubes were separated into A (front) and B (back) sections and analyzed by gas chromatography according to NIOSH Method 2005 with the following modifications.

- Desorption Process: 1 hour with sonication in 1.0 ml methanol containing 1.0 microliter per milliliter (μL/ml) ethyl benzene as an internal standard.

Gas Chromatograph:	Hewlett-Packard Model 5890 equipped with a flame ionization detector.
Column:	30 meter (M) x 0.32 mm fused silica capillary column coated internally with 1.0 micron SPB-5.
Oven Conditions:	Programmed from 110 °C (held for 6 minutes) to 250 °C at a rate of 50 °C/minute.

Known amounts of the proprietary chemical, aniline and *o*-toluidine were spiked onto the A section of silica gel tubes and were desorbed the same as the samples. A select number of tube samples were analyzed for *o*-toluidine and aniline in addition to the proprietary chemical to check for filter break through. There was no *o*-toluidine and aniline detected on any of the tubes. The NIOSH calculated LOD for the proprietary chemical silica gel tube samples was 10 µg/sample and the calculated LOQ was 30 µg/sample.

a. Personal Air Sampling

A total of 46 workers over the three workshifts in Department 245 participated in the personal air sampling. Personal air sampling consisted of 51 total samples (46 TWA and 5 peak). A total of 11 air sample blanks, and several unused media sets not handled during the survey, were submitted for analysis along with the field samples for analytical instrument calibration.

b. Area Air Sampling

Area air samples were collected with the same sampling trains as the personal samples. The areas were collected in the same manner as the personal samples, for the complete workshift, changing the filter media after about 100 liters of sample volume. Twenty-four area air samples were collected over the three workshifts monitored. The area monitoring was conducted on a worst case basis by positioning the samplers where, of all the areas in the process that operators could be during a workshift, the air concentrations of *o*-toluidine and aniline were judged likely to be the highest. Since the sampling media was the same as for the personal samples, the finished samples were handled in exactly the same way at the end of the work shift and in the analytical laboratory.

2. Skin Contact Sampling Rationale and Methods

a. Dermal Liquid Contact Indicator Badges

The scientific literature was reviewed when considering possible techniques to assess the potential for dermal contact with liquid process chemicals and residuals. There were several reports of

dermal monitoring methods, but they were all for pesticides, and used either gauze or cloth patches as sampling media. Since *o*-toluidine and aniline are relatively volatile compounds, it was obvious that these types of media would not retain these chemicals if they were contacted. Therefore monitors were developed that could be placed on the workers, and would retain any *o*-toluidine and aniline that was contacted. These monitors were cotton pouches containing silica gel. This method was laboratory tested for recovery and retention stability over time. The pesticide monitoring literature was reviewed for the appropriate locations to place the monitors on the workers. Based on the literature, and observations of the workers performing their job tasks, which showed that the majority of contact with process surfaces was to the upper body, it was decided to focus the monitoring on that area. To accomplish this five silica gel samplers, or dermal liquid contact indicator badges, henceforth referred to as liquid indicator badges, were placed on each worker monitored, one each at each shirt lapel, each forearm, and on the chest.

The liquid indicator badges were placed on and removed from the workers at the same time the air sampling trains were attached. It was determined by laboratory testing that it was not necessary to change the badges during the workshift. After removal, the badges were placed in pre-labeled 20 ml scintillation vials which were then capped, shrink-banded and refrigerated until sample analysis.

At the analytical laboratory the silica gel from each liquid indicator badge sample was desorbed in 8 ml of absolute ethanol for 1.5 hours in a sonication bath. After the desorption period, 1 ml aliquots of each sample were transferred to autosampler vials and analyzed by gas chromatography with flame ionization detection (GC/FID), using a HP5890 GC equipped with a 30 m DB-5 fused silica capillary column for *o*-toluidine, aniline, and the proprietary chemical. All analyses were performed in the splitless injection mode. The resultant sample recoveries were corrected for dilution effects.

The calculated LOD for *o*-toluidine, aniline and the proprietary chemical for the liquid indicator badge samples were 3.00, 4.00 and 1.00 μg/sample respectively, and the calculated LOQ was 9.00, 12.0 and 3.00 μg/sample respectively. See Appendix A for additional details regarding this sampling and analytical method.

These silica gel liquid indicator badges were intended to indicate the potential for dermal contact with process chemicals only. They were not developed or used as a method to quantitate dermal exposure or absorption. It was anticipated that the silica gel would act as a passive air monitor of *o*-toluidine and aniline. Therefore, in order to determine the amount of *o*-toluidine and aniline on the liquid contact indicators that could be due to absorption of liquid, liquid indicator badges were also

placed with the area air samplers for subsequent comparison.

b. Glove Sampling

A method of using silica gel to indicate potential liquid contact of process chemicals to the skin of the hands could not be developed for the exposure survey. The complicating factor was the absorption of moisture from the skin by the silica gel, which would be a discomfort to the workers, and an interference to the collection of process chemicals. Therefore, it was decided to use thin, pure cotton gloves, with no dyes or chemical treatments, that could be worn underneath the workers regular work gloves. The gloves were tested in the laboratory for purity, and the analytical method was tested for recovery and retention stability over time.

The gloves were given to the workers at the same time the air sampling trains and liquid indicator badges were attached, and the workers were directed to wear the cotton gloves underneath their usual work gloves when they were worn. The workers usually only wore their work gloves while actually in the process area, so they were instructed to remove the cotton gloves after removing their work gloves (without touching the cotton gloves with their work gloves) and to place them inside each respective work glove. This procedure was reversed when the gloves were put back on. The gloves were collected at the same time as the air and liquid indicator badge media at the end of the work shift. They were then placed in 40 ml brown glass bottles, which were then capped, shrink banded and refrigerated until laboratory analysis.

At the analytical laboratory the glove samples were extracted with ethanol and analyzed by GC according to NIOSH Method 2002 with the following modifications.

Extraction Process:	8 hours by shaking in 80 ml ethanol containing 1.0 µl/ml ethyl benzene as an internal standard.
Gas Chromatograph:	Hewlett-Packard Model 5710A equipped with a flame ionization detector.
Column:	30 M x 0.32 mm fused silica capillary column coated internally with 1.0 micron DB-5.
Oven Conditions:	Programmed from 120 °C (held) for 8 minutes) to 250 °C at a rate of 32 °C/minute and held for 4 minutes.

The calculated LOD for the gloves for *o*-toluidine, aniline and the proprietary chemical was 70, 80 and 70 µg/sample respectively, and the calculated LOQ was 210, 260 and 220

µg/sample respectively. See Appendix A for additional detail about the glove sampling and analytical method.

c. Surface Wipe Sampling

Observation of process operators performing job tasks indicated that operators routinely contact process surfaces in performance of their jobs. Therefore, it was appropriate to conduct surface wipe sampling in areas where workers routinely made contact with process surfaces to determine if residual liquid process chemicals were present, and thereby indicate potential dermal exposure from this route. Based on a review of the literature, and consultation with our analytical laboratory, it was decided to use hexane cleaned cotton gauze pads to wipe process surfaces where workers routinely performed job tasks. Sampling locations were selected by first observing process operators at their various work stations, and making note of the surfaces that were most often handled. The surfaces were sampled by removing the gauze pad from the storage jar, holding the pad firmly in a gloved hand (clean latex), and making several passes over the surfaces (including switches, levers, etc.) handled by operators in that particular area. The surface wipe sample was then returned to the jar which was then capped, shrink-banded and refrigerated until analysis. The surface wipe samples were extracted and analyzed by GC according to NIOSH Method 2002 with the following modifications.

Extraction Process:	8 hours by shaking in 20 ml ethanol containing 1.0 µl/ml ethyl benzene as an internal standard.
Gas Chromatograph:	Hewlett-Packard Model 5710A equipped with a flame ionization detector.
Column:	30 M x 0.32 mm fused silica capillary column coated internally with 1.0 micron DB-5.
Oven Conditions:	Programmed from 120 °C (held for 8 minutes) to 250 °C at a rate of 32 °C/minute and held for 4 minutes.

Liquid standards were prepared of known amounts of *o*-toluidine, aniline and the proprietary chemical and spiked into 1 ml of extraction solvent. The calculated LOD for *o*-toluidine, aniline and the proprietary chemical was 20.0 µg/sample, and the calculated LOQ was 60.0, 70.0 and 60.0 µg/sample respectively. See Appendix A for additional detail about the wipe sampling and analytical method.

d. Bulk Sampling

Since the residual chemicals present on process surfaces and the

airborne chemicals present throughout the process would most likely emanate from the process reactant, there would be finished products dusts present, and the fact that the process reactant chemical composition changes as it progresses through the reaction stages, it was appropriate to evaluate the presence of *o*-toluidine, aniline and 4-aminobiphenyl (a potential contaminant of the aniline starting chemical and of diphenylamine, which is an intermediate of the Wingstay® process) in the process reactant at various stages of the process. To accomplish this it was decided to collect samples of bulk process material from all of the intermediate stages of the process where a sample could be extracted, as well as of starting *o*-toluidine and aniline and finished products. Quality assurance (QA) samples were routinely collected by Goodyear of starting, ending and intermediate process chemicals and taken to the QA laboratory for analysis. Portions of all QA samples were taken by transferring about 60 milliliters from a freshly collected sample into a glass jar, which was then capped, shrink-banded, and refrigerated until analysis.

The six liquid bulks were prepared for analysis by diluting 10 μl of each bulk with 2 ml of methanol. The bulk samples were also analyzed directly (without dilution) by injection of 0.2 μl aliquots of each in the gas chromatograph. The three solid samples were dissolved in methanol and sonicated for thirty minutes. The approximate concentration was 2 mg/ml each. A 0.38 μg/ml 4-aminobiphenyl standard was prepared in methanol to establish GC/mass spectrometer (MS) analysis conditions and to estimate the approximate concentration of 4-aminobiphenyl in the bulks. The injection volume was 1 μl for all analyses except those analyzed directly without dilution. The MS was operated in the full-scan mode (40-500 amu) or the selected-ion monitoring (SIM) mode at medium resolution. This mode is about 100 times more sensitive than full scan mode. In the latter case, the molecular ion at m/e 169.0813 and other fragment ions characteristic of 4-aminobiphenyl were monitored during the expected chromatographic elution time of the compound. A mass spectrometer response at the correct retention time indicates its presence. In the full-scan mode, the entire mass spectrum was used for compound identification. See Appendix A for detailed information about the bulk process sampling and analytical methods.

3. Urine Sampling Rationale and Methods

Each participant in the biological monitoring was asked to complete a questionnaire concerning work history and possible confounding factors such as active smoking or exposure to sidestream tobacco smoke. Participants were provided with 500 ml polypropylene containers to collect a urine sample immediately before reporting to work (preshift) and immediately before leaving for the day (postshift). The sample bottle was labeled only with the person's study identification number, not his/her

name. Each sample was split into two 50 ml vials, one of which contained 5 grams (g) of citric acid to preserve it for *o*-toluidine and aniline analysis in the NIOSH laboratory. Urine in the second vial was analyzed for creatinine and cotinine concentration at a contract laboratory. Each pair of vials was coded with a random number so that the laboratories performing the analyses did not know whether the sample was obtained preshift or postshift or whether the donor was from Department 245 or 145. For approximately 10% of samples a second pair of 50 ml vials was prepared and coded with a different random number. These "blind-splits" were used to determine how well laboratory measurements of the same sample agreed. The result from the primary samples were used in the epidemiological analysis and reported to participants. The date and time of each sample, and the random vial numbers assigned to it, were recorded in a logbook with the donor's study identification number. The 50 ml vials of urine were placed on dry ice immediately after preparation and preserved in that manner until placement in a -65 °C freezer at NIOSH in Cincinnati, Ohio.

The laboratory methods for analysis of *o*-toluidine and aniline in urine, including quality control procedures, are described in Appendix B.

a. Statistical Methods for Analyzing and Reporting Urine Data

1. Statistical Analysis Methods

As presented in Appendix B, which describes the analytical method used in the urine analyses, the detection limit for *o*-toluidine was 0.6 µg/liter (L) and for aniline was 1.4 µg/L. Values below the limit of detection were reported by the laboratory and included in the statistical analyses because the alternative, which was to substitute the measured value with the LOD/square root of 2 (Hornung and Reed, 1987), was considered to be less precise. Those samples giving no analytical response were assigned the LOD/square root of two, which was 0.99 µg/L for *o*-toluidine and 0.43 µg/L for aniline; there were three such samples for *o*-toluidine and 14 for aniline.

Preshift and postshift means were calculated to evaluate differences in *o*-toluidine and aniline urine concentration between the exposed and unexposed groups of workers, between nonsmokers and smokers within exposure group, and between exposed groups of Wingstay®, Morfax® and maintenance workers within Department 245. Paired t-tests were used to test the difference in preshift and postshift samples within each subgroup, and unpaired t-tests were used to test the difference between preshift means and postshift means between subgroups. When necessary, the data were log transformed to achieve normality.

For descriptive purposes, the mean air, dermal, and urine levels

in each of thirteen job categories were calculated. Correlation coefficients were calculated between *o*-toluidine and aniline levels in personal air and urine samples. Correlation coefficients were also calculated between preshift and postshift values for both *o*-toluidine and aniline.

Multiple regression was used to evaluate the relationship between the outcome variables and the explanatory variables. The outcome variables for the regression models are postshift urinary *o*-toluidine and aniline (μg/L) and the difference between preshift and postshift urinary *o*-toluidine and aniline (μg/L). The explanatory variables are air concentration of *o*-toluidine and aniline and smoking status (yes or no). The potential confounding effects of age, sex and ethnic background (categorized as white and "all other") were evaluated using multiple regression as well. Since none of these factors was a significant predictor of *o*-toluidine or aniline concentration, they were not included in the final models. The regression analyses were restricted to the 32 individuals who had personal air samples and preshift and postshift urine measurements. The residuals of the regression models were tested and, when necessary, appropriate transformations were used to achieve normality and homoscedasicity.

2. Reporting Methods

The dermal indicator badge sampling data were not included in the analysis because they essentially duplicated the results of the personal air sampling data (due to passive absorption from the air) but were less precise. Results of peak air sampling, and glove samples above the limit of detection were not included in the analysis because they were available for only a few individuals (4 individuals had peak air sample measurements and 7 individuals had glove results above the limit of detection). Peak air sampling and glove results were, however, factors in identifying high exposure jobs.

Subsequent to conducting the survey, we became aware of potential problems in using creatinine concentration as a correction for the dilution or concentration of the urine (Boeniger, 1991). In particular, there is some evidence of a diurnal variation in creatinine excretion rate (milligrams creatinine per hour), with a tendency towards higher excretion rates 8 to 12 hours after awakening (Curtis, 1970). Since the parameters of interest in this study included postshift minus preshift concentration of *o*-toluidine and aniline, which would be effected by a diurnal variation in creatinine excretion rate, we have presented urine concentrations of *o*-toluidine and aniline without correction for creatinine in the body of the report. Parallel statistical analyses conducted using the creatinine corrected values (i.e. μg aniline/mg creatinine) had similar results. Selected analyses using creatinine corrected data are presented in Appendix D.

Urinary cotinine level was also obtained but was not used in the analyses because it could not be measured in 14/171 urine samples due to insufficient volume. (This was not a significant problem because the main purpose of the cotinine analysis was to analyze for the effect of passive smoking. Since the effect of active smoking in the unexposed was very small, and the differences between the exposed and unexposed very large, passive smoking was not an issue in the analysis.) Urine cotinine results, like all other test results have been reported to individual participants.

a. Expressing the Variabilities of Individual Sample Results

When reporting the individual urine test results to the workers, it is important to account for the laboratory variability in the urine measurements. Hence, an interval estimate for a workers' measurement was given, in addition to simple point estimates.

This interval used the median coefficient of variation (standard deviation divided by the mean) from the combined laboratory/field splits (see Appendix B which describes the urine methods). In contrast to the standard deviation, which increased with higher urinary concentrations, the coefficient of variation was statistically invariant among levels of exposure. It therefore provided the best overall summary of the variability in the analytic method. For any individual urine concentration, an interval estimate was constructed as follows:

$$\text{Urine Conc.} \pm (1.96)(\text{coefficient of variation})(\text{Urine Conc.})$$

Effectively, this adds and subtracts 1.96 standard deviations from the urine concentration. The median coefficient of variation from combined lab/field split data was 0.13 for *o*-toluidine and 0.16 for aniline. For example, if a worker had an aniline level of 1.4, the 95% confidence interval for his value would range from:

$$1.4 \pm (1.96)(0.16)(1.4) = 1.4 \pm 0.44 = 1.0 \text{ to } 1.9$$

V. EVALUATION CRITERIA

A. Health Effects of Chemicals Used in Department 245

1. In Animals

Two of the chemicals used in this department, *o*-toluidine and aniline, are primary aromatic amines for which there is some evidence of carcinogenicity. The IARC reviewed the carcinogenicity of *o*-toluidine and aniline in 1982 (IARC, 1982). Regarding *o*-toluidine, the IARC concluded that "there is

sufficient evidence for the carcinogenicity of *o*-toluidine hydrochloride (HCl) 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." Regarding aniline, the IARC concluded that "there is limited evidence for the carcinogenicity of aniline HCl in experimental animals. The available epidemiologic data are insufficient to allow a conclusion as to the carcinogenicity of aniline." The IARC classification of these chemicals remained the same in a follow-up evaluation concluded in 1987 (IARC, 1987).

A comparison of the carcinogenicity of *o*-toluidine and aniline in experimental animals is possible because they have been tested in similar experiments (NCI, 1978, NCI, 1979). In experiments with 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).

Other process chemicals used in Department 245 have some evidence of carcinogenicity in animals. In recent NTP bioassays, the Morfax® intermediate 2-mercaptobenzothiazole (CAS Number 149-30-4) has shown "equivocal evidence" of carcinogenicity in the mouse and weak evidence in the rat (NTP-TR-332,88), and hydroquinone (CAS Number 123-31-9) has shown "some evidence" of carcinogenicity in male and female rats and in female mice. Diphenylamine, which was used (approximately 1972-1985) as a chemical added to Wingstay® 200 to manufacture the product RWC4396, and has always been (since 1957) an intermediate of the Wingstay® reaction, can be contaminated with the known bladder carcinogen 4-aminobiphenyl. Diphenylamine itself was selected for chronic bioassay study by NTP in July, 1990.

2. In Humans

The epidemiologic data available for *o*-toluidine and aniline have been extremely limited. Case (1954), in a large study of mortality due to bladder cancer in British dyestuff workers, found no evidence that workers exposed to aniline alone had an increased risk of dying from this tumor. Ott and Langer (1983)

studied workers exposed to aniline and/or *o*-toluidine and found two bladder cancer deaths observed vs. two expected. The IARC cites several reports regarding *o*-toluidine and aniline. None are adequate epidemiologic studies from which the risk can be calculated for bladder cancer in workers exposed to *o*-toluidine, but not also exposed to other carcinogenic aromatic amines. 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.

A summary of the NIOSH investigation of bladder cancer incidence at the Niagara Falls Goodyear plant was published in the Journal of the National Cancer Institute in March, 1991 (83:7:502-506). In summary, the study found that among the 1749 individuals ever employed at the plant, there were 13 cases of bladder cancer observed and 3.61 expected based on New York State incidence rates. The ratio of observed to expected cases (also known as the standardized incidence ratio, or SIR) of 3.60 was found to be highly statistically significant ($p<0.0001$), indicating that this risk was very unlikely to have occurred by chance. Among 708 workers who had ever been assigned to Department 245, there were 7 cases observed and 1.08 expected (SIR=6.48; $p<0.0001$). Among 288 workers considered to have possible exposure to *o*-toluidine and aniline, there were 4 cases observed and 1.09 expected (SIR=3.66; $p=<0.03$). The SIR among 681 workers considered "probably unexposed" was not significantly different from 1.00.

Among workers who had ever been assigned to Department 245, bladder cancer risk increased with longer duration of work. There were no cases observed among employees who worked in the department for less than 5 years. Among workers employed in the department for 5 to 10 years, there was 1 case observed and 0.11 expected (SIR=8.79; $p=<.11$). Among workers employed in the Department for 10 or more years, there were 6 cases observed and 0.22 expected (SIR=27.2; $p=<.0000001$). Because the bladder cancer risk at the plant was greatest among workers with possible and definite exposure to chemicals in Department 245, and increased with longer duration of work in the Department, NIOSH investigators concluded that there was a clear epidemiological association between exposure to *o*-toluidine and aniline in Department 245 and bladder cancer (JNCI March, 1991).

Based on the bladder cancer incidence study at the Goodyear Niagara Falls facility, and on an independent review of additional human and animal data in the scientific literature, NIOSH concluded in a recent Hazard Alert (NIOSH, 1990) that *o*-toluidine and aniline are potential occupational carcinogens as defined in the OSHA Carcinogen Policy [29 CFR 1990].

B. Absorption, Metabolism and Biological Monitoring for *o*-Toluidine and Aniline

In rats orally administered C-14 labelled *o*-toluidine, the major route of excretion is in the urine, with over 90% of administered dose appearing in the urine in the first 24 hours (Cheever et al, 1980). Unchanged *o*-toluidine represented 21% of the compound excreted. In rats administered C-14 labelled *o*-toluidine by injection, 53% of the total dose was recovered in the urine at 24 hours, and only 5% of compound excreted in the urine was unchanged *o*-toluidine (Son et al, 1980). These studies concluded that like many other aromatic amines, *o*-toluidine is metabolized in the rat primarily through ring hydroxylation with subsequent conjugation. The metabolism of *o*-toluidine has not been studied in humans, but from the rat studies we can infer that measurement of unchanged *o*-toluidine in a urine sample collected after the workshift might provide a reasonable index of *o*-toluidine exposure.

In humans, 20 to 40% of aniline absorbed by respiration, and 13 to 40% of aniline absorbed dermally, is metabolized to *p*-aminophenol and rapidly excreted in urine (Dutkiewicz and Piotrowski, 1961a, 1961b). Eighty-nine percent of *p*-aminophenol is eliminated within 24 hours post exposure (Dutkiewicz and Piotrowski, 1961b). Only a small amount is eliminated as unchanged aniline (Dutkiewicz and Piotrowski, 1961b). The ACGIH has recommended a Biological Exposure Index (BEI) of 10 mg/L of *p*-aminophenol in the urine (ACGIH, 1986). Aniline is a metabolite of phenylhydroxyamine, nitrobenzene, acetanilide, phenacetin, and the disinfectant phenazopyridine. Aniline is also a product of degradation of a variety of pesticides such as Propham, Carbetamide, Fenuron or Siduron (ACGIH, 1986). Thus, potential exposure to these compounds should be considered in the interpretation of an unusually high urine aniline result.

