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I. SUMMARY

On September 16, 1990, the National Institute for Occupational Safety and Health (NIOSH) received a request from the Morton International Chemical Company to evaluate exposure of employees to *o*-toluidine and aniline at their Specialty Chemical Group facility in Paterson, New Jersey. This facility is a dye works which has been using *o*-toluidine and aniline since at least 1970, and aromatic amines since 1929. All airborne exposures measured for *o*-toluidine and aniline by the company since 1982 have been below their respective Occupational Safety and Health Administration (OSHA) permissible exposure limits (PELs) and American Conference of Governmental Industrial Hygienists' (ACGIH) threshold limit values (TLVs) in effect at the time of exposure monitoring. Nevertheless, during annual bladder cytology examinations in the winter of 1989-90, three workers were diagnosed as having "bladder dysplasia."

Personal air, skin liquid contact indicator (dermal) badges, and glove samples were collected on workers to measure airborne exposure to *o*-toluidine and aniline and indicate potential dermal contact with liquid chemical. Area air and dermal badge samples were collected from representative locations to measure air exposure potential and evaluate the amount of passive absorption of chemical from the air by the dermal badges. Surface 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. Pre- and post-shift urine specimens were collected from a sample of workers before and after the workshift to assess absorption of *o*-toluidine and aniline from all possible exposure routes to these chemicals.

Twelve current employees who on the basis of an evaluation of industrial hygiene records, chemical processes, and job titles and tasks were considered the most likely to be exposed (probably exposed group) to *o*-toluidine and aniline had their urine analyzed. Based upon job descriptions, eight of the workers least likely to be exposed (presumably unexposed group) were also included in the study and had their urine analyzed.

To account for other sources of *o*-toluidine, aniline or chemically similar substances, participating individuals were asked to complete a questionnaire concerning cigarette smoking habits, passive exposure to smoke, use of medications during the previous week (some drugs have metabolites similar to those of *o*-toluidine and aniline), non-work exposure to chemicals (hobbies or second jobs), and work in specific areas during the day of urine collection. In addition to measuring *o*-toluidine and aniline (or their metabolites) in the urine, cotinine concentration was measured as a quantitative measure of exposure to cigarette smoke.

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The personal time weighted average (TWA) air sample results for presumably unexposed workers had no detectable o-toluidine, but one worker had a detectable aniline exposure of 2 micrograms per cubic meter ($\mu g/M^3$). The personal TWA air sample results for the probably exposed workers for o-toluidine ranged from less than 8.7 (the lowest detectable concentration) to 164 $\mu g/M^3$, and for aniline ranged from less than 1.3 (the lowest detectable concentration) to 25 $\mu g/M^3$.   The TWA area air sample o-toluidine concentrations ranged from less than 8.7 to 510 $\mu g/M^3$, and area aniline concentrations ranged from less than 1.3 to 34 $\mu g/M^3$.   Personal dermal badge sample results for the probably exposed workers for o-toluidine ranged from less than 28 (the lowest detectable concentration) to 211 μg; aniline was not detected (less than 31 μg) in any of these dermal badge samples. For the presumably unexposed group, the personal dermal badge sample results for o-toluidine and aniline ranged from less than 28 to 60 μg and from less than 31 to 55 μg, respectively. No o-toluidine or aniline was detected in any of the personal glove samples.

Post-shift urine samples from the unexposed workers averaged 1.56 ± 2.08 micro-grams per liter ($\mu g/L$) o-toluidine and 2.01 ± 1.96 $\mu g/L$ aniline, while the pre-shift samples averaged 1.60 ± 2.08 $\mu g/L$ o-toluidine and 3.11 ± 5.13 $\mu g/L$ aniline. Post-shift urine samples from the probably exposed workers averaged 15.97 ± 14.33 $\mu g/L$ o-toluidine and 4.76 ± 2.75 $\mu g/L$ aniline, while the pre-shift samples averaged 2.08 ± 2.33 $\mu g/L$ o-toluidine and 2.72 ± 2.65 $\mu g/L$ aniline. o-Toluidine and aniline concentrations in pre-shift urine samples from exposed workers were similar to concentrations in unexposed workers; the post-shift sample means were significantly higher for exposed workers.

All airborne personal exposures measured for o-toluidine and aniline were below the OSHA PELs and the ACGIH TLVs. However, average urinary concentrations of aniline among exposed workers were approximately two times greater than among probably unexposed workers, while average urinary concentrations of o-toluidine in exposed workers were approximately eight times greater than those in the probably unexposed workers. These differences were statistically significant, and were not explained by differences in smoking habits or any other factor between the exposed and probably unexposed groups other than their potential occupational exposure to o-toluidine and aniline. Although the exact relationship between bladder cancer with o-toluidine and aniline exposure is not known, NIOSH considers both chemicals to be potential occupational carcinogens and recommends that exposures be reduced to the lowest feasible concentration. Morton International has attempted to control exposure through engineering controls and personal protective equipment, yet the post-shift urinary o-toluidine concentrations in particular demonstrate that workers in the facility are occupationally exposed to o-toluidine. In order to minimize the potential for a health hazard associated with long term exposure to these chemicals, NIOSH recommends that a review of current control practices be made to identify any further interventions that may reduce occupational exposure.

PREFACE

The Hazard Evaluations and Technical Assistance Branch of NIOSH conducts field investigations of possible health hazards in the workplace. These investigations are conducted under the authority of Section 20(a)(6) of the Occupational Safety and Health Act of 1970, 29 U.S.C. 669(a)(6) which authorizes the Secretary of Health and Human Services, following a written request from any employer and authorized representative of employees, to determine whether any substance normally found in the place of employment has potentially toxic effects in such concentrations as used or found.

The Hazard Evaluations and Technical Assistance Branch also provides, upon request, medical, nursing, and industrial hygiene technical and consultative assistance to federal, state, and local agencies; labor; industry; and other groups or individuals to control occupational health hazards and to prevent related trauma and disease.

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

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II. INTRODUCTION

In September 1990, the Corporate Director for Occupational Safety and Health of the Morton International Specialty Chemical Group requested assistance from the National Institute for Occupational Safety and Health (NIOSH) in evaluating worker exposure to *o*-toluidine and aniline at their facility in Paterson, New Jersey. The request was initiated because of concern about "bladder dysplasia" diagnoses in three members of the workforce. This plant is a dye works which has been using *o*-toluidine and aniline since at least 1970, and aromatic amines since 1929. A NIOSH health hazard evaluation[1] at the Goodyear Tire and Rubber Company in Niagara Falls, New York, had found an elevated risk of bladder cancer (Standardized Incidence Ratio 6.48, p = 0.0001) in workers employed in a department which has used *o*-toluidine and aniline since 1957. Based on this investigation, and a subsequent review of the human and animal data in the scientific literature, NIOSH concluded in a 1990 Hazard Alert that *o*-toluidine and aniline are potential occupational carcinogens as defined in the Occupational Safety and Health Administration (OSHA) carcinogen policy (29 CFR 1990).[2] Both *o*-toluidine and aniline are aromatic amines for which the International Agency for Research on Cancer (IARC) believes there is some evidence of carcinogenicity.[3] Therefore, NIOSH recommends reducing occupational exposure to these two chemicals to the lowest feasible concentration.

At the Goodyear Niagara Falls plant, *o*-toluidine and aniline concentrations in the urine of exposed workers were significantly higher than in unexposed workers, even though all historical air sampling levels had been below the OSHA permissible exposure limit.[4]

NIOSH investigators explored the possibility of conducting an epidemiologic study of bladder cancer incidence among current and former Morton workers. However, as no company records prior to 1970 exist, and as records for current workers do not include adequate work histories, an epidemiologic study of incidence was not feasible.

A survey of current exposures in the dye manufacturing processes was conducted from June 11 through 13, 1991. Because both *o*-toluidine and aniline have potential for absorption through the skin, as well as by inhalation, methods were developed to measure exposure through multiple routes. Personal air and dermal monitoring was conducted, surface wipe samples were collected from several work locations, and bulk samples were obtained at various stages of the process. Urine samples were collected from both exposed and presumably unexposed workers to analyze for concentrations of *o*-toluidine and aniline. This report contains the results of the environmental and urine monitoring.

Participating workers will receive a copy of this report as well as their individual results.

III. BACKGROUND

      A.   Description of the Plant, Processes, and Products

The plant opened in 1929 for the production of dyes, and moved to its present location in 1945. The plant was purchased by Morton International in 1968 from the original owners. In the early 1970s, products of the plant, then known as Morton-Norwich Products, Inc., included: disperse dyes, solvent dyes, fluorescent brightening agents, toners and lake pigments, polyethylene glycol monolaurate and polyethylene glycol mono-oleate, quaternary ammonium salts, corrosion and rust inhibitors, and dispersing agents. By 1977, only dyes were being produced.[5]

At present the facility produces:

- Liquid dyes: used for petroleum colorants, permanent marker, ball point pen and flexographic gravure inks, for lacquers and enamels, for decorative foil coatings, and marker dyes used for fuel tracing and tax regulation.

- Solid dyes: used for plastics and petroleum products.

1. Dye Process Descriptions

Since 1971, *o*-toluidine, aniline, and other liquid raw materials have been brought in on tank trucks and fed by hose to underground storage tanks (see Figure 1 for plant layout). From there they are pumped as needed to storage tanks in Building 11 (which is adjacent to the tank farm). Before 1971, *o*-toluidine and aniline were brought in drums.

Other liquid raw materials (acids, caustics, solvents, amines, etc.) are stored in either underground or above ground storage tanks, or in drums. Powdered raw materials are stored in Building 10 in either bags or drums.

Two dye intermediates are made on site (Building 2 and Building 13) for use in the production of liquid dyes in Building 11.

All dyes manufactured at this facility are produced on a batch-wise basis. Batches are run in response to inventory requirements.

a. Liquid Dye Production Procedures in Building 11

o-Toluidine and/or aniline are starting components that are used in dye manufacturing at this site. The main reaction is a diazo-coupling reaction which occurs in DC tanks. There are multiple DC tanks used for the production of liquid dyes. Liquid bulk raw materials are transferred by pipes to the DC tanks from underground storage tanks. Intermediates are piped in from storage tanks located in Buildings 2 and 13. The liquid bulk raw materials and intermediates are charged via a closed system. The DC tanks are under negative pressure during the transfer of all raw materials

and intermediates. Raw materials other than liquid bulk chemicals are added via a vacuum pump to the tank through the hatch.

After the reaction is completed, the mixture separates in the tank into two layers consisting of an aqueous/organic mix. The aqueous layer is drained from the reactor through a discharge valve at the bottom of the reactor. During separation, an operator monitors a valve and determines by means of a sight glass when the aqueous layer has been discharged.

The organic mix is transferred to one of several stripping kettles located on the second floor where water is removed by refluxing. The kettles are equipped with exhaust ventilation that is used in the event the kettles are opened. After stripping, the product is transferred to a holding tank, and then through a filter into a storage tank. Several liquid dye products are produced by blending primary dye colors (red, blue, yellow) in mixing tanks. The product is packed into drums (on occasion, product is loaded into tank trucks) by a filling pipe which extends into the drum. Local exhaust ventilation is provided for packaging.

b. Liquid Dye Production Procedures in Building 5

Aniline is used in the manufacturing of one product and *o*-toluidine is not used for the manufacturing of any product in Building 5.

The production of liquid dye in Building 5 is similar to the production of liquid dyes in Building 11. Liquid raw materials are piped in from storage tanks or vacuum loaded into a kettle. Some raw materials are added manually to the tank through the hatch. After a portion of raw materials is added to the kettle, the contents are transferred to a tank for further processing and raw material additions, and then returned to a kettle. This step is repeated several times. The separation of the aqueous and organic layers occurs in a tank with the organic layer transferred to a kettle. In the kettle, the product is stripped and then filtered. Other dye colors are made by blending various dye colors. On the first floor, the product is packed into drums.

c. Solid Dye Production Procedures

Solid dyes are made in Building 2 and do not use or contain *o*-toluidine or aniline.

