Exposure to *o*-Toluidine, Aniline, and Nitrobenzene in a Rubber Chemical Manufacturing Plant: A Retrospective Exposure Assessment Update

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Key words

Ortho-toluidine; Aniline; Nitrobenzene; Bladder cancer; Occupational epidemiology; Retrospective exposure assessment; Job-exposure matrix

Abstract

The National Institute for Occupational Safety and Health previously conducted a retrospective cancer incidence and mortality study of workers employed at a rubber chemical manufacturing plant. Compared to New York State incidence, the bladder cancer risk was 6.5 times higher for workers considered to have definite exposure to *ortho*toluidine and aniline, and 4 times higher for workers with possible exposure. Exposure characterization in the original study utilized a surrogate measure based *only* on departments in which each worker was ever employed. As part of an update of that study, some departments in the three original exposure *groups* were reclassified based on a follow-up site visit; interviews with employees, management, and union representatives; and review of records including exposure data. An additional evaluation of department-job combinations, rather than only departments, was used to stratify exposure into four *categories*. An approximate rank of "relative" exposure level for each department-job-year combination was also

assigned using a ranking scale of 0 to 10. The ranks were supported by quantitative exposure levels and by professional judgment. The numerical ranking scale was applied to each worker by multiplying the exposure rank by duration for each job held based on comprehensive individual work histories. The cumulative rank scores for this cohort ranged from 0 to 300 unit-years. The medians of the cumulative rank scores for the exposure categories showed very good agreement with increasing exposure classifications (e.g., 0.72, 4.6, 11, 14 unit-years for the four exposure categories). Workers' breathing zone air sampling data collected at this plant from 1976-2004 were well below published occupational exposure limits for these chemicals but additional cases of bladder cancer have been reported. The exposure assessment revisions and rank estimates will be used to analyze the updated mortality and bladder cancer incidence data.

Word count 291 (JOEH max = 325)

Introduction

In 1988, the National Institute for Occupational Safety and Health (NIOSH) began a Health Hazard Evaluation of a rubber chemical manufacturing plant in New York State, where eight cases of bladder cancer had been reported among current and former employees between 1973 and 1988.[(1)] Workers at the plant were occupationally exposed to *ortho*toluidine, aniline, and nitrobenzene. Biological monitoring conducted by NIOSH in 1990 determined that both before and at the end of the workday, exposed workers had significantly higher urinary levels of *o*-toluidine and aniline compared to unexposed workers.[(2)] Evaluation of hemoglobin (Hb) adducts, biomarkers that reflect longer term exposures, showed mean *o*-toluidine Hb adduct levels to be 10 times higher in exposed workers than in unexposed workers at this plant and more than 100 times higher than the means in unexposed populations previously studied.[(3-7)]

A NIOSH retrospective cancer incidence study of 1,749 workers ever employed at this plant through 1988 identified 13 cases of bladder cancer versus 3.61 expected based on bladder cancer rates in New York State rate (excluding those of New York City) [standardized incidence ratio (SIR) = 3.6; 90% confidence interval (CI) = 2.1-5.7].[(8)] Bladder cancer incidence was elevated among workers considered to be definitely (DE) and possibly (PE) exposed to *o*-toluidine and aniline with 6.5-fold and nearly 4-fold elevations, respectively.[(8)] Furthermore, bladder cancer risk was strongly associated with increased duration of employment in the department where *o*-toluidine and aniline were used, with a 27-fold excess risk among workers with 10 or more years of employment compared to workers with less than 5 years of employment. A retrospective cohort mortality study at this plant showed excess bladder cancer mortality among DE workers, but the excess, based on a single death, was not statistically significant [standardized mortality ratio (SMR) = 3.8; 95% CI = 0.1-21.1].[(9)] This finding was not unexpected given that the overall relative survival rate of bladder cancer is approximately 80%, five years after diagnosis.[(10-11)]

Recent classification of *o*-toluidine as carcinogenic to humans by the International Agency for Research on Cancer[(12-13)] and reports of 19 additional bladder cancer cases among the cohort[(14-15)] have prompted NIOSH to update the mortality and bladder cancer incidence studies of this plant. Work histories were extended through 2006 for workers actively employed in 1988, and additional work histories were compiled for workers hired after 1988. The goal of this article is to describe the revised exposure assessment schemes which will be used to evaluate if there is an increased cancer incidence and mortality risk in workers from exposure to *o*-toluidine, aniline, or nitrobenzene. The revised exposure assessment was performed by researchers who were blinded to disease status.

METHODS

The exposure assessment revision required us to evaluate the manufacturing process; review historical records and exposure monitoring data; conduct a site visit and plant walkthrough; and interview current and former employees, company management, and union representatives.[(16)]

Description of Manufacturing Processes

The plant opened in 1946 for production of polyvinyl chloride (PVC). In 1957, production of a rubber antioxidant began and it was still being manufactured through 2006. In addition, several rubber accelerators were produced from the mid-1950s until 1970; one accelerator continued to be produced from 1970 to 1994. Both the antioxidant and accelerators were synthesized and packaged in parallel operations in the same rooms of the rubber chemicals department. Liquid chemicals were received by tractor trailer or rail cars and pumped into storage tanks; solid chemicals were stored in a warehouse adjacent to the rubber chemicals process rooms. Over time, the potential for exposure was affected by a sequence of process, engineering control, and work practice modifications as well as production alterations implemented at the plant (Table 1).

Antioxidant production involved *o*-toluidine, aniline, hydroquinone, toluene (until 1992) or xylene (1992-2006), and a proprietary catalyst. Phenol and diphenylamine are by-products of the reaction. *o-T*oluidine and aniline were pumped from storage tanks to the premix tank. The premix solution was pumped to a reactor and mixed with a catalyst to start the reaction. After the reactant was degassed, the product was filtered or centrifuged; solidified and formed into flakes or pastilles; and packaged for shipment.[1-2]

Accelerant chemicals included a mixture of nitrobenzene, aniline, and benzothiazole, which were blended prior to a series of reactions in enclosed autoclaves. Following the reactions, the product flowed out the top of the reactor into a holding tank; was quenched with water; and processed through centrifugal and fluid bed dryers. After drying, the finished powder was conveyed by gravity to a vacuum bagger.[1-2]

Review of Historical Records and Exposure Monitoring Data

Published and unpublished technical documents were reviewed including exposure monitoring data; material safety data sheets; a summary of process changes; process specifications; volumes of raw materials purchased since 1960; results of laboratory analyses for process intermediates; accident and injury reports for 1994-1998; and results of urinary analyses.