Both *o*-toluidine and aniline are present in the urine of individuals who are not occupationally exposed to these compounds. One possible source is cigarette smoke. Both *o*-toluidine and aniline are major aromatic amine components of mainstream and sidestream cigarette smoke. Patrianakos and Hoffman (1979) found 162 nanogram (ng) *o*-toluidine and 364 ng aniline per cigarette in mainstream smoke and 3030 ng *o*-toluidine and 10,800 ng aniline per cigarette in sidestream smoke. El Bayoumy et al (1986) found that smokers excreted 6.30 (SD 3.70) μg *o*-toluidine and 3.10 (SD 2.60) μg aniline per 24 hour period, while non-smokers excreted 4.10 (SD 3.20) μg *o*-toluidine and 2.80 (SD 2.50) μg aniline per 24 hour period. Although the differences in *o*-toluidine and aniline in urine of nonsmokers and smokers were not statistically significant, exposure to cigarette smoke is a potential confounder in evaluating the urine concentration of these chemicals due to occupational exposure.

C. Environmental Monitoring Criteria

The OSHA (OSHA: 29 CFR 1910.1000, 1989), NIOSH (NIOSH Testimony on OSHA's Proposed Rule on Air Contaminants, August 1, 1988) and ACGIH (ACGIH: TLVs and BEIs for 1989-1990) personal air exposure standards and recommendations for *o*-toluidine and aniline in effect on the date of the survey are stated below and shown in Table II in the Tables and Figures section of this report. The OSHA TWA PEL for *o*-toluidine and aniline was 22,000 and 19,000 ug/M^3 (5 ppm), and the NIOSH/ACGIH REL/TLV was 9000 and 8000 ug/M^3 (2 ppm). Since that time, the NIOSH recommended exposure level for these chemicals has been lowered to the lowest feasible limit (NIOSH Alert: Preventing Bladder Cancer from Exposure to *o*-Toluidine and Aniline, 1990), and the OSHA PEL and ACGIH TLV (ACGIH: TLVs and BEIs for 1990-1991) are unchanged. There were no exposure standards in existence for the liquid indicator badge or glove monitoring methods. Also, there were no ACGIH BEI's in effect on the date of the survey, but an intent to establish a BEI for Aniline of 50 mg/g of creatinine was in effect, and is now an established BEI.

VI. EXPOSURE CHARACTERIZATION SURVEY RESULTS

A. Participation Rates and Characteristics of Participants

The Department 245 job titles and job task descriptions that have been used in analyzing the environmental and urine data are shown in Figures 4 and 5. A total of 58 exposed workers and 33 unexposed workers participated in the survey. Five exposed workers participated only in the environmental survey. Participation rates (in either the environmental or urine portions of survey) were 33/52 (64%) among unexposed workers, 27/33 (82%) among Wingstay® workers, 19/21 (90%) among Morfax® workers, and 7/10 (70%) among maintenance workers. Overall, the participation rate was 86/116, or 74%.

Table III provides details about the demographic characteristics and smoking habits of participants in the urine portion of the survey. Among the 53 participants from the exposed group (including currently exposed maintenance workers), 32 provided both preshift and postshift urine samples and had personal air sample results. The relatively low percentage of individuals with all types of samples (60%) is partly explained by 7 participants in the urine portion of the survey having been sampled on the shift when no environmental monitoring was performed. The exposed group was significantly younger than the unexposed, but the two groups did not differ significantly with respect to sex, ethnic background or smoking status.

B. Environmental and Biological Monitoring Results

1. Airborne Sampling Results

A K-S distribution fitting test performed for all of the airborne environmental data indicated that they were lognormally distributed as expected. Therefore, in addition to the individual sample results, geometric means of these data were calculated and are discussed in the appropriate results sections to follow.

a. Personal Air Sampling Results

The personal air sample results are shown in Table II. This table shows that all of the 51 personal air samples for Department 245 employees had detectable levels of *o*-toluidine and aniline present, but only three had detectable levels of the proprietary chemical. The personal air monitoring results for *o*-toluidine, aniline and the proprietary chemical were all well below their respective OSHA, ACGIH and NIOSH PEL/TLV/REL's (see Table II) in effect on the date of the survey.

The employee showing the highest *o*-toluidine (1630 $\mu g/M^3$) TWA air exposure was a Maintenance Operator for Department 245, which was not surprising because maintenance operators have the potential for elevated air exposure from process liquids during disassembly, cleaning and maintenance of process fixtures. This indicates that Maintenance operators may have a greater exposure potential than the other two groups of workers in Department 245 (Wingstay® and Morfax®).

A Production Operator, Wingstay® Utility had the second highest *o*-toluidine (1520 $\mu g/M^3$) and the highest aniline (726 $\mu g/M^3$) TWA exposure levels. He also had the highest peak exposures to *o*-toluidine (7170 $\mu g/M^3$) and aniline (4150 $\mu g/M^3$), which was measured during cleaning of the sparkler filter. This was not surprising since this operator performed sparkler filter cleaning twice during the work shift. This indicates that the sparkler cleaning operation presents an additional exposure to the Production Operator, Wingstay® Utility above that received by the other Wingstay® process operators.

Also, a Production Operator, Wingstay® Packaging, who assisted the Utility Operator (mentioned previously) with sparkler filter cleaning, had the third highest *o*-toluidine (1087 $\mu g/M^3$) and the second highest aniline (581 $\mu g/M^3$) TWA air exposure measured. This also indicates that Sparkler filter cleaning presents additional exposure to the two Wingstay® operators performing the task.

For the proprietary chemical, only three personal TWA air samples had detectable levels, these were 185 $\mu g/M^3$ for a Maintenance Operator, and 336 and 385 $\mu g/M^3$ each for two Production Operators

in Wingstay® packaging. The relationship between air exposure to the proprietary chemical and urine aniline concentration could not be evaluated because so few air samples had detectable levels, and, therefore, further discussion of the proprietary chemical monitoring results will be limited.

b. Airborne Exposure by Process

The geometric means of the personal TWA air samples are shown graphically in Figure 6. The proprietary chemical results are not shown in Figure 6 because 94% (3/51) of the samples had non-detectable levels. This Figure shows that the exposures to *o*-toluidine and aniline are generally higher in the Wingstay® than in the Morfax® process. Also, as shown in Figure 7, the area samples collected in the Morfax® charge room had higher concentrations of *o*-toluidine, which is not used in the process, than aniline. This indicates that workers in the Morfax® process are exposed to chemicals that are not used in the Morfax® process, such as *o*-toluidine, and that air concentrations of *o*-toluidine were present throughout Department 245 regardless of process. This may be partially explained by the close proximity of the two processes in the Department, the volatility of *o*-toluidine which would allow any that was emanating from process fixtures in the Wingstay® process to rapidly migrate throughout the Department, and the significant extent of operator mobility.

c. Area Air Sample Results

The individual area air sample results are shown in Table IV, and the geometric area results are presented graphically in Figure 7. All 24 area air samples had detectable levels of *o*-toluidine and aniline, with 2 detectable for the proprietary chemical. The highest area air sample for *o*-toluidine was measured (2460 ug/M^3) in the reactor/degasser area in the Wingstay® process. This was expected since *o*-toluidine is a major starting chemical used in the Wingstay reaction. The highest aniline area concentration (1440 ug/M^3) was measured by the Wingstay® premix tank in the mezzanine area. This was also expected since aniline is a major starting chemical present in the premix. The fact that *o*-toluidine was measured in the Morfax® charge room on all three samples collected there also indicates that *o*-toluidine is present in Morfax® process areas, even though it is not a starting or intermediate chemical of that process.

2. Dermal Sampling Results

The potential for dermal exposure may have been reduced from that in existence during the May, 1988 NIOSH initial visit by protective measures that had been implemented prior to the 2/27-3/9/90 exposure characterization survey. These measures included: the wearing of gloves by most workers during at least a portion of the workshift; the wearing of Tyvek® suits during sparkler filter cleaning and *o*-toluidine and aniline rail tank

car unloading operations, and; the use of top loading/unloading rail cars. However, the fact that seven glove samples had detectable levels of *o*-toluidine suggests that opportunities for direct dermal contact with process chemicals containing *o*-toluidine still exist.

a. Dermal Liquid Contact Indicator Passive Air Absorption Analysis and Personal Badge Monitoring Results

These silica gel liquid contact indicator badges were intended to indicate the potential for dermal contact with liquid or residual process chemicals only. They were not developed or used as a method to quantitate dermal exposure or absorption. It was anticipated that the silica gel would passively absorb *o*-toluidine and aniline from the air. Therefore, in order to subsequently determine how much of the *o*-toluidine and aniline (amine) absorbed by the liquid contact indicators was absorbed by actual contact with liquid or residual chemical, and how much from the air, area liquid indicator badges were placed as area samplers beside the sorbent tube area air samplers. The data from these pairs of samples should give an estimate of the relationship of air concentration of amine with the levels of amine on the badges.

Using the sorbent tube area air and companion liquid indicator badge data shown in Table IV in the Tables and Figures section, calculations were performed in order to estimate the contribution of passive air sampling to the *o*-toluidine and aniline levels on the indicator badges, and thereby compute an estimate of *o*-toluidine and aniline representing a possible dermal exposure to liquid or residual amine.

The total quantity of amine collected passively from the air by the badges was calculated using the equation:

(Equation 1) $$Q = Ctr$$

Where: Q = total quantity of amine collected passively from the air in μg
C = the air concentration of amine
t = the sampling time in minutes
r = the apparent sampling rate in M^3/minute

Then: The uptake rate of amine (Q/t) is:

(Equation 2) $$Q/t = Cr$$

Using equation 2, the uptake rate for each area badge was computed, and the relationship between these uptake rates and the air concentrations from the corresponding area sorbent-tube samples was estimated by linear regression. The results are

tabulated as follows:

TABLE V
Linear Regression of Amine Uptake of
Airborne Area Liquid Indicator Badge and Sorbent Tube Sample Pairs

	Slope (M^3/min)	Intercept (μg/min)	Number of Points
o-Toluidine	0.00040	0.116	13
Aniline	0.00106	-0.057	9

The air and badge pairs with nondetectable data were excluded from the calculations. Using the slopes (R) and the intercepts (b) from the linear regressions, the quantity of amine collected by each badge sample through passive sampling was calculated. The badge amine levels were then adjusted to exclude the quantity of amine collected through passive sampling (Q). The following equation was used for this combined operation:

(Equation 3) $$A = M - Q = M - t(Cr + b)$$

Where: A = the adjusted amine quantity on the badge in μg
M = the measured quantity of amine on the badge in μg

These calculations indicated that there were only two indicator badge sets that may have had amine collected due to contact with and the absorption of liquid chemical. These badge sets were collected on a Maintenance Operator working in Department 245, and a Production Operator, Wingstay® Utility. It is a reasonable conclusion that some degree of contact of the dermal liquid contact indicator badges worn by these workers with liquid chemical could have occurred because, Maintenance Operators often dissemble and work with process fixtures that could contain process liquids, and the Production Operators, Wingstay® Utility perform cleaning of the sparkler filter, which involves contact with vapors and residue from process liquids. Also, this Maintenance Operator had the highest *o*-toluidine air level measured, detectable glove *o*-toluidine levels, and a substantial increase in urinary (pre vs. post shift) *o*-toluidine level. The Production Operator, Wingstay® Utility had the highest aniline and second highest *o*-toluidine TWA air exposure, the highest *o*-toluidine and aniline peak air exposure, and one of the 3 highest postshift urine *o*-toluidine levels measured. These badge sample sets were collected on the individuals shown with an * in Table II.

b. Glove Sample Results

The Glove monitoring results are also shown in Table II. Seven

of the 43 glove pairs collected had detectable levels of *o*-toluidine. Four of those seven were Wingstay® workers, 3 were Maintenance workers, and none were Morfax® workers. This was expected because *o*-toluidine is not used in the Morfax process, and Maintenance operators work in both processes. The highest *o*-toluidine glove level (180 μg) was for an area Manager, Wingstay®. This result is not peculiar because the area managers move throughout the process and occasionally assist, or even briefly relieve process operators.

Nine of the 43 glove pairs had detectable levels of aniline. Four of these were from Wingstay® operators, four were from Maintenance, and one was from a Morfax® operator. The highest aniline glove result (230 μg) was for a Maintenance operator. This was expected since they work in both processes and open up process fixtures to remove and repair them, and thereby could directly contact process liquids. The proprietary chemical was only detected on one sample set, which was also a Maintenance operator. Again, this was expected for the same reasons previously stated. The fact that, seven glove pairs had detectable *o*-toluidine concentrations and nine had detectable aniline concentrations, the cotton gloves would probably not retain all of the amine they absorb during the workshift, and the relatively high LOD of the glove analytical method (70 and 80 μg per glove set for *o*-toluidine and aniline respectively), indicates that a significant potential for dermal contact by the hands of Department 245 process and Maintenance operators to *o*-toluidine and aniline exists.

c. Surface Wipe Sample Results

The surface wipe sample results are shown in Table VI. Three of the sixteen wipes collected had detectable levels of *o*-toluidine. All sixteen were non-detectable for aniline and the proprietary chemical. The three wipes with detectable *o*-toluidine levels were collected in the Wingstay® process. Two of these were collected from surfaces around the reactor/degasser that would be routinely handled by process operators. This location also had the highest area air level measured for *o*-toluidine. These results indicate that, there is some degree of *o*-toluidine residual present on Wingstay® surfaces, especially around the reactor/degasser, and present the potential for continual skin contact, and support the assumption that the glove results indicate the potential for skin exposure from process surfaces.

d. Bulk Process Sample Results

The bulk sample results are shown in Table VII. Seven of the nine process bulk samples collected (*o*-toluidine and aniline starting chemical were excluded) were analyzed for the presence of *o*-toluidine and aniline by full scan gas chromatography and mass spectrometry (GC/MS) with a sensitivity of 2.3 μg/ml of sample aliquot. All nine bulk samples were analyzed for the

presence of 4-aminobiphenyl (a potential contaminant in raw aniline and the low yield Wingstay® intermediate diphenylamine) by GC/MS in selected-ion monitoring (SIM) mode. This mode is an order of magnitude more sensitive than the full scan mode at 0.23 ng/ml of sample aliquot, and can detect analytes at the ion level. *o*-Toluidine was detected in 4 of the 7 samples analyzed by GC/MS full scan. The detection of *o*-toluidine in the Morfax® reactor feed was unanticipated since *o*-toluidine is not a starting or intermediate chemical in that process. Detection in the other three was expected since they were Wingstay® process reactants. Aniline was detected in all seven process samples, which was expected since aniline is a starting chemical in both processes.

Trace amounts of 4-aminobiphenyl were detected in three of the nine bulk samples analyzed. This was not unreasonable for the aniline raw chemical or the Morfax® reactor feed since aniline has been known to contain trace contamination of 4-aminobiphenyl resulting from aniline condensation. However, we do not have an explanation for the detection of 4-aminobiphenyl in the *o*-toluidine starting chemical, except that the identification of the chromatographic chart peaks at this high level of sensitivity can be very difficult, and is not an absolute identification. It is conceivable that other compounds could complicate the identification of the 4-aminobiphenyl peak. In any event, the levels of 4-aminobiphenyl that would be present if the peak identification is correct, would be too low to measure environmentally or biologically.

Because of the complex chemical matrix of the seven process bulk samples, quantitative analysis for those samples could not be performed. Also, the amounts of 4-aminobiphenyl detected by SIM in the three samples previously mentioned was too low to quantitate. This method can detect the presence of chemical ions, but can not quantitate ionic levels.

3. Urine Sample Results

a. Urine *o*-Toluidine and Aniline Levels by Exposure and Smoking Status

Among unexposed workers the mean urine *o*-toluidine concentration was 1.1 µg/L in preshift samples and 2.7 µg/L in postshift samples; the mean urine aniline concentration was 2.7 µg/L in preshift samples and 3.8 µg/L in postshift samples. Among exposed workers the mean urine *o*-toluidine concentration was 18.5 µg/liter in preshift samples and 104 in postshift samples; the mean urine aniline concentration in preshift samples was 17.4 µg/liter and in postshift samples was 32.3 µg/liter (Table VIII). For *o*-toluidine, the preshift mean in the exposed group is 16.8 times higher than in the unexposed, while the postshift mean in the exposed is 38.4 times that in the unexposed. For aniline, the preshift mean in the exposed group is 6.4 times higher than

in the unexposed and the postshift mean in the exposed is 8.5 times that in the unexposed (Table VIII). If the 95th percentile of the unexposed distribution is used to define the upper limit of normal, 79% of preshift aniline concentrations among the exposed workers are elevated (>5.7 μg/L), as are 98% of their postshift aniline concentrations (95th percentile: 9.1 μg/L). The differences between the exposed and unexposed groups were even stronger for *o*-toluidine. A total of 83% of preshift samples from the exposed fell on or above the 95th percentile for the unexposed (3.60 μg/L), as did all of their postshift samples (95th percentile: 5.60 μg/L).

As shown in Table VIII, both the unexposed and the exposed groups have higher levels of *o*-toluidine in the postshift than the preshift samples. The rise in the unexposed group is about 1.5-fold, while the rise in the exposed group is about 6-fold. Both the unexposed and the exposed groups show higher levels of aniline in the postshift than in the preshift samples, but in both groups the rise is less than 2-fold.

Since both *o*-toluidine and aniline are present in cigarette smoke, we also examined urinary excretion of these compounds by smoking status separately for the unexposed (Table IX) and the exposed (Table X) groups. In the unexposed group *o*-toluidine levels were virtually identical in smokers and nonsmokers, but smokers had significantly higher aniline levels than nonsmokers. Higher concentrations of *o*-toluidine and aniline were seen in the postshift than in the preshift samples in both non-smokers and smokers (Table IX), though the increase in aniline concentration in smokers was not statistically significant.

Among unexposed workers, smoking did not increase urinary *o*-toluidine at all and aniline concentration increased an average of only 2 to 3 μg/L, but among exposed workers there were large differences between smokers and nonsmokers, except for preshift *o*-toluidine. Smokers and non-smokers did not differ greatly in their *o*-toluidine preshift values, but the mean postshift level among smokers averaged 51.7 μg/L higher than the postshift levels among nonsmokers. The mean preshift aniline level among smokers was 7.20 μg/L greater than the level in nonsmokers, while the mean postshift level was 22.5 μg/L greater in smokers than non-smokers.

C. Relationship of Urine Levels to Personal Air Exposure Levels

1. By Exposure Group

Table XI presents the urine and Table XII the airborne *o*-toluidine and aniline levels for exposed workers by Department or group (Wingstay®, Morfax® or Maintenance). Despite the fact that *o*-toluidine is not a starting product in the Morfax® reaction, the ratio of *o*-toluidine:aniline levels in air and urine samples

were very similar in the Wingstay® and Morfax® Departments (Table XIII top). For both *o*-toluidine and aniline, air and urine concentrations measured among Wingstay® workers were, on average, 2 to 3 times those among Morfax® workers (Table XIII, bottom). Thus, the urine and air data are consistent in showing that Morfax® workers are exposed to both *o*-toluidine and aniline, and that Wingstay® workers have substantially higher exposure to both chemicals.

Analysis of exposures of Maintenance workers is limited by their small numbers. The preshift means for *o*-toluidine and aniline were lower than those of Wingstay® and Morfax® workers, the postshift mean for aniline was in between those of Wingstay® and Morfax® workers, while the postshift mean for *o*-toluidine was higher than that for Wingstay® workers. The air levels measured in maintenance workers also show a substantial potential exposure comparable to that of Wingstay® workers.

2. By Job Title

Table XIV shows preshift and postshift urine concentrations of *o*-toluidine and aniline, and Table XV shows airborne levels of *o*-toluidine and aniline, by job category within Department 245. The job category with the highest postshift urinary concentrations of both *o*-toluidine and aniline is "Production Operator, Wingstay® Utility"; other job categories with high levels of *o*-toluidine and aniline are "Chemical Operator, Wingstay® reactor," "Area Manager," and "Maintenance." In general, jobs associated with high urinary concentrations of *o*-toluidine and aniline also showed high air levels.

3. By Individual (correlation analysis)

Aniline and *o*-toluidine air levels obtained from personal samplers were highly correlated with each other ($r=.90$, $p=.0001$). Aniline and *o*-toluidine levels in preshift urine samples ($r=.75$, $p=.0001$) and postshift ($r=.68$, $p=.0001$) urine samples were also highly correlated. Preshift and postshift aniline levels were highly correlated with each other ($r=.61$, $p=.0001$), while preshift and postshift *o*-toluidine levels were not ($r=.21$, $p=.17$).

4. By Individual (Regression Analysis)

For both *o*-toluidine and aniline, air level during the day of the survey appears to be a significant predictor of postshift urine concentration and the difference between postshift and preshift urine concentration (Table XVI). Inclusion of a dichotomous variable for smoking in the model improved the fit of the model but did not markedly change the coefficients or p values for the air level variable.

VII. DISCUSSION

A. Discussion of Urine Results Interpretation

The regression analyses suggest that both personal air measurements and smoking status are predictors of urinary *o*-toluidine and aniline concentrations in exposed workers. The exact relationships between air level and smoking status and the outcome variables tested should be interpreted with caution because of the overall small sample size.

It is somewhat surprising that smoking is a predictor of urinary *o*-toluidine and aniline. The results in the unexposed group show no difference between smokers and nonsmokers for *o*-toluidine, and while there is a difference for aniline, it is of very small magnitude compared to the effect of exposure itself. Among the exposed group, the average *o*-toluidine and aniline concentration among smokers are higher than that among nonsmokers, but this is somewhat dependent on high urine concentrations in a few smokers and may be due to chance.

If there is a real difference in urinary *o*-toluidine and aniline levels between exposed smokers and nonsmokers, one possible explanation is that smoking enhances the absorption of aniline and *o*-toluidine into the body. The most direct mechanisms for this would be that (1) aniline and *o*-toluidine present on the skin of the hands contacts the lips, resulting in ingestion, and/or that (2) the hands contact the cigarette, and the *o*-toluidine and aniline which are deposited on the cigarette are inhaled in the cigarette smoke. The breakroom also contains measurable air concentrations of *o*-toluidine and aniline, which may enrich the *o*-toluidine and aniline exposure of smokers, who may inhale more deeply (while smoking) than nonsmokers. It is also possible that smokers metabolize the chemicals differently, resulting in higher concentrations of the metabolites measured by the method used in this study (which measures the parent compound and the acetylated derivatives). While it is known that compounds in cigarette smoke induce enzyme systems involved in aromatic amine metabolism (Butler, MA et al, 1989), not enough is known about the metabolism of *o*-toluidine and aniline to assess how likely this explanation is.