The main reaction is a condensation reaction. The liquid raw materials are primarily charged through the hatch by vacuum pump or piped in from storage tanks. Solid materials are manually added through the hatch. The tanks are equipped with exhaust ventilation that is used when tanks are

opened. The solid dye is filtered, washed, and loaded onto trays for drying. The dye trays are put on stack racks and loaded into Building 8 ovens. In Building 4, the dried solid dye is ground and packaged.

B.   Description of Engineering and Administrative Exposure Controls

1.   Engineering Controls

The tanks and kettles in the dye processing buildings are equipped with local exhaust ventilation, and local exhaust fans are located near the dye packaging operations. Also, raw *o*-toluidine and aniline are transported from bulk storage tanks to the dye reaction vessels through an enclosed pipe system.

2.   Administrative Controls

Morton International administers personal protective equipment, respiratory protection, and hazard communication programs, and provides annual medical exams at the Paterson facility.

All employees are provided with and required to wear cotton work uniforms, hard hats, safety glasses, and chemically resistant safety footwear. Safety equipment provided for protection during performance of specific tasks includes gloves, face shields, respiratory protection, and Tyvek® or Saranex® suits.

The respiratory protection program consists of annual qualitative fit testing with irritant smoke, and employee training and medical surveillance.

Annual hazard communication training has been provided for *o*-toluidine and aniline at the Paterson facility since 1985. Also, the top five chemicals contained in a raw material or product are labeled on the appropriate containers/pipes in accordance with the New Jersey Right-to-Know law.

Annual medical exams are provided for the employees working in the dye processing areas. The examination contents were developed and are reviewed by a Board Certified Occupational Physician. The general contents of the exams include:

► Medical History

► Physical Examination

► Blood Tests:

  ! Chemistry   ! Cholesterol Profile

> ! CBC   ! PSA (Added since survey)

- ▸ Electrocardiogram - Conducted at discretion of company physician or at employee request.

- ▸ Chest X-Ray - Conducted on semi-annual basis; abnormal tests followed up via an established protocol.

- ▸ Urinalysis

- ▸ Urine Cytology, including RBC in Urine - Conducted on semi-annual basis; abnormal tests followed up via an established protocol.

- ▸ Vision Testing

- ▸ Audiometry

- ▸ Pulmonary Function Spirometric Testing

C. Description and History of the Workforce

Current personnel records do not always include details of work assignments and work history, and there are no production records prior to 1970 or monitoring records from before 1986, making it impossible to estimate past exposures. It is known that all current and former production workers have been male. Some employees have worked in Building 2 (solid dyes) and later in Building 11 (liquid dyes); some former production workers are now in maintenance; however, there has not been a substantial amount of job rotation. Sixteen of the 55 unionized workers have been at the plant 20 years or more.

IV. **STUDY DESIGN AND METHODS**

A. Study Population

At the time of the survey, 95 individuals were employed at the Paterson facility. There were two production shifts, 8 a.m. to 4 p.m. and 4 p.m. to midnight, 5 days a week. Employees were assigned to the day or afternoon shift on a permanent basis (but may bid for rotation to the other shift). All employees except the office workers and the security guards, even those not working directly with *o*-toluidine and aniline, have potential exposure to these substances.

Participants in the study included the 12 production workers who were judged to be the most highly exposed (probably exposed), based on observation of the job tasks, and a comparison group of eight workers from other areas of the plant

considered very unlikely to have contact with *o*-toluidine and aniline (presumably unexposed).

B. Strategy for Environmental and Biological Monitoring

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 for dye production operations. These included airborne vapor/mists (inhalation) and skin contact with process liquid chemical spills and residuals (dermal), since there is OSHA skin notation for both chemicals.[4] The potential inhalation exposure source was identified as airborne process vapor, and the potential dermal exposure sources as liquid chemical contact with spills or process surfaces contaminated with residual chemicals.

Personal air samples were collected to measure inhalation exposure, and dermal indicator badge and glove samples were collected on workers to detect contact with liquid chemicals. Area air samples were collected from representative locations throughout the dye production areas 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 from the air by this type of sampler. Wipe samples were collected from several representative work surfaces to indicate potential dermal exposure to workers not wearing gloves in the process areas to residual *o*-toluidine and aniline. Bulk samples were taken of process starting chemicals, process reactant at various intermediate stages of the process, and finished products. The bulk samples were collected to quantitate the presence of *o*-toluidine, aniline, the potential aniline contaminant 4-aminobiphenyl (a known human bladder carcinogen), diphenylamine (known to sometimes be contaminated with 4-aminobiphenyl), hydroquinone and 2-aminofluorene (which have shown evidence of carcinogenicity in animal studies), and the known human carcinogen 2-naphthylamine.

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.

1. Air Sampling Rationale and Methods

The validated techniques available for *o*-toluidine and aniline 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 *o*-toluidine and aniline. 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, OSHA method 73 was used as described in Appendix A.

The OSHA method 73 collection media consisted of 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 connected by tubing to an SKC Model 224-PCXR7 personal air sampling pump set in the 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 air volume not exceeding 100 liters (L) was collected in accordance with the OSHA 73 method for full shift time-weighted average (TWA) exposure monitoring. Several of the same type of sampling pumps were also calibrated in high flow mode at 2000 cc/minute with the same sampling train to evaluate short-term peak exposures 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 within the limit of detection of the analytical method.

The filter and pump sampling trains were placed on the workers at the beginning of the work-shift for the TWA sampling so that the air inlet was fastened in the breathing zone. The air sampling media was changed at mid-shift after about 100 L of air had been collected. For peak exposure sampling of job tasks with higher airborne exposure potential, an additional sampling pump and media train, pre-calibrated at 2000 cc/minute, were placed on the worker (in the same way as the TWA 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 turned off and removed at completion of the work task. At the end of the shift, or peak sampling period, the sampling train was removed and the cassettes were sealed and logged in. The sampling pump calibration was again checked and recorded at this time. All samples were refrigerated upon return to the NIOSH Hamilton facility until laboratory analysis.

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 (front) and B (back) 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 field samples. To each field and QC sample, 3 ml of deionized (DI) water, 1 ml 0.5 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, field samples, and QC spikes were derivitized by the addition of 25 microliters (μL) 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 of each was then transferred to gas chromatograph (GC) vials for analysis.

The analysis was performed on a HP5890 GC equipped with an electron capture detector. A 30 meter (M) x 0.25 mm internal diameter (ID) fused silica DB-5 capillary column was used at an initial temperature of 110 degrees centigrade ($^{\circ}$C) for 5 minutes and then increased at 10°C/minute intervals up to 150°C. The NIOSH calculated limit of detection (LOD) for each acid treated filter was 8.7 microgram per cubic meter (μg/M^3) for o-toluidine and 1.3 μg/M^3 for aniline. The calculated limit of quantitation (LOQ) was 26 μg/M^3 for o-toluidine and 5.2 μg/M^3 for aniline. The calculated LODs and LOQs for o-toluidine and aniline were based on the analytical LODs of 0.6 and 0.1 μg/sample, respectively, and the analytical LOQs of 2.0 and 0.4 μg/sample, respectively.

a. Personal Air Sampling

A total of 20 workers over the two workshifts participated in the personal air sampling. Personal air sampling consisted of 21 total samples (20 TWA and 1 peak). A total of seven air sample blanks, and six unused media sets not handled during the survey, were submitted for analysis along with the field samples for QC and analytical instrument calibration.

b. Area Air Sampling

The area air samples were also collected as TWA samples for the complete workshift, changing the filter media after about 100 L of sample volume. Twelve area air samples were collected over the two workshifts monitored. The area monitoring was conducted by positioning the samplers in the process where operators would be expected to spend most of the workshift. 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 workshift and in the analytical laboratory.

2. Skin Contact Sampling Rationale and Methods

a. Dermal Sampling

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. However, it was uncertain if liquid *o*-toluidine and aniline would be retained by the cloth patches if they were contacted. Therefore, monitors were developed that could be placed on the workers, and would retain any liquid *o*-toluidine and aniline that was contacted. These monitors were cotton pouches containing silica gel that were fitted with paper tabs for labeling and handling purposes. 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 most of the dermal monitoring effort in that area of the body. To accomplish this, seven silica gel dermal liquid contact indicator badge samplers, or dermal badges, were placed on each worker monitored, one each at each shirt lapel, each forearm, on the chest, and on the cuff of each pant leg.

The pre-labeled dermal badges were placed on and removed from the workers by handling only the paper tabs (to prevent inadvertent contamination), at the same time the air samplers were attached. It was previously determined by laboratory testing that it was not necessary to change the badges during the workshift. After removal, the paper tabs were removed from the dermal badges using sterile gloves and the badges were then placed in pre-labeled 20 ml scintillation vials. Then 5 ml of pure ethanol was added to stabilize any amine present and the vials were capped and shrink-banded. The samples were refrigerated at the NIOSH Hamilton facility until sample analysis.

At the analytical laboratory the silica gel from each dermal badge sample was desorbed in 8 ml of pure 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 GC with flame ionization detection (GC/FID), using a HP5890 GC equipped with a 30 m DB-5 fused silica capillary column for *o*-toluidine and aniline. All analyses were performed in the splitless injection mode. The resultant sample recoveries were corrected for dilution effects.

The calculated LODs for *o*-toluidine and aniline for the dermal badge samples were 28 and 31 µg/sample, respectively, and the calculated LOQ was 84 and 93 µg/sample, respectively. See Appendix A for additional details regarding this sampling and analytical method.

These silica gel dermal 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 subsequently 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 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. Prior to the survey, 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 samplers and dermal 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 to the outside of 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 dermal badge media at the end of the workshift. They were then placed in 120 ml amber glass bottles, 20 ml of pure ethanol was added to stabilize any amine in the sample, and the vials were capped and shrink-banded. The samples were refrigerated at the NIOSH Hamilton facility until sample analysis.

At the analytical laboratory, the glove samples were extracted with ethanol and analyzed by GC according to NIOSH Method 2002 with modifications as described in Appendix A. The calculated LOD for the analysis of the gloves for *o*-toluidine and aniline was 240 and 270 µg/sample, respectively, and the calculated LOQ was 720 and 810 µg/sample, respectively. See Appendix A for additional details of 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 decided 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 the NIOSH analytical laboratory, it was decided to use hexane-extracted 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 120 ml amber glass 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 wipe samples were then returned to the jar, 10 ml of pure ethanol added to stabilize any amine present, and they were capped and shrink-banded. The samples were refrigerated at the NIOSH Hamilton facility until sample analysis.

The wipe samples were extracted and analyzed by GC according to NIOSH Method 2002 with modifications as described in Appendix A. Liquid standards were prepared of known amounts of *o*-toluidine and aniline and spiked into 1 ml of extraction solvent. The calculated LOD for *o*-toluidine and aniline was 70 and 80 µg/sample, respectively, and the calculated LOQ was 210 and 240 µg/sample, respectively.
See Appendix A for additional detail of the surface wipe sampling and analytical method.

d. Bulk Sampling

The airborne and residual surface chemicals present at any process location are most likely composed of the process chemicals within the process at that location. Also, the chemical composition of the process reaction chemicals changes as they progress through the various reaction stages. Therefore, it was decided to evaluate the amounts of *o*-toluidine, aniline, and the other previously mentioned bulk sample analytes within the system at the 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 the starting materials *o*-toluidine and aniline, and of finished products. QA samples were routinely collected by Morton of starting, ending, and intermediate process chemicals and taken to the QA laboratory for analysis. Portions of all available QA samples were taken by transferring about 60 ml from a

freshly collected sample into a glass jar, which was then capped and shrink-banded. The samples were refrigerated at the NIOSH Hamilton facility until sample analysis.

The 13 bulk dye samples collected were analyzed by GC in conjunction with mass spectrometry. The samples were analyzed to confirm the presence and approximate concentration of *o*-toluidine, aniline, diphenylamine, hydroquinone, 4-aminobiphenyl, 2-naphthylamine, and 2-aminofluorene.