In the original study, personnel records were microfilmed for all workers employed at the plant from 1946 through 1988, including office and salaried personnel. These data were coded and entered into an electronic database. Electronic personnel records provided by the company for this study update were also used to supplement and update the work histories. When discrepancies existed, the data were manually reviewed and compared with existing microfilmed records. If no microfilm was available, the data most recently provided were used. Using these records, a comprehensive job directory of departments and all of the job titles within each department for the entire cohort time frame, 1954-2006, was tabulated with personal identifying data expunged.[17] This listing contained 225 unique department-job title combinations.

NIOSH received exposure monitoring data collected by the company which were organized by department, job, and time period. The data included personal breathing zone exposure data from 1976 to 2004 for the three chemicals of interest (i.e., aniline, *o*-toluidine, and nitrobenzene). Results of air monitoring data obtained by NIOSH at this factory in 1990 were also reviewed for this assessment.[2]

Site Visit, Plant Walkthrough, and Interviews

A plant walkthrough was conducted by NIOSH investigators along with company management and union representatives to observe the facility in relation to historical reports and descriptions. During the site visit, we held meetings with company and union representatives and current and former employees who worked during the 1957-1988 period. In addition to group discussions, one-on-one informal interviews were held with 15 current and retired workers and several management and union representatives. The following topics were addressed during the interviews: progression of jobs and department changes during employment; basic job duties; perceived effects of process changes; times and activities when chemicals would potentially contact their skin or clothes; and employee movement between processes, departments, and areas of plant.

After the site visit, a list of follow-up questions was submitted for clarification of worker-reported jobs and departments, differences between similar jobs in the same department, and confirmation of possible exposures for some jobs. Replies were provided by the company, corporate industrial hygiene staff, and union representatives.[17]

Revision of Exposure Assessment

Three different schemes were developed for revision of the exposure assessment. First, new information was used to update the original three-group exposure assessment based only on department. Next, a more comprehensive classification scheme incorporated job title and department to create four new exposure categories. Finally, relative exposure ranks were developed and assigned to each department-job combination by year identified in the updated and expanded work histories. The four new exposure categories and assigned relative ranks were applied to the 225 department-job title combinations previously tabulated in the directory.[17] Relative ranks were adjusted contingent upon installation of exposure controls and process changes made over five time intervals. All exposure assessments were blinded to personal identifiers linking names, employee numbers, job titles, and disease status. Revised exposure groups, categories, and ranks were reviewed by company industrial hygiene and engineering staff and union representatives. Minor adjustments were made to the assignments based on their comments. Then, relative ranks were applied to the unique individual work histories and cumulative and average rank scores were calculated for each cohort member.

Statistical Analyses

Company collected TWA breathing zone exposure data were summarized by department and time period using simple descriptive statistics. Log-normality was assessed graphically using quantile-quantile plots. Samples reported as below the limit of detection were treated as left-censored at the limit of detection and maximum likelihood methods were used to estimate the geometric mean and geometric standard deviation.[18] For workers in the cohort, employment tenure and cumulative rank were summarized using simple descriptive statistics including median, range, and the Pearson correlation coefficient. All statistical analyses were performed using SAS Software (version 9.2, SAS Institute Inc., Cary, NC).

Results

Review of Work History Records

A thorough review of employee work history information did not identify any new relevant records for updating the exposure assessment. Time cards and other records which characterize specific tasks conducted at a given time were not available. Furthermore, while maintenance work orders were used, many tasks, especially minor repairs, were done as needed without waiting for an order.

Examination of existing job descriptions for jobs from the 1970s through the mid-1990s showed that they were too generic to assess exposure potential; the descriptions merely confirmed what had been discovered from workplace observations, employee interviews, and follow-up questions.

Summary of Exposure Data

In 1990, NIOSH collected 45 full-shift time weighted average (TWA) breathing zone air samples throughout the rubber chemicals department (Table II) for antioxidant (n = 17), accelerant (n = 18), maintenance (n = 7), and recycle (n = 3) personnel.[2] Although aniline and *o*-toluidine were detected in every sample, the concentrations were less than a quarter of the occupational exposure limits published by OSHA, ACGIH, and the German MAK commission[19-21]; the geometric means (GMs) were an order of magnitude lower than these limits. The GMs for both *o*-toluidine and aniline were similar for the antioxidant and maintenance personnel (0.096 versus 0.086, and 0.041 versus 0.037 ppm for *o*-toluidine and aniline, respectively). For the accelerator workers, their GM concentrations were approximately half than that of those measured on antioxidant and maintenance personnel. With the exception of the recycle process, *o*-toluidine GM concentrations were two times higher compared to that of the aniline GM concentrations. Nitrobenzene was not detected in approximately 93% of the TWA measurements with a minimum detectable concentration near 0.02 ppm.

A summary of the company's data from 1976 - 2004 is provided in Table III. The patterns of exposure for both *o*-toluidine and aniline were similar; as time progressed from 1976 exposure concentrations decreased (Figure 1 and 2). These graphs show that the company's exposure data were log-normally distributed and were approximately an order of magnitude higher for 1976-1979 and 1980-1994 than for 1995-2004 time periods. Exposure concentrations were greatest for employees in the rubber chemicals department; however, levels for each of these analytes in this department were still very low relative to their respective occupational exposure limit (OEL) (Table IV). The aniline TWA GMs in the rubber chemicals department were 0.081, 0.015, and 0.0021 ppm, respectively, for the time periods 1976-1979; 1980-1994; and 1995-2004. For *o*-toluidine, the GMs in this department were 0.10, 0.015, and 0.0028 ppm, for these same eras. For comparison, the ACGIH 8-hour threshold limit values (TLV)® for these aromatic amine compounds are 2 ppm[20]. Consistent with the NIOSH data, nitrobenzene was rarely detected after 1985 (> 94% was below the limit of detection [LOD]); prior to that date the GM was 0.012 ppm (geometric standard deviation [GSD] = 2.8), nearly 100 times lower than the TLV for nitrobenzene [20].

Coding of New Work History Reports

Work history records were extended for 314 workers and added for 128 workers (113 of whom were hired after 1989) resulting in a total of 8,391 work history records for 1,877 workers. Based on the updated records, three new departments and eight new jobs were identified.

Plant Walkthrough Findings

Historically, the majority of workers were assigned either to the PVC or rubber chemicals departments. By the time of the walkthrough, PVC production equipment had been disassembled and the building was razed. Likewise, much of the equipment associated with production of rubber accelerants had been removed. Although, chemical manufacturing was not occurring during the walkthrough of NIOSH's site visit, antioxidants are still being manufactured at this factory. Engineering modifications and work practice procedures implemented to minimize exposures in the rubber chemicals department were confirmed during the walkthrough. No new controls had been implemented beyond those described in Table I.