For both *o*-toluidine and aniline, the metabolites that we measured represent a fraction of the absorbed dose. We do not know the exact fraction and did not assume that it would necessarily be similar for *o*-toluidine and aniline. We are therefore somewhat surprised to note that the ratio of *o*-toluidine concentration to aniline concentration in the urine samples of about 2 to 3:1 parallels the ratio in the environmental samples.

Individual urine sample results should be interpreted with caution. There are several sources of variability in these

results. One is the variability in the laboratory method, which can be expressed by the 95% confidence interval. Using the formula described in the Statistical Methods for Analyzing and Reporting Urine Data, Statistical Analysis Methods section of the report, the 95% confidence intervals are fairly wide. For example, the 95% confidence interval for an *o*-toluidine level of 50 µg/L is 37 µg/L to 63 µg/L; the 95% confidence interval for an *o*-toluidine level of 100 µg/L is 75 µg/L to 125 µg/L. Furthermore, the amount of *o*-toluidine or aniline measured in the postshift urine sample may be related to many factors: the preshift concentration, the total absorbed dose during the workday, the time of day during which that dose was absorbed, the rate of metabolism (which may differ between different individuals), and the relative ratio of the metabolites measured to those not measured (which may also differ between different individuals). The metabolism of aromatic amines is complex (Gorrod and Monson, 1986, Beland and Kadlubar, 1986) and both genetic and environmental factors may influence the amount of a specific metabolite measured in a spot sample (Butler et al 1989 and Lang and Kadlubar, 1990). Thus, we believe that individual urine results should be interpreted with caution. In particular, comparison of one individual to others **cannot be used to monitor adherence to work practice or personal protective controls**. High urine concentrations observed in an individual should not be interpreted as resulting from non-adherence since he or she may have higher levels for metabolic reasons.

The most important use of urinary monitoring results for the Goodyear, Niagara Falls plant would be in tracking urinary levels in groups of workers over time as exposure controls are installed. In tracking Department 245 workers over time, one would expect that the average urinary concentration of *o*-toluidine and aniline would go down as exposure controls are implemented, even though there will still be variation among individuals due to differences in the exposure potential of different jobs as well as factors such as smoking status and differences in metabolism. A second possible use may be in identifying for possible intervention job categories with consistently high exposures. A third possible use might be in documenting exposures after an incident resulting in possible overexposure.

B. Jobs and Operations of Particular Concern

1. Morfax® Operators

All Morfax® operators had measurable air exposure levels, and higher post than pre-shift urine levels of *o*-toluidine. This shows that Morfax® workers are exposed to and are absorbing *o*-toluidine into their bodies during the workshift. This may be partially explained by the mobility of the workers, the close proximity of the two processes at several locations (see Figure 8), and the volatility of *o*-toluidine allowing any Wingstay®

process emissions to rapidly migrate throughout Department 245.

2. Wingstay® Area Managers

One Wingstay® Area Manager had the highest postshift urine *o*-toluidine value measured in the survey. Another had a relatively high urine value, detectable *o*-toluidine on his gloves, but an air exposure level below the arithmetic mean of the exposure range. The relatively low air exposure level and the fact that *o*-toluidine was detected on the gloves, suggest that dermal absorption may have accounted for some of the total bodily absorption during the workshift by this manager.

Finding exposure in the Wingstay® Area Managers was not surprising since they continually move during the workshift monitoring the process, assisting operators when necessary, and occasionally relieving operators for brief periods.

3. Maintenance Operators

One Maintenance operator had the highest *o*-toluidine air level measured, detectable glove *o*-toluidine levels, and a substantial urine pre vs. post shift *o*-toluidine level. Also, three of the seven glove sets with detectable *o*-toluidine were from Maintenance operators. This indicates that Maintenance operators may have a greater air and skin exposure potential than the other two Department 245 groups of workers. This was not surprising because Maintenance operators have the potential for elevated air exposure and dermal contact with process liquids during disassembly, cleaning and maintenance of process fixtures.

4. Production Operator, Wingstay® Utility

One of these operators had the highest aniline and second highest *o*-toluidine TWA air exposure, the highest *o*-toluidine and aniline peak air exposure, and one of the 3 highest postshift urine *o*-toluidine levels measured.

It was anticipated that some of the higher levels would be found in these workers because they are responsible for cleaning the sparkler filter. This operation involves opening up a process hatch and working with a hot steel filter assembly that has process reactant vapors coming off, and residual process liquid present on its surfaces. This operation is described in more detail in the following section.

5. Production Operator, Wingstay Packaging

A Production Operator, Wingstay® Packaging, who assisted the Utility Operator mentioned in the previous section with sparkler filter cleaning, had the third highest *o*-toluidine and the second highest aniline TWA air exposure measured, and post shift *o*-toluidine and aniline urine levels well above the mean

concentrations. This also indicates that sparkler filter cleaning presents additional exposure to the two Wingstay® operators performing the task.

6. Sparkler Filter Cleaning Operation

During sparkler filter cleaning, a Production Operator, Wingstay® Utility is required to remove a large process hatch cover, hoist out a catalyst filtering assembly (which measures about three feet in diameter and four feet in length), disassemble the ten to twelve steel catalyst filter sections, remove and replace the used filters from each filter section, and reassemble and replace the filter assembly. During the hoist removal of the sparkler filter assembly, the operator is standing on a platform looking down into the filter vessel, which is at process temperature (hot). Steaming vapors emanate from the filter vessel and assembly during the filter assembly removal and filter changing operation. The filter assembly is hoisted up and over the top of the vessel, moved laterally and lowered about eight feet to the floor. Retaining bolts are removed from the threaded rods over which the filter sections are stacked. The Wingstay® Utility Production Operator is assisted by a Production Operator, Wingstay® Packaging during disassembly and dumping of the used filter sections (about 30 minutes). The operators bend over the assembly, pull each circular steel filter holding plate off of the steel rods, and scrape off the spent filters into a waste cart. Vapors are still emanating from the hot steel plates and filtrate during the filter disassembly and cleaning. New filters are placed in the steel holding plates one section at a time, the filter plate sections are restacked over the threaded rods, and the bolts are reinstalled and tightened. The assembly is hoisted up high enough to clear the process vessel, moved laterally until above the vessel and lowered into position. The hatch cover is repositioned, and the hatch dogs tightened. The entire operation takes 60 to 90 minutes to complete. Personal protective equipment worn by the operators during the cleaning operation consisted of a Tyvek® suit, rubber gloves, a half-mask chemical cartridge respirator, and a full face shield over the respirator. It was obvious during the cleaning operation that the facial skin of the operators was intermittently in contact with the rising vapors.

During this cleaning operation the tyvek suit, gloves, and respiratory protective equipment worn by the operators became soiled with the process catalyst filtrate, which would contain liquid residue from the process, and condensate from the vapors emanating from the filter assembly. Handling of the protective equipment during removal presents an additional potential for dermal contact by the operators.

VIII. CONCLUSIONS

The potential for dermal exposure may have been reduced from that in existence during the May, 1988 visit by protective measures that had been implemented prior to the 2/27-3/9/90 exposure characterization survey. These measures included: the wearing of gloves by most workers during at least a portion of the workshift, the wearing of Tyvek® suits during sparkler filter cleaning and *o*-toluidine and aniline rail tank car unloading operations, and the use of top loading/unloading rail cars. However, the fact that seven glove samples had detectable levels of *o*-toluidine suggests that opportunities for direct dermal contact with process chemicals containing *o*-toluidine still exist.

A. Airborne Exposure Conclusions

The personal and area air monitoring results presented in Tables II and IV shows that all workers and areas monitored had measurable levels of *o*-toluidine and aniline. The GM personal air exposure results illustrated in Figure 6 show that the exposures to *o*-toluidine and aniline are generally higher in the Wingstay® than in the Morfax® process. Also, the area samples collected in the Morfax® charge room had higher concentrations of *o*-toluidine, which is not used in the process, than aniline. This indicates that workers in the Morfax® process are exposed to chemicals that are not used in the Morfax® process, such as *o*-toluidine, and that air concentrations of *o*-toluidine were present throughout Department 245. This may be partially explained by the close proximity of the two processes, the volatility of *o*-toluidine which would allow any that was emanating from process fixtures in the Wingstay® process to rapidly migrate throughout the Department, and the significant extent of operator mobility.

The employee showing the highest TWA *o*-toluidine air exposures was a Maintenance Operator for Department 245, which was not surprising because Maintenance operators have the potential for elevated air and skin exposure from process liquids during disassembly, cleaning and maintenance of process fixtures. This indicates that Maintenance operators may have a greater exposure potential than the other two Department 245 groups of workers.

A Production Operator, Wingstay® Utility had the second highest *o*-toluidine and the highest aniline TWA exposure levels, and had the highest peak exposures to *o*-toluidine and aniline, which was measured during cleaning of the sparkler filter. This was not surprising since this operator performed sparkler filter cleaning twice during the work shift. This indicates that the sparkler cleaning operation presents an additional exposure to the Production Operator, Wingstay® Utility above that received by the other Wingstay® process operators.

Also, a Production Operator, Wingstay® Packaging, who assisted

the Utility Operator mentioned in the previous paragraph with sparkler filter cleaning, had the third highest *o*-toluidine and the second highest aniline TWA air exposure measured. This also indicates that sparkler filter cleaning presents additional exposure to the two Wingstay® operators performing the task.

B. Dermal Exposure Conclusions

1. Liquid Contact Indicator Badges

An analysis of the relative contribution of air and liquid absorption on the badges showed that the levels on two of the badges was not due to absorption from the air only. The analysis showed that the badges collected on a Maintenance operator working in Department 245, and a Production Operator, Wingstay® Utility had loading that could have been the result of liquid absorption. This seems a reasonable conclusion since Maintenance Operators often dissemble and work with process fixtures that could contain process liquids, and the Production Operators, Wingstay® Utility perform cleaning of the sparkler filter, which involves contact with vapors and residue from process liquids. Also, this Maintenance operator had the highest *o*-toluidine air level measured, detectable glove *o*-toluidine levels, and a substantial urine pre vs. post shift *o*-toluidine level; and, the Production Operator, Wingstay® Utility had the highest aniline and second highest *o*-toluidine TWA air exposure, the highest *o*-toluidine and aniline peak air exposure, and one of the 3 highest postshift urine *o*-toluidine levels measured.

2. Glove Samples

Of the 43 glove sample sets collected, seven had detectable levels of *o*-toluidine and nine of aniline. The highest *o*-toluidine level was for a Wingstay® Area Manager, which was not surprising since Area Managers move throughout the process assisting and sometimes briefly relieving operators. The highest aniline level was for a Maintenance operator, which was not unexpected since they dissemble process components which often contain process liquids. The detectable levels of *o*-toluidine and aniline found on the glove samples suggests that the potential for dermal contact with liquid or residual *o*-toluidine and aniline exists in Department 245.

3. Surface Wipe Samples

Three of the surface wipe samples collected in the Wingstay® process area had measurable levels of *o*-toluidine. Two of these were of surfaces in the reactor/degasser area routinely handled by process operators. This indicates that the potential for operator contact with residual *o*-toluidine present on process surfaces exists.

4. Bulk Samples

o-Toluidine was detected in 4 of the 7 samples analyzed by GC/MS full scan. The detection of *o*-toluidine in the Morfax® reactor feed was unexpected since *o*-toluidine is not a starting or intermediate chemical in that process. Aniline was detected in all seven process samples, which was expected since aniline is a starting chemical in both processes.

Trace amounts of 4-aminobiphenyl were detected in three of the nine bulk samples analyzed. This was not unexpected for the aniline raw chemical or the Morfax® reactor feed since aniline has been known to contain trace contamination of 4-aminobiphenyl resulting from aniline condensation. However, we do not have an explanation for the detection of 4-aminobiphenyl in the *o*-toluidine starting chemical. The amount of 4-aminobiphenyl detected by SIM was too low to quantitate. This method can detect the presence of chemical ions, but can not quantitate at the ionic level. Also, the identification of the chromatographic chart peaks at this high level of sensitivity can be very difficult, and is not an absolute identification. It is conceivable that other compounds could complicate the identification of the 4-aminobiphenyl peak. However, the levels of 4-aminobiphenyl that would be present if the peak identification is correct and bulk materials contaminated the work place, would be too low to measure environmentally or biologically.

C. Urine Results Conclusions

Urine *o*-toluidine and aniline concentrations were elevated in all Department 245 workers tested. There was no overlap of urine levels between exposed and unexposed workers. This is unequivocal evidence that Department 245 workers are absorbing *o*-toluidine and aniline into their bodies during the workshift. A total of 89% *o*-toluidine and 91% aniline TWA air concentration measurements were below 0.1 ppm (385 ug/M^3). Despite their low absolute values, the air concentrations of *o*-toluidine and aniline showed a consistent difference between Wingstay® and Morfax® processes and were significantly related to the urine *o*-toluidine and aniline concentrations. This indicates that *o*-toluidine and aniline air concentrations during the workshift contributed to the increased postshift urine levels. A urine *o*-toluidine and aniline monitoring program could be utilized to track urinary levels in groups of workers over time as exposure controls are installed, identify job categories with consistently high exposures for possible intervention, and document exposures after a possible overexposure incident.

VI. Recommendations

A. General Recommendations

Due to the demonstrated increased risk of workers in Department 245 developing bladder cancer, which is most likely associated with exposure to *o*-toluidine and aniline, and the observation (in January 1990) of poor process integrity (e.g., leaking pumps, valves and other process fixtures) that was presenting the potential for worker exposure to these chemicals, the NIOSH investigators provided a letter of recommendations to the Goodyear Tire and Rubber Company (1/30/90). The recommendations stated that Goodyear should tighten process integrity, clean up spills, improve housekeeping, investigate installation of engineering exposure controls, and implement a personal protective program as necessary to immediately reduce exposure potential to workers in Department 245. NIOSH subsequently recommended in a Hazard Alert (NIOSH, 1990) that exposures to *o*-toluidine and aniline throughout the U.S. be reduced to the lowest feasible concentration.

Since the environmental monitoring data shows that detectable exposure levels of *o*-toluidine and aniline are present throughout Department 245, the urine monitoring data shows conclusive evidence that Department 245 workers are absorbing *o*-toluidine and aniline into their bodies, and an elevated risk of bladder cancer was found for workers in Department 245, the Goodyear Tire and Rubber Company should take immediate steps to reduce exposures to process chemicals (especially *o*-toluidine and aniline) in Department 245 to the lowest feasible concentration. The potential for release of process chemicals into the air of the work environment, and for contact of these chemicals with the workers' skin, must be minimized through the use of engineering controls, improved work practices, and personal protective equipment.

B. Specific Recommendations

To facilitate the necessary reduction of worker exposure to Department 245 process chemicals, the following specific recommendations are provided.

1. Process Integrity Evaluation Recommendation

Perform an engineering evaluation of all the process components such as transfer pumps and pipes, holding tanks, vessels, valves, reactors, etc., of Department 245 for integrity, and replace or modernize any leaking or ageing components.

2. Engineering Exposure Control Evaluation Recommendation

Conduct a detailed evaluation of all work stations/areas, QC

sampling ports, etc, to identify any locations where engineering exposure controls may be installed to eliminate or reduce the escape of process chemicals, intermediates, byproducts, and finished products to the work environment. This should be accomplished through the use of enclosed processes, separation of the worker from the processes, and design and installation of appropriate ventilation. The following engineering controls should be considered.

a. Enclosed Systems

Use enclosed systems for unloading bulk chemicals. Such systems should be equipped with snap-lock or other types of transfer hose connections for quick hookups and disconnections. A purging system should be included to remove excess chemicals from the transfer hose before disconnection.

b. Redundant Controls

Use redundant controls such as double mechanical seals for process pumps and for other rotating or reciprocal equipment, or other types of back-up leak protection to prevent the release of chemical liquid or vapor to the work environment.

c. Enclosed Sampling Ports

Use enclosed systems for sampling process liquids (e.g., lines and vessels with snap-lock fittings). The sampling ports should be equipped with a system to purge the port after sampling and before disconnection of the sampling vessel.

3. Sparkler Filter Replacement Recommendation

To reduce the frequency of exposure to process temperature vapors, expedite permanent replacement of the sparkler filter with a filtering system that does not require frequent opening of process fixture covers.

4. Particulate Control Recommendation

Enclose the vibrating conveyor, and any other particulate transports, and install dust collection engineering controls to reduce fugitive dust escaping into the process areas.

5. Dust Removal Recommendation

Implement an immediate, followed by periodic vacuum dust cleaning of Department 245.

6. Personal Protective and Work Practice Programs Recommendation

Develop and institute a comprehensive personal exposure

protection program for use only when adequate or complete engineering exposure control is not possible. This program should be conducted on site by a qualified full time in house safety specialist and include: identification of the proper types of gloves, coveralls, respirators and other appropriate protective gear based on the exposures identified for each job description; annual quantitative respirator fit testing; a periodic respirator cleaning and maintenance program; routine inspection and replacement of gloves, coveralls, etc.; and, development of work practices to help control exposure. If specific industrial hygiene expertise in the area of PPE is not available in house, such expertise should be obtained from consultants knowledgeable in this area. Examples of work practices that can be used to control exposures are:

a. The maintenance of good general housekeeping so that leaks and other process integrity problems can be readily detected and corrected.

b. The use of clear labeling for all drums or containers in the work area that hold process chemicals (this labeling must conform with the requirements of the OSHA Hazard Communication Standard [29 CFR 1910.1200]).

c. The preventive maintenance of process equipment to prevent deterioration and subsequent development of leaks, this maintenance should include regular inspection of potential leak sites.

d. The use of proper hygiene practices to minimize skin absorption, such as the proper use and removal of protective clothing, prohibition of eating and smoking in work areas, and proper materials handling.

e. While the sparkler filter remains in operation, the following personal protective recommendations are provided to reduce worker exposure to the lowest feasible level during the filter cleaning operation. The optimal personal protective equipment for workers involved in sparkler filter cleaning would be a positive pressure, full-face, air-line respirator operated in a positive pressure mode and worn underneath a level A chemically resistant protective suit ensemble of a material such as Saranex-Tyvek® to reduce vapor, liquid, and particulate exposure to o-toluidine and aniline. For the hot weather season encapsulating suits designed for use with Vortex tubes that have appropriate outlet valves to reduce filling the suit with air should be used. Cooling vests and other devices can also be used in conjunction with Vortex tubes to alleviate heat stress. Also, the protective suits should be used only once (single use) since they can not be effectively decontaminated. Workers must don their PPE ensemble in a designated clean area, and not in the contaminated work area. Also, the workers must be in clean, not dirty, work uniforms

before donning the PPE ensemble. The dirty PPE ensemble should be doffed in an area near the Sparkler filter where contaminants are minimal. This area is a contamination reduction zone.

Additionally, the impact of the PPE program instituted should be monitored for its positive effect on reducing worker exposure to *o*-toluidine and aniline during the sparkler cleaning operation.

The concept of full body protection and protection level (ensembles) is presented in Volume I of "Field Guide, Guidelines for the Selection of Chemical Protective Clothing, 3rd edition" (Schwope et al., 1988), Additionally, information for the chemical resistance of protective clothing, as applied to specific chemical classes, is presented in Volume II, and, contamination reduction zones are discussed in Volume I of this set. The two volume set can be purchased form the ACGIH, Inc. 6500 Glenway Avenue, Building D-7, Cincinnati, Ohio 45211-4438 as publication number 0460. For evaluation of the PPE program, the elements of a PPE program and assessment of its success is discussed in the two volume set of "Chemical Protective Clothing" (Johnson and Anderson, 1991). This reference is available from the AIHA, PO Box 8390, Akron, Ohio 44320.

7. Worker Training Recommendation

Provide worker training regarding: the possible carcinogenic effects of exposure, the importance of avoiding skin contact, specific work practices, and the use of appropriate protective equipment, including gloves and respiratory protection.

8. Smoking Control Recommendation

Although there are several explanations (including chance variation) for the increased levels of *o*-toluidine and aniline in the urine of exposed smokers compared to nonsmokers, it would be prudent to make efforts to reduce the probability of increased exposure among smokers. Measures would include an evaluation of the air supply in the breakroom, decontamination of the hands (washing) and clothing (vacuuming) before entering the breakroom, and frequent cleaning of the breakroom to prevent contamination of the surfaces. In addition, smoking cessation programs should be offered to employees to both reduce the possibility of increased exposure to *o*-toluidine and aniline through smoking and the likelihood of developing bladder cancer, and separate break rooms should be provided for smokers.

9. Urine Monitoring Recommendation

A voluntary program of urine monitoring should be established for workers in Department 245, including maintenance workers and other personnel who are working within the department. This program should be established and monitored with the Union/Management Health and Safety Committee so as to have

maximum participation among the employees. The eventual goal of such a program would be to control exposure to o-toluidine and aniline to such a degree that the urinary concentrations do not differ from those in the unexposed population.