The samples were prepared for analysis by dissolving known amounts (approximately 220 to 250 milligrams [mg]) of each bulk dye into 25 ml of methylene chloride. In the case of the bulk *o*-toluidine and aniline, a syringe was used to inject 25 µl of the sample into 25 ml of methylene chloride. Calibration standards containing the seven analytes were prepared in methylene chloride at three concentration levels, 0.01, 0.1, and 1 µg/ml, respectively. An additional standard was prepared in methylene chloride at the concentration level of 0.5 µg/ml each. A spiking solution that contained the internal standard, octafluoronaphthalene, was prepared in methylene chloride at a concentration of 50 µg/ml. See Appendix A for additional detail of the bulk sampling and analytical method.

3. Urine Sampling Rationale and Methods

The 12 workers with the apparently highest exposure and eight presumably unexposed workers participated in the biological monitoring portion of the survey. This sample size is more than adequate to detect a difference in urinary *o*-toluidine concentration between probably exposed and unexposed workers using nonparametric tests. Detecting a difference (if one exists) between the mean level of *o*-toluidine and aniline (or their metabolites) in the urine of the probably exposed and unexposed workers was the major objective of the study.

At the Morton International, Paterson, New Jersey facility, production workers are potentially exposed to both *o*-toluidine and aniline. Based on our understanding of the processes and job categories at Morton, we concluded that any worker assigned to an area where *o*-toluidine and aniline were used should be considered definitely exposed to these chemicals. Workers assigned to Maintenance, Janitorial/Yard, and Shipping departments were considered possibly exposed. These definitely and possibly exposed workers constitute the exposed group. Workers never employed in the production area were considered presumably unexposed. The presumably unexposed group includes male plant gate guards and male and female office workers (male administrators periodically enter the production area).

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 side-stream tobacco smoke. Participants were provided with 500 ml polypropylene containers to collect a urine sample immediately before reporting to work (pre-shift) and immediately before leaving for the day (post-shift). Probably exposed workers were asked (at the request of Company representatives) to collect the pre-shift sample after arriving at work (the protocol called for pre-shift collection at home, just before leaving for work). Probably exposed workers were asked to collect the post-shift sample after showering or at least after removing their outer work clothes and washing their hands. (Presumably unexposed office workers were not asked to remove their working clothes or shower before collecting the sample.) The sample bottle was labeled only with the employee's study identification number, not his or her name. Each sample was split into two 20 ml vials; one vial contained 2 grams (g) of citric acid to preserve the urine for *o*-toluidine and aniline analysis in the NIOSH laboratory. Urine in the second vial was analyzed for creatinine and cotinine concentration by a NIOSH contract laboratory. (One post-shift specimen had insufficient urine for a sample to be sent for creatinine and cotinine testing.) 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 pre-shift or post-shift or whether the donor was from the probably exposed or the presumably unexposed workers. For approximately 10% of the urine samples, a second pair of 20 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. (After the lab analysis was completed, the average of all blind splits of a sample was used as the value for that sample in the analysis.) The date and time of each sample, and the random vial numbers assigned to it, were recorded in a logbook with the employee's study identification number. The vials were placed on dry ice as soon as possible after the urine was added to the vials and preserved in that manner until placement in a -65°C freezer at the NIOSH Taft facility laboratories in Cincinnati, Ohio. NIOSH Method SOP T4-29 was the laboratory method for analysis of *o*-toluidine and aniline in urine as described in Appendix B.

C.   Statistical Methods

With the recently developed NIOSH analytical method used in the urine analyses (Appendix B), the LOD for *o*-toluidine was 0.6 micrograms per liter (µg/L) and for aniline was 1.4 µg/L. Some quantitative values below the LOD were reported by the laboratory. These values were included in the statistical analyses because

the alternative, which was to substitute $LOD/\sqrt{2}^6$, was considered to be less precise. Those samples for which there was no analytical response (the quantity of analyte was below the LOD) were assigned the $LOD/\sqrt{2}$, which was 0.42 µg/L for *o*-toluidine and 0.99 µg/L for aniline.

Because the number of participants was small and the distribution of results therefore unpredictable, it was decided to use statistical tests that are not based on distributional assumptions. Armitage[7] discusses the justification for using such distribution-free methods. The nonparametric Wilcoxon rank-sum test[8] was used to compare the levels of the outcome variables in the exposed and presumably unexposed groups. The differences, for individual workers, in pre- and post-shift levels was compared with the Wilcoxon signed-rank test, which is appropriate for paired samples.[8]

Pre-shift and post-shift means were calculated to evaluate differences in *o*-toluidine and aniline urine concentration between the exposed and presumably unexposed groups of workers and between nonsmokers and smokers within the exposed group (as there was only one smoker in the presumably unexposed group, this comparison was not made). Paired t-tests were used to test the difference in pre-shift and post-shift samples within each subgroup, and unpaired t-tests were used to test the difference between pre-shift means and post-shift means between subgroups. Parallel analyses were performed with log-transformed data.

For descriptive purposes, the arithmetic mean air and urine levels and highest dermal level for exposed and unexposed were calculated. Correlation coefficients between *o*-toluidine and aniline levels in personal air and urine samples were calculated.

Correlation coefficients between pre-shift and post-shift values of both *o*-toluidine and aniline were also calculated.

Multivariate linear regression was used to evaluate the relationship between the outcome variables and the exposure variables. The outcome variables for the regression models are post-shift urinary o-toluidine or aniline (µg/L) or the difference between pre-shift and post-shift urinary o-toluidine and aniline (µg/L). The exposure variables include two continuous variables, air concentration and pre-shift level of *o*-toluidine or aniline, and two categorical variables, smoking and exposure status (yes or no). The variables were retained in the final model if they were statistically significant.

All analyses were performed with SAS/DOS 6.04 statistical software.[9]

V.   EVALUATION CRITERIA

A. Health Effects of Chemicals Used

1. In Animals

Two of the chemicals used at Morton, *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.[3] Regarding *o*-toluidine, the IARC concluded that "there is sufficient evidence for the carcinogenicity of *o*-toluidine hydro-chloride (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." The IARC classification of these chemicals remained the same in a follow-up evaluation concluded in 1987.[10] 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."

A comparison of the carcinogenicity of *o*-toluidine and aniline in experimental animals is possible because they have been tested in similar experiments.[11,12] 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.[13,14]

2. In Humans

The epidemiologic data available for *o*-toluidine and aniline have been limited. In a large study of bladder cancer in British dyestuff workers, Case[15] found no evidence that workers exposed to aniline alone had an increased risk of bladder tumor. Ott and Langner[16] 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 of bladder cancer in workers exposed to *o*-toluidine, but not also exposed to other carcinogenic

aromatic amines, can be calculated. One recent study reported a 72-fold increase (eight cases observed vs. 0.11 expected) of bladder cancer among 116 workers involved in manufacturing 4-chloro-*o*-toluidine between 1929 and 1970.[17] *o*-Toluidine was also present at this plant, although exposure to 4-chloro-*o*-toluidine was thought to be more extensive.

In December 1989, NIOSH released the first report of the investigation of bladder cancer incidence at the Goodyear Tire and Rubber Company, Niagara Falls, New York facility.[18] A summary report of the study was published in the Journal of the National Cancer Institute.[19] In summary, that 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 seven 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 four cases observed and 1.09 expected (SIR=3.66; $p=<0.03$). The SIR among 681 workers considered "presumably 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 under five years. Among workers employed in the department for 5 to 10 years, there was one case observed and 0.11 expected (SIR=8.79; $p\leq 0.11$). Among workers employed in the Department for 10 or more years, there were six cases observed and 0.22 expected (SIR=27.2; $p\leq 0.0000001$). 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 that department, NIOSH investigators concluded that there was a clear epidemiological association between exposure to *o*-toluidine and aniline in Department 245 and bladder cancer.[19]

Based on the bladder cancer incidence study at the Goodyear Niagara Falls facility,[18,19] and on an independent review of additional human and animal data in the scientific literature, NIOSH concluded in a 1990 Hazard Alert[20] that *o*-toluidine and aniline are potential occupational carcinogens as defined in the OSHA Carcinogen Policy [29 CFR 1990].[2]

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

In rats orally administered ^{14}C labeled *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.[21] Unchanged *o*-toluidine represented 21% of the compound excreted. In rats administered ^{14}C 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.[22] 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.[23,24] Eighty-nine percent of *p*-aminophenol is eliminated within 24 hours post exposure.[24] Only a small amount is eliminated as unchanged aniline.[24] Aniline is a metabolite of phenylhydroxyamine, nitrobenzene, acetanilide, phenacetin (a medication no longer sold commercially in the United States), and the disinfectant phenazopyridine. Aniline is also a product of degradation of a variety of pesticides such as propham, carbetamide, fenuron, or siduron.[25] Thus, potential exposure to these compounds (for example by a home gardener) should be considered in the interpretation of a high urine aniline result. The current method for *p*-aminophenol analysis requires that the samples be analyzed by a particular colorimetric method based on the indophenol reaction and has a detection limit of 10 milligrams per liter (mg/L).[25, 28] For these reasons, another method, with a lower limit of detection, was developed by NIOSH researchers. This method, including quality control procedures, is described in Appendix B.

Both *o*-toluidine and aniline typically 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 side-stream cigarette smoke. Patrianakos and Hoffman[26] found 162 nanograms (ng) of *o*-toluidine and 364 ng of aniline per cigarette in mainstream smoke and 3030 ng of *o*-toluidine and 10,800 ng of aniline per cigarette in side-stream smoke. El Bayoumy et al[27] found that smokers excreted 6.30 (standard deviation [SD] 3.70) µg of *o*-toluidine and 3.10 (SD 2.60) µg of aniline per 24-hour period, while non-smokers excreted 4.10 (SD 3.20) µg of *o*-toluidine and 2.80 (SD 2.50) µg of 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 contribution of occupational exposure to the urine concentration of these chemicals.

The established American Conference of Governmental Industrial Hygienists' (ACGIH) biological exposure index (BEI) for aniline is 50 mg/g of creatinine,[25, 28] but there is no BEI established for *o*-toluidine.

C. Environmental Criteria

As a guide to the evaluation of the hazards posed by workplace exposures, NIOSH representatives employ environmental criteria for assessment of chemical and physical agents. These criteria are intended to suggest levels of exposure to which most workers may be exposed up to 10 hours per day, 40 hours per week for a working lifetime without experiencing adverse health effects. It is important to note, however, that not all workers will be protected from adverse health effects if their exposures are maintained below these levels. A small percentage may experience adverse health effects because of individual susceptibility, a pre-existing medical condition, and/or a hypersensitivity (allergy). In addition, some hazardous substances may act in combination with other workplace exposures, the general environment, or with medications or personal habits of the worker to produce health effects, even if the occupational exposures are controlled at the limits set by the evaluation criteria. Also, some substances are absorbed by direct contact with the skin and mucous membranes, and thus the overall exposure may be increased above measured airborne concentrations. Evaluation criteria typically change over time as new information on the toxic effects of an agent become available.

The primary sources of environmental criteria for the workplace are the following: NIOSH Criteria Documents and Recommended Exposure Limits (RELs), ACGIH Threshold Limit Values (TLVs), and the OSHA Permissible Exposure Limits (PELs). These values are usually based on a TWA exposure, which refers to the average airborne concentration of a substance over the entire 8- to 10-hour workday. Concentrations are usually expressed in parts per million (ppm) or milligrams per cubic meter (mg/M^3). In addition, for some substances there are short-term exposure limits (STELs) or ceiling limits which are intended to supplement the TWA limits where there are recognized toxic effects from short-term exposures.

The OSHA standards are required to take into account the feasibility of reducing exposures in various industries where the agents are used; whereas, the NIOSH RELs are based primarily on concerns relating to the prevention of occupational disease. In evaluating the exposure levels and NIOSH recommendations for reducing exposures, it should be noted that employers are legally required to meet the requirements of OSHA PELs and other OSHA standards.