During the walkthrough, areas of potential exposure other than production areas were identified which included the wastewater treatment building, tank farm, laboratory and shop areas, and possibly the cafeteria and locker room/shower areas. Surfaces throughout the plant were observed to be contaminated with dust or sticky residue; surface contamination was also visually observed on cabinet doors, handles, and bench tops in the laboratory, albeit to a less degree than in the manufacturing areas. Break and dressing areas, however, were reasonably clean. Some surface wipes from the original study reported by NIOSH in 1992[2] did find quantitative levels of o-toluidine on levers, valves and railings, however, the visual observations of this study update were only used to qualitatively assess the potential for dermal contact with contaminated surfaces.

Interview Findings

Tasks reported by employees to have the highest potential for inhalation exposure and skin contact were: changing the sparkler filters; manually connecting transfer lines to rail cars (historic); unclogging frozen recycle pipe lines; repairing and maintaining pumps and pipes, including removing obsolete chemical pipe lines; collecting raw material and recycle samples; and handling hoses by maintenance workers which caused unknown liquids to drip on them. Several workers reported that personal protective equipment was infrequently used prior to the 1990 NIOSH Health Hazard Evaluation and Alert publication.[1,22]

Laboratory workers reported that several vinyl chloride and accelerator tests caused noticeable chemical vapors in the laboratory. Although ventilated lab hoods were available, some tests were reportedly conducted without local exhaust ventilation. Some laboratory technicians also acted as shift monitors, checking for leaks throughout the plant on a regular basis using direct reading instrumentation.

Workers also reported that guards were required to walk throughout the plant buildings on a regular basis, thus having potential intermittent exposure, and that exposure was likely none to minimal for a few non-production jobs including accountants, office workers, sanitary engineer, and janitor.

Revision of Exposure Assessment Classifications

The three revised exposure schemes are described briefly below; additional details are available in the full NIOSH report.[17]

Updated Original Exposure Groups

The original 3-group exposure scheme classified all job titles within an entire department as either definitely exposed (DE), possibly exposed (PE), or probably not exposed (PNE) (Table V). There was no extent or intensity of exposure implied in these definitions. The exposure groups were applied to the cohort based strictly on whether a worker ever worked in the department. The exposure groups of some departments were revised as described below:

The maintenance department was reassigned from PE to DE. Employee interviews and written job descriptions revealed that maintenance personnel worked in all areas of the plant making repairs; often liquid chemicals would contact their hands and clothing. A few maintenance jobs specified "bench work" in the shop, with the caveat that all employees were expected to work in the plant as required. Further, interviews and site observations showed that bench work included repairing parts that were contaminated or contained bulk amounts of the chemicals of concern.

All laboratory departments including quality control, and research and development were reassigned from PNE to DE since physical observations and employee interviews indicated that laboratory workers were exposed daily in the laboratory while handling samples and conducting analyses. These workers also entered the plant to collect process samples and monitor the air quality.

Some work histories included the department designation "temporary assignment from headquarters" or "none assigned". Employee interviews indicated that these workers probably would have worked in assignments similar to plant associates with the same job, and may have worked anywhere during work stoppages including the rubber chemicals department. All jobs associated within these 'departments' (e.g., chemical engineer, engineer, quality control, area manager, etc.) were reassigned from PNE to PE because it is not known to which area of the plant they were actually assigned.

Exposure Categories Based on Department and Job

A second exposure classification scheme was developed to incorporate both department and job title. This was necessary because some jobs originally classified as belonging to a PNE department likely had mild to moderate exposure on an irregular basis (e.g., guards) or on a regular basis (e.g., laboratory personnel). Conversely, some jobs originally classified as PE or DE likely had no or minimal exposure (e.g., secretaries and accountants assigned to the "definitely exposed" rubber chemicals department). Thus, four new exposure categories were developed: definitely exposed moderate/high and regularly (DER), probably exposed low and regularly (PER), probably exposed low and irregularly/occasionally (PEI), and probably not exposed (PNE). These categories broadly account for intensity and frequency of exposure. Examples of jobs assigned to each of these categories are presented in Table VI.

Exposure Ranks Based on Department, Job, and Year

An approximate rank of "relative" exposure level was assigned for each of the 225 department-job combinations by time period; a condensed summary of the assigned rank values extrapolated from these combinations[17] is presented in Table VII. A ranking scale of 0 to 10, which was not chemical specific, was selected to provide latitude to characterize exposures of different job titles based on relative exposures interpreted over five time periods: 1954-1960; 1961-1969; 1970-1979; 1980-1994; and 1995-2005. Most jobs in the two categories with regular exposure (i.e., DER and PER) had the higher ranks. Except for the "off-site" workers, there were no "0" ranks assigned prior to 1995 as it was assumed that all workers occasionally went into the plant, or could be exposed to low levels due to the proximity of offices to chemical buildings allowing vapor intrusion through windows, doors, or air intakes. The rationale for each time period follows:

1954-1960 - The rubber chemicals department was established in 1954 and the production of an accelerator began which required the use of aniline and nitrobenzene. *o*-Toluidine was introduced in 1957 when antioxidant synthesis was initiated. Given the lack of exposure information for this era, other than production volume was about half of that for the highest production eras 1970-1979 (and 1980-1994), ranks of 1-5 were assigned; these are approximately half of the exposure rank values for that 1970-1979 period (when exposure controls were less effective than in 1980-1994).

1961-1969 - Based on chemical purchase and manufacturing records, a substantial increase in antioxidant production, and subsequent use of *o*-toluidine and aniline, occurred after 1960 which continued to increase through this decade. The much greater antioxidant production resulted in a small reduction of accelerator manufacturing but both aniline and *o*-toluidine use increased in the 1960s. Exposure ranks were raised accordingly, especially for those who worked regularly in the rubber chemicals department. In this era, the ranks ranged from 1-3 and from 3-9, respectively, for PNE/PEI and PER/DER exposure categories.

1970-1979 - In 1970, the expansion of the rubber chemicals department with the addition of a second production line was completed. This allowed equipment to be dedicated for synthesis of accelerator and antioxidant simultaneously. The highest ranks were assigned for this period. For most PER and DER jobs, the 1960s ranks were increased in value by one. The highest value (10) was assigned to production personnel (including line supervision and managers) who worked in the rubber chemicals buildings. With the exception of jobs in the warehouse which was attached to the rubber chemicals department, all other job ranks remained the same as those in 1960-1969.