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XII. TABLES AND FIGURES

TABLE II
SUMMARY RESULTS FOR PERSONAL AIR AND GLOVE SAMPLES
COLLECTED AT THE GOODYEAR NIAGARA FALLS PLANT
DEPARTMENT 245 DURING 3/6-8/90

JOB TITLE OR SAMPLE LOCATION	ORTHO-TOLUIDINE OSHA/NIOSH & ACGIH PEL/REL = 22,000/9,000 µg/M³ TWA for Air No PEL's for Gloves		ANILINE OSHA/NIOSH & ACGIH PEL/REL = 8,000 µg/M³ TWA for Air No PEL's for Gloves		Proprietary Chemical OSHA/NIOSH & ACGIH PEL/REL = 5,000 µg/M³ TWA for Air No PEL's for Gloves	
	AIR[1] (µg/M³) TWA[2]	GLOVE[3] total µg/glove set	AIR µg/M³ TWA	GLOVE total µg/glove set	AIR µg/M³ TWA	GLOVE total µg/glove set
Area Manager Wingstay®	558	80.0	242	N.D.[4]	N.D.	N.D.
Area Manager Wingstay®	392	N.T.[5]	136	N.T.	N.D.	N.T.
Area Manager Wingstay®	370	180	112	100	N.D.	N.D.
Production Operator* Wingstay® Utility	305	N.D.	86.2	N.D.	N.D.	N.D.
Production Operator Wingstay® Utility	1,520	N.D.	726	90.0	N.D.	N.D.
Same Operator As Above - Cleaning Sparkler Filter (Peak Sample)	7,170	"	4,150	"	N.D.	"
Same Operator As Above - Cleaning Sparkler Filter (Peak Sample)	324	"	125	"	N.D.	"
Production Operator Wingstay® Utility	263	N.D.	103	N.D.	N.D.	N.D.
Same Operator As Above - Cleaning Sparkler Filter (Peak Sample)	6,990	"	4,047	"	N.D.	"
Production Operator Wingstay® Packaging	615	N.D.	327	N.D.	N.D.	N.D.
Production Operator Wingstay® Packaging	244	130	77.7	220	336	N.D.
Production Operator Wingstay® Packaging	407	N.D.	198	N.D.	N.D.	N.D.
Production Operator Wingstay® Packaging	155	N.D.	60.6	N.D.	N.D.	N.D.
Production Operator Wingstay® Packaging	229	140	86.0	100	385	N.D.
Production Operator Wingstay® Packaging	1,087	N.D.	581	N.D.	N.D.	N.D.
Chemical Operator Wingstay® Utility	398	N.D.	138	N.D.	N.D.	N.D.
Chemical Operator Wingstay® Utility	398	N.D.	112	N.D.	N.D.	N.D.
Same Operator As Above - Unloading Aniline Rail Car (Peak Sample)	767	"	167	"	N.D.	"

TABLE II
SUMMARY RESULTS FOR PERSONAL AIR AND GLOVE SAMPLES COLLECTED AT THE GOODYEAR NIAGARA FALLS PLANT DEPARTMENT 245 DURING 3/6-8/90

JOB TITLE OR SAMPLE LOCATION	ORTHO-TOLUIDINE OSHA/NIOSH & ACGIH PEL/REL=22,000/8,000 µg/M³ TWA for Air No PEL's for Gloves		ANILINE OSHA/NIOSH & ACGIH PEL/REL=8,000 µg/M³ TWA for Air No PEL's for Gloves		Proprietary Chemical OSHA/NIOSH & ACGIH PEL/REL=5,000 µg/M³ TWA for Air No PEL's for Gloves	
	AIR[1] (µg/M³) TWA[2]	GLOVE[3] total µg/glove set	AIR µg/M³ TWA	GLOVE total µg/glove set	AIR µg/M³ TWA	GLOVE total µg/glove set
Chemical Operator Wingstay® Utility	483	N.D.	101	N.D.	N.D.	N.D.
Same Operator As Above - Unloading Toluidine Rail Car (Peak Sample)	1,250	"	108	"	N.D.	"
Chemical Operator Wingstay® Reactor	599	N.D.	195	N.D.	N.D.	N.D.
Chemical Operator Wingstay® Reactor	378	N.D.	197	N.D.	N.D.	N.D.
Maintenance Operator Department 245	332	100	123	200	N.D.	N.D.
Maintenance Operator Department 245	257	N.D.	112	140	N.D.	N.D.
Maintenance Operator Department 245	241	100	112	230	185	N.D.
Maintenance Operator* Department 245	1,630	90.0	318	N.D.	N.D.	N.D.
Maintenance Operator Department 245	257	N.D.	112	110	N.D.	N.D.
Maintenance Operator Department 245	237	N.D.	83.9	N.D.	N.D.	760
Maintenance Operator Department 245	524	N.T.	227	N.T.	N.D.	N.T.
Chemical Operator C-2 Building	87.4	N.D.	57.0	N.D.	N.D.	N.D.
Chemical Operator C-2 Building	302	N.D.	241	N.D.	N.D.	N.D.
Chemical Operator C-2 Building	448	N.D.	389	N.D.	N.D.	N.D.
Area Manager Morfax®	150	N.T.	61.8	N.T.	N.D.	N.T.
Area Manager Morfax®	304	N.D.	85.7	N.D.	N.D.	N.D.
Production Operator Morfax® Packaging	246	N.D.	78.3	N.D.	N.D.	N.D.
Production Operator Morfax® Packaging	157	N.D.	68.2	N.D.	N.D.	N.D.
Production Operator Morfax® Packaging	301	N.D.	98.1	90.0	N.D.	N.D.
Production Operator Morfax® Packaging	412	N.D.	114	N.D.	N.D.	N.D.
Production Operator Morfax® Packaging	140	N.D.	53.9	N.D.	N.D.	N.D.

TABLE II
SUMMARY RESULTS FOR PERSONAL AIR AND GLOVE SAMPLES COLLECTED AT THE GOODYEAR NIAGARA FALLS PLANT DEPARTMENT 245 DURING 3/6-8/90

JOB TITLE OR SAMPLE LOCATION	ORTHO-TOLUIDINE OSHA/NIOSH & ACGIH PEL/REL = 22,000/8,000 µg/M³ TWA for Air No PEL's for Gloves		ANILINE OSHA/NIOSH & ACGIH PEL/REL = 8,000 µg/M³ TWA for Air No PEL's for Gloves		Proprietary Chemical OSHA/NIOSH & ACGIH PEL/REL = 5,000 µg/M³ TWA for Air No PEL's for Gloves	
	AIR[1] (µg/M³) TWA[2]	GLOVE[3] total µg/glove set	AIR µg/M³ TWA	GLOVE total µg/glove set	AIR µg/M³ TWA	GLOVE total µg/glove set
Chemical Operator Morfax® Reactor	301	N.D.	117	N.D.	N.D.	N.D.
Chemical Operator Morfax® Reactor	249	N.D.	72.2	N.D.	N.D.	N.D.
Chemical Operator Morfax® Reactor	298	N.D.	110	N.D.	N.D.	N.D.
Chemical Operator Morfax® Reactor	433	N.D.	150	N.D.	N.D.	N.D.
Chemical Operator Morfax® Reactor	146	N.D.	82.6	N.D.	N.D.	N.D.
Chemical Operator Morfax® Steam Stripper	161	N.D.	69.9	N.D.	N.D.	N.D.
Chemical Operator Morfax® Steam Stripper	147	N.D.	60.6	N.D.	N.D.	N.D.
Chemical Operator Morfax® Steam Stripper	371	N.D.	161	N.D.	N.D.	N.D.
Chemical Operator Morfax® Charge Room	166	N.D.	91.3	N.D.	N.D.	N.D.
Chemical Operator Morfax® Charge Room	215	N.D.	112	N.D.	N.D.	N.D.
Chemical Operator Morfax® Charge Room	128	N.D.	71.6	N.D.	N.D.	N.D.

* = This operator had *o*-toluidine and aniline levels on the dermal liquid contact indicator badges that were likely due to absorption of liquid chemical.

1. The limit of detection for *o*-toluidine, aniline and the proprietary chemical for the air samples was 3, 4 and 100 micrograms per cubic meter respectively.
2. All air samples collected for the full work shift except for peaks collected only for duration of specific tasks.
3. The limit of detection for *o*-toluidine, aniline and the proprietary chemical for the glove sets was 70, 80 and 70 micrograms per glove set respectively.
4. N.D. = Analyte not detected during sample analysis.
5. N.T. = This type of sample not taken with this sample set.

Table III
Summary Of Urine Survey Participant Characteristics

Characteristic	Not Exposed	Exposed[1]
Urine Samples Provided		
Preshift only	2	2
Postshift only	1	4
Pre and postshift	33	47
Participant Characteristics		
Number male (%)	30 (90.9)	50 (94.3)
Number female (%)	3 (9.1)	3 (5.7)
Mean age	51.6	46.6
Number smokers (%)	12 (36.4)	21 (39.6)
Number nonsmokers (%)	21 (63.6	32 (60.4)
Ethnicity white (%)	25 (75.8)	46 (86.8)
Ethnicity other (%)	8 (24.2)	7 (13.2)

1. One individual, counted here as a participant in the exposed group, was omitted from subsequent statistical summaries because his urine had an exceptionally high aniline concentration which would have unduly influenced the statistical analysis.

TABLE IV
SUMMARY RESULTS FOR
AREA AIR SORBENT TUBE AND LIQUID INDICATOR BADGE SAMPLE PAIRS
COLLECTED AT THE GOODYEAR NIAGARA FALLS PLANT, DEPARTMENT 245
DURING 3/6-8/90

SAMPLE LOCATION	ORTHO-TOLUIDINE OSHA/NIOSH & ACGIH PEL/REL=22,000/9,000 µg/M³ TWA for Air - No PEL's for Dermal		ANILINE OSHA/NIOSH & ACGIH PEL/REL=8,000 µg/M³ TWA for Air - No PEL's for Dermal		Proprietary Chemical OSHA/NIOSH & ACGIH PEL/REL=5,000 µg/M³ TWA for Air - No PEL's for Dermal	
	AIR[1] (µg/M³) TWA[2]	DERMAL[3] µg/sample	AIR µg/M³ TWA	DERMAL µg/sample	AIR µg/M³ TWA	DERMAL µg/sample
Break Room Area	36.8	N.T.[4]	3.90	N.T.	N.D.[5]	N.T.
Break Room Area	98.2	N.D.	19.5	N.D.	N.D.	N.D.
Break Room Area	150	64.0	58.7	N.D.	156	N.D.
Morfax® Charge Room Area	160	N.T.	92.5	N.T.	N.D.	N.T.
Morfax® Charge Room Area	116	144	78.7	N.D.	N.D.	N.D.
Morfax® Charge Room Area	169	N.D.	114	N.D.	N.D.	N.D.
Flaker Area	1,210	264	351	216	N.D.	N.D.
Holding Tank Area	756	N.T.	219	N.T.	N.D.	N.T.
Holding Tank Area	2,310	368	669	224	N.D.	N.D.
Holding Tank Area	1,760	296	613	184	N.D.	N.D.
Knock Out Tank Area	1,260	N.T.	470	N.T.	N.D.	N.T.
Knock Out Tank Area	763	144	331	64.0	N.D.	N.D.
Reactor/Degasser Area - Wingstay®	1,420	336	583	272	N.D.	N.D.
Reactor/Degasser Area - Wingstay®	2,460	552	784	376	200	N.D.
Mezzanine Area - Premix	1,760	N.T.	1,380	N.T.	N.D.	N.T.
Mezzanine Area - Premix	1,560	376	1,350	640	N.D.	N.D.
Mezzanine Area - Premix	1,660	288	1,440	624	N.D.	N.D.
Pump House Area	828	N.T.	263.7	N.T.	N.D.	N.T.
Pump House Area	561	112	125	N.D.	N.D.	N.D.
Pump House Area	557	128	161	48.0	N.D.	N.D.
Reactor Mezzanine Area - Wingstay®	888	N.T.	280	N.T.	N.D.	N.T.
Reactor Mezzanine Area - Wingstay®	456	128	199	N.D.	N.D.	N.D.
Reactor Mezzanine Area - Wingstay®	S.I.[6]	304	S.I.	216	N.D.	N.D.
Reactor #1 Area - Wingstay®	2,330	N.T.	675	NT	N.D.	N.T.

1. The limit of detection for *o*-toluidine, aniline and the proprietary chemical for the air samples was 3, 4 and 100 micrograms per cubic meter respectively.
2. All area air samples collected for the full work shift.
3. Only one liquid indicator badge was placed with each area air sample. The limit of detection for the liquid indicator badges for *o*-toluidine, aniline and the proprietary chemical was 24, 32, and 8 micrograms per sample respectively.
4. N.D. = Analyte not detected during sample analysis.
5. N.T. = This type of sample not taken with this sample set.
6. S.I. = Sample result invalid due to pump failure.

TABLE VI
ANALYTICAL RESULTS FOR SURFACE WIPE SAMPLES COLLECTED AT THE GOODYEAR NIAGARA FALLS PLANT, DEPARTMENT 245 DURING 3/6-8/90

WIPE SAMPLE LOCATION	ANALYTE CONCENTRATION IN MICROGRAMS PER SAMPLE[1]		
	ORTHO-TOLUIDINE	ANILINE	PROPRIETARY CHEMICAL
Break Room Window Sill	N.D.[2]	N.D.	N.D.
Break Room Window Sill	N.D.	N.D.	N.D.
Pump House Chart Covers	N.D.	N.D.	N.D.
Pump House Chart Covers	N.D.	N.D.	N.D.
Charge Room Chart Covers	N.D.	N.D.	N.D.
Charge Room Chart Covers	N.D.	N.D.	N.D.
Nailax Reactor-Degasser Levers and Pump Switches	50.0	N.D.	N.D.
Nailax Reactor-Degasser Levers and Pump Switches	40.0	N.D.	N.D.
Holding Tank Area Valves and Stair Rails	N.D.	N.D.	N.D.
Holding Tank Area Valves and Stair Rails	N.D.	N.D.	N.D.
Pre-mix Mezzanine Area Poker, Gate & Ladder	N.D.	N.D.	N.D.
Pre-mix Mezzanine Area Poker, Gate & Ladder	N.D.	N.D.	N.D.
Reactor Mezzanine Reactor Valve Handles	N.D.	N.D.	N.D.
Reactor Mezzanine Reactor Valve Handles	N.D.	N.D.	N.D.
Knock-out Tank Area Valves, Switches & Rails	20.0	N.D.	N.D.
Knock-out Tank Area Valves, Switches & Rails	N.D.	N.D.	N.D.

1. The limit of detection for *o*-toluidine, aniline and the proprietary chemical was 20 micrograms per sample for wipe samples.
2. N.D. = Analyte not detected by sample analysis.

TABLE VII
ANALYSIS RESULTS FOR BULK PROCESS SAMPLES COLLECTED AT THE GOODYEAR NIAGARA FALLS PLANT DEPARTMENT 245 DURING 3/6-8/90

PROCESS MATERIAL	GC/MS FULL SCAN IDENTIFICATION[1]			GC/MS SIM[2] DETECTION
	ORTHO-TOLUIDINE	ANILINE	4-AMINOBIPHENYL	4-AMINOBIPHENYL
Raw Ortho-toluidine	N.T.[3]	N.T.	N.D.[4]	Yes
Raw Aniline	N.T.	N.T.	N.D.	Yes
Morpholine	Yes	Yes	N.D.	N.D.
Wingstay® Recycle	Yes	Yes	N.D.	N.D.
Wingstay® Final Product	Yes	Yes	N.D.	N.D.
Morfax® Reactor Feed	Yes	Yes	N.D.	Yes
Morfax® Final Product	N.D.	Yes	N.D.	N.D.
Mercaptobenzothiazole	N.D.	Yes	N.D.	N.D.
Benzothiazole	N.D.	Yes	N.D.	N.D.

1. GC/MS with a detection limit of 2.3 micrograms per sample.
2. GC/MS selected ion monitoring with a sensitivity of 0.23 nanograms per sample.
3. Sample not tested for this analyte.
4. Analyte not detected by sample analysis.

Table VIII
Urinary *o*-Toluidine And Aniline Concentrations In Unexposed And Exposed Workers

A. Urinary *o*-Toluidine Concentration (μg/L)[4]

Exposure Group	Preshift Mean (n)	Postshift Mean (n)[5]	Paired T-test[1] (n)
Unexposed	1.1 (n=32)	2.7 (n=32)	.0001 (n=31)
Exposed	18.5 (n=48)	103.7 (n=52)	.0001 (n=46)
Unpaired t-test[2]	.0001	.0001	

B. Urinary Aniline Concentration (μg/L)[3]

Exposure Group	Preshift Mean (n)	Postshift Mean[5] (n)	Paired T-test[1] (n)
Unexposed	2.7 (n=32)	3.8 (n=32)	.01 (n=31)
Exposed	17.4 (n=48)	32.3 (n=52)	.0001 (n=46)
Unpaired t-test[2]	.0001	.0001	

1. The paired t-test tests the significance of the difference between preshift and postshift samples by individual. Data were log transformed to achieve normality.
2. The unpaired t-test tests the difference between the exposed and unexposed groups for both preshift and postshift means. Data were log transformed to achieve normality.
3. In the unexposed, 13/32 preshift samples and 8/32 postshift samples were below the LOD for aniline of 1.4. In the exposed, 1/48 preshift samples and 0/52 postshift samples were below the LOD for aniline of 1.4.
4. In the unexposed, 15/32 preshift and 1/32 postshift samples were under the LOD for *o*-toluidine of 0.6. In the exposed, 2/48 preshift and 0/52 postshift samples were below the LOD of 0.6.
5. The total number of postshift samples in exposed workers (52) is two greater than the total number of exposed individuals who submitted postshift samples (50) in Table I because two individuals provided postshift urine samples on two survey days.

Table IX
Urinary *o*-Toluidine And Aniline Concentrations In Unexposed Workers By Smoking Status

A. Urinary *o*-Toluidine Concentration (μg/L)[4]

Smoking Status	Preshift Mean (n)	Postshift Mean (n)	Paired T-test[1] (n)
Nonsmokers	1.2 (n=20)	2.8 (n=21)	.0001 (n=20)
Smokers	1.0 (n=12)	2.6 (n=11)	.0001 (n=11)
Unpaired t-test[2]	.60	.74	

B. Urinary Aniline Concentration (μg/L)[3]

Smoking Status	Preshift Mean (n)	Postshift Mean (n)	Paired T-test[1] (n)
Nonsmokers	1.8 (n=20)	2.7 (n=21)	.04 (n=20)
Smokers	4.1 (n=12)	5.8 (n=11)	.15 (n=11)
Unpaired t-test[2]	.02	.01	

1. The paired t-test tests the significance of the difference between preshift and postshift samples by individual. Data were log transformed to achieve normality.
2. The unpaired t-test tests the difference between smokers and nonsmokers for both preshift and postshift means. Data were log transformed to achieve normality.
3. In the nonsmokers, 12/20 preshift samples and 7/21 postshift samples were below the LOD for aniline of 1.4. In the smokers, 1/12 preshift samples and 1/11 postshift samples were below the LOD for aniline of 1.4.
4. In the nonsmokers, 10/20 preshift and 1/21 postshift samples were under the LOD for *o*-toluidine of 0.6. In the smokers, 5/12 preshift and 0/12 postshift samples were below the LOD of 0.6.

Table X
Urinary *o*-Toluidine And Aniline Concentrations In Exposed Workers By Smoking Status

A. Urinary *o*-Toluidine Concentration (μg/L)

Smoking status	Preshift Mean (n)	Postshift Mean (n)	Paired T-test[1] (n)
Nonsmokers	17.5 (n=29)	83.9 (n=32)	.0001 (n=29)
Smokers	20.0 (n=19)	135.6 (n=20)	.0001 (n=17)
Unpaired t-test[2]	.10	.05	

B. Urinary Aniline Concentration (μg/L)

Smoking status	Preshift Mean (n)	Postshift Mean (n)	Paired T-test[1] (n)
Nonsmokers	14.6 (n=29)	23.6 (n=32)	.0001 (n=29)
Smokers	21.8 (n=19)	46.1 (n=20)	.0002 (n=17)
Unpaired t-test[2]	.06	.003	

1. The paired t-test tests the significance of the difference between preshift and postshift samples by individual. Data were log transformed to achieve normality.
2. The unpaired t-test tests the difference between smokers and nonsmokers for both preshift and postshift means. Data were log transformed to achieve normality.

Table XI
Urinary *o*-Toluidine And Aniline Concentrations By Job Area Within Exposure Group

A. Urinary *o*-Toluidine Concentration (μg/L)

Job/area	Preshift Mean (n)	Postshift Mean (n)	Paired T-test[1](n)
Morfax®	12.9 (n=19)	52.4 (n=19)	.0001 (n=19)
Wingstay®	27.9 (n=26)	130.4 (n=26)	.0001 (n=20)
Maintenance	3.9 (n=7)	144.1 (n=7)	.001 (n=7)
Unpaired t-test[2]	.0001	.09	

B. Urinary Aniline Concentration (μg/L)

Job/area	Preshift Mean (n)	Postshift Mean (n)	Paired T-test[1](n)
Morfax®	9.9 (n=19)	18.2 (n=19)	.0001 (n=19)
Wingstay®	27.0 (n=22)	44.3 (n=26)	.0008 (n=20)
Maintenance	7.7 (n=7)	25.6 (n=7)	.0004 (n=7)
Unpaired t-test[2]	.009	.0001	

1. The paired t-test tests the significance of the difference between preshift and postshift samples by individual. Data were log transformed to achieve normality.
2. The unpaired t-test tests the difference between Wingstay® and Morfax® workers for both preshift and postshift means. Data were log transformed to achieve normality.

Table XII
Airborne *o*-Toluidine and Aniline Levels By Job Area

A. *o*-Toluidine

Exposure Group	Air Levels ($\mu g/m^3$)		
	Mean	Geometric Mean	n
Morfax®	312.3	244.2	17
Wingstay®	516.6	442.3	15
Maintenance	595.2	401.2	4
t-test[1] Geometric Mean	.0001		

B. Aniline

Exposure Group	Air Levels ($\mu g/m^3$)		
	Mean	Geometric Mean	n
Morfax®	122.8	95.6	17
Wingstay®	240.3	190.2	16
Maintenance	163.1	145.0	4
t-test[1] Geometric Mean	.004		

1. The unpaired t-test tests the difference between Wingstay® and Morfax® workers for both geometric mean air and dermal levels. Data were log transformed to achieve normality.