For *o*-toluidine and aniline, the OSHA PELs are 8-hour TWAs of 22,000 and 19,000 $\mu g/M^3$, respectively (or 5 ppm each);[4] the ACGIH TLVs are 8-hour TWAs of 8800 and 7600 $\mu g/M^3$, respectively (or 2 ppm each)[28] as shown in Table I. (Both OSHA and the ACGIH criteria listed skin absorption to be a potential route of exposure for these two compounds.) The NIOSH RELs for these chemicals are

the lowest feasible concentrations.[29] There are no published environmental criteria for the dermal badge or glove sampling methods.

VI. RESULTS

A. Participant Characteristics

Participant characteristics are summarized as follows:

Summary Of Urine Survey Participant Characteristics		
Characteristics	**Not Exposed**	**Exposed**
Number male (%)	6 (75)	12 (100)
Number female (%)	2 (25)	0 (0)
Mean age	46.0	47.4
Number smokers (%)	1 (12.5)	6 (50.0)
Number nonsmokers (%)	7 (87.5)	6 (50.0)
Ethnicity white (%)	5 (62.5)	3 (25.0)
Ethnicity other (%)	3 (37.5)	9 (75.0)

B. Environmental Monitoring Results

The personal air, dermal badge, and glove sample results are shown in Tables I and II. The summary sample results for each worker monitored are presented by job title, with worker identifiers excluded, in Table I. The results for all personal samples collected are presented in Table II. The results for each area air and dermal badge sample set are tabulated in Table III. The surface wipe sample results are shown in Table IV.

1. Air Sampling Results

a. Personal Air Sampling Results

As previously discussed, the air sampling filters were changed at mid-shift after approximately 100 L of air volume. When the TWA air concentrations were calculated for a full shift sample, the total weight of analyte found for both filters for the given worker or area was used. In the

cases where both filters had no detected concentrations of o-toluidine and/or aniline, the result is reported as ND. However, when only one of the two filters for a given worker or area sample had a detectable level of o-toluidine and or aniline, and the other filter was ND, the value of LOD/$\sqrt{2}$ was substituted for the ND filter when adding the weights of analyte to use for the TWA calculation for that sample. This technique for estimating average concentration in the presence of ND values is described in detail by Hornung and Reed.[6] The LOD/$\sqrt{2}$ substitution technique was also used in the calculation of the geometric mean values for the personal and area air exposure levels.

The personal air sample results are shown in Tables I and II. These tables show that 9 of the 20 personal air samples collected had detectable levels of o-toluidine, and all of these workers were in the probably exposed group. The o-toluidine exposure levels for the probably exposed group samples ranged from ND to 164 µg/M³, with a geometric mean of 37.9 µg/M³. Twelve of 20 personal air samples had detectable levels of aniline present, including one worker from the presumably unexposed group. The aniline exposure levels for the probably exposed group ranged from ND to 25 µg/M³, with a geometric mean of 7.6 µg/M³. All of the personal air monitoring results for o-toluidine and aniline were well below their respective OSHA PELs and ACGIH TLVs (see Table I).

The employee showing the highest o-toluidine (164 µg/M³) and aniline (25 µg/M³) TWA air exposure was a Diazo-Coupling Operator for Building 11. Another Diazo-Coupling Operator for Building 11 had the second highest (23 µg/M³) aniline air exposure. Both of these workers were involved in the production of a liquid dye which uses both o-toluidine and aniline in the process.

A Kettle Operator for Building 11 had the second highest o-toluidine (130 µg/M³) TWA exposure level. This worker was involved in the production of a liquid dye which uses o-toluidine. A peak sample also collected on this worker while adding raw materials to the batch (through a hatch opening in the top of Tank 6) was ND for o-toluidine and aniline. All other o-toluidine and aniline TWA exposure levels were below 100 µg/M³.

These results indicate that the highest exposures to o-toluidine and aniline occur to the workers in Building 11 (all in the probably exposed group). This conclusion is supported by the fact that all of the o-toluidine TWA results for the workers in Buildings 5, 7, 15 and 16 were ND and the aniline results for these workers were all 5 µg/M³ or less.

b. Personal Airborne Exposure by Process

All personal TWA *o*-toluidine samples that were detectable were collected on workers assigned to the liquid dye process areas (Buildings 11 and 13) who were included in the probably exposed group. The TWA *o*-toluidine samples for all workers in all other buildings were ND. Aniline TWA levels were detectable for the Building 11 and Building 5 liquid dye workers, and the Warehouse Building (Building 16) workers monitored. These results were expected for the 11 workers in the probably exposed group because aniline was used in all dyes produced by the workers sampled during the survey. However, the detectable level of aniline (2 $\mu g/M^3$) for the warehouse worker monitored was not expected. This may have been the result of the worker briefly going into a production area or being exposed to side-stream cigarette smoke.

c. Area Air Sampling Results

The area air sample results are shown in Table III. All area air sample results for *o*-toluidine ranged from ND to 510 $\mu g/M^3$ with a geometric mean value of 54.4 $\mu g/M^3$. The aniline area air sample results ranged from ND to 47 $\mu g/M^3$ with a geometric mean value of 9.3 $\mu g/M^3$. Area air samples were collected in Buildings 11, 5, 7, 13. and 17, at locations that would most likely be representative of the air concentrations of *o*-toluidine and aniline in the proximity of where operators work for most of the shift. All Building 11 areas had detectable levels of *o*-toluidine ranging from 16 $\mu g/M^3$ by the Drumout Station to 510 $\mu g/M^3$ by the Diazo-Coupling Charging Tank #5. This is not surprising since *o*-toluidine is used in the liquid dye products that were processed in Building 11 during the sampling. The only other building where *o*-toluidine was detected was in Building 17 on the counter at the Guard Station. This was unexpected because the personal sample for *o*-toluidine for the Guard was ND, and there are no dye production operations in Building 17. This may have been the result of contamination carried in from a process area or from side-stream cigarette smoke.

All Building 11 area samples had detectable concentrations of aniline ranging from 7 $\mu g/M^3$ by the Drumout Station to 47 $\mu g/M^3$ by the Diazo-Coupling Charging Tank #5. This was expected because aniline is used in the products that were processed in Building 11 during the sampling. The only other building where aniline was detected was in Building 5 during production of aniline based liquid dyes.

2. Skin Contact Sampling Results

NIOSH investigators anticipated that the silica gel would passively adsorb *o*-toluidine and aniline from the air. Therefore, in order to subsequently determine how much of the *o*-toluidine and aniline adsorbed by the dermal

badges was adsorbed by actual contact with liquid or residual chemical, and how much from the air; area dermal badges were placed as area samplers beside the sorbent tube area air samplers. The data from these pairs of samples were intended to give an estimate of the relationship of air concentration of amine with the levels of amine on the badges. However, since o-toluidine was only detected on two of the area badges and aniline was not detected on any, there was not sufficient data to perform this analysis.

a. Personal Dermal Sampling Results

Tables I and II show that seven of the eight dermal badge sets with detectable levels of o-toluidine were collected from workers in Building 11. Seven of 11 personal dermal badge sets collected from employees who worked in Building 11 had at least one dermal badge with a detectable level of o-toluidine. Only one of the workers with a detectable dermal badge level had detectable results on more than one (two) dermal badge. The detected o-toluidine levels for the dermal badges ranged from 28 to 211 µg/sample. The employee with the highest measured dermal badge level (Diazo-Coupling Operator, 211 µg) also had the highest personal air measurement for o-toluidine (164 µg/M^3).

The only detectable o-toluidine dermal badge results for personnel not working in Building 11 were for a nonsmoking clerk working in Building 15 (42 µg), who also had the only detectable aniline result (55 µg) of all personal dermal badges collected, and for the warehouse worker (60 µg) discussed previously. This worker reportedly left the facility for approximately one hour during the workshift while wearing all sampling media. Therefore, it is possible that the worker was in the proximity of a smoker, and o-toluidine and aniline were collected by the dermal badge from side-stream cigarette smoke. Also, minor laboratory instrument error or sample contamination could cause low level false-positive results (especially for concentrations this close to the LOD of 28 and 31 µg for o-toluidine and aniline respectively).

b. Area Dermal Sampling Results

As shown in Table III, two of the 12 area dermal badges collected had detectable levels of o-toluidine present (34 µg each). Both of these samples were collected in Building 11 in areas (Kettle #6 and Diazo-Coupling Tank #5 during o-toluidine based liquid dye processing) where o-toluidine and aniline were being used in the process, and where the area air levels were the highest. Therefore, it is likely that these badges adsorbed o-toluidine from the air. Since the o-toluidine levels detected on the dermal badges were just above the limit of detection (28 µg) in the two areas where the area air levels were the highest; it is not surprising that

o-toluidine was not detected on the other area dermal badges collected where the area air levels were lower. Aniline was not detected on any of the area dermal badges. Since the area air levels of *o*-toluidine (315 and 510 µg/M^3) were much greater than aniline (13 and 47 µg/M^3) for these two areas, it is not surprising that aniline was not detected by the dermal badges.

c. Glove Sampling Results

Neither *o*-toluidine nor aniline were detected on any of the thirteen pairs of glove samples collected on production employees in Buildings 5, 11, and 13 as shown in Tables I and II.

d. Surface Wipe Sampling Results

One surface wipe sample had detectable levels of both *o*-toluidine and aniline (see Table IV). This sample was collected by wiping the three lift handles for the Building 11 Kettle #6 cover during the processing of an *o*-toluidine based liquid dye. It was expected that *o*-toluidine and aniline could be detected on this sample because *o*-toluidine and aniline are both used during liquid dye production, and the cover is opened during the process for the addition of reactants. These results indicate that residual *o*-toluidine and aniline are present on the surface of the kettle, and therefore, the potential for dermal contact exists for workers who might inadvertently handle the kettle cover without gloves.

One other surface wipe sample, which was collected from the surface of the operators table in the Building 7 control room, had a detectable level of *o*-toluidine present. This result was unexpected since detectable air levels were not found and no dyes are produced in this building. This may have been the result of contamination carried in from a process area.

e. Bulk Sampling Results

Eleven bulk samples of *o*-toluidine, aniline, various dye products, and intermediates were analyzed for *o*-toluidine, aniline diphenylamine, hydroquinone, 4-aminobiphenyl, 2-naphthylamine, 1-naphthylamine, and 2-aminofluorene. Aniline was present in all samples with a range of 0.7 ppm to 4200 ppm, with the highest value obtained form an intermediate process sample. Aniline was obtained from *o*-toluidine at 33 ppm.

o-Toluidine levels ranged from none detected to 2700 ppm (the highest level being a liquid dye intermediate), and was present in 9 of 11 product/intermediate samples. Seven of these samples were less than or

equal to 69 ppm. *o*-Toluidine was present in aniline at 67 ppm, and in one liquid dye product at 1600 ppm.

Diphenylamine was present in one liquid dye at 2300 ppm, not detected in seven samples (including aniline and *o*-toluidine) and detected in five other samples at 18 ppm or less.

Hydroquinone was detected at trace levels in an aniline based liquid dye and an intermediate. Trace levels of 2-naphthylamine were detected in 5 samples. Trace levels of 4-aminobiphenyl were detected in three samples at levels of 3.8 ppm or less. 2-Aminofluorene was not detected in any of the samples.

A major peak was observed near the retention time of 2-naphthylamine in samples of a production intermediate (aniline based liquid dye), one liquid dye (no aniline or *o*-toluidine), one solid dye (no aniline or *o*-toluidine) and *o*-toluidine. The NIOSH laboratory determined that the most likely compound was 1-naphthylamine, which is recognized by NIOSH as an occupational bladder carcinogen.[29] Figure 2a shows the GC/selected ion microscopy (GC/SIM) results obtained for 2-naphthylamine during the analysis of a liquid dye. In order to characterize the unknown peak, a 1-naphthylamine standard was analyzed under the same GC/SIM conditions to confirm the suspected compound. The results in Figure 2b show that the retention time of the standard was an exact match with the peak for the liquid dye. It also shows that a trace amount of 2-naphthylamine was present in the standard. The approximate concentration of 1-naphthylamine in the four samples was: 5 ppm in the liquid dye intermediate; 860 ppm in the liquid dye; 21 ppm in the solid dye, and 6 ppm in *o*-toluidine. Peak areas from the 2-naphthylamine standards were used to estimate the 1-naphthylamine concentrations.