1980-1994 - In the late 1970s and early 1980s, the company initiated a more concerted effort aimed at lowering workers' exposures (Table I). This included establishment of an air monitoring program for aniline, nitrobenzene, and *o*-toluidine; installation of enclosed charging systems and ventilated control room; process equipment and operation modifications; and improved exhaust ventilation including raising the height of outside air intakes. A number of additional controls had been implemented around 1991-1992, but the air sampling results did not show that the overall air levels were noticeably lowered in the early 1990s. Even though production volume appeared to be relatively consistent through this period, the exposure ranks were lowered to reflect these changes. The GM exposure concentrations presented in Table III also show that the TWA concentrations for 1980-1994 were substantially lower than those for 1976-1979. Hence, ranks ranged from 1-8 based on departments and jobs for years 1980 through 1994. The ranks for PNE and PEI jobs remained the same as the two previous eras, except for the PVC Utility operator who was assigned to work in the recycle area in 1980. The PER ranks were assigned 3 or 4 consistent with those from 1961-1969. The DER rank values (6-8) were assigned one integer less than those of the 1960s since in the 1980s there were more exposure controls, process and operational changes aimed to lower the potential for exposure.

1995–2006 - Air levels of aniline and *o*-toluidine were substantially lower in and after 1995, presumably due to cessation of accelerator production. Thus, 1995 was used as the start of a distinct exposure era. Production of antioxidant continued from 1995-2005 with few additional exposure controls (Table I). Air levels were fairly consistent in the rubber chemical production areas from year to year within this era. Hence, assigned exposure ranks ranged from 0-3 for the 1995-2006 time period.

Table VIII lists the tenure, average, and cumulative exposure ranks by exposure classification and rank quartiles. At least half of the cohort members were in the definitely exposed group (DE) or category (DER). The PNE subsets contained the second largest number of the workers. An increasing trend was apparent for both average and cumulative ranks with increasing exposure for the three-group and four-category exposure classifications. When cumulative rank was plotted against employment tenure (in years) for the DER, PER, PEI, and PNE categories, the hierarchy of ranks was reasonably consistent with the assigned exposure categories and duration of employment, as shown in Figure 3.

Discussion

The objective of this exposure characterization was to reassess workers' exposures to three chemicals of interest (i.e., aniline, *o*-toluidine, and nitrobenzene) that epidemiology studies can use to examine the relation between mortality or bladder cancer incidence with exposure. The updated original exposure groups by department and new categories by department and job presented in this article will be used in a similar manner as the original epidemiology analyses.[8-9] However, exposure assessment schemes based only on exposure strata by department or job title do not differentiate between short- and long-term exposure durations. One way to incorporate the duration of work within this cohort was to assign exposure ranks by department, job, and year so that average and cumulative exposure estimates can be calculated. The assigned rank multiplied by duration (recorded in days) yields a cumulative exposure score for the worker's duration of employment. The range of estimated cumulative exposures is much broader and more continuous than the three-group or four-categories of exposure.

Observed differences in the NIOSH exposure measurements between workers in the accelerant and antioxidant processes (Table II) could not be accounted for by this exposure reassessment because company job titles did not sufficiently identify the process to which a given worker was assigned. Further, employee interviews indicated that workers regularly conducted different jobs within the department.

Although the company provided personal air monitoring data from 1976 to 2004, they were not directly used to develop quantitative exposures for the cohort. First of all, there were no air sampling data prior to 1975, which represents twenty exposure years for this cohort, including a period when controls were not yet implemented (Table I). The company sampling strategy also emphasized jobs, tasks, and locations where high levels might exist. Thus, jobs suspected to be highly exposed tended to be the jobs most frequently sampled. For some jobs, very limited sample days and tasks were monitored; furthermore, not all potentially exposed jobs were sampled.

During some early time periods, the limit of detection (LOD) was simply reported as 10% of the TLV; it was not based on the measured LOD for the analytical instrumentation and procedures. Moreover, LODs varied over time depending on the analytical methods utilized. Company records were also inconsistent in regards to reporting 'equal to' versus 'less than' the LOD. This is particularly important since a substantial amount of the company data for *o*-toluidine and aniline was recorded as either not detected, detected at or near the LOD, or measured at a concentration less than the lowest minimum detectable concentration observed in previous non-detected results. Use of censoring methods with this data could introduce bias since these exposure estimates would be derived inconsistently.

Occupational exposure criteria published by NIOSH, OSHA, ACGIH, and the German MAK commission each contain skin notations for aniline, *o*-toluidine, and nitrobenzene (Table IV) to warn that appreciable absorption and systemic distribution will occur from direct skin contact with these chemicals. In the most recent review, the International Agency for Research on Cancer (IARC) classified *o*-toluidine as carcinogenic to humans (Group 1), and also concluded that skin absorption was a critical determinant of occupational exposure.[12-13] Using *o*-toluidine in urine and hemoglobin adducts, Korinth et al. demonstrated that percutaneous absorption of *o*-toluidine in rubber industry workers can be significant.[23] Penetration of *o*-toluidine through human skin in vitro has also been shown to occur.[24] Hence, air exposure measurements do not reflect total exposure dose for those workers with substantial skin contact to *o*-toluidine. Frequent skin contact with chemicals and process intermediates and inconsistent use of PPE were reported by workers at this facility, especially prior to 1989, even though the company reported that PPE policies were established about a decade earlier. Skin exposure and absorption vary by task, work practices, use of personal protective equipment, and skin condition, factors which cannot be adequately evaluated in this retrospective study. Moreover, the types of gloves that we observed to be used (and re-used) were not impermeable to aromatic amine and nitro compounds for more than a few hours.[25]

Surrogate exposure measures work well as long as enough is known about the work tasks in relation to exposures so that workers are assigned to the correct exposure strata. In retrospective cohort studies, it is often not possible to assign exposures to each employee based on detailed work histories derived from individual interviews and employment records. The major source of exposure misclassification occurs when employees work in areas of the plant or conduct tasks other than those for their assigned departments or jobs (e.g., when replacing an absent co-worker). If such substitutions were frequent and unknown, then this could be a serious source of bias. Employee interviews and job descriptions, however, indicated that workers at this plant generally worked in their assigned departments.