Table XIII
Comparison Of Relative Values Of Various Exposure Measures By Department

Ratio of *o*-Toluidine:Aniline			
Department	Air	Preshift Urine	Postshift Urine
Morfax®	2.5	1.3	2.9
Wingstay®	2.0	1.0	2.9
Maintenance	2.2	0.5	5.6
Ratio of Wingstay®:Morfax®			
Chemical	Air	Preshift Urine	Postshift Urine
o-Toluidine	2.0	2.2	2.5
Aniline	2.5	2.7	2.4

Table XIV
o-Toluidine Concentrations In Urine Collected From Individuals Working In Department 245, By Job/Area
(μg *o*-toluidine per liter urine)

Job/area	Preshift			Postshift		
	n	Mean	Range	n	Mean	Range
Chemical Operator, Morfax® Steam Stripper	3	13.3	6.5-26.2	3	49.2	31.4-83.0
Chemical Operator, Morfax® Reactor	4	12.0	4.4-22.0	4	50.4	42.4-60.2
Chemical Operator, Morfax® Charge Room	2	17.6	13.0-22.2	2	43.6	42.4-44.7
Production Operator, Morfax® Packaging	6	13.8	2.9-32.5	6	52.4	21.7-111.4
Area Manager, Morfax®	3	12.4	8.0-18.7	3	70.6	30.5-114.6
Chemical Operator, Wingstay® Reactor	5	59.3	13.8-178.3	6	138.9	44.1-289.7
Chemical Operator, Wingstay® C2 Building	3	11.8	0.3-28.9	3	64.3	38.8-82.1
Chemical Operator, Wingstay® Utility	2	17.3	9.8-24.8	3	70.0	64.4-80.6
Production Operator, Wingstay® Utility	3	23.1	11.7-38.4	2	289.8	105.1-474.4
Production Operator, Wingstay® Packaging	4	16.2	3.2-33.9	6	70.2	14.1-143.5
Production Operator, Wingstay® Utility/ Packaging	2	10.5	8.7-12.4	2	111.9	59.7-164.1
Area Manager, Wingstay®	3	30.8	10.2-48.8	4	231.8	76.1-527.0
Maintenance	7	3.9	.30-9.0	7	144.1	61.0-487.9

Table XIV (continued)
Aniline Concentrations In Urine Collected From Individuals Working In Department 245, By Job/Area
(μg aniline per liter urine)

Job/area	Preshift			Postshift		
	n	Mean	Range	n	Mean	Range
Chemical Operator, Morfax® Steam Stripper	3	5.8	5.1-7.0	3	22.0	10.5-35.1
Chemical Operator, Morfax® Reactor	4	9.4	4.2-13.0	4	17.8	15.0-21.7
Chemical Operator, Morfax® Charge Room	2	16.1	5.1-27.2	2	22.8	22.4-23.3
Production Operator, Morfax® Packaging	6	9.3	3.1-11.3	6	15.7	6.4-26.0
Area Manager, Morfax®	3	10.0	7.2-11.9	3	18.9	14.9-24.8
Chemical Operator, Wingstay® Reactor	5	27.5	18.0-52.4	6	47.6	22.7-100.7
Chemical Operator, Wingstay® C2 Building	3	4.8	0.8-9.1	3	26.9	13.7-38.1
Chemical Operator, Wingstay® Utility	2	11.5	9.5-13.4	3	16.0	13.8-17.3
Production Operator, Wingstay® Utility	3	42.8	14.2-75.1	2	87.6	52.0-123.3
Production Operator, Wingstay® Packaging	4	40.2	9.6-91.0	6	39.3	11.5-101.4
Production Operator, Wingstay® Utility/ Packaging	2	22.6	11.6-33.6	2	47.1	40.3-53.8
Area Manager, Wingstay®	3	28.7	6.6-43.1	4	58.5	27.3-111.0
Maintenance	7	7.7	2.0-15.3	7	25.6	13.2-39.0

Table XV
Airborne Levels Of *o*-Toluidine And Aniline By Job[1]

Job/Area	n	*o*-Toluidine Air Levels ($\mu g/m^3$)		Aniline Air Levels ($\mu g/m^3$)	
		Mean	G.M.	Mean	G.M.
Chemical Operator, Morfax® Steam Stripper	3	226.5	206.5	97.2	88.1
Chemical Operator, Morfax® Reactor	4	251.1	241.1	95.1	93.3
Chemical Operator, Morfax® Charge Room	2	171.1	165.5	91.8	89.5
Production Operator, Morfax® Packaging	6	471.5	318.9	180.6	113.7
Area Manager, Morfax®	3	226.9	212.7	73.8	72.8
Chemical Operator, Wingstay® Reactor	6	469.7	460.7	180.7	179.3
Chemical Operator, Wingstay® C2 Building	3	374.9	367.7	315.3	306.4
Chemical Operator, Wingstay® Utility	4	440.3	438.2	106.3	106.1
Production Operator, Wingstay® Utility	3	891.6	632.2	414.5	273.1
Production Operator, Wingstay® Packaging	6	498.5	395.2	250.4	181.2
Area Manager, Wingstay®	4	475.1	467.8	189.3	181.7
Maintenance	7	595.2	401.2	163.1	145.0

1. No air samples were collected from individuals working in the job category "Production Operator Wingstay 100 Utility/Packaging".

Table XVI
Regression Models Relating Airborne With Urine Levels

A. *o*-Toluidine

Outcome	Factor		1 Factor Models		2 Factor Models
			Air	Smoke	Air/Smoke
Post Toluidine (Log trans)	Model r2[1]		.19	.13	.30
	Air	Cf[2]	.0008		.0007
		p	.01		.01
	Smoke	Cf[3]		.52	.47
		p		.05	.05
Post-Pre Toluidine (Sqrt trans)	Model r2[1]		.33	.16	.46
	Air	Cf[2]	.005		.004
		p	.0006		.0005
	Smoke	Cf[3]		2.8	2.5
		p		.02	.01

1. Model R2 = percent of overall variation in the outcome variable explained by the predictor variables.
2. Cf = coefficient for the term for air level in the regression.
3. Cf = coefficient for the term for smoking in the regression.

Table XVI (continued)
Regression Models Relating Airborne With Urine Levels

B. Aniline

Outcome	Factor		1 Factor Models		2 Factor Model
			Air	Smoke	Air/Smoke
Post Aniline	Model r2		.46	.15	.52
	Air	Cf	.09		.09
		p	.0001		.0001
	Smoke	Cf		19.8	13.6
		p		.03	.05
Post-Pre Aniline	Model r2		.24	.11	.30
	Air	Cf	.06		.05
		p	.005		.01
	Smoke	Cf		14.1	10.5
		p		.06	.12

1. Model R2 = percent of overall variation in the outcome variable explained by the predictor variables.
2. Cf = coefficient for the term for air level in the regression.
3. Cf = coefficient for the term for smoking in the regression.

FIGURE I
Starting And Intermediate Chemicals Found In Department 245

Wingstay® Products (Diaryl-*p*-phenylenediamine)	Morfax® (Kagarax) (*4*-morpholinyl-*2*-benzothiazole disulfide)
Chemicals Present As Starting Materials	
o-Toluidine	Morpholine
Aniline	Aniline
Hydroquinone	Carbon Disulfide
Toluene	Proprietary Chemical
Phenol	Sulfur
Ferric Chloride	Sodium Hydroxide
Diphenylamine (RWC4396 only)	Marcaptobenzothiazole
Sodium Carbonate	Isopropyl Alcohol
Mixed Xylidines	Sodium Sulfide
Diaryl *p*-Phenylene	Chlorine
	Benzothiazole
	Sulfuric Acid
	Paraffinic Oil
Chemicals That Are Present As Process Intermediates (formed during process)	
Wingstay® Products (Diaryl-*p*-phenylenediamine)	**Morfax® (Kagarax) (*4*-morpholinyl-*2*-benzothiazole disulfide)**
Diphenylamine	Mercaptobenzothiazole
Phenol	Benzothiazole
Diaryl *p*-Phenylene	Sodium Hypochlorite

FIGURE 2

Wingstay® 100 Process Chemistry

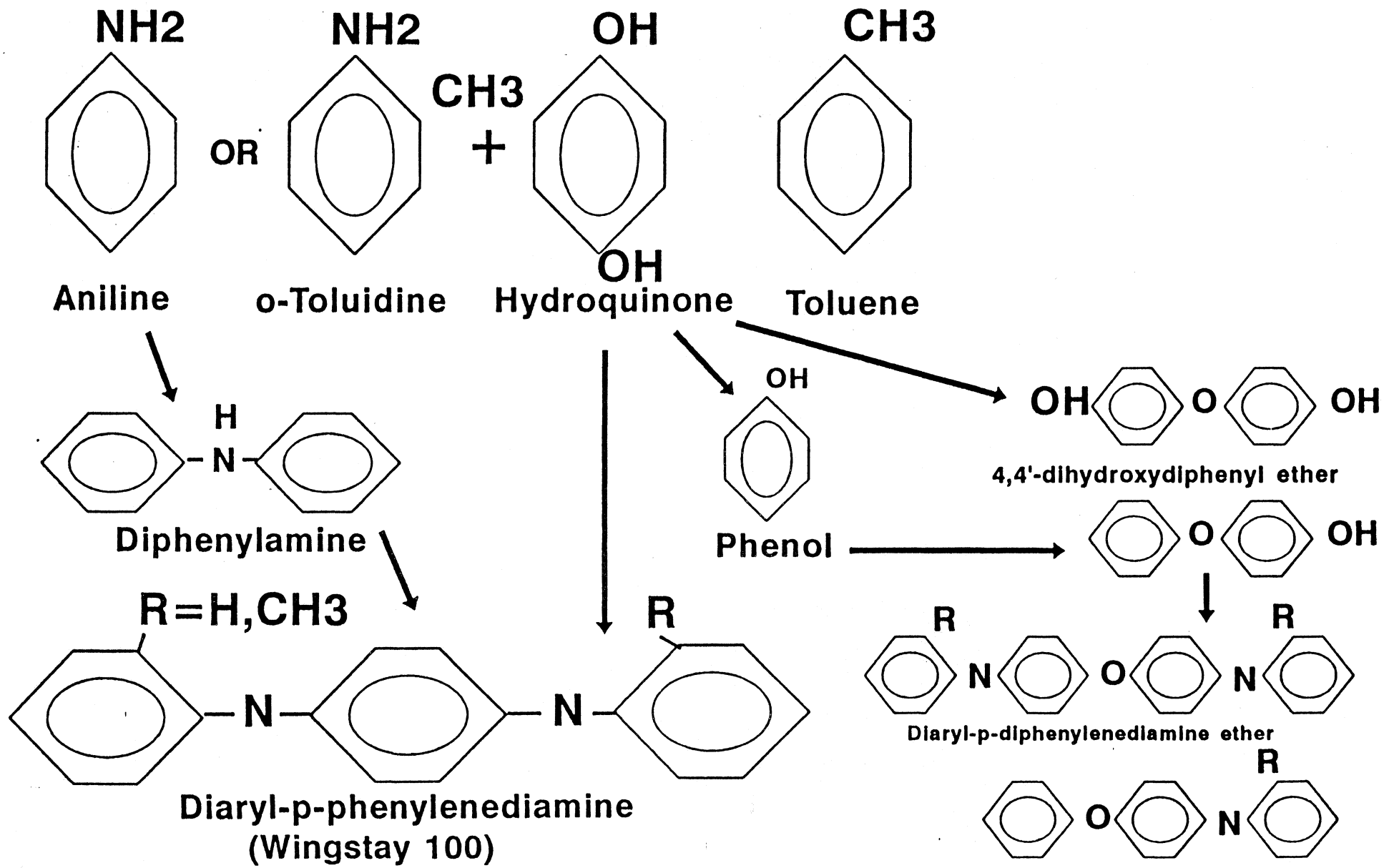


FIGURE 3

Morfax® Process Chemistry

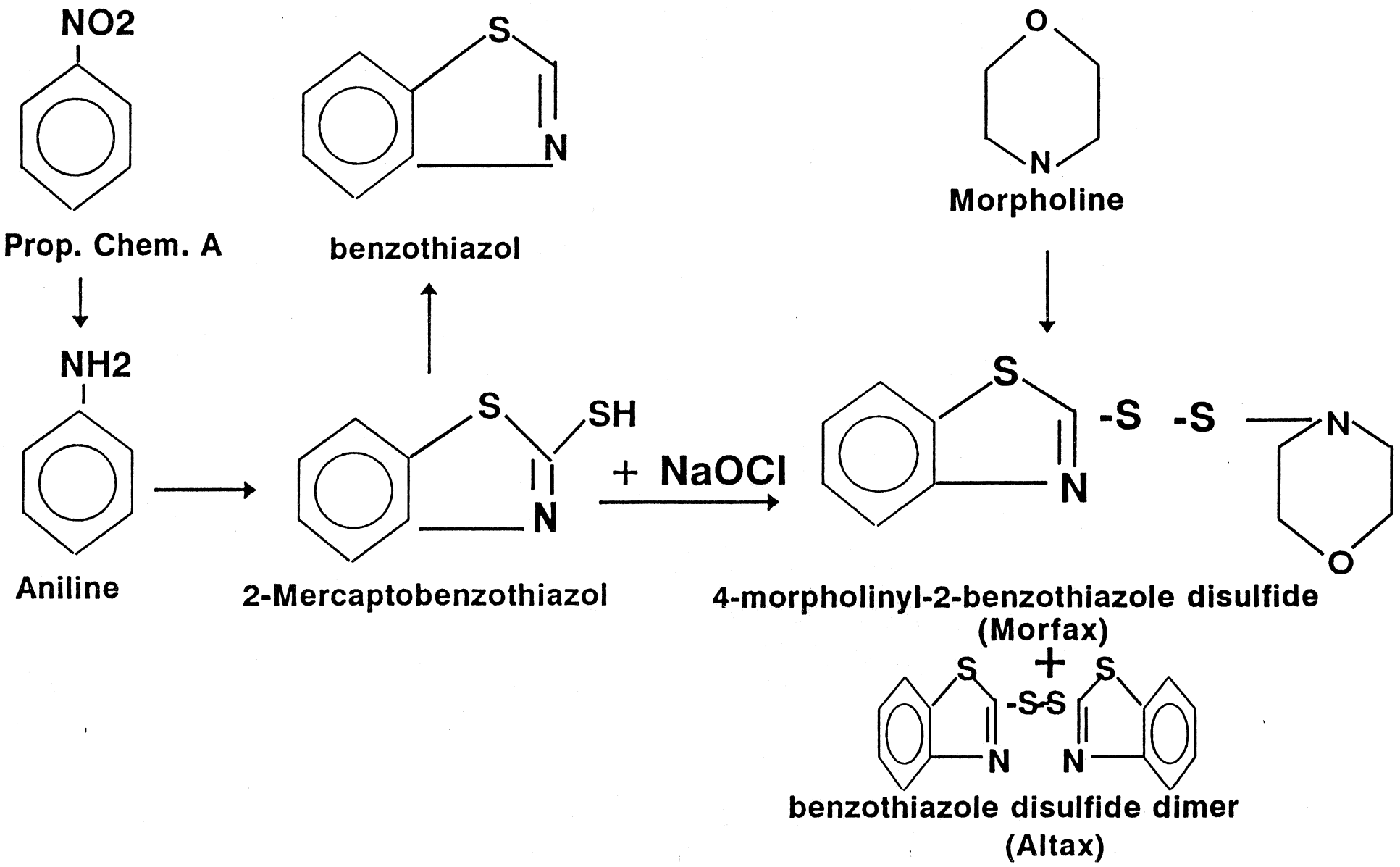


FIGURE 4
WINGSTAY® Job Titles and Job Task Descriptions

Job Title	Tasks
Area Manager, Wingstay®	1. Supervise 7-20 hourly employees who report directly to him/her in the operation of plant systems to maximize production and product quality. 2. Obtain maximum production from the equipment with regard to meeting customer specifications with the least amount of downtime. 3. Direct laboratory and maintenance personnel as necessary to achieve optimum results. 4. Receive information from previous Area Manager as to production specifications, equipment breakdown, and what maintenance will be required to put equipment back into production. 5. Receive overall priorities from the Operations Manager and make necessary changes in personnel and equipment to achieve these priorities.
Chemical Operator, Wingstay® Reactors (2 per shift)	1. Charge reactor. 2. Fill pre-mix tank. 3. Transfer reactor to degasser. 4. Neutralize degasser. 5. Pull vacuum cuts on degasser. 6. Transfer degasser to holding tanks. 7. Make up neutralizer. 8. Sample finished product holding tanks. 9. Sample recycle tank.

FIGURE 4
WINGSTAY® Job Titles and Job Task Descriptions

Job Title	Tasks
Chemical Operator, C-2 Building (1 per shift)	1. Start extraction. 2. Start bleach manufacture. 3. Start isopropyl alcohol (isol) recovery. 4. Sample all processes. 5. Clean process strainers. 6. Make-up brine.
Chemical Operator, Wingstay® Utility (3 per day shift, 1 per other shifts)	1. Cover for operator absences (Wingstay® and Morfax®). 2. Transport bagged raw material. 3. Unload and sample tank farm raw materials. 4. Haul trash. 5. General housekeeping.
Production Operator, Wingstay® Utility (1 per shift)	1. Clean sparkler filter. 2. Load hydroquinone to pre-mix tanks. 3. Clean hercules filter. 4. Load Wingstay® rejects to the tar knockout tank. 5. Clean pre-mix strainer. 6. Load Wingstay® tank car.
Production Operator, Wingstay® Packaging (2 per shift)	1. Bag Wingstay® and stack on skid. 2. Drumming liquid Wingstay®. 3. Flaking Wingstay® to drums. 4. Start up Wingstay® flaker. 5. Clean system. 6. Help clean sparkler filter.

FIGURE 4
WINGSTAY® Job Titles and Job Task Descriptions

Job Title	Tasks
Maintenance Operator, Department 245	1. Maintain and install all machinery, equipment and miscellaneous mechanical devices throughout the plant. 2. Read and interpret detailed drawings or blue prints of machines and pipe systems. 3. Align work, set up equipment, fit keys, make file fits, fit bearings, drill, tap ream holes and other mechanical operations necessary for maintenance and installation work. 4. Use precision measuring instruments, and machinist tools such as steel taps, level, scale, protractor, scraper, hammer, chisel, wrenches, etc.. 5. Make sketches, measure pipe jobs, cut thread and fit pipe for water, steam, air, oil and vinyl chloride. 6. Install gauges, regulators, strainers, condensers, syphons, diaphragms, thermostats, etc.. 7. Know various metals and their characteristics. 8. Install packing and gaskets. 9. Know the function of valves and make the proper selection for a job and be able to repair valves. 10. Practice all safety and fire rules.

FIGURE 5
Morfax® Job Titles And Job Task Descriptions

Job Title	Tasks
Area Manager Morfax®	1. Supervise 7-20 hourly employees, who report directly to him/her, in the operation of plant systems to maximize production and product quality. 2. Obtain maximum production from the equipment with regard to meeting customer specifications with the least amount of downtime. 3. Direct laboratory and maintenance personnel as necessary to achieve optimum results. 4. Receive information from previous Area Manager as to production specifications, equipment breakdown, and what maintenance will be required to put equipment back into production. 5. Receive overall priorities from the Operations Manager and make necessary changes in personnel and equipment to achieve these priorities.
Chemical Operator, Morfax® Steam Stripper	1. Fill pellet tank with raw materials for start-up. 2. Circulate pellet tank to pelletizer. 3. Start autoclaves venting to system. 4. Switch to new feed blend tank & flush lines with isopropyl alcohol. 5. Monitor system and take readings. 6. Pump up completed blend & isopropyl alcohol flush lines. 7. Shut system down. 8. Clean pelletizer with caustic soda.

FIGURE 5
Morfax® Job Titles And Job Task Descriptions

Job Title	Tasks
Chemical Operator, Morfax® Reactor (2 per shift)	1. Add raw materials to make up tank. 2. Pump make-up tank to feed tank & flush lines. 3. Start up Reactor. 4. Relieve charge room operator. 5. Monitor & sample sulfur recovery unit. 6. Take tank farm tank levels and temperature readings.
Chemical Operator, Morfax® Charge Room (1 per shift)	1. Make up sulfur & carbon disulfide mixture batches. 2. Make up benzothiazole, aniline & proprietary chemical blend. 3. Make up sodium hydroxide. 4. Monitor & adjust water levels in sulfur & carbon disulfide mixture pump pots. 5. Monitor pumping ratio readings. 6. Monitor sulfur recovery unit on natural gas (when charge room is down).
Production Operator, Morfax® Packaging (2 per shift)	1. Bag Morfax®. 2. Add Morfax® rework to rework hopper. 3. Empty dust collector. 4. Clean dryer and change dryer grids. 5. Clean lines with sodium sulfide. 6. Housekeeping (sweeping & shoveling Morfax®)

FIGURE 6

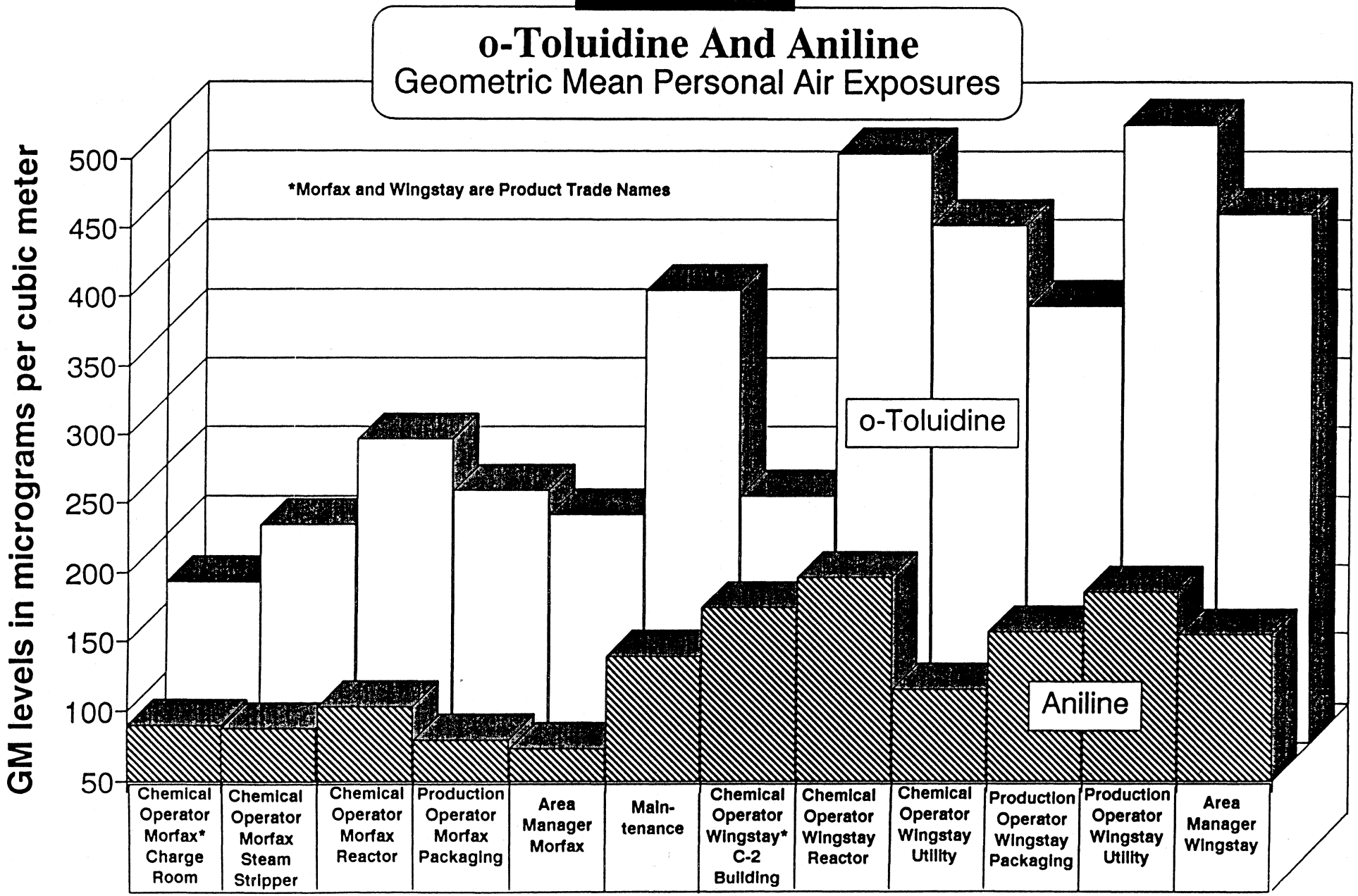

o-Toluidine And Aniline
Geometric Mean Personal Air Exposures
*Morfax and Wingstay are Product Trade Names
GM levels in micrograms per cubic meter
500
450
400
350
300
250
200
150
100
50
o-Toluidine
Aniline
Chemical Operator Morfax* Charge Room
Chemical Operator Morfax Steam Stripper
Chemical Operator Morfax Reactor
Production Operator Morfax Packaging
Area Manager Morfax
Main-tenance
Chemical Operator Wingstay* C-2 Building
Chemical Operator Wingstay Reactor
Chemical Operator Wingstay Utility
Production Operator Wingstay Packaging
Production Operator Wingstay Utility
Area Manager Wingstay