The LOD was estimated at less than 0.5 ppm for all analytes except 2-aminofluorene, which was 5 ppm.

C.   Urine Monitoring Results

Urine samples were collected from 20 employees, including 12 that were considered probably exposed and 8 considered presumably unexposed. Of these, there were seven *o*-toluidine and nine aniline samples below the LOD.

As laboratory tests for cotinine confirmed self-reported smoking status, the self-reported status was used as an exposure variable.

The group results are presented in Table V. Two types of statistical tests were performed: parametric t-tests and nonparametric Wilcoxon scores. Analyses

were done with and without creatinine correction and with and without data log-transformed to achieve a normal distribution. Results were similar for all analyses. The results presented here are for non-log-transformed data without creatinine correction. Appendix C presents the rationale for not using creatinine correction on these data.

In the t-test comparison, there were no significant pre-shift differences between exposed and unexposed workers in urine levels of aniline or *o*-toluidine. Post-shift levels of both *o*-toluidine and aniline were significantly higher in exposed workers (Table V). An analysis by smoking status was performed for the exposed (there was only one smoker in the unexposed group). For aniline, exposed smokers had higher levels than did exposed nonsmokers (statistically significantly higher for pre-shift levels). Exposed nonsmokers, however, had higher levels of *o*-toluidine than did exposed smokers. The difference was statistically significant for post-shift levels (Table V).

Exposed and unexposed worker groups were compared for differences in pre- or post-shift levels of aniline or *o*-toluidine with the nonparametric Wilcoxon rank sum test. There were no differences between exposed and unexposed in pre-shift levels of either chemical. However, the post-shift levels were significantly different. For aniline, the post-shift sum of scores was 56 for unexposed workers (84 expected) and 154 for exposed workers (126 expected). The probability of such differences occurring by chance is 0.03. For *o*-toluidine, the post-shift sums of scores were 41 for unexposed workers (84 expected) and 169 for exposed workers (126 expected). The probability of such differences occurring by chance is 0.001.

The pre- to post-shift change in level was compared for both chemicals and both groups of workers with the Wilcoxon signed-rank sum test. There were no significant pre- to post-shift changes for either chemical in unexposed workers. However, the pre- to post-shift changes for both chemicals were significant in exposed workers. For aniline, the positive score (higher post-shift than pre-shift level) was 67 in exposed workers (39 expected), while the negative score (lower post-shift than pre-shift level) was 11 (39 expected). The probability of such a result occurring by chance is 0.015. For *o*-toluidine, the positive score was 78 (39 expected) and the negative score was 0 (39 expected). The probability of such a result occurring by chance is 0.001.

Within the exposed group there are six Diazo-Coupling Operators and four Kettle Operators. We compared aniline and *o*-toluidine levels for these two groups. Pre-shift aniline was significantly higher in Diazo-Coupling Operators (mean 3.36 vs. 0.97, p<0.02), while pre-shift *o*-toluidine was significantly higher in Kettle Operators (mean 2.82 vs. 2.07, p<0.05). However, if smoking is controlled for, the urine level differences between job titles are not significant (66% of Diazo-Coupling Operators and 25% of Kettle Operators are smokers).

D. Comparison of Biological and Environmental Levels of *o*-Toluidine and Aniline

Linear regression analyses were performed to determine which exposure factors were associated with post-shift levels of aniline and *o*-toluidine. The original model for aniline included the TWA aniline air level, the pre-shift urine level of aniline, the highest dermal badge level of aniline, smoking status, and whether or not that individual was in the "probably exposed" group. In that model, only the TWA aniline air level and smoking status proved significant ($p < 0.05$). A simpler model, including only the two factors that had proved significant in the original model, was equally good in accounting for inter-individual variation in post-shift urine levels of aniline, explaining 83% of the overall variation in the outcome. The coefficients and significance levels for the model are: for air, coefficient 0.15 (for each $\mu g/m^3$ TWA), p-value 0.0006; for smoking status, coefficient 4.69 (for current smokers vs. nonsmokers), p-value 0.0001.

The original model for o-toluidine included the TWA *o*-toluidine air level, the pre-shift urine level of *o*-toluidine, the highest dermal badge level of *o*-toluidine, smoking status, and whether or not that individual was in the "probably exposed" group. In that model, significant independent variables included the TWA *o*-toluidine air level, the pre-shift *o*-toluidine level, and the highest dermal badge level of *o*-toluidine. A simpler model, including only pre-shift *o*-toluidine and the TWA *o*-toluidine air level, accounted for 81% of the inter-individual variation in post-shift urine levels of *o*-toluidine. The coefficients and significance levels for the model are: air, coefficient 0.21, p-value 0.0001; pre-shift urine level, coefficient 2.01, p-value 0.005.

VII. CONCLUSIONS

A. Environmental Monitoring Conclusions

1. Airborne Exposure Sampling Conclusions

All airborne levels measured for *o*-toluidine and aniline were below their respective OSHA PELs and ACGIH TLVs. The NIOSH RELs for *o*-toluidine and aniline are the lowest feasible concentration.[20] Nine of 12 personal TWA air measurements for the probably exposed group had detectable levels of *o*-toluidine. The highest personal TWA *o*-toluidine air levels were measured in Building 11 for workers involved in production of *o*-toluidine/aniline based liquid dyes. Nine of the 11 workers monitored that were working in Building 11 had detectable TWA exposure to *o*-toluidine. The airborne *o*-toluidine exposure levels were generally much higher than aniline. *o*-Toluidine was not detected for any personal TWA air samples for the presumably unexposed group. Detectable personal TWA aniline air exposures were measured on 11 of the 12 workers in the probably exposed group. Aniline was detected for

one worker in the presumably unexposed group. This may have been the result of side-stream cigarette smoke or an excursion into a dye processing area such as Building 11.

o-Toluidine was detected in all of the general area TWA samples for Building 11. *o*-Toluidine also was detected in Building 17 at the Guard Station. This may have been the result of contamination carried in from a process area or side-stream cigarette smoke. Airborne aniline was detected in all areas where dye production was underway except for the Building 13 intermediate dye production area.

2. Skin Contact Exposure Sampling Conclusions

    a. Dermal Sampling

        Seven of the 12 workers in the probably exposed group had detectable *o*-toluidine levels on one of their seven dermal badges, and all seven of these workers performed tasks in Building 11. One probably exposed group worker (Diazo-Coupling Operator, Buildings 11 and 13) had a detectable level on two of his seven badges. Aniline was not detected on any of the dermal badges for the probably exposed group. Two of the eight workers from the presumably unexposed group had a detectable level of *o*-toluidine on one of their dermal badges. The Building 15 worker reportedly left the facility while wearing the badges and could have been in contact with side-stream cigarette smoke. In the case of the Building 16 worker, an excursion into a dye production area is most likely. Additionally, the dermal monitoring sampling and analytical method used during the survey at the Morton International, Paterson, New Jersey facility is developmental and has not been extensively field validated. Consequently, these low level results may have been due to minor laboratory instrument error or sample contamination.

        There were not enough detectable dermal area sample results to analyze the relative contributions of liquid versus airborne absorption of *o*-toluidine and aniline by the badges.

    b. Glove Sampling

        All of the glove sample results were non-detectable. This indicates that any exposure to workers' hands to *o*-toluidine and aniline liquid is occurring at levels below the LOD of the glove analytical method.

    c. Surface Wipe Sampling

Measurable levels of *o*-toluidine and aniline were wiped from the Building 11, Kettle #6 cover lift handles during *o*-toluidine based liquid dye production. This indicates that *o*-toluidine and aniline liquid/residue is present on surface areas handled by operators during liquid dye production. Therefore, the involved workers' clothing could become contaminated with *o*-toluidine and aniline, which could subsequently result in dermal exposure when the workers handle their work clothes.

There was a detectable *o*-toluidine wipe sample collected from the surface of the operators work table in the Building 7 control room. This may have been the result of contamination carried in from a process area.

d. Bulk Sampling

o-Toluidine and aniline were detected in the bulk samples where it was anticipated. It was not surprising that a trace amount of 4-aminobiphenyl was detected in aniline since there has been concern about the possibility of its formation in aniline by condensation.[30] However, the detection of higher levels of 4-aminobiphenyl in an aniline based liquid dye than in aniline was unexpected. This process may be concentrating the existing 4-aminobiphenyl present in aniline, or promoting further condensation of aniline. In any case, the trace amount of 4-aminobiphenyl that would be present in the work place from the quantities found would most likely be too low to measure environmentally or biologically. The level of diphenylamine measured in a non *o*-toluidine/aniline based liquid dye indicates that it must be utilized in, or a byproduct of, the process. The trace quantities of hydroquinone, 2-naphthylamine and 1-naphthylamine found would also most likely be too low to measure environmentally or biologically.

B. Urine Monitoring Conclusions

Post-shift urine *o*-toluidine and aniline concentrations were significantly elevated in the group of exposed workers, compared with their own pre-shift levels or with post-shift levels in the group of presumably unexposed workers. This result supports the hypothesis that exposed workers are absorbing *o*-toluidine and aniline into their bodies during the workshift.

We had planned that if the results were to show a statistically significant difference in mean aniline and *o*-toluidine levels between the group of most exposed and the group of least exposed workers, we would consider additional testing if needed to determine which jobs and tasks within the plant are associated with high urine levels of aromatic amines. However, the results of the Wilcoxon signed-rank sum tests (page 19, 29, 68) show that the entire group of exposed workers have post-shift levels higher than pre-shift levels of *o*-toluidine and

nearly all have higher post-shift levels of aniline. Therefore everyone working with either chemical should be considered exposed.

The regression analyses suggest that personal air measurements and smoking status are predictors of post-shift urinary aniline concentrations in exposed workers, and that personal air and dermal patch measurements are predictors of post-shift urinary o-toluidine concentrations. Caution should be used in interpreting the relative weight of air level and smoking status in determining the outcome because of the overall small sample size. This is especially true in light of our finding that urinary levels of aniline were higher in exposed smokers than in nonsmokers, and significantly higher for pre-shift levels, while urinary levels of o-toluidine were higher in exposed nonsmokers than in smokers, and significantly higher for post-shift levels. That is, one would have expected smoking to have similar effects on aniline and o-toluidine levels. The differences with respect to aniline may have been affected by the choice of analyte (aniline instead of its metabolite, p-aminophenol).

The differences between two categories of exposed workers (six Diazo-Coupling Operators and four Kettle Operators) are not consistent: pre-shift aniline is higher in the former, pre-shift o-toluidine in the latter, and there are no post-shift differences. The lack of consistency in the results and the small size of the study population mean that the most likely explanation for the results is random variation (including variation in exposure levels on the day samples were taken, in personal background levels of the two chemicals, and in the analysis of samples).

Despite their low absolute values, the air concentrations of o-toluidine and aniline were significantly related to the urine o-toluidine and aniline concentrations. This supports the hypothesis that o-toluidine and aniline air concentrations during the workshift contributed to the increased post-shift urine levels. A urine o-toluidine and aniline monitoring program could be utilized if feasible 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.

It is somewhat surprising that smoking is a predictor of urinary aniline but not of o-toluidine. If there is a real difference in urinary aniline levels between exposed smokers and exposed nonsmokers, one possible explanation is that smoking may enhance the absorption of aromatic amines into the body. The most direct mechanisms for this would be that: (1) substances present on the skin of the hands contact the lips, resulting in ingestion, and/or that (2) the hands contact the cigarette, and the aromatic amines deposited on the cigarette are inhaled in the cigarette smoke. The break room was found to contain measurable air concentrations of o-toluidine, which may add to the o-toluidine 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[31], not enough is known about the metabolism of *o*-toluidine and aniline to assess how likely this explanation is. In addition, none of these hypotheses can explain a mechanism whereby aniline would be absorbed but *o*-toluidine would not be.