Ideally, it would be beneficial to determine the etiology of the observed bladder cancer incidence at this plant. Based on a comprehensive review of the literature, IARC classified *o*-toluidine as carcinogenic to humans [12-13] as did Deutsche Forschungsgemeinschaft MAK commission[26]; and aniline is not known to induce bladder cancer in animals or humans. [27] The air monitoring data collected by NIOSH showed that *o*-toluidine levels were usually at least two times higher than the aniline levels measured from the same sample. Post-shift urine concentrations measured by NIOSH from exposed workers were also substantially higher for *o*-toluidine than for aniline.[2,4] The impact of workers' exposures to any one of these chemicals cannot be determined independently because of concurrent exposures. Aniline and *o*-toluidine were used simultaneously from 1957-2005, while nitrobenzene was also used in the same areas from 1970-1994. The antioxidant and accelerator processes were parallel in the same buildings, with overlapping equipment. Moreover, personnel records identified the department and job title for each worker, but did not specify whether their assignment was for the antioxidant or accelerator process. Consequently, it is not possible to approximate workers' exposures to each chemical based on assigned jobs and work histories. Thus, the ability to definitively distinguish the causative agent is not possible with this cohort. Other cohort studies of workers exposed to aromatic amines at dyestuff and rubber chemical manufacturers have implicated *o*-toluidine as contributing to excess risk of bladder cancer(28-29) but these workers also had mixed exposures. However, *o*-toluidine has been proven to be genotoxic to humans by high DNA adducts in bladder cancer patients (30) Moreover, using hemoglobin adduct measurements obtained from this study cohort, Ward et al. concluded the *o*-toluidine exposure substantially exceeded aniline exposure.(4) Hence, based on the weight of this evidence, the authors of these studies proposed that *o*-toluidine was the most likely cause for the excess bladder cancer incidence in the dyestuff and rubber chemical industries.(4,12,13,26,28,29,31)

Even though both NIOSH and company sampling data emphasized high potential exposure jobs in the rubber chemicals department, the data shows the TWA breathing zone exposures to be well below occupational exposure limits. Despite these low exposures, an elevated risk of bladder cancer has been reported in the cohort.(8,31) This suggests that the OELs may not be sufficiently protective or that skin absorption of these chemicals presents an important contribution to the observed morbidity, or both.

Conclusions

This article presents the methodology and rationale used to create a retrospective exposure assessment developed for a cohort of workers employed between 1954 - 2006 at a rubber chemical manufacturer that used *o*-toluidine, aniline, and nitrobenzene. Three new exposure assessment schemes were developed based on available data for this project. First, the original exposure-department groups were updated to reclassify some departments. Second, four exposure categories were created based on department-job combinations, as opposed to only department. Further, an approximate rank of the "relative" exposure level was assigned to each job title-department combination over time to calculate average and cumulative exposure scores for each cohort member based on their personal work histories. Company exposure records from 1975 – 2004 showed a decreasing trend over time and nearly all breathing zone TWA measurements were well below published occupational exposure limits, yet bladder cancer cases were still reported. Thus, these new exposure categories and ranking scores will be used to analyze updated mortality and bladder cancer incidence data in follow-up epidemiology studies.

Acknowledgments

The authors wish to acknowledge the company workers, management, and union staff who provided valuable input into the exposure reassessment activities. The authors also wish to thank Scott Henn for quality inspection of air monitoring data, Lian Luo and Pi-hsueh Chen for programming support, and Kim Jenkins, Jean Geiman and Denise Giglio for assistance with work histories and data coding.

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Figures

Figure 1: o-Toluidine air sampling results from 1976-1979

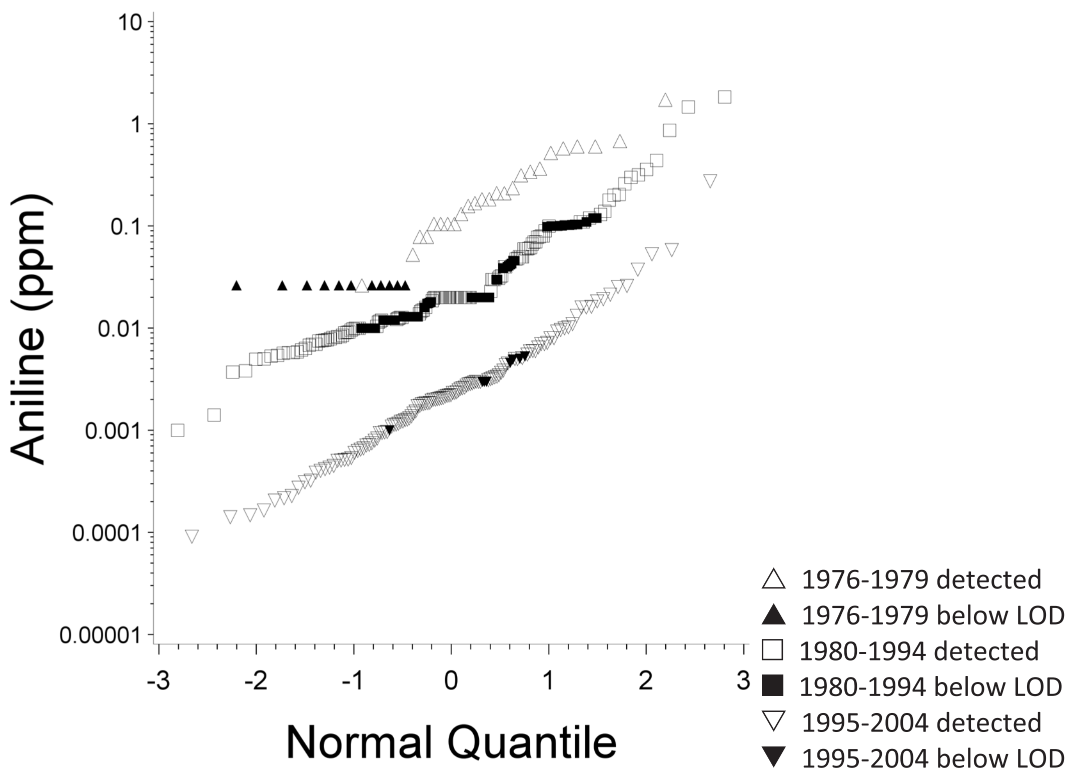
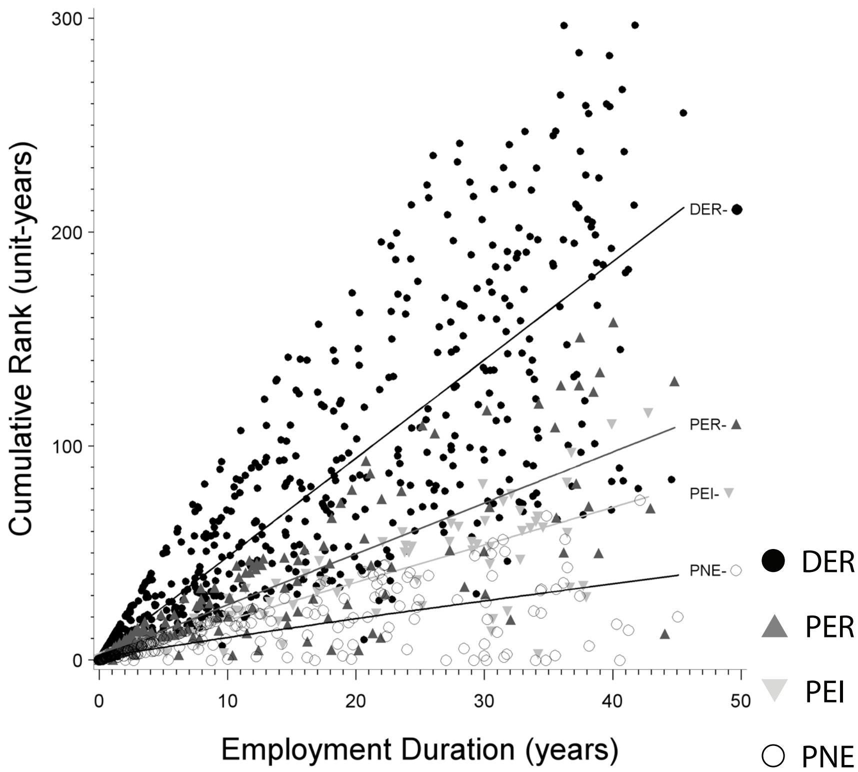