FIGURE 7

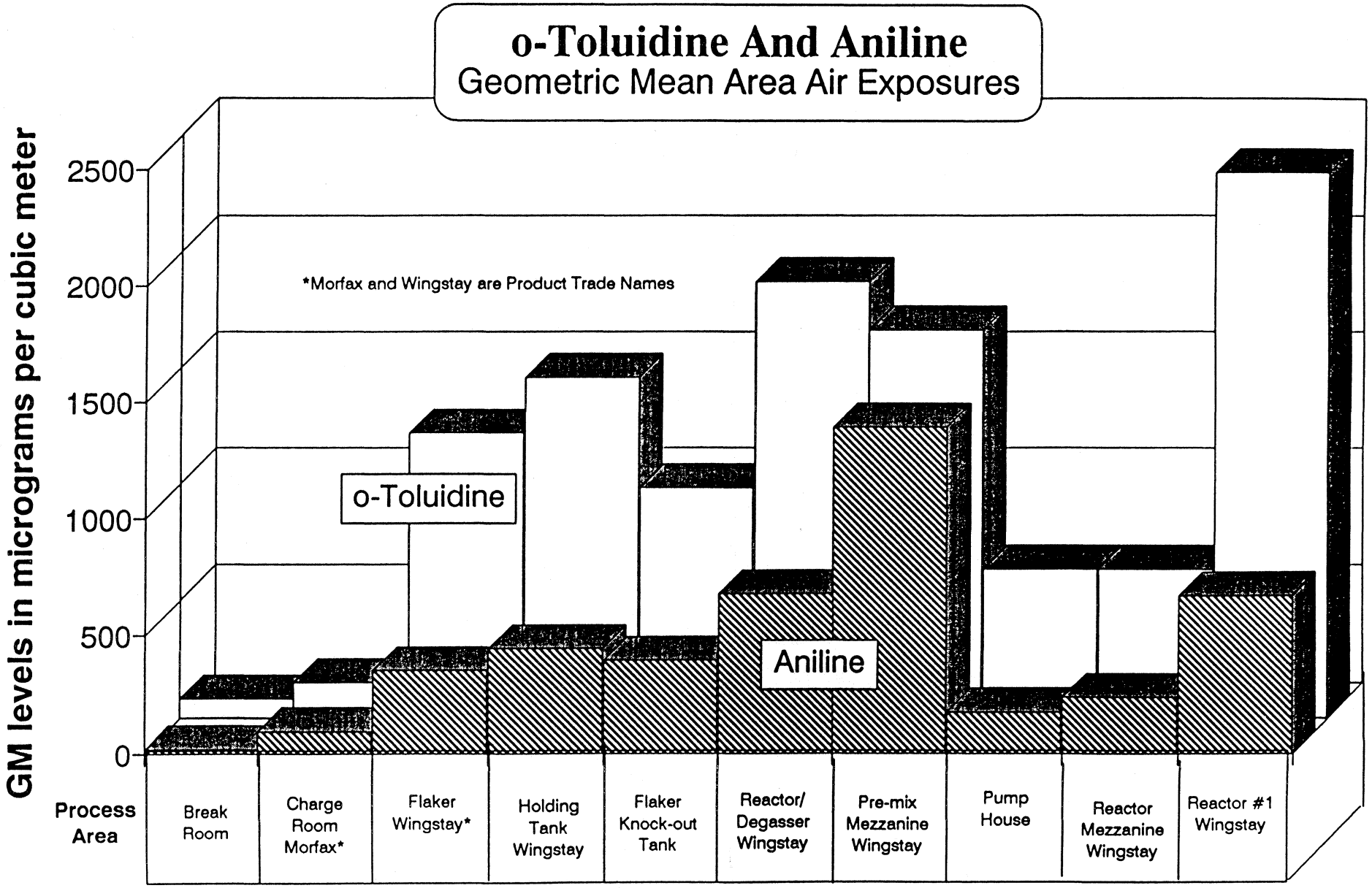
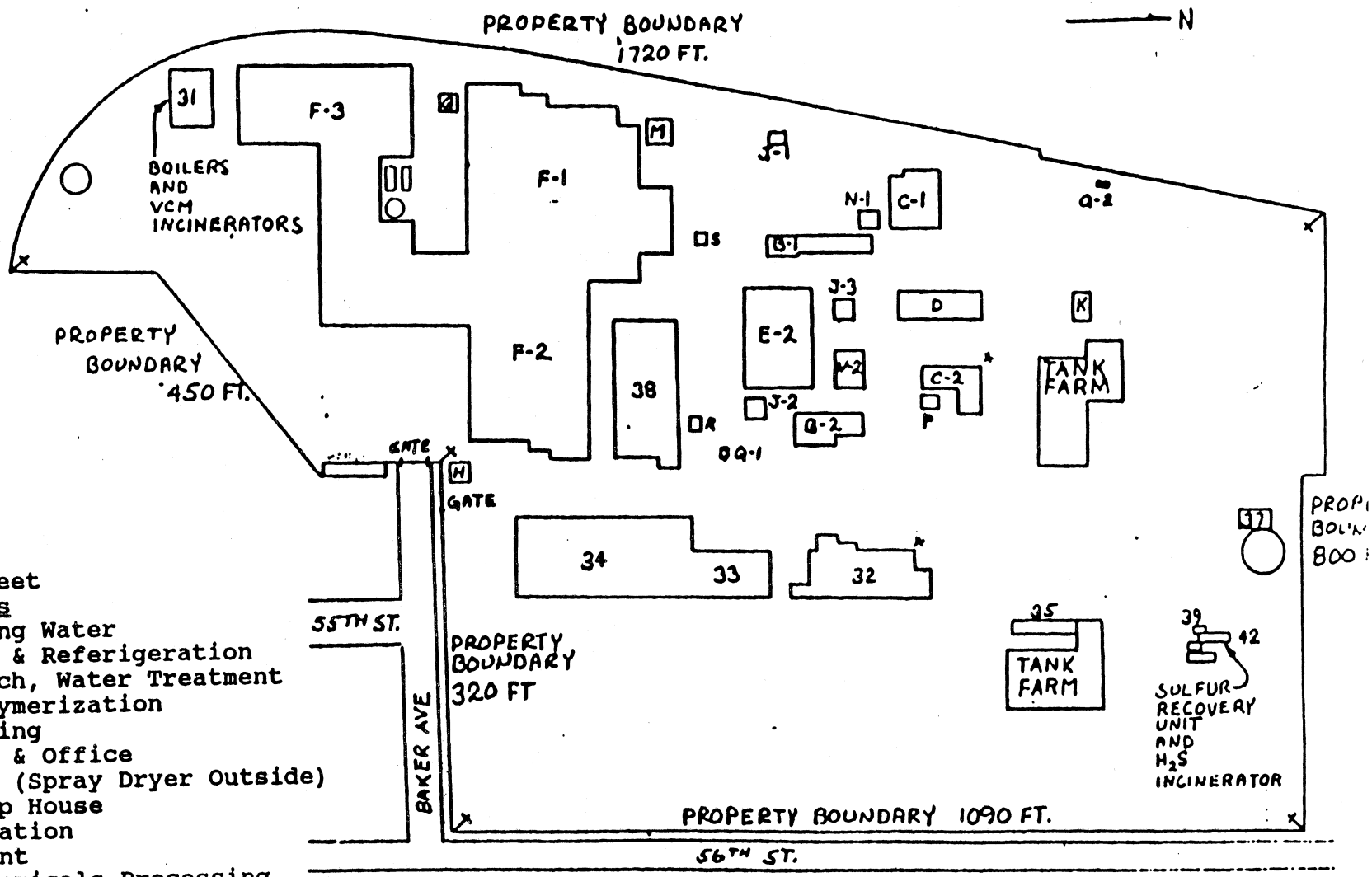

o-Toluidine And Aniline
Geometric Mean Area Air Exposures
GM levels in micrograms per cubic meter
2500
2000
1500
1000
500
0
*Morfax and Wingstay are Product Trade Names
o-Toluidine
Aniline
Process Area
Break Room
Charge Room Morfax*
Flaker Wingstay*
Holding Tank Wingstay
Flaker Knock-out Tank
Reactor/ Degasser Wingstay
Pre-mix Mezzanine Wingstay
Pump House
Reactor Mezzanine Wingstay
Reactor #1 Wingstay

FIGURE 8

Goodyear Niagara Falls, Plant Layout



Scale 1"=193 feet

Major Buildings

B-1	B-2 Cooling Water
C-1	VC Unload & Referigeration
C-2	Iso, Bleach, Water Treatment
E-2	Vinyl Polymerization
F-1	Vinyl Drying
F-2	Warehouse & Office
F-3	Warehouse (Spray Dryer Outside)
K	Vinyl Pump House
N-2	Referigeration
31	Steam Plant
32	Rubber Chemicals Processing
33	Rubber Chemicals Finishing
34	Rubber Chemicals Offices & Warehouse
35	Rubber Chemicals Pump House
37	Air Compressors and Fire Water
39, 42	Sulfur Removal, Etc.

GOODYEAR TIRE AND RUBBER COMANY
NIAGARA FALLS, NEW YORK
33.5 Acres

FIGURE 9

Wingstay® Process Flow Diagram

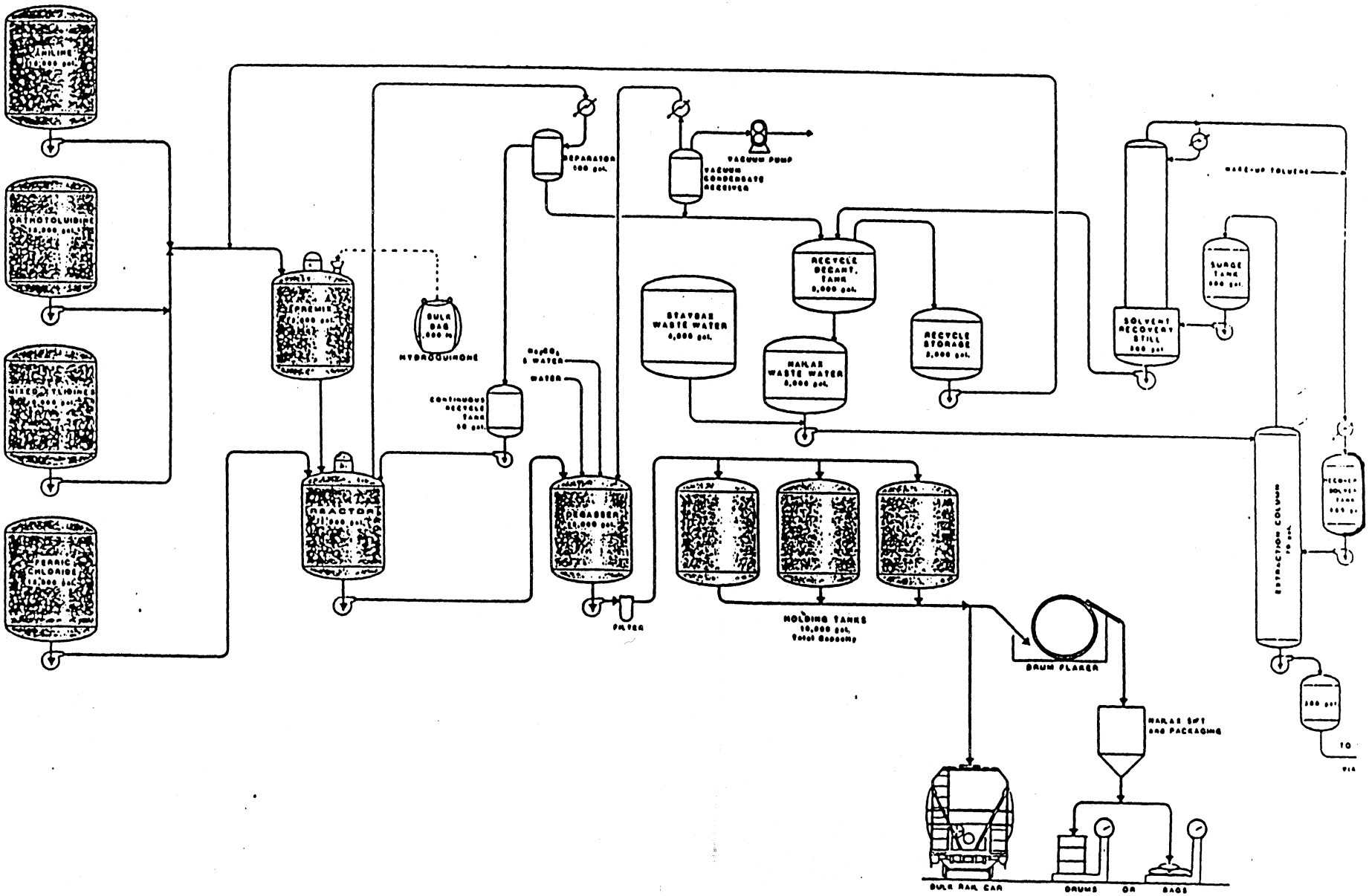
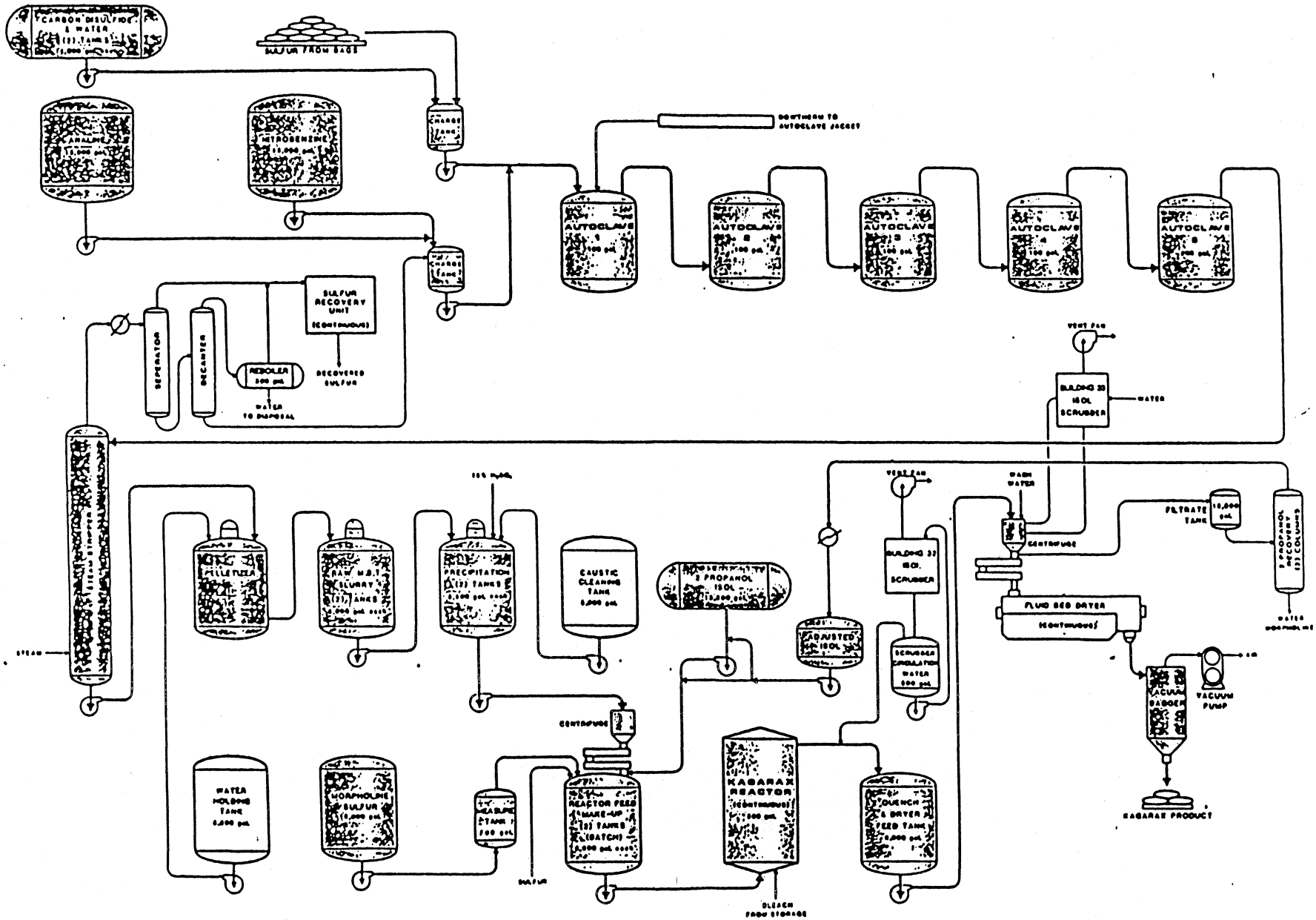


FIGURE 10

Morfax® Process Flow Diagram



XIII. APPENDICES

A. Appendix A: Environmental Monitoring and Analysis Methods

1. Air Monitoring and Analysis Methods

a. Air Monitoring Methods

The OSHA 73 method used two stacked sulfuric acid treated 37 mm diameter 0.8 μm pore size glass fiber filters (GFF) in a closed face cassette. The filters were separated by a spacer using no support pads for either filter. The filter cassette was followed in line by a 520/260 milligram (mg) silica gel tube. This media assembly was connected by tubing to an SKC Model 224-PCXR7 personal air sampling pump set in low-flow mode and each pump was pre-calibrated to operate at 400 cubic centimeters per minute (cc/minute) with a variable limiting orifice. A total air volume not exceeding 100 liters was sampled in accordance with the OSHA 73 method. A preliminary laboratory study showed that the proprietary chemical was not trapped by the filters and did not interfere with the collection of aniline and *o*-toluidine while passing through the filters.

The filter tube and pump sampling trains were placed on the workers at the beginning of the work shift such that the air inlet was fastened in the breathing zone. The air sampling media was changed at mid-shift after about 100 liters of air flow. At the end of the shift the sampling train was removed, the cassettes plugged, the tubes capped, and both were later stored in refrigeration until laboratory analysis. The sampling pump calibration was checked and logged in at this time as well.

Passive area air sampling for all three agents was also conducted in tandem with the airdrawn area samples using the dermal monitoring badges which are described in the Dermal Sampling section.

b. Air Sample Analysis Methods

Samples were prepared by placing the two filters in separate 20 ml scintillation flasks designated as the A and B sections of each sample. Quality control (QC) spikes were received on dry acid treated filters in 20 ml scintillation flasks and were treated the same as the samples. To each sample and QC, 3 ml of deionized (DI) water, 1 ml .5 N NaOH, and 2 ml of toluene were added. They were then shaken for 10 minutes and the phases allowed to separate prior to transferring at least 1 ml of the toluene layer into 4 ml wisp vials.

All standards, samples, and QC spikes were derivitized by the addition of 24 ml of heptafluorobutyric acid anhydride (HFAA). They were then shaken for 10 seconds and the reaction allowed to

process for 10 minutes, after which, 1 ml of Ph 7.0 phosphate buffer was used to wash away the excess HFAA by shaking vigorously for 10 seconds and allowing phases to separate. The toluene layer was then transferred to a gas chromatograph (GC) vials for analysis.

The analysis was performed on a HP5890 GC equipped with an electron capture detector. A 6' x 2 millimeter (mm) internal diameter (ID) glass column packed with 3% OV-101 on 100/120 mesh Suplcoport was used for separation of the analyte, at an isothermal temperature of 100 °C.

The NIOSH calculated limit of detection (LOD) for the filter samples was 0.4 µg/sample for aniline, and 0.3 µg/sample for *o*-toluidine. The calculated limit of quantitation (LOQ) was 2 µg/sample for aniline, and 1 µg/sample for *o*-toluidine.

The silica gel tubes were separated into A (front) and B (back) sections and analyzed by gas chromatography according to NIOSH Method 2005 with the following modifications.

Desorption Process:	1 hour with sonication in 1.0 ml methanol containing 1.0 microliter per milliliter (µL/ml) ethyl benzene as an internal standard.
Gas Chromatograph:	Hewlett-Packard Model 5890 equipped with a flame ionization detector.
Column:	30 meter (m) x 0.32 mm fused silica capillary column coated internally with 1.0 micron SPB-5.
Oven Conditions:	Programmed from 110 °C (held for 6 minutes) to 250 °C at a rate of 50 °C/minute.

Known amounts of the proprietary chemical, aniline and *o*-toluidine were spiked onto the A section of silica gel tubes and were desorbed the same as the samples. The calculated LOD and LOQ for proprietary chemical A were 10 and 20 µg/sample respectively.

2. Dermal Monitoring and Analysis Methods

a. Liquid indicator badge Monitoring Method

Five silica gel samplers, or liquid indicator badges, were placed on each worker monitored, one each at each shirt lapel, each forearm, and on the chest. The liquid indicator badges were placed on and removed from the workers at the same time the air sampling trains were attached. It was determined by laboratory testing that it was not necessary to change the badges during the

workshift. After removal, the badges were placed in pre-labeled 20 ml scintillation vials which were then capped, shrink banded and refrigerated until sample analysis.

b. Liquid indicator badge Analysis Method

The silica gel from each liquid indicator badge sample was desorbed in 8 ml of absolute ethanol for 1.5 hours in a sonication bath. After the desorption period, 1 ml aliquots of each sample were transferred to autosampler vials and analyzed by gas chromatography with flame ionization detection (GC/FID), using a HP5890 GC equipped with a 30 m DB-5 fused silica capillary column for *o*-toluidine, aniline, and proprietary chemical A. All analyses were performed in the splitless injection mode. The resultant sample recoveries were corrected for dilution effects.

The calculated limits of detection for aniline, *o*-toluidine and the proprietary chemical for the liquid indicator badge samples were 4.00, 3.00 and 1.00 µg/sample respectively, and the calculated limits of quantitation were 12.0, 9.00 and 3.00 µg/sample respectively.

c. Glove Monitoring Method

The gloves were given to the workers at the same time the air sampling trains and liquid indicator badges were attached, and the workers were directed to wear the cotton gloves underneath their usual work gloves when they were worn. The workers usually only wore their work gloves while actually in the process area, so they were instructed to remove the cotton gloves after removing their work gloves (without touching the cotton gloves with their work gloves) and to place them inside each respective work glove. This procedure was reversed when the gloves were put back on. The gloves were collected at the same time as the air and liquid indicator badge media at the end of the work shift. They were then placed in 40 ml brown glass bottles, which were then capped, shrink banded and refrigerated until laboratory analysis.

d. Glove Analysis Method

The glove samples were extracted with ethanol and analyzed by gas chromatography according to NIOSH Method 2002 with the following modifications.