Therefore, the most likely explanation is that the observed effect of smoking on aniline levels is a chance occurrence and that the air concentrations are the primary influence on urinary levels, for both aniline and *o*-toluidine. (This is the same conclusion that was reached for a previous NIOSH study of the effects of aniline and *o*-toluidine.)

Urine sample results for an individual (rather than for groups of workers) 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 previously described, 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 post-shift urine sample may be related to many factors: the pre-shift 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,[32,33] and both genetic and environmental factors may influence the amount of a specific metabolite measured in any sample.[30,34] Thus, we believe that individual urine results should be interpreted with caution. In particular, comparison of one individual to another 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 to work practices or use of personal protective controls since he or she may have higher levels for metabolic reasons.

The most important use of urinary monitoring results for the Paterson plant would be in tracking urinary levels in groups of workers over time as exposure controls are installed. In tracking Building 11 workers over time, one would expect that the average post-shift 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, differences in metabolism, and urine concentration. A second possible use may be in identifying job categories with consistently high exposures for possible intervention. A third

possible use might be in documenting exposures after a potential overexposure incident.

VIII. RECOMMENDATIONS

A. General Recommendations

NIOSH has recommended that occupational exposures to *o*-toluidine and aniline be reduced to the lowest feasible concentration[20].

Since both the air and urine monitoring documented exposure to *o*-toluidine and aniline among dye process workers, Morton International should take steps to reduce exposures to process chemicals (especially *o*-toluidine and aniline) in dye manufacturing operations 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, should be minimized through the use of engineering controls, improved work practices, and personal protective equipment.

B. Specific Recommendations

To facilitate the reduction of worker exposure to *o*-toluidine and aniline, the following industry standard controls, that were compiled for and presented in the NIOSH, "Alert for Preventing Bladder Cancer from Exposure to *o*-Toluidine and Aniline" of December 1990,[20] are offered as a guideline. This guideline details available control methods that can be used to enhance the *o*-toluidine and aniline exposure controls currently in place at the Paterson facility, and thereby help reduce exposures to *o*-toluidine and aniline to the lowest feasible concentrations.

1. Process Integrity Evaluation Recommendation

Perform an engineering evaluation of all the process components such as transfer pumps and pipes, holding and coupling tanks, valves, vessels, kettles, reactors, etc., of the various dye manufacturing processes, 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. The reduction of worker exposure 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. 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 person 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 personal protective equipment (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]).[35]

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

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

e. Workers should 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 removed in an area 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.

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."[36] 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. This two-volume set can be purchased from ACGIH, 1330 Kemper Meadow Drive, Cincinnati, Ohio 45240 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."[37] This reference is available from the American Industrial Hygiene Association (AIHA), 2700 Prosperity Avenue, Suite 250, Fairfax, Virginia 22031.

4. 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.

5. Smoking Control Recommendation

Although there are several explanations (including chance variation) for the increased levels of aniline in the urine of exposed smokers compared to nonsmokers,[38,39] it would be prudent from a public health standpoint to offer a smoking cessation program to employees to reduce the possibility of increased exposure to *o*-toluidine and aniline through smoking.

NIOSH recommends elimination of involuntary exposure to environmental tobacco smoke (second-hand smoke). Therefore, smoking should not be allowed in the break room and should be prohibited throughout the plant or restricted to smoking lounges with appropriate ventilation.[40]

6. Urine Monitoring Recommendation

A voluntary program of urine monitoring should be established for workers in dye processing operations at the Paterson facility, including maintenance workers and other personnel who are working within the dye processing departments. 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 occupationally unexposed population.

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	ORTHO-TOLUIDINE OSHA & ACGIH[1] PEL/TLV=22,000/ 8,800 µg/M³ TWA for Air - No PEL's for Dermal/Gloves			ANILINE OSHA & ACGIH[1] PEL/TLV=19,000/ 7,600 µg/M³ TWA for Air - No PEL's for Dermal/Gloves		
JOB TITLE, WORK AREA, AND CLASSIFICATION,	**AIR[2] (µg/M³) TWA[3]**	**DERMAL[4] average µg/sample set**	**GLOVE[5] total µg/glove set**	**AIR (µg/M³) TWA**	**DERMAL average µg/sample set**	**GLOVE total µg/glove set**
Supervisor, Building 11 Diazo-Coupling and Kettle	44	4	N.D.[6]	10	N.D.	N.D.
Chemical Operator, Building 11 Diazo-Coupling Operator	92	6	N.D.	18	N.D.	N.D.
Chemical Operator, Building 11 Diazo-Coupling Operator	164	30	N.D.	25	N.D.	N.D.
Chemical Operator, Building 11 Diazo-Coupling Operator	25	N.D.	N.D.	5	N.D.	N.D.
Chemical Operator, Building 11 Diazo-Coupling Operator	42	N.D.	N.D.	7	N.D.	N.D.
Chemical Operator, Building 11 & 13 Diazo-Coupling Operator	123	12	N.D.	23	N.D.	N.D.
Chemical Operator, Building 11 & 13 Diazo-Coupling Operator[7]	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Chemical Operator, Building 11 Kettle Operator	95	5	N.D.	19	N.D.	N.D.
Chemical Operator, Building 11 Kettle Operator	36	7	N.D.	7	N.D.	N.D.
Chemical Operator, Building 11 Kettle Operator[7]	130	4	N.D.	7	N.D.	N.D.
Same Operator as Above Charging Raw Materials to *o*-toluidine based liquid dye batch in Tank 6 (Peak Sample)	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Chemical Operator, Building 11 Kettle Operator	N.D.	N.D.	N.D.	3	N.D.	N.D.
Chemical Operator, Building 5 Aniline Based Liquid Dye Operator	N.D.	N.D.	N.D.	5	N.D.	N.D.

TABLE I
SUMMARY RESULTS FOR PERSONAL AIR, DERMAL BADGE, AND GLOVE SAMPLES COLLECTED AT THE MORTON INTERNATIONAL PATERSON FACILITY
FOR THE PROBABLY EXPOSED GROUP **- DURING JUNE 11-13, 1991**

TABLE I (continued) SUMMARY RESULTS FOR PERSONAL AIR, DERMAL BADGE, AND GLOVE SAMPLES COLLECTED AT THE MORTON INTERNATIONAL PATERSON FACILITY *FOR THE PRESUMABLY UNEXPOSED GROUP* - DURING JUNE 11-13, 1991						
JOB TITLE, WORK AREA, AND CLASSIFICATION	**ORTHO-TOLUIDINE** OSHA & ACGIH[1] PEL/TLV=22,000/ 8,800 µg/M[3] TWA for Air - No PEL's for Dermal/Gloves			**ANILINE** OSHA & ACGIH[1] PEL/TLV=19,000/ 7,600 µg/M[3] TWA for Air - No PEL's for Dermal/Gloves		
	AIR[2] (µg/M[3]) TWA[3]	**DERMAL[4] average µg/sample set**	**GLOVE[5] total µg/glove set**	**AIR (µg/M[3]) TWA**	**DERMAL average µg/sample set**	**GLOVE total µg/glove set**
Engineer, Building 7 Boiler Operator	N.D.	N.D.	N.T.[8]	N.D.	N.D.	N.T.
Chief Engineer, Building 7 Boiler Operator	N.D.	N.D.	N.T.	N.D.	N.D.	N.T.
Head Watchman, Building 17 Security Guard	N.D.	N.D.	N.T.	N.D.	N.D.	N.T.
Traffic Manager, Building 16	N.D.	9	N.T.	2	N.D.	N.T.
Office Manager, Building 15	N.D.	N.D.	N.T.	N.D.	N.D.	N.T.
Plant Accountant, Building 15[9]	N.D.	N.T.	N.T.	N.D.	N.T.	N.T.
Plant Receptionist, Building 15	N.D.	N.T.	N.T.	N.D.	N.T.	N.T.
Clerk, Building 15[10]	N.D.	6	N.T.	N.D.	8[7]	N.T.

1. NIOSH recommends that exposure to *o*-toluidine and aniline be reduced to the lowest feasible concentration.[20]
2. The limit of detection (LOD) for *o*-toluidine and aniline for the air samples was 8.7 and 1.3 micrograms per cubic meter respectively. When the filters from both halves of the shift were reported as not detected it is shown in the table as N.D. When the sample from one half of the shift was N.D., and the other was detectable, the value of (LOD/$\sqrt{2}$) was substituted for the N.D. sample when calculating the TWA.[6]
3. All air samples collected for full work shift except for peaks collected only for duration of specific tasks.
4. The LOD for the dermal samples for *o*-toluidine and aniline was 28 and 31 micrograms per sample respectively.
5. The LOD for *o*-toluidine and aniline for the gloves was 240 and 270 micrograms per glove respectively.
6. N.D. = Analyte not detected during sample analysis.
7. Dermal badges were worn underneath employee's protective clothing.
8. N.T. = This type of sample not taken on this employee.
9. Dermal badges for forearms were placed on the sleeves of the employee's short sleeved shirt.
10. Employee left the facility during the work shift wearing the sampling media.

			DERMAL SAMPLES BY BODY LOCATION µg/sample							DERMAL	GLOVE
TABLE II **INDIVIDUAL RESULTS FOR PERSONAL AIR, DERMAL BADGE, AND GLOVE SAMPLES** **COLLECTED AT THE MORTON INTERNATIONAL PATERSON FACILITY** *FOR THE PROBABLY EXPOSED GROUP* **- DURING JUNE 11-13, 1991**											
JOB TITLE, CLASSIFICATION, AND WORK AREA	**Analyte**	**AIR (µg/ M³) TWA**	**Right Lapel**	**Left Lapel**	**Right Forearm**	**Left Forearm**	**Chest**	**Left Leg**	**Right Leg**	**average µg/sample set**	**total µg/glove set**
Supervisor, Diazo-Coupling and Kettle, Building 11	*o*-Toluidine	44	N.D.	N.D.	N.D.	N.D.	28	N.D.	N.D.	4	N.D.
	Aniline	10	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Chemical Operator, Diazo-Coupling Operator, Building 11	*o*-Toluidine	92	N.D.	N.D.	N.D.	40	N.D.	N.D.	N.D.	6	N.D.
	Aniline	18	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Chemical Operator, Diazo-Coupling Operator, Building 11	*o*-Toluidine	164	N.D	N.D	N.D.	N.D.	N.D.	N.D.	211	30	N.D.
	Aniline	25	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Chemical Operator, Diazo-Coupling Operator, Building 11	*o*-Toluidine	25	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D..	N.D..
	Aniline	5	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Chemical Operator, Diazo-Coupling Operator, Building 11	*o*-Toluidine	42	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
	Aniline	7	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Chemical Operator, Diazo-Coupling Operator, Building 11 & 13[1]	*o*-Toluidine	123	N.D.	N.D.	41	44	N.D.	N.D.	N.D.	12	N.D.
	Aniline	23	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Chemical Operator, Diazo-Coupling Operator, Building 11 & 13	*o*-Toluidine	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
	Aniline	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Chemical Operator, Kettle Operator, Building 11	*o*-Toluidine	95	N.D.	32	N.D.	N.D.	N.D.	N.D.	N.D.	5	N.D.
	Aniline	19	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Chemical Operator, Kettle Operator, Building 11	*o*-Toluidine	36	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	51	7	N.D.
	Aniline	7	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.