Figure 2: Aniline air sampling results from 1976-1979 and 1980-1994 and 1995-2004

Figure 3: Cumulative rank versus duration of employment (n=1874 workers)



Tables

Table 1: Timeline of Changes or Procedures which may have Impacted Exposure to o-Toluidine, Aniline, and Nitrobenzene in the Rubber Chemicals Department

Date	Change or Procedure
1954	Initiated manufacturing of rubber chemical, mercaptobenzothiazole; introduced aniline
1957	Started anti-oxidant production; introduced *o*-toluidine; aniline use increased
1960	Increased production volume of antioxidant and accelerators; amount of chemical use steadily increased through this decade
1970	Completed rubber chemical building expansion and installed a second production line adjacent to the first in same space; accelerator and antioxidant production increased and occurred concurrently; introduced nitrobenzene; aniline and *o*-toluidine use increased
1975/76	Initiated air monitoring program for *o*-toluidine and aniline
1978	Installed premix reactor feed system operated from a control room to replace manual charging operation; improved exhaust ventilation; lowered operating temperature installed fluid bed dryer for accelerator process
~ 1980	Company personal protective equipment (PPE) policies reportedly established
1980	Installed closed system to feed liquid catalyst

Date	Change or Procedure
1981	Raised height of air intake stacks to bring fresh air into building; installed closed plate and frame type filter but did not replace sparkler filter
1987	Provided workers the option to have towels and work clothes laundered by a vendor
1991	Implemented program to reduce antioxidant recycle material; implemented procedure to weld pipes to minimize potential for leaky threads; installed vacuum lines from product holding tanks; provided worker training program and improved PPE program to minimize skin contact with liquid aniline or *o*-toluidine during sparkler filter cleaning and other operations (PPE included gloves, boots, supplied air respirators, and coveralls with hoods)
1992	Installed redundant leak protection controls; installed local exhaust ventilation for process sampling; installed samplers for raw materials from tank car/trucks; initiated/implemented monthly ventilation system performance check system; initiated/implemented quantitative fit testing for respirators
1993	Renovated a change room/shower facility with dirty and clean sides which allowed workers the opportunity to more effectively wash and change clothes before leaving the plant; implemented routine cleaning/decontamination of the change-room/shower facility; improved worker training program for proper work and personal hygiene practices
1994	Installed centrifuge equipment to reduce the need to change out sparkler filters[A]
1995	Ceased production of accelerant and removed unnecessary process equipment; quantities of aniline reduced and nitrobenzene no longer used
1997	Modified the pastille finishing line system so that it was more enclosed
1998	Installed automatic bagging system for pastille packaging; installed hand washing sink in break room, separate from sink for dish washing

[A] Sparkler filter is still used when the centrifuge is inoperable and for some specialty antioxidants.

Table 2: Summary of TWA breathing zone exposure data collected by NIOSH in the rubber chemicals department, 1990 (ppm)

Description	Parameter	o-Toluidine	Aniline	Nitrobenzene[C]
Anti-oxidant process[A] (n = 17)	Min – Max GM (GSD)	0.035 – 0.35 0.096 (1.74)	0.016 – 0.19 0.041 (2.00)	0.067 – 0.076 n.a.
Maintenance (n = 7)	Min – Max GM (GSD)	0.054 – 0.37 0.086 (2.02)	0.022 – 0.083 0.037 (1.60)	0.037 n.a.

Description	Parameter	o-Toluidine	Aniline	Nitrobenzene[C]
Recycle process[B] (n = 3)	Min – Max GM (GSD)	0.020 – 0.10 0.052 (2.35)	0.015 – 0.10 0.046 (2.72)	ND n.a.
Accelerant process[A] (n = 18)	Min – Max GM (GSD)	0.029 – 0.099 0.051 (1.50)	0.014 – 0.042 0.023 (1.36)	ND n.a.
All jobs (n = 45)	Min – Max GM (GSD)	0.020 – 0.37 0.070 (1.84)	0.014 – 0.19 0.032 (1.83)	ND – 0.076 n.a.

Notes: TWA-time-weighted average; ppm-parts per million; GM-geometric mean; GSD-geometric standard deviation; ND-not detected; n.a.-no data available

[A] Jobs include chemical, production, and utility operators, and area managers.

[B] Job only includes chemical operators.

[C] Nitrobenzene was only detected in 3 (out of 45) TWA measurements; descriptive statistics were not calculated.

Table 3: Summary of company-collected TWA breathing zone exposure data by analyte, department, and time period

Analyte	Department	Time period	No. Samples	% < LOD	Range (ppm) lower limit	-	Range upper limit	GM (ppm)[A]	GSD[A]
o-toluidine	Rubber chemicals	1976-1979	30	27	ND (<0.023)	-	1.8	0.10	45.9
		1980-1994	200	26	0.0025	-	1.5	0.015	3.2
		1995-2004	127	6	0.00021	-	0.22	0.0028	3.8
	Maintenance	1980-1994	43	40	0.00051	-	0.12	0.0049	4.4
		1995-2004	63	6	ND (<0.0001)	-	0.24	0.0014	5.6
	Laboratory	1980-1994	4	25	0.0018	-	0.002		
		1995-2004	1	100	ND (<0.0020)				

Analyte	**Department**	**Time period**	**No. Samples**	**% < LOD**	**Range (ppm) lower limit**	**-**	**Range upper limit**	**GM (ppm)[A]**	**GSD[A]**
	Warehouse	1980-1994	2	100	ND (<0.008)				
		1995-2004	11	55	0.00020	-	0.0020		
	Vinyl chemicals	1980-1994	39	97	ND (<0.00044)	-	0.056		
Aniline	Rubber chemicals	1976-1979	36	31	0.026	-	1.7	0.081	5.3
		1980-1994	200	38	0.0010	-	1.8	0.015	3.9
		1995-2004	127	6	0.000091	-	0.27	0.0021	4.0
	Maintenance	1980-1994	43	51	0.00069	-	0.39	0.0042	3.5
		1995-2004	63	8	ND (<0.00013)	-	0.25	0.00091	4.7
	Laboratory	1980-1994	4	25	0.0018	-	0.0038		
	Warehouse	1980-1994	2	100	ND (<0.096)- ND (<0.10)				
		1995-2004	11	64	ND(<0.00017)	-	0.0020		
	Vinyl chemicals	1980-1994	38	95	ND (<0.00053)	-	0.00095		
Nitrobenzene[B]	Rubber Chemicals	1976-1979	6	17	0.020	-	0.16	0.038	2.7
		1980-1994	90	60	ND (<0.0010)	-	0.11	0.0044	3.8

Notes: TWA-time-weighted average; LOD-limit of detection; ppm-parts per million; GM-geometric mean; GSD-geometric standard deviation; ND-not detected.