Extraction Process: 8 hours by shaking in 80 ml ethanol containing 1.0 µl/ml ethyl benzene as an internal standard.

Gas Chromatograph: Hewlett-Packard Model 5710A equipped with a flame ionization detector.

Column:	30 m x 0.32 mm fused silica capillary column coated internally with 1.0 micron DB-5.
Oven Conditions:	Programmed from 120 °C (held) for 8 minutes) to 250 °C at a rate of 32 °C/minute and held for 4 minutes.

The calculated limits of detection for the gloves for aniline, o-toluidine and the proprietary chemical were 80, 70 and 70 µg/sample respectively, and the calculated limits of quantitation were 260, 210 and 220 µg/sample respectively.

e. Wipe Sample Monitoring Method

The surfaces were sampled by removing the gauze pad from the storage jar, holding the pad firmly in a gloved hand (clean latex), making several passes over the surfaces (including switches, levers, etc.) handled by operators in that particular area. The wipe sample was then returned to the jar which was then capped, shrink-banded and refrigerated until analysis.

f. Analysis Methods for Wipe Samples

The wipe samples were extracted and analyzed by GC according to NIOSH Method 2002 with the following modifications.

Extraction Process:	8 hours by shaking in 20 ml ethanol containing 1.0 µl/ml ethyl benzene as an internal standard.
Gas Chromatograph:	Hewlett-Packard Model 5710A equipped with a flame ionization detector.
Column:	30 m x 0.32 mm fused silica capillary column coated internally with 1.0 micron DB-5.
Oven Conditions:	Programmed from 120 °C (held for 8 minutes) to 250 °C at a rate of 32 °C/minute and held for 4 minutes.

Liquid standards were prepared of known amounts of proprietary chemical A, aniline and o-toluidine and spiked into 1 ml of extraction solvent.

The calculated LOD for aniline, o-toluidine and the proprietary chemical was 20.0 µg/sample, and the calculated LOQ was 70.0, 60.0 and 60.0 µg/sample respectively.

3. Bulk Sampling and Analysis Methods

a. Bulk Sampling Method

Bulk samples of bulk process material were collected from all of the intermediate stages of the process where a sample could be extracted, as well as of starting *o*-toluidine and aniline and finished products. Quality assurance (QA) samples were routinely collected by Goodyear of starting, ending and intermediate process chemicals and taken to the QA laboratory for analysis. Portions of all QA samples were taken by transferring about 60 milliliters from a freshly collected sample into a glass jar, which was then capped, shrink-banded, and refrigerated until analysis.

b. Analysis Methods for Bulk Samples

The six liquid bulks were prepared for analysis by diluting 10 μl of each bulk with 2 ml of methanol. The bulk samples were also analyzed directly (without dilution) by injection 0.2 μl aliquots of each in the gas chromatograph. The three solid samples were dissolved in methanol and sonicated for thirty minutes. The approximate concentration was 2 mg/ml each. A 0.38 μg/ml 4-aminobiphenyl standard was prepared in methanol to establish GC/MS analysis conditions and to estimate the approximate concentration of 4-aminobiphenyl in the bulks. The injection volume was 1 μl for all analyses except those analyzed directly without dilution. The mass spectrometer was operated in the full-scan mode (40-500 amu) or the selected-ion monitoring (SIM) mode at medium resolution. This mode is about 100 times more sensitive than full scan mode. In the latter case, the molecular ion at m/e 169.0813 and other fragment ions characteristic of 4-aminobiphenyl were monitored during the expected chromatographic elution time of the compound. A mass spectrometer response at the correct retention time indicates its presence. In the full-scan mode, the entire mass spectrum was used for compound identification.

B. Appendix B: Urine Sample Analysis Method

1. Quality Assurance Procedures for *o*-Toluidine and Aniline

The 209 urine samples received at the analytical laboratory were analyzed in 17 lots using NIOSH Standard Operating Procedure (SOP) T4-29 *Quantitation of o-Toluidine and Aniline in Urine*, presented in appendix C. In addition to the procedure for the method, the SOP gives information on the range, specificity, precision, and accuracy. The SOP was followed as written with the following exception. For Lots 1 through 8, all 8 ml of the butyl chloride layer was used in Section 6.4.7; in Lot 9, 7 ml was used.

A number of steps were taken to document the quality of the results of the analysis of the urine samples for *o*-toluidine and aniline. Some are described in the SOP. Section 6.3 of the SOP stipulates that quality control samples, samples of pure water, and duplicates of previously analyzed field samples be analyzed along with each lot of samples. Other steps were implemented in the field and remained unknown to the laboratory chemists until after the results were reported. Field investigators submitted quality control samples and duplicate portions of field samples (blind splits), all coded as field samples. These steps and their outcome are presented below. All Tables and Figures referred to in the following sections (a through e) can be found in section 2 of Appendix B.

a. Standards Traceability.

Aniline hydrochloride, acetanilide, and *o*-toluidine were purchased from Aldrich Chemical Co., and their identities were confirmed by mass spectroscopy. *N*-acetyl-*o*-toluidine was synthesized from acetic anhydride and *o*-toluidine, and its identity was confirmed by mass spectroscopy and melting point. Standards were prepared using class A volumetric pipets and flasks. The analytical balances were calibrated with NIST traceable standard weights.

b. Quality Control Urine Samples

For all but the last lot of analyses (Lot 17), two to five quality control samples were included in the analyses. These samples were prepared per Section 7.2 of the SOP, all from the same pool of urine from non-exposed persons. The analysis results for these samples are presented in Tables B-I and B-II and in Figures B-1 and B-2. Samples for the levels QC1, QC2, and QC3 were prepared using standard solutions of *o*-toluidine and aniline; samples for QC4 were prepared from a standard solution of *N*-acetyl-*o*-toluidine and acetanilide.

The precision, expressed as relative standard deviation, reflects

both within-lot and between-lot variation. The high imprecision of determining the level of *o*-toluidine in the blank is a result of the variability of the method at the limit of detection. The equivalency of the recoveries for the samples prepared with the acetyl derivatives and those prepared with the free amines at a similar concentration suggests that the yield of the hydrolysis step was quantitative for acetanilide and about 90% for *N*-acetyl-*o*-toluidine.

The graphs of recovery as a function of time in storage, shown in Figures B-1 and B-2, reveal that the samples were stable as stored. The dip in recovery between days 20 and 80 reflects the influence of an important, but unknown, factor affecting the method. The results for the field samples were not corrected for recovery.

c. Replicate Samples

In each lot at least two previously analyzed urine samples were reanalyzed. The results for the 38 pairs are presented in Table B-III. In addition, the field investigators split 17 urine voidings and submitted each portion as a separate sample. The results for the analysis of these duplicate samples are presented in Table B-IV. The results in Tables B-III and B-IV provide the best estimate of the precision of the analysis of the field samples. Statistical analysis of the combined results revealed that the relative standard deviation did not vary significantly over the entire concentration range. This suggests that the method was equally precise throughout the range measured. For *o*-toluidine the median relative standard deviation was 0.13; for aniline it was 0.16.

d. Blind Quality Control Samples

A chemist not associated with the laboratory analyzing the samples prepared 20 quality control samples, which were submitted labeled as field samples. The results for these samples are in Tables B-V and B-VI.

The precision and accuracy of the analysis of these samples appeared worse than would be expected when compared to the results of our quality control samples and the replicated field samples. A possible explanation lies in the manner in which each set of quality control samples was prepared. Our laboratory quality control samples for a given concentration were aliquoted from the same standard solution in urine (Section 7.2 of the SOP). In comparison, the blind quality control samples were prepared by first aliquoting blank urine into 50-ml samples and then spiking each individual portion with 1 to 100 µL of standard solution. The decreased precision and accuracy in analyzing the blind quality control samples reflected the additional component of variation introduced by this method of making up the samples. Such variation is eliminated by preparing a single standard

solution in urine and dividing that pool into smaller samples.

e. Reagent Blanks

To check on contamination introduced by the reagents in the procedure, two or three samples of Milli-Q™ purified water were analyzed with each lot of field samples, except the last. Table B-VII gives the average levels found for each lot. The results for the field samples and quality control samples were corrected for these background concentrations.

2. Tables and Figures for Appendix B

TABLE B-I
Results of Analysis of Quality Control Samples for Aniline

LOT	DATE ANALYZED[a]	CONCENTRATION (µg/L)				
		BLANK	QC1	QC2	QC3	QC4[b]
0	8/23/90	3.9[c]	6.5[d]	20[d]	78[d]	19[d]
1	9/13/90	3.6		16		16
2	9/17/90		5.0		63	16
3	9/20/90	3.1		13	63	13
4	10/25/90		5.9			13
5	11/6/90			15	56	
6	11/15/90		6.9			17
7	11/21/90			18	70	
8	12/3/90		7.5			18
9	12/7/90			CONTAM[e]	82	
10	12/13/90		8.0			20
11	12/18/90			20	77	
12	1/31/91		12			20
13	2/8/91	4.5[f]	7.4	20	80	21
14	2/14/91			18		19
15	2/20/91	4.6[f]	8.4	20	75	22
16	3/27/91	4.4[f]	6.9	19	71	20
17	4/4/91					
AVERAGE		4.0	7.5	18	71	18
RSD[g] (%)		14	26	14	12	16
NOMINAL VALUE[h]		3.9	6.8	18	77	19
RECOVERY (%)		103	109	97	93	96

[a] All quality control samples were prepared on 8/17/90 except QC4, which was prepared on 8/23/90.
[b] Urine pool spiked with acetanilide, rather than aniline. Data expressed in terms of free aniline.
[c] Average of 5 samples.
[d] Average of 3 samples.
[e] QC sample analyzed, but results were invalid due to contamination.
[f] Average of 2 samples.
[g] Relative standard deviation.
[h] The nominal value is the concentration of added aniline plus the background concentration.

TABLE B-II
Results of Analysis of Quality Control Samples for *o*-Toluidine

LOT	DATE ANALYZED[a]	CONCENTRATION FOUND µg/L				
		BLANK	QC1	QC2	QC3	QC4[b]
0	8/23/90	0.12[c]	4.0[d]	19[d]	94[d]	13[d]
1	9/13/90	NP[e]		17		12
2	9/17/90		2.7		75	11
3	9/20/90	1.8		16	71	11
4	10/25/90		3.6			9.1
5	11/6/90			15	66	
6	11/15/90		4.0			13
7	11/21/90			17	83	
8	12/3/90		5.0			14
9	12/7/90			CONTAM[f]	100	
10	12/13/90		3.8			15
11	12/18/90			21	100	
12	1/31/91		3.4			15
13	2/8/91	3.2[g]	7.7	25	91	15
14	2/14/91			22		17
15	2/20/91	NP,NP	4.1	19	98	16
16	3/27/91	NP,0.65	4.2	19	92	14
17	4/4/91					
AVERAGE			4.2	19	87	13
RSD[h] (%)			32	17	14	17
NOMINAL VALUE[i]		0.12	4.2	20	102	16
RECOVERY (%)			101	93	86	83

[a] All quality control samples were prepared on 8/17/90 except QC4, which was prepared on 8/23/90.
[b] Urine pool spiked with N-acetyl-o-toluidine, rather than *o*-toluidine. Data expressed in terms of free *o*-toluidine.
[c] Average of 5 samples.
[d] Average of 3 samples.
[e] NP indicates no chromatographic peak detected.
[f] QC sample analyzed, but results were invalid due to contamination.
[g] Average of 2 samples.
[h] Relative Standard Deviation.
[i] The nominal value is the concentration of added *o*-toluidine plus the background concentration.

TABLE B-III
Results of Replicate Analysis of Field Samples

ANILINE				*o*-TOLUIDINE			
#[a]	(N)[b]	AVERAGE CONCENTRATION (µg/L)	% RSD	#[a]	(N)[b]	AVERAGE CONCENTRATION (µg/L)	%RSD
179[c]	2	NP		179[c]	2	NP	
230[c]	2	NP		230[c]	2	NP	
226	2	1.0	65	226	2	NP & 0.9	
231	2	1.1	1	157	2	NP & NP	
157	2	3.3	46	231	2	0.75	15
173	2	3.6	7	229	3	3.2	21
235	2	4.2	39	235	2	4.8	23
164	3	5.2	64	173	2	5.6	14
435	3	8.0	19	164	3	7.1	63
151	2	9.5	25	273	3	11	9
229	3	9.6	36	249	2	12	26
158	2	12	28	443	3	18	58
380	2	12	1	158	2	19	4
273	3	12	13	135	2	22	7
249	2	14	55	435	3	23	43
159	2	17	11	247	3	24	8
187	3	18	11	151	2	25	8
443	3	19	44	124	2	33	3
124	2	23	3	330	2	33	9
310	2	27	11	380	2	36	6
135	2	27	10	388	2	39	27
354	2	29	4	279	2	40	5
330	2	35	22	152	2	60	9
162	3	35	10	159	2	64	8
194	3	38	11	347	3	67	30
388	2	41	39	194	3	72	7
279	2	43	6	354	2	82	4
152	2	43	11	187	3	89	10
184	3	48	16	310	2	92	12
219	2	48	29	304	2	96	1
347	3	49	15	383	2	102	17
247	3	49	15	171	2	105	30
171	2	52	50	162	3	116	14
170	2	54	38	170	2	164	32
459	2	64	5	219	2	207	54
383	2	106	7	184	3	234	9
304	2	113	1	459	2	290	13
278[c]	2	123	4	278[c]	2	474	9
334[c]	2	529	18	334[c]	2	458	22

[a] Field sample number.
[b] Number of sample aliquots analyzed.
[c] Samples analyzed using less sensitive detector amplification.

TABLE B-IV
Results for Blind Split Samples.

o-TOLUIDINE			ANILINE		
SAMPLE NUMBERS	AVERAGE CONCENTRATION (µg/L)	RELATIVE STD. DEV. (%)	SAMPLE NUMBERS	AVERAGE CONCENTRATION (µg/L)	RELATIVE STD. DEV. (%)
193/201	NP & 1.5		285/442	0.86	23
285/442	1.1	7	255/313	1.4	20
255/313	1.2	1	193/201	2.5	7
233/267	5.1	19	213/235	4.4	6
213/235	5.5	17	233/267	5.0	24
121/212	11	15	121/212	6.8	5
244/265	13	26	195/206	8.0	43
195/206	25	41	244/265	11	30
244/265	36	12	323/450	13	3
124/133	40	24	330/377	15	14
128/145	41	10	124/133	20	16
441/462	46	12	172/242	21	11
172/242	49	13	149/246	22	12
330/377	73	15	244/265	36	3
149/246	82	16	128/145	56	43
215/251	130	17	215/251	56	22
323/450	530	11	441/462	2500	6

TABLE B-V
Results for Blind Spiked Urines

SAMPLE NUMBER	ANILINE CONCENTRATION (µg/L)				
	ADDED	FOUND	AVERAGE	% RSD	PERCENT RECOVERY
329	0.0	7.8	4.6	61	
344	0.0	3.7			
468	0.0	2.4			
312	5.6	13	16	25	154
345	5.6	14			
343	5.6	20			
273	11	12	15	22	98
399	11	15			
443	11	19			
279	28	43	46	17	144
402	28	56			
388	28	41			
331	55	75	86	45	144
375	55	130			
415	55	54			
286	110	135	120	13	103
383	110	106			
304	110	113			
334[a,b]	552	528	880	57	158
425[b]	552	1233			

[a] Analyzed in duplicate.
[b] Samples analyzed using less sensitive detector amplification.

TABLE B-VI
Results for Blind Spiked Urines

SAMPLE NUMBER	*o*-TOLUIDINE CONCENTRATION (μg/L)				
	ADDED	FOUND	AVERAGE	% RSD	PERCENT RECOVERY
329	0.0	0.7	0.5[a]	89[a]	
344	0.0	0.8			
468	0.0	NP			
312	6.4	9.1	14	31	128
345	6.4	16			
343	6.4	17			
273	13	11	14	28	77
399	13	12			
443	13	18			
279	32	40	44	18	121
402	32	53			
388	32	39			
331	64	70	82	43	120
375	64	122			
415	64	55			
286	128	120	106	12	80
383	128	102			
304	128	96			
334[b,c]	640	458	758	56	118
425[c]	640	1059			

[a] NP was included in the computation as 0.0 μg/L.
[b] Analyzed in duplicate.
[c] Samples analyzed using less sensitive detector amplification.

Table B-VII
Results for Water Blanks

Lot Number	Concentration (μg/L)[a]	
	Aniline	*o*-Toluidine
1	0.5	-
2	0.9	0.6
3	2.6	-
4	1.1[b]	-
5	0.2	-
6	0.7[c]	-
7	-	-
8	1.2	-
9	0.4	-
10	1.2	-
11	1.8	-
12	2.8	-
13	-	1.1
14	3.3	-
15	0.4	-
16	0.1[c]	-

[a] Average of two samples. Samples with no peak detected are averaged as 0 μg/L, except that "-" indicates no peak was detected in any of the samples.
[b] One sample.
[c] Average of three samples.

FIGURE B-1

o-Toluidine Concentration in Quality Control Samples

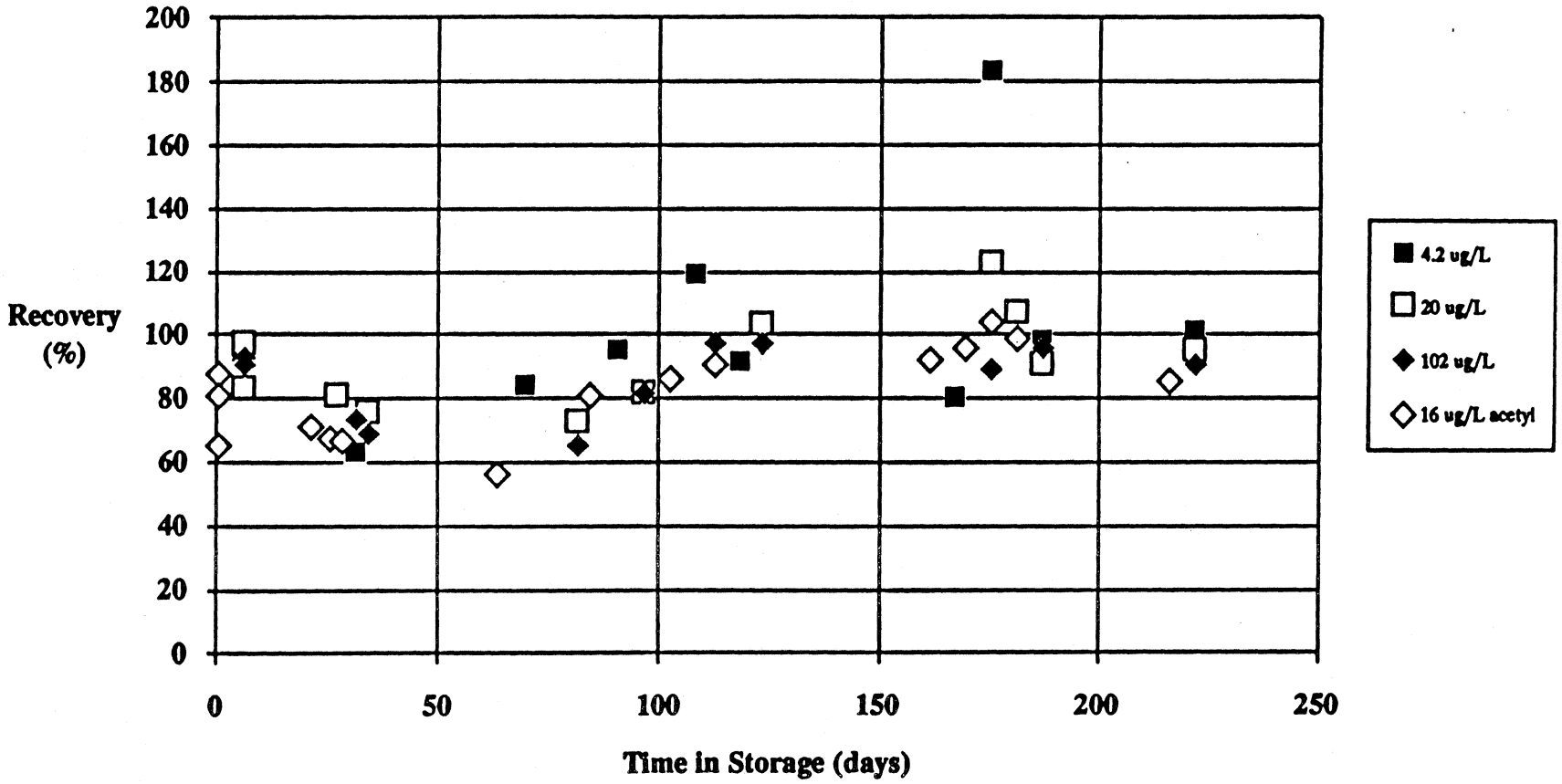
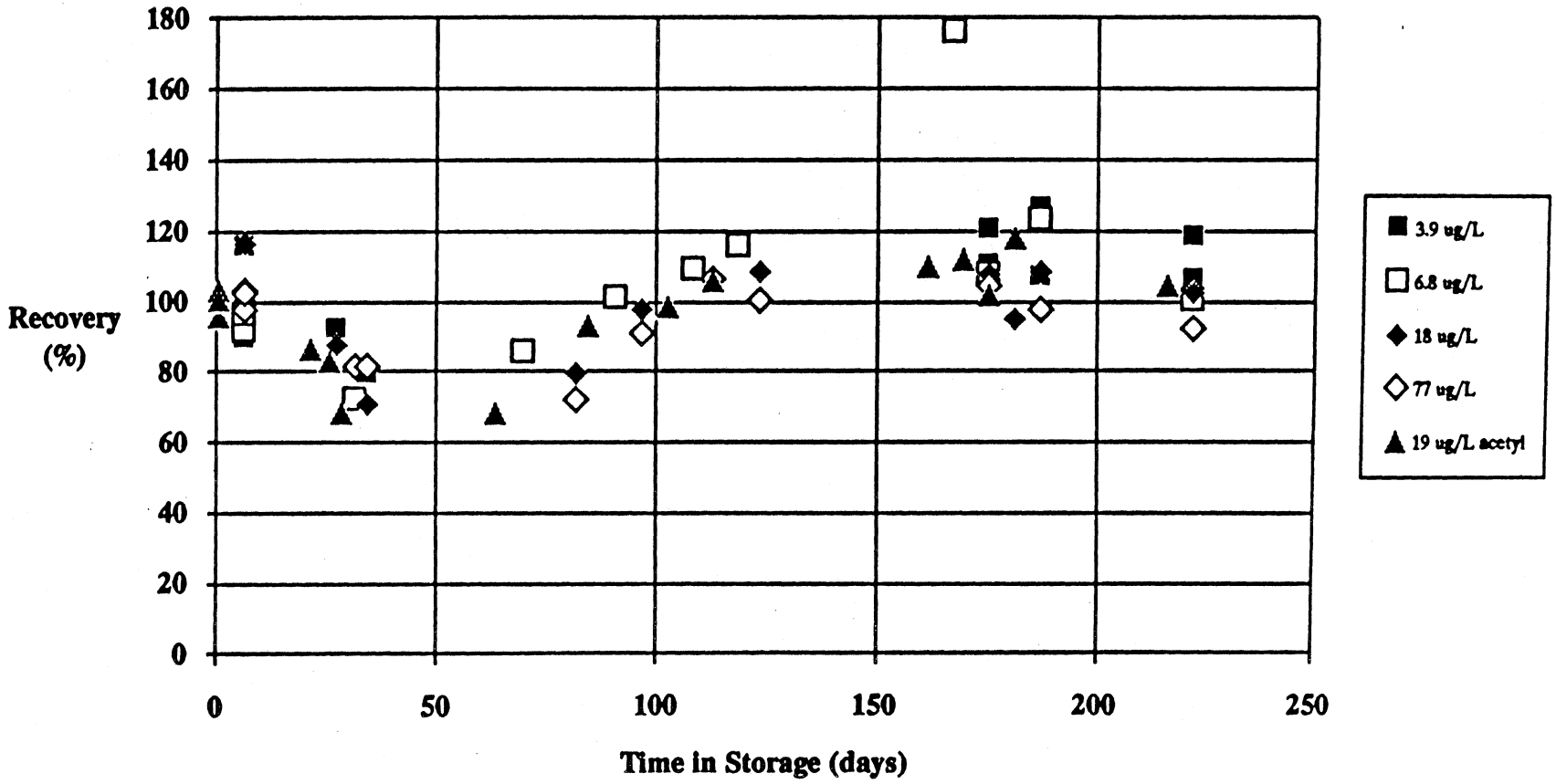


FIGURE B-2

Aniline Concentration in Quality Control Samples



C. Appendix C: Standard Operating Procedure For Urine Analysis

STANDARD OPERATING PROCEDURE

NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH
Division of Biomedical and Behavioral Science
SOP No. T4-29

Date Indexed: June 3, 1991

Title: Quantitation of *o*-Toluidine and Aniline in Urine

Section: Analytical Toxicology Section

Branch: Applied Biology Branch

SYNOPSIS

This method quantifies the aniline and *o*-toluidine present in urine, including metabolites converted by base hydrolysis back to aniline and *o*-toluidine. Urine samples are made 6.25 *M* in sodium hydroxide and heated at 80 °C for 2 h to convert the metabolites acetanilide and *N*-acetyl-*o*-toluidine to free aniline and *o*-toluidine. The neutral and basic compounds are extracted from the hydrolysate with butyl chloride, and the basic compounds are extracted from the butyl chloride solution with 0.1 *M* aqueous HCl. An aliquot of the acidic extract is subjected to ion-interaction reversed-phase liquid chromatography with coulometric electrochemical detection.