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JOB TITLE, CLASSIFICATION, AND WORK AREA	Analyte	AIR (µg/ M³) TWA	DERMAL SAMPLES BY BODY LOCATION µg/sample							DERMAL average µg/sample set	GLOVE total µg/glove set
			Right Lapel	Left Lapel	Right Forearm	Left Forearm	Chest	Left Leg	Right Leg		
Chemical Operator, Kettle Operator, Building 11	*o*-Toluidine	130	N.D.	N.D.	N.D.	28	N.D.	N.D.	N.D.	4	N.D.
	Aniline	7	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Same Operator as Above Charging Raw Materials to *o*-Toluidine Based Liquid Dye Batch in Tank 6 (Peak Sample)	*o*-Toluidine	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
	Aniline	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Chemical Operator, Kettle Operator, Building 11[1]	*o*-Toluidine	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.[2]	N.D.	N.D.	N.D.
	Aniline	3	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.[2]	N.D.	N.D.	N.D.
Chemical Operator, Aniline Based Liquid Dye Operator, Building 5	*o*-Toluidine	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
	Aniline	5	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D

TABLE II
INDIVIDUAL RESULTS FOR PERSONAL AIR, DERMAL BADGE, AND GLOVE SAMPLES COLLECTED AT THE MORTON INTERNATIONAL PATERSON FACILITY
FOR THE PROBABLY EXPOSED GROUP **- DURING JUNE 11-13, 1991**

JOB TITLE, CLASSIFICATION, AND WORK AREA	Analyte	AIR (µg/M³) TWA	DERMAL SAMPLES BY BODY LOCATION µg/sample							DERMAL average µg/sample set	GLOVE total µg/glove set
			Right Lapel	Left Lapel	Right Forearm	Left Forearm	Chest	Left Leg	Right Leg		
Engineer, Boiler Operator, Building 7	o-Toluidine	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.T.
	Aniline	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.T.
Engineer, Boiler Operator, Building 7	o-Toluidine	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.T.
	Aniline	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.T.
Head Watchman, Security Guard, Building 17	o-Toluidine	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.T.
	Aniline	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.T.
Traffic Manager Building 16	o-Toluidine	N.D.	60	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	9	N.T.
	Aniline	2	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.T.
Office Manager Building 15	o-Toluidine	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.T.
	Aniline	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Plant Accountant Building 15	o-Toluidine	N.D.	N.T.	N.T.	N.T.[3]	N.T.[3]	N.T.	N.T.	N.T.	N.T.	N.T.
	Aniline	N.D.	N.T.	N.T.	N.T.[3]	N.T.[3]	N.T.	N.T.	N.T.	N.T.	N.T.
Plant Receptionist Clerk Building 15	o-Toluidine	N.D.	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.
	Aniline	N.D.	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.
Clerk Building 15[4]	o-Toluidine	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	42	N.D.	6	N.T.
	Aniline	N.D.	N.D.	55	N.D.	N.D.	N.D.	N.D.	N.D.	8	N.T.

1. Dermal badges were worn underneath employee's protective clothing.
2. The left leg dermal sample was dropped on the floor of the break room during sample clip-on.
3. Dermal badges for forearms were placed on the sleeves of the employee's short sleeved shirt.
4. Employee left the facility during the work shift wearing sampling media.

SAMPLE LOCATION	ORTHO-TOLUIDINE OSHA & ACGIH[1] PEL/REL=22,000/8,800 µg/M³ TWA for Air - No PEL's for Dermals		ANILINE OSHA & ACGIH[1] PEL/REL=19,000/7,600 µg/M³ TWA for Air - No PEL's for Dermals	
	AIR[2] (µg/M³) TWA[3]	DERMAL[4] µg/sample	AIR µg/M³ TWA	DERMAL µg/sample
Building 11 - *o*-Toluidine Based Liquid Dye Process By Kettle #6	191	N.D.[5]	31	N.D.
Building 11 - *o*-Toluidine Based Liquid Dye Process By Kettle #6	315	34	13	N.D.
Building 11 - Diazo Coupling Charging Tank #5	510	34	47	N.D.
Building 11 - *o*-Toluidine/Aniline Based Liquid Dye Stripping Process By Kettle #1	141	N.D.	28	N.D.
Building 11 - By Tank #4	138	N.D.	26	N.D.
Building 11 - *o*-Toluidine/Aniline Based Liquid Dye Process Between Diazo Coupling Tanks #1 and #2	99	N.D.	15	N.D.
Building 11 - By Drumout Station	16	N.D.	7	N.D.
Building 11 - By Kettle #7	58	N.D.	10	N.D.
Building 5 - By Tank #40	N.D.	N.D.	37	N.D.
Building 7 - In Control Room	N.D.	N.D.	N.D.	N.D.
Building 13 - Intermediate Dye Process Area	N.D.	N.D.	N.D.	N.D.
Building 17 - By Guard Station	72	N.D.	N.D.	N.D.

TABLE III
SUMMARY RESULTS FOR AREA AIR AND DERMAL BADGE SAMPLES
COLLECTED AT THE MORTON INTERNATIONAL PATERSON FACILITY
DURING JUNE 11-13, 1991

1. NIOSH recommends that exposure to *o*-toluidine and aniline be reduced to the lowest feasible concentration.[20]
2. The limit of detection (LOD) for *o*-toluidine and aniline for the air samples was 8.7 and 1.3 micrograms per cubic meter respectively. When the filters from both halves of the shift were reported as not detected it is shown in the table as N.D. When the sample from one half of the shift was N.D., and the other was detectable, the value of (LOD/√2) was substituted for the N.D. sample when calculating the TWA.[6]
3. All area air sample results are a time weighted average.
4. The LOD for the dermal samples for *o*-toluidine and aniline was 28 and 31 micrograms per sample respectively.
5. Analyte not detected by sample analysis.

TABLE IV ANALYTICAL RESULTS FOR SURFACE WIPE SAMPLES COLLECTED AT THE MORTON INTERNATIONAL PATERSON FACILITY DURING JUNE 11-13, 1991		
WIPE SAMPLE LOCATION	**ANALYTE CONCENTRATION IN MICROGRAMS PER SAMPLE[1]**	
	ORTHO-TOLUIDINE	**ANILINE**
Building 11 - Kettle 6 Running *o*-Toluidine Based Liquid Dye 3 Cover Handles and Vessel Lift Handle	Detected	Detected
Building 11 - Kettle 1 Running *o*-Toluidine/Aniline Based Liquid Dye 2 Cover Handles and Lift Chain	N.D.	N.D.
Building 11 - DC 5 Running *o*-Toluidine/Aniline Based Liquid Dye 1 Cover Handle and 2 Feed Pipe Handles	N.D.	N.D.
Building 7 - Boiler Control Room Surface of Operators Table	Detected	N.D.
Lunch Room - Dining Table Surface	N.D.	N.D.
Building 5 - Tank No. 40 Pump Probe, Hatch Handle and Sampling Can Wire	N.D.	N.D.

1. The limit of detection for *o*-toluidine and aniline for the wipe samples was 70 and 80 µg/sample, respectively.

TABLE V
Urinary Aniline and *o*-toluidine Concentrations (μg/L)[1]
by Exposure Group and by Smoking Status Within the Exposed Group

Exposure/Smoking	Aniline		*o*-Toluidine	
	Pre-shift	Post-shift	Pre-shift	Post-shift
Unexposed (n=8)	3.1 ± 5.1	2.0 ± 2.0	1.6 ± 2.1	3.7
Exposed (n=12)	2.7 ± 2.7	4.8 ± 2.8^2	2.1 ± 2.3	16.0 ± 14.3^2
Exposed Nonsmokers (n=6)[3]	0.8 ± 0.4	2.8 ± 2.2	2.3 ± 3.1	25.0 ± 15.3
Exposed Smokers (n=6)	4.6 ± 2.6^4	6.7 ± 1.7^4	1.9 ± 1.4	6.9 ± 1.7^4

1. In unexposed workers, 2/8 pre-shift and 2/8 post-shift sample concentrations were below the limit of detection (LOD) for aniline of 1.4 and 1/8 pre-shift and 3/8 post-shift samples were under the LOD for *o*-toluidine of 0.6. In exposed workers, 3/12 pre-shift and 2/12 post-shift samples were below the LOD of aniline and 3/12 pre-shift samples were below the LOD of *o*-toluidine.
2. Significant ($p<0.05$) differences between exposed and unexposed samples in unpaired t-tests.
3. The unexposed group included only one smoker, so it was not subdivided by smoking status.
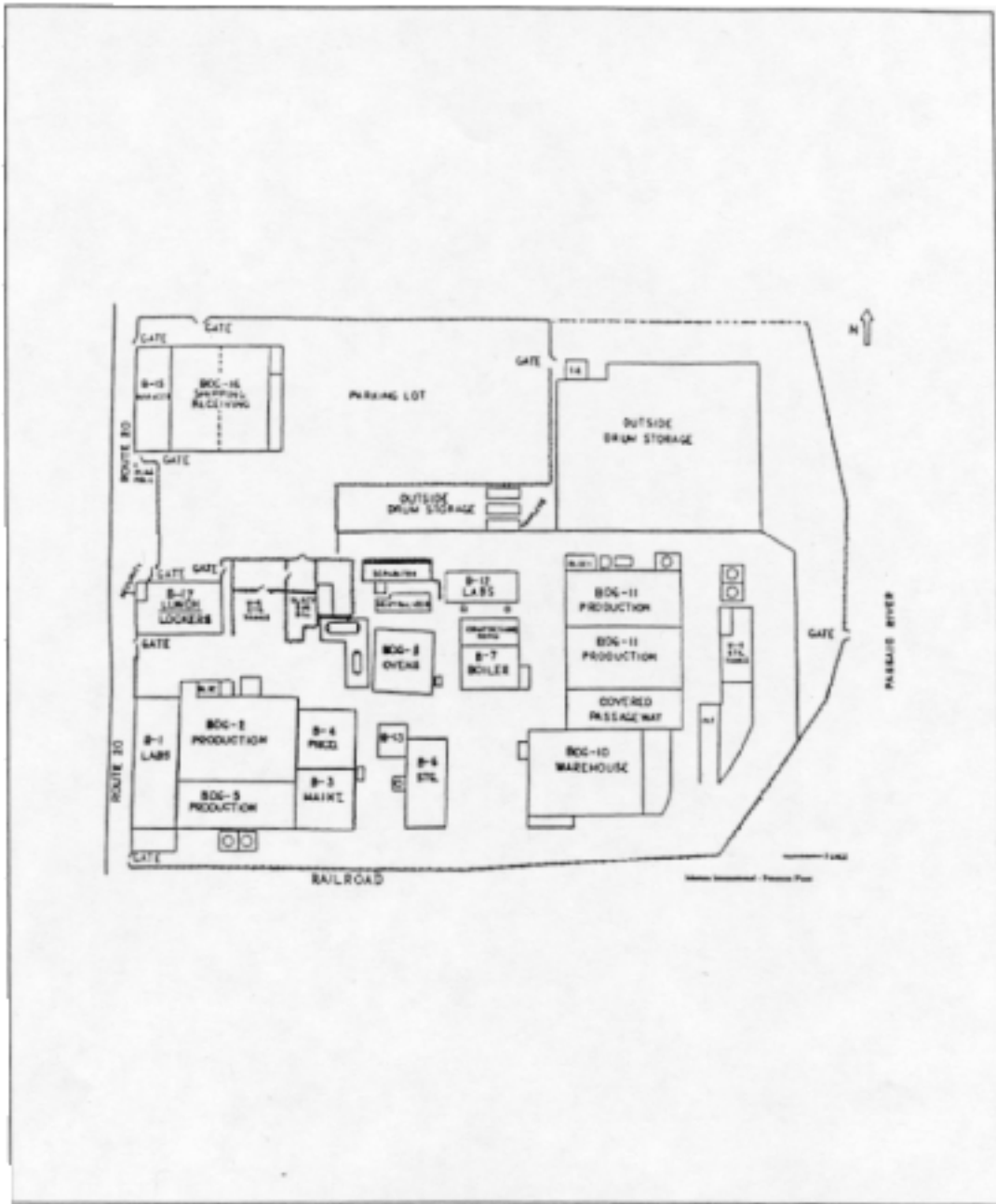4. Significant ($p<0.05$) differences between nonsmoker and smoker samples in unpaired t-tests.