[A] Geometric mean (GM) and standard deviation (GSD) were estimated using maximum likelihood estimation. Samples reported as ND (non-detect) (< LOD) were treated as left-censored at the limit of detection (LOD). GM and GSD not reported for analyte-department-time period combinations with fewer than 15 uncensored values.

[B] For nitrobenzene, all samples were ND for maintenance (n=11); laboratory (n=40); warehouse (n=2); and vinyl (n=2) personnel from 1985-1994; no samples were collected for these jobs before 1985. After 1985, nitrobenzene samples were ND in 94% of the samples, inclusive of the rubber chemical.

Table 4: Occupational exposure limitsA, skin, and carcinogenic classifications

Source	Established	o-Toluidine (CAS no. 95-53-4)	Aniline (CAS no. 62-53-3)	Nitrobenzene (CAS no. 98-95-3)
OSHA PEL	1971/1971/1971[B] "	5 skin	5 skin	1 skin
NIOSH REL	1990/1990/1988 " "	LFC[C] skin NIOSH – Ca[D]	LFC skin NIOSH – Ca	1 skin -
ACGIH TLV®	1982/1980/1948 1982/1961/1961 1996/1996/1996	2 skin ACGIH-A3 [E]	2 skin ACGIH-A3	1 skin ACGIH-A3
DFG MAK commission	n.a.[F] /1994/n.a. 1992/1994/2003 2007/2007/2007	n.e.[F] skin Category-1 [G]	2 skin Category-4	n.e. skin Category-3B
IARC	2008/1987/1996 "	Group 1[H] skin	Group 3 skin	Group 2B skin

[A] Reported as 8-hour TWA (ppm).

[B] Established dates for o-toluidine, aniline, and nitrobenzene, respectively.

[C] Lowest (feasible) measureable concentration, NIOSH Alert.[(22)]

[D] NIOSH-Ca, potential occupational carcinogen.[(32)]

[E] ACGIH-A3, confirmed animal carcinogen with unknown relevance to humans.[(20)]

[F] n.a = not applicable; n.e. = not established.

[G] MAK commission redefined their classifications which changed the assignment for *o*-toluidine from category 2 to 1, causes cancer in man; germ cell mutation category 3B.[(26)]

[H] IARC modified the classification for *o*-toluidine from Group 2B to 1,carcinogenic to humans.[(12-13)]

Table 5: Definitions Used for Original and Updated Exposure Groups Based on Department Only

Exposure Category	Original Definition [(1)]	Updated Definition [(17)]
Definitely exposed (DE)	Employees who had ever worked in the Rubber Chemicals department	Employees who had ever been assigned to the Rubber Chemicals, Maintenance, or Laboratory departments
Possibly exposed (PE)	Employees who had ever worked in the Maintenance, Yard/Janitor, or Shipping, Packaging, & Warehouse departments, but had never worked in the Rubber Chemicals department	Employees who had ever worked in the Yard/Janitor, Shipping, Packaging, & Warehouse, Temporary Assignment from Headquarters or None Assigned departments, but had never worked in the Rubber Chemicals, Maintenance, or Laboratory departments

Exposure Category	Original Definition [1]	Updated Definition [17]
Probably not exposed (PNE)	Employees who had never worked in the Rubber Chemicals, Maintenance, Yard/Janitor, or Shipping, Packaging, & Warehouse departments	Employees who had never worked in the Rubber Chemicals, Maintenance, Laboratory, Yard/Janitor, Shipping, Packaging, & Warehouse, Temporary Assignment from Headquarters, or None Assigned departments

Table 6: Definitions of Job Exposure Categories Based on Department and Job

Exposure Category	Definition
Definitely exposed moderate/ high and regularly (DER)	Assigned department-job combinations which required working regularly and in direct contact with *o*-toluidine, aniline, and/or nitrobenzene Examples: Rubber chemical worker, Maintenance worker
Probably exposed low and regularly (PER)	Assigned department-job combinations which required working regularly around but not in direct contact with *o*-toluidine, aniline, and/or nitrobenzene Examples: Shipping, packaging, & warehouse worker, Laboratory technician, Painter, Chemical engineer, Co-op worker
Probably exposed low and irregularly/occasionally (PEI)	Assigned department-job combinations which required working occasionally around and not in direct contact with *o*-toluidine, aniline, and/or nitrobenzene Examples: Safety engineer, Nurse, Laboratory supervisor, Guard, Janitor, Yard worker, Shipping, packaging, & warehouse dispatcher
Probably not exposed (PNE)	Department-job combinations which did not require working around or in direct contact with *o*-toluidine, aniline, and/or nitrobenzene Examples: Accounting staff, Secretary, Switchboard operator

Table 7: Condensed Summary of Exposure Classifications and Ranks Assigned for Various Departments and Jobs[A]

Exposure Classifications[B]

- Original Groups
- Revised Groups
- New Categories

Assigned Exposure Ranks[B]

- 1954-1960
- 1961-1969
- 1970-1979
- 1980-1994
- 1995-2006

Job Name	Original Groups	Revised Groups	New Categories	1954-1960	1961-1969	1970-1979	1980-1994	1995-2006
Offsite location jobs	PNE	PNE	PNE	0	0	0	0	0