1.0 Range

1.1 The limit of detection for *o*-toluidine was estimated using data from the analysis of 18 urine samples fortified to 1.4-15 µg/L plus 5 unfortified urine samples (blank level 0.12 µg/L), all from the same pool. Linear regression of the measured concentration for each sample against the nominal concentration gave a line of slope 0.94 with a standard error of estimate of 0.18 µg/L, from which was calculated a detection limit for *o*-toluidine of 0.6 µg/L in urine. Similarly, using data from the analysis of 18 urine samples fortified with aniline to 4.8-15 µg/L plus 5 unfortified urine samples (blank level 3.9 µg/L), the detection limit for aniline was estimated to be 1.4 µg/L in urine.

1.2 Using the instrumental conditions of section 6.5, the upper limit of detection is approximately 35 µg/L of *o*-toluidine or aniline in urine. The integrator, range 1024 mV, is saturated by signals produced from standards for higher levels. The upper limit of detection can be extended by reducing the injection volume to 5 µL,

decreasing the detector gain to 2 x 10, and/or diluting the original urine sample.

2.0 Interferences

2.1 To be an interference a compound must 1) make it through the sample work-up to the dilute HCl extract--i.e. be a basic compound or neutral compound significantly soluble in both water and butyl chloride, 2) have a retention time close to that of aniline or *o*-toluidine, 3) escape complete oxidation at a potential of 400 mV, and 4) be oxidized at 600 mV.

2.2 Compounds eluting within three standard deviations of the average retention times of the standards are identified as aniline and *o*-toluidine. Additional evidence for the identity of a chromatographic peak is obtained by analyzing the 0.1 *N* HCl extract at two electrode potentials at which *o*-toluidine and aniline are oxidized to different extents--e.g., 520 mV and 600 mV. If the response ratio for an unknown is close to that of standards at the same potentials, then the unknown has an increased likelihood of being pure aniline or *o*-toluidine.

3.0 Precision and Accuracy

3.1 Precision and recovery were determined by fortifying a pool of urine with *o*-toluidine and aniline and analyzing samples of the pool over a period of 220 days. The results were:

Compound	Concentration (µg/L)	Relative Standard Deviation (%)	Average Recovery (%)
o-Toluidine	4.2	32	101
	20	17	93
	102	14	86
Aniline	3.9 (blank)	14	
	6.8	26	109
	18	14	97
	77	12	93

The unfortified urine contained 3.9 µg/L of aniline and 0.12 µg/L of *o*-toluidine.

3.2 A pool of urine was fortified with acetanilide and *N*-acetyl-*o*-toluidine at concentrations corresponding to 19 µg/L of aniline and 16 µg/L of *o*-toluidine in urine. Aliquots of this pool were analyzed over 220 days. For aniline the precision was 16% relative standard deviation and the average recovery was 96%. For *o*-toluidine the

precision was 17% relative standard deviation and the average recovery was 83%.

4.0 Apparatus

4.1 The HPLC system consisted, in sequence, of a 5-L mobile-phase reservoir, a Whatman in-line nylon degasser/filter of 0.2-µm pore size, a Waters Model 510 HPLC pump, a pulse dampener, an in-line filter of 0.2-µm pore size, an electrochemical guard cell, a Waters WISP auto-injector, a Waters Nova-Pak™ C18 guard column, a Nova-Pak™ C18 300-mm X 4.6-mm analytical column within a Waters Model CHM column oven, an in-line filter of 0.2-µm pore size, and an ESA Model 5100A electrochemical detector. The electrochemical detector is interfaced with a Hewlett-Packard Model 3396A recording integrator, in turn interfaced with an IBM XT computer running Visions 96™.

4.2 Bottle, 4-L.

4.3 pH meter.

4.4 Bottles, 2-oz (60-mL) and 8-oz polypropylene

4.5 Scintillation vials, 10-mL polypropylene

4.6 Vortex mixer.

4.7 Rotary mixer, Roto-Torque™.

4.8 Centrifuge tubes, 15-mL with teflon lined caps, disposable.

4.9 Reagent dispenser, 8-mL.

4.10 WISP vials, 1-mL.

4.11 Water bath set at 80 °C.

4.12 Volumetric pipets, 5-mL, disposable.

4.13 Pipets, 2-mL, disposable.

4.14 Micropipets, 1-mL.

4.15 Syringes, 3-cm^3 plastic, disposable.

4.16 Pipette, pasteur-type, disposable.

4.17 Syringe filters, Anotop™ 10 with 0.2-µm pore size.

4.18 Volumetric flasks, 2-L, 1-L and 50-mL class A.

5.0 Chemicals and Reagents

5.1 Water, Milli-Q™ purified.

5.2 Sodium dihydrogen phosphate monohydrate ($NaH_2PO_4 \cdot H_2O$), ACS reagent grade.

5.3 Methanol, HPLC grade.

5.4 Sodium dodecyl sulfate (SDS), chromatographic grade.

5.5 Aniline hydrochloride, 99+%.

5.6 *o*-Toluidine, 99+%.

5.7 Phosphoric acid, 85%, ACS reagent grade.

5.8 Butyl chloride, HPLC grade.

5.9 Sodium hydroxide, ACS reagent grade.

5.10 Hydrochloric acid, 0.1 *N*, Fisher certified.

5.11 Citric acid, anhydrous, ACS reagent grade.

5.12 Mobile phase. Add 23.0 g of $NaH_2PO_4 \cdot H2O$ and 6 mL of 8.5% phosphoric acid to a 2-L volumetric flask. Bring to volume with water. Adjust to pH 3.3 ± 0.05 with 8.5% phosphoric acid or 50% NaOH. Add 1333 mL of methanol and 200 ± 0.5 mg sodium dodecyl sulfate to a 4 L bottle. After all the solid dissolves, add the 2 L of buffer solution (89 m*M* in PO_4^{3-}) and mix thoroughly. The mobile phase is now 60 mg/L in sodium dodecyl sulfate and 53 m*M* in PO_4^{3-}.

6.0 Procedure

6.1 *Cleaning and Maintaining Equipment*

6.1.1 Rinse all glassware and caps with methanol, then with 0.1 *N* HCl, and finally with purified water before use.

6.1.2 Clean electrodes and columns by flushing with 1:1 methanol-water (v/v).

6.1.3 After changing mobile phase, run the LC system for 16 h to allow the system to reach equilibrium and, thus, the retention times to stabilize.

6.1.4 When the LC system is not in use, replace the buffered mobile phase with 1:1 methanol-water (v/v). If scheduling requires leaving the buffered mobile-phase in the system, maintain a flow fate of 0.1 L/min. Buffered

mobile phase can plug a column with salt crystals, leaves residue at every leaking point, and is more abrasive than pure solvent mobile phases to the pump seals.

6.2 *Collection and Shipping of Samples*

Collect field urine samples in 8-oz wide-mouth polypropylene bottles. Measure the volume or the specific gravity and weight of each voiding. Transfer a 50-mL aliquot to a 2-oz polyethylene bottles containing 5 g of citric acid, used as a preservative. Immediately freeze the samples on dry ice and store them at -65 °C until analysis.

6.3 *Batch protocol.*

With each batch of 20 field samples, analyze 2 quality-control samples, 2 blank samples of purified water, and 2 field samples analyzed in the previous batch. Order the batch of LC runs by *standard, unknown, unknown, standard, unknown, ..., standard*. Within that order, randomize the order of the standards and unknowns separately.

6.4 *Sample preparation.*

6.4.1 Weigh 1.00 g ± one pellet of NaOH into 15-mL centrifuge tubes.

6.4.2 Prepare three labels for each unknown and one for the standard solutions, using MMMDDXX for the sample-number code. MMM is the month and DD the day the samples are thawed and prepared for LC analysis. XX is the LC run number. Affix the labels for each unknown to a 15-mL centrifuge tube containing 1 g of sodium hydroxide, an empty 15-mL centrifuge tube, and a 1-mL WISP vial. Attach the labels for the standard solutions to 1-mL WISP vials.

6.4.3 Warm the urine samples to room temperature, mix each sample well, and transfer 4-mL aliquots of each to the correspondingly labeled centrifuge tube containing 1 g of sodium hydroxide. Return the unused portion of each sample to the freezer.

6.4.4 Heat for 2 h in the 80 °C water bath.

6.4.5 After the samples are cooled to room temperature, dispense 8 mL of butyl chloride into each tube.

6.4.6 Tumble the tubes for 10 min on the Roto-Torque™ at setting "6 high," then centrifuge the tubes at 3000 rpm for 5 min.

6.4.7 Transfer a 5-mL aliquot of each butyl chloride (upper) layer to the correspondingly labeled 15-mL centrifuge tube.

6.4.8 Add 1 mL of 0.1 *N* HCl to the butyl chloride solutions.

6.4.9 Tumble the tubes for 10 min on the Roto-Torque™ at setting "6 high." Centrifuge the tubes at 3000 rpm for 5 min.

6.4.10 Remove the aqueous (lower) layer with a Pasteur-type pipette and transfer it to the barrel of a 3-mL plastic syringe previously fitted with an 10-mm (0.2-μm pore size) filter.

6.4.11 Insert the plunger and transfer the aqueous solution to the correspondingly labelled 1-mL WISP vial for LC analysis.

6.4.12 Order the samples and standard solutions (Step 7.1.3) in the WISP carrousel per the batch protocol (Section 6.3) and start the HPLC runs.

6.5 *Settings for the Liquid Chromatography System*

Injection volume:	50 μL
Run time, unknowns:	60 min
Standards:	25 min
Mobile phase flow rate:	0.8 mL/min
Detector gain:	10 X 15
Potential, guard cell:	1000 mV
electrode 1:	400 mV
electrode 2:	600 mV
Response time:	4 s
Column-oven temperature:	30 °C
Integrator parameters:	
chart speed	0.1 cm/sec
threshold	0
attenuation	10
peak width	0.5 min

6.6 *Samples above the Range of the Detector.*

6.6.1 If a sample gives a chromatographic peak for aniline or *o*-toluidine with a height greater than the range of the detector (about 8,400,000 peak-height units or 7000 pg *o*-toluidine or aniline injected), reanalyze (step 6.4.12) the extract using a 5-μL injection. The response of the LC system has been found to be linear with injection volume.

6.6.2 If the reanalysis of the sample with a 5-μL injection results in a response above the range of the detector,

reanalyze (step 6.4.12) the extract at a gain of 10 x 2 with standard solutions covering the new range.

6.7 *Confirmation of Peak Identity.*

6.7.1 Analyze the unknown extract with two standard solutions of concentrations near that of the unknown with detector electrode 2 at 600 mV. Run one standard before and one standard after the unknown.

6.7.2 Reanalyze the three solutions with detector electrode at 520 mV.

6.7.3 For each solution, calculate the response ratios for *o*-toluidine and aniline by dividing the peak heights at 600 mV by the peak heights at 520 mV. Determine the averages and standard deviations of the response ratios for the standard solutions. If the response ratio for an unknown peak is within three standard deviations of the average for that peak in the standard solutions, there is increased likelihood that the component is pure *o*-toluidine or aniline.

7.0 Calibration

7.1 *Standard solutions*

7.1.1 Prepare duplicate standard solutions of *o*-toluidine and aniline at the following concentrations:

100 mg/L. Dissolve 100 mg of *o*-toluidine and 139 mg of aniline hydrochloride (equivalent to 100 mg of aniline) in 0.1 *N* HCl in a 1-L volumetric flask.

1000 µg/L. Dilute 1.00 mL of the 100-mg/L standard solution to 100 mL.

100 µg/L. Dilute 1.00 mL of the 100-mg/L standard solution to 1 L.

Store these stock solutions in the refrigerator.

7.1.2 Label ten 50-mL volumetric flasks with the concentrations listed in the table below. Using the table, prepare the standard solutions listed by diluting the indicated volume of stock standard solution to 50 mL with mobile phase. Alternate the use of the duplicate stock standard solutions such that every other standard solution is made from the alternate stock standard solution.

Concentration of Standard Solutions (µg/L)	Volume (mL) of Stock Standard Solution	
	1000 µg/L	100 µg/L
140	7.0	
120	6.0	
80	4.0	
60	3.0	
40	2.0	
20	1.0	
10		5.0
8		4.0
6		3.0
4		2.0
2		1.0

7.1.3 Analyze these standard solutions with the unknowns starting at step 6.4.12.

7.1.4 The standard solutions are stable at 4 °C for at least 2 weeks. Nonetheless, prepare one half of the standard solutions fresh for each batch.

7.2 *Quality-control samples.*

7.2.1 Collect 1 L of fresh urine from unexposed non-smoking individuals, who are not taking medication.

7.2.2 To each liter of fresh urine add 100 g of citric acid.

7.2.3 Add 10, 5, 1, and 0 mL of stock 1000-µg/L standard solution to four 250-mL volumetric flasks and dilute to the mark with acidified urine. The nominal concentrations of these samples--40, 20, 4, and 0 µg/L, respectively--must be corrected for the average concentration of *o*-toluidine and aniline in the unfortified urine.

7.2.4 Aliquot each urine solution into a 10-mL polypropylene scintillation vial and store at -65 °C.

8.0 Calculations

8.1 Using the peak heights from the chromatograms of the standard solutions and the computed quantities of analyte injected, determine the calibration equations for *o*-toluidine and aniline by quadratic regression of peak height (H, integrator units) against quantity injected (Q, pg):

$$H = aQ^2 + bQ + c$$

where a, b, and c are the regression coefficients. The quantity injected is the product of the concentration of the standard solution (pg/μL) and injection volume (μL).

8.2 Using the data from the chromatograms of the standard solutions for the batch, compute the retention-time windows for *o*-toluidine and aniline. The range for each window is the average plus and minus three times the standard deviation. Use these ranges to identify aniline and *o*-toluidine in the chromatograms of the unknown samples. Check the peak assignments for the unknowns with a plot of retention time of each analyte against run number, including all the chromatograms in the batch. On this plot the retention times of the unknowns should fall in line with the retention times of the adjacent standards. If more than one peak is within this retention window, choose that with retention time closest to the adjacent standard solutions.

8.3 Calculate the concentration (C, μg/L) of analyte found in the unknowns as follows:

$$C = 1.6\{-b + [b^2 - 4a(c - H)]^{0.5}\}/(2aIV)$$

where I is the volume (μL) injected into the LC, V is the original volume (mL) of urine taken for analysis, 1.6 corrects for the use of only 5/8 of the butyl chloride layer, and a, b, c, and H are as defined in Section 8.1.

8.4 Average the concentrations of *o*-toluidine and aniline in the blank water samples. Subtract these averages from the respective concentrations in the other unknown samples to correct for background contamination.

9.0 Storage of Data

Combine all print-outs of chromatographic data and work sheets for the batch, place them in a binder, and store them in room 310. Label the binders with the title *Aniline - o-Toluidine Analysis*, the source of the samples, the HETA number, and the dates of the analysis.

D. Appendix D: Creatinine Correction Methods

Creatinine concentration has been used for correction of urine concentration in spot urine samples because creatinine is thought to be excreted at a constant rate independent of urine flow. However, according to a recent review (Boeniger, 1991) there are a number of reasons why adjustment for creatinine may introduce error into the analysis of an industrial chemical in urine, particularly when preshift and postshift samples are being compared.

Creatinine concentration (in terms of mg/hr) shows marked intraindividual variability (Curtis, 1970) and in many individuals exhibits a diurnal pattern with the lowest excretion in overnight or first morning urine samples and a peak in late afternoon or early evening (Curtis, 1970). Therefore, correction for creatinine may reduce the difference in postshift versus preshift means.

This effect was observed in the current study, as shown in Table D-I, which shows the creatinine corrected values for each group beneath the uncorrected values. While creatinine correction did reduce the difference between preshift and postshift means, it did not markedly effect the relationship between the exposed and the unexposed groups. For example, the uncorrected ratio of postshift *o*-toluidine between the exposed and unexposed is 38.4; the ratio using creatinine corrected data is 39.1. Table D-II shows the regression analyses using creatinine corrected urine data as the outcome (Table XVI in the body of the report shows the regression results for the uncorrected data). With the exception of the regression with postshift minus preshift aniline as the outcome variable, the results of the regressions using creatinine corrected data are similar to those using *o*-toluidine and aniline concentration in suggesting that both air concentration and smoking status are predictors of urine *o*-toluidine and aniline level.

Table D-I
Urinary o-Toluidine And Aniline Concentrations In Unexposed And Exposed Workers
Comparison Of Creatinine Corrected And Uncorrected Data

A. Urinary *o*-Toluidine Concentration

Exposure Group	Unit	Preshift Mean (n)	Postshift Mean (n)	Paired T-Test[1] (n)
Unexposed	ug/L	1.1 (n=32)	2.7 (n=32)	.009 (n=31)
	ug/creat[3]	0.7 (n=32)	1.8 (n=32)	.03 (n=31)
Exposed	ug/L	18.5 (n=48)	103.7 (n=52)	.0001 (n=46)
	ug/creat[3]	17.9 (n=48)	71.2 (n=52)	.0001 (n=46)
Unpaired t-test[2]	ug/L	.0001	.0001	
	ug/creat[3]	.0001	.0001	

B. Urinary Aniline Concentration

Exposure Group	Unit	Preshift Mean (n)	Postshift Mean (n)	Paired T-test[1] (n)
Unexposed	ug/L	2.6 (n=32)	3.7 (n=32)	.01 (n=31)
	ug/creat[3]	1.6 (n=32)	2.8 (n=32)	.03 (n=31)
Exposed	ug/L	17.4 (n=48)	32.3 (n=52)	.0001 (n=46)
	ug/creat[3]	15.1 (n=48)	21.9 (n=52)	.0009 (n=46)
Unpaired t-test[2]	ug/L	.0001	.0001	
	ug/creat[3]	.0001	.0001	

1. The paired t-test tests the significance of the difference between preshift and postshift samples by individual. Data were log transformed to achieve normality.
2. The unpaired t-test tests the difference between the exposed and unexposed groups for both preshift and postshift means. Data were log transformed to achieve normality.
3. The units of creatinine are (ug aniline or *o*-toluidine/mg creatinine) x 1000.

Table D-II
Regression Models Relating Airborne With Urine Levels Corrected for Creatinine

A. o-Toluidine

Outcome	Factor		1 Factor Models		2 Factor Models
			Air	Smoke	Air/Smoke
Post Toluidine (Log trans)	Model r2[1]		.07	.25	.30
	Air	Cf[2]	.02		.02
		p	.14		.16
	Smoke	Cf[3]		40.3	38.8
		p		.003	.004
Post-Pre Toluidine (Sqrt trans)	Model r2[1]		.10	.23	.31
	Air	Cf[2]	.03		.02
		p	.08		.09
	Smoke	Cf[3]		38.3	36.4
		p		.005	.006

1. Model R2 = percent of overall variation in the outcome variable explained by the predictor variables.
2. Cf = coefficient for the term for air level in the regression.
3. Cf = coefficient for the term for smoking in the regression.

Table D-II (continued)
Regression Models Relating Airborne With Urine Levels Corrected for Creatinine

B. Aniline

Outcome	Factor		1 Factor Models		2 Factor Model
			Air	Smoke	Air/Smoke
Post Aniline	Model r2[1]		.16	.31	.40
	Air	Cf[2]	.02		.02
		p	.02		.05
	Smoke	Cf[3]		12.6	11.2
		p		.001	.002
Post-Pre Aniline	Model r2[1]		.0008	.11	.12
	Air	Cf[2]	-.002		-.006
		p	.88		.58
	Smoke	Cf[3]		7.7	8.1
		p		.06	.05

1. Model R2 = percent of overall variation in the outcome variable explained by the predictor variables.
2. Cf = coefficient for the term for air level in the regression.
3. Cf = coefficient for the term for smoking in the regression.