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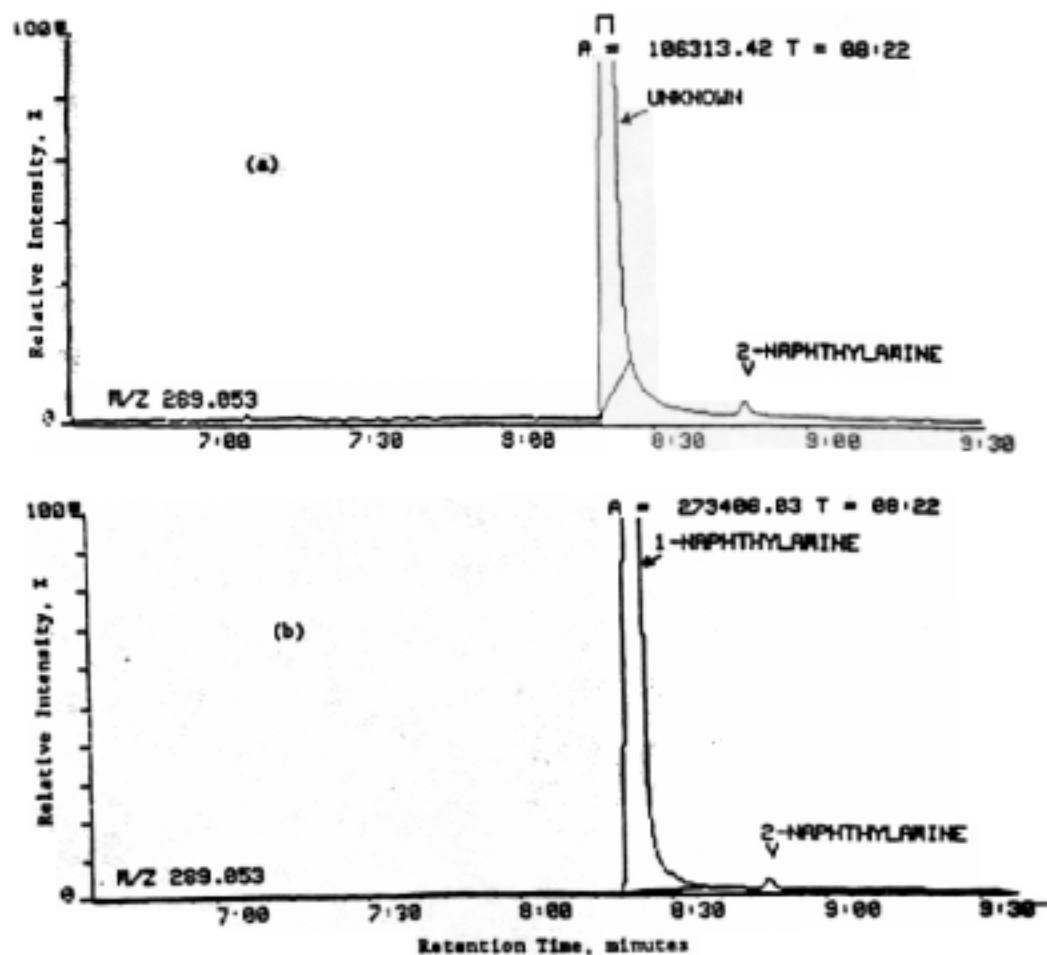
Figure 2. Mass chromatogram of m/z 289.053 obtained from the GC/SIM analysis of: (a) 4.6 μg of a non o-toluidine/aniline based liquid dye ; and (b) PFP derivative of a 1-naphthylamine standard.

Appendix A. Environmental Sampling and Analytical Methods

1. Air Sampling and Analytical Methods

   a. Sampling Method

   The OSHA 73 method used two stacked sulfuric acid treated 37 mm diameter
   0.8 µm pore size glass fiber filters in a closed face cassette. The filters were
   separated by a spacer using no support pads for either filter. This media assembly
   was connected by tubing to a personal air sampling pump pre-calibrated to operate
   at 400 cc/minute. A total air volume not exceeding 100 L was sampled in
   accordance with the OSHA 73 method.

   The filter 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 L of air flow. At the end
   of the shift the sampling train was removed, and the cassettes were plugged and
   logged in. The sampling pump calibration was checked and logged in at this time
   as well. At the NIOSH facility the samples were stored in refrigeration until
   laboratory analysis.

   The pre-labeled dermal badges were placed on and removed from the workers, by
   handling only the paper tabs, at the same time the air samplers were attached. The
   gloves were given to the workers at the same time the air samplers and dermal
   badges were attached, and the workers were directed to wear the cotton gloves
   underneath their usual work gloves when they were worn.

   Passive area air sampling for *o*-toluidine and aniline was also conducted in tandem
   with the air drawn area samples using the dermal monitoring badges which are
   described in the Dermal Sampling section.

   b. Analytical Method

   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 field and QC sample, 3 ml of
   DI water, 1 ml 0.5 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 25 µL 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 GC vials for analysis.

The analysis was performed on a HP5890 GC equipped with an electron capture detector. A 30 m x 0.5 mm ID fused silica DB-5 capillary column was used at an initial temperature of $110^{\circ}C$ for 5 minutes and then increased at $10^{\circ}C$/minute up to $150\ ^{\circ}C$. The NIOSH calculated LOD for each acid treated filter was 8.7 $\mu g/m^3$ for *o*-toluidine and 1.3 $\mu g/m^3$ for aniline. The calculated LOQ was 26 $\mu g/m^3$ for *o*-toluidine and 5.2 $\mu g/m^3$ for aniline.

The NIOSH calculated LOD was 0.1 μg/sample for aniline, and 0.6 μg/sample for *o*-toluidine. The calculated LOQ was 0.4 μg/sample for aniline, and 2 μg/sample for *o*-toluidine.

When only one of the two filters for a given worker or area air sample had a detectable level of *o*-toluidine and or aniline, and the other filter was ND, the value of LOD/$\sqrt{2}$ was substituted for the ND filter, and the resulting weights of analyte were added to use for the TWA calculation for that sample. This technique for estimating average concentration in the presence of ND values is described in detail by Hornung and Reed[6].

2. Dermal and Glove Sample Analytical Methods

The silica gel from each dermal 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 GC/FID, using a HP5890 GC equipped with a 30 m DB-5 fused silica capillary column for *o*-toluidine and aniline. All analyses were performed in the splitless injection mode. The resultant sample recoveries were corrected for dilution effects.

The calculated limits of detection for *o*-toluidine and aniline for the dermal badge samples were 28 and 31 μg/sample respectively, and the calculated limits of quantitation were 84 and 93 μg/sample, respectively.

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 $\mu l/ml$ 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 120ºC (held) for 8 minutes) to 250ºC at a rate of 32ºC/minute and held for 4 minutes.

The calculated LODs for the gloves for *o*-toluidine and aniline were 240 and 270 µg/sample respectively, and the calculated LOQ were 720 and 810 µg/sample, respectively.

3. Surface Wipe Sample Analytical Method

The wipe samples were extracted and analyzed by gas chromatography 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 120ºC (held for 8 minutes) to 250ºC at a rate of 32ºC/minute and held for 4 minutes.

Liquid standards were prepared of known amounts of *o*-toluidine and aniline and spiked into 1 ml of extraction solvent.

The calculated LODs for *o*-toluidine and aniline was 70 and 80 µg/sample respectively, and the calculated LOQs were 210 and 240 µg/sample, respectively.

4. Bulk Sample Analytical Method

The 13 bulk dye samples collected at the Morton International Chemical Company, Paterson, New Jersey facility, were analyzed by gas chromatography in conjunction with mass spectrometry. The samples were analyzed to confirm the presence and approximate concentration of *o*-toluidine, aniline, diphenylamine, hydroquinone, 4-aminobiphenyl, 2-naphthylamine, and 2-aminofluorene.

The samples were prepared for analysis by dissolving known amounts (approximately 220 to 250 mg) of each bulk dye into 25 ml of methylene chloride. In the case of the bulk *o*-toluidine and aniline, a syringe was used to inject 25 µl of the sample into

25 ml of methylene chloride. Calibration standards containing the seven analytes were prepared in methylene chloride at three concentration levels, 0.01, 0.1, and 1 µg/ml, respectively. An additional standard was prepared in methylene chloride at the concentration level of 0.5 µg/ml each. A spiking solution that contained the internal standard octafluoronaphthalene was prepared in methylene chloride at a concentration of 50 µg/ml.

Since the bulk dyes were extremely complex, it was necessary to develop a derivatization procedure for improved detection and specificity of the analytes. Prior to analysis, 1.8 ml of each sample, standard, and blank, were pipetted from stock solutions into 4 ml sample vials with teflon lined caps. Next, 30 µl of triethylamine was added to each vial followed by 200 µl of the derivatizing reagent pentafluoropropionic anhydride (PFP). The solutions were allowed to stand overnight. The next day, 20 µl of the internal standard was added to each vial, giving a final concentration of 0.5 µg/ml.

The GC was equipped with a 30 m by 0.25 mm DB-5.625 capillary column. The oven was temperature programmed from $80^{\circ}C$ to $250^{\circ}C$. The mass spectro-meter (MS) was operated in the full scan mode (40-500 amu) or the SIM mode at about 3000 resolution. GC/MS analysis conditions were optimized in the full scan mode with 1 µl injection of the 0.5 mg/ml standard.

Full scan data obtained from these analyses were used to determine the correct operating parameters for the GC/SIM procedure. In this procedure, the molecular ion of the PFP derivative was monitored during the expected chromatographic elution time (see Table A-I below). A MS response at the correct retention time indicates it presence. The area response obtained during analysis was compared to the areas form the standard to estimate the concentration. The limit of detection was estimated at less than 0.5 ppm for all analytes except 2-aminofluorene, which was 5 ppm.

The detection limits were based on a signal-to-noise ratio of 3:1.

TABLE A-I IONS MONITORED DURING GC/SIM ANALYSIS OF THIRTEEN BULK DYE PROCESS SAMPLES	
PFP DERIVATIVE	**MOLECULAR ION**
o-Toluidine	253.053
Aniline	239.036
Diphenylamine	315.068
Hydroquinone	401.995
4-Aminobiphenyl	315.068
2-Naphthylamine	289.053
2-Aminofluorene	327.078

Appendix B. Urine Sample Analytical Method

Fifty-one samples were shipped from Morton International (HETA 90-391) to NIOSH on June 13 and 14, 1991. In addition, 39 samples were delivered to a contract laboratory for creatinine/cotinine testing. The samples sent to NIOSH were stored at -68ºC. The analysis of the samples for *o*-toluidine and aniline was initiated December 1991, using SOPT4-29 with two modifications. The mobile phase was changed to 37.5% methanol and 65 mg/L SDS and the voltages for electrodes 1 and 2 were changed to 370 and 650 millivolts, respectively.

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.

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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

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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 rate 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

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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	Volume (mL) of Stock Standard Solution	
(µg/L)	1000 µg/L	100 µg/L
140	7.0	
120	6.0	
80	4.0	
60	3.0	
41	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

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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.

Appendix C. Creatinine Correction Method

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, 1993)[1] there are a number of reasons why adjustment for creatinine may introduce error into the analysis of an industrial chemical in urine, particularly when pre-shift and post-shift samples are being compared.

Creatinine concentration (in terms of mg/hr) shows marked intraindividual variability[2] 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. Therefore, correction for creatinine may reduce the difference in post-shift versus pre-shift means.

Since the parameters of interest in this study included post-shift minus pre-shift 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.

   1.   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 worker's measurement will be given, in addition to simple point estimates.

      This interval will use 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 increases with higher urinary concentrations, the coefficient of variation is statistically invariant among levels of exposure.

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[1]Boeniger MF, Lowry LK, Rosenberg J [1993}. Interpretation of urine results used to estimate chemical exposure with emphasis on creatinine adjustments: a review. AIHJ 54:615-627.

[2]Curtis G and Fogel M [1970]. Creatinine excretion: diurnal variation and variability of whole and part-day measures. Psychosom Med 32:337-350.

It therefore provides the best overall summary of the variability in the analytic method. For any individual urine concentration, an interval estimate will be constructed as follows:

Urine Conc. +/- (1.96)(coefficient of variation)(Urine Conc.)

Effectively, this adds and subtracts 1.96 standard deviations from the urine concentration.