Job Name	Orig-inal Groups	Revised Groups	New Catego-ries	1954-1960	1961-1969	1970-1979	1980-1994	1995-2006
Front office jobs[C]	PNE	PNE	PNE	1	1	1	1	0
Sales agents	PNE	PNE	PNE	1	1	1	1	0
All PVC Dept.[D], Powerhouse operator, Rubber Compounds	PNE	PNE	PNE	1	2	2	2	[E]
Hourly (non Rubber Chemicals)	PNE	PNE	PNE	1	2	2	2	1
Lab - Secretary/stenographer	PNE	DE	PNE	1	2	2	2	1
Guard (non-PVC)	PNE	PNE	PEI	1	2	2	2	1
Clerks	PNE	PNE	PEI	1	2	2	2	1
Dispatchers	PE	PE	PEI	1	2	2	2	1
Rubber Chemicals - Clerks, Secretary/stenographer	DE	DE	PEI	1	2	2	2	1
Trainers OBT, (non-PVC)	DE	DE	PEI	1	2	2	2	1
Maintenance - Electrician	PE	DE	PEI	2	3	3	3	1
Maintenance - Painter	PE	DE	PEI	2	3	3	3	2
Nurse, Safety engineer	PNE	PNE	PEI	2	3	3	3	2
Dept -Yard, Janitor (non-PVC)	PE	PE	PEI	2	3	3	3	1
Shipping, Warehouse, Scaleman, Lift truck operator (non-PVC)	PE	PE	PEI	2	2	3	2	2
PVC Utility operator	PNE	PE	PEI	2	2	2	4[F]	2
Chemist, Lab supervisor	PNE	DE	PER	2	3	3	3	2
Engineer, Co-op, Squad	PNE	DE	PER	2	3	4	3	2
Lab technician, Quality control	PNE	DE	PER	3	4	5	4	2
Chemical engineer, R & D engineer (non-PVC)	PNE	DE	PER	3	4	5	4	2
Helper	PNE	DE	PER	3	4	5	4	2
Antioxidant packaging operator	DE	DE	DER	4	7	8	6	2
Maintenance - Craftsman, Welder, Foreman, Supervisor	PE	DE	DER	4	7	8	6	2
Maintenance - Mechanics, Millwright, Pipefitter	PE	DE	DER	4	7	8	6	3
Rubber Chemicals jobs[G]	DE	DE	DER	5	9	10	8	3

Abbreviations: (3-Group) PNE –probably not exposed; PE – possibly exposed; DE – definitely exposed / (4-Category) PNE – probably not exposed; PEI – probably exposed low and irregularly/occasionally; PER – probably exposed low and regularly; DER – definitely exposed moderate/high and regularly.

[A] Extrapolated from 225 department-job title combinations.[17]

[B] Original and revised exposure groups based only on department;[4,31] new categories based on department and job title; assigned ranks based on department-job title and era.

[C] Front office jobs include Secretary, Stenographers, Data processors, Draftsman, Accounting staff, Operator.

[D] PVC department includes Trainer, Yard attendant, Janitor, and all production jobs but not the Utility operator.

[E] Production jobs assigned to these departments in this era were assigned the same exposure rank as rubber chemical department.

[F] The PVC Utility Operator worked in the recycle area, which began processing *o*-toluidine in 1980; rank of 4 was assigned between 1980 and 1994.

[G] Rubber chemicals jobs include Chemical operator, Production operator, Utility operator, Foreman, Supervisor, Section head, Area manager (non-PVC).

Table 8: Distribution of employment tenure and rank scores by exposure classification for 1877 workers in the cohort

Original 3-group[E]

Metric Classification	No. workers	Total years of employment[A]	Years in highest category[A]	Cumulative rank[A,B]	Pearson Correlation[C]	Average rank[A,D]
PNE	769 (41%)	0.73 (0.005-45)	0.73 (0.005-45)	1.3 (0-160)	0.72	2.0 (0.0-8.0)
PE	312 (17%)	8.5 (0.005-45)	2.3 (0.003-41)	18 (0.005-240)	0.82	3.0 (0.08-8.0)
DE	796 (42%)	2.3 (0.005-46)	0.53 (0.005-36)	11 (0.049-300)	0.86	6.8 (0.46-10)

Revised 3-group[F]

Metric Classification	No. workers	Total years of employment[A]	Years in highest category[A]	Cumulative rank[A,B]	Pearson Correlation[C]	Average rank[A,D]
PNE	609 (32%)	0.50 (0.005-45)	0.50 (0.005-45)	0.84(0-75)	0.73	2.0 (0.0-7.5)
PE	184 (10%)	1.8 (0.005-41)	0.70 (0.003-39)	4.2(0.02-110)	0.92	2.4 (0.08-8)
DE	1084 (58%)	3.5 (0.005-46)	1.3 (0.005-39)	13 (0.005-300)	0.85	5.0 (0.14-10)

Alternative 4-category

Metric Classification	No. workers	Total years of employment[A]	Years in highest category[A]	Cumulative rank[A,B]	Pearson Correlation[C]	Average rank[A,D]
PNE	592 (32%)	0.46 (0.005-45)	0.46 (0.005-45)	0.72 (0.0-75)	0.75	2.0 (0.0-3.0)
PEI	170 (9%)	2.3 (0.005-43)	0.89 (0.002-41)	4.6 (0.02-120)	0.89	2.4 (0.08-3.0)
PER	199 (11%)	3.5 (0.005-45)	2.0 (0.005-39)	11 (0.02-160)	0.84	3.4 (0.14-5.0)
DER	916 (49%)	3.5 (0.005-46)	0.92 (0.005-39)	14 (0.05-300)	0.88	6.0 (0.46-10)

Cumulative rank

Metric Classification	No. workers	Total years of employment[A]	Years in highest category[A]	Cumulative rank[A,B]	Pearson Correlation[C]	Average rank[A,D]
Q1: < 0.81	469 (25%)	0.11 (0.005-41)	0.11 (0.005-41)	0.31 (0-0.80)	n.a.[C]	2.0 (0-10)
Q2: 0.81 - < 4.7	469 (25%)	0.56 (0.082-36)	0.28 (0.005-17)	1.9 (0.81-4.6)	n.a.	3.0 (0.04-10)
Q3: 4.7 - < 34	469 (25%)	4.4 (0.49-45)	2.7 (0.005-36)	13 (4.7-34)	n.a.	2.8 (0.17-10)
Q4: ≥ 34	470 (25%)	24 (3.6-46)	11 (0.14-36)	81 (34-300)	n.a.	4.2 (0.91-10)

Notes: PNE-probably not exposed; PE-possibly exposed; DE-definitely exposed; PEI-probably exposed low and irregularly, occasionally; PER-probably exposed low and regularly; DER-definitely exposed moderate/high and regularly; Q1-Q4-quartiles.

[A] Median (range).

[B] Cumulative rank is the product of the assigned exposure rank and the number of days in the job, summed over all jobs worked. The units are *unit*-years.

[C] Pearson correlations were calculated between total years of employment and cumulative rank. These correlations are not applicable for quartiles because the quartiles are based on cumulative rank scores.

[D] Average rank is cumulative rank (*unit*-years) divided by duration of employment (years).

[E] Ward et al. (1991).(4)

[F] Carreón et al. (2010).(31)

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