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Risk Assessment for o-Toluidine and Bladder Cancer Incidence

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Abstract

Background.—Elevated bladder cancer incidence has been reported in a cohort of 1,875 workers manufacturing chemicals used in the rubber industry and employed any time during 1946–2006. ortho-Toluidine (OT), an aromatic amine, was the prime suspect agent. Using the available environmental data and process characterization, previous investigators assigned ranks to volatile chemical air concentrations across time in departments and jobs, reflecting probabilities of exposure and use of personal protective equipment for airborne and dermal exposures. Aniline, another aromatic amine, was present at comparable concentrations and is known to be an animal carcinogen but produced lower levels in post-shift urine and of hemoglobin adducts than OT in a group of workers.

Methods.—A quantitative risk assessment was performed based on this same population. In this work, cumulative OT exposures were estimated a) based on previously assigned ranks of exposure intensity and reported actual exposures in jobs with the highest assigned rank, and b) directly from the historical environmental sampling for OT. Models of bladder cancer incidence were evaluated taking into account possible *healthy worker survivor effects*.

Results.—Under various assumptions regarding workforce turnover, the excess lifetime risk of bladder cancer from OT exposure at 1 ppb was estimated to be in the range 1–7 per thousand.

Conclusions.—The current ACGIH TLV and OSHA standards for OT are 2 ppm and 5 ppm, respectively, one thousand-fold higher than the exposure estimated here for 1–7 per thousand excess lifetime risk.

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INTRODUCTION

In 1988 in response to a request from the Oil, Chemical and Atomic Workers International Union concerning bladder cancer, NIOSH performed a Health Hazard Evaluation (HHE) at a rubber chemicals manufacturing plant in Niagara Falls, NY. That investigation and several others that followed in that rubber chemicals cohort (RCC) identified increased bladder cancer incidence in workers exposed to o-toluidine (OT) and aniline (AN).[1–4] Aromatic amines such as OT, benzidine, and 2-naphthylamine are identified by the International Agency for Research on Cancer (IARC) as carcinogenic in humans (Group 1).[5] That decision was based, in part, on sufficient evidence in humans of exposure-related increased cancer of the urinary bladder. Aniline (AN) shares the same molecular structure at the amine group as do benzidine and β-naphthylamine whereas OT has an adjacent methyl group, and aniline is classified as a Group 2A carcinogen based on animal studies and mechanistic evidence by IARC. [6] Aniline, although present at comparable concentrations in a sample of the RCC, produced substantially lower levels than OT in post-shift urine samples (by a factor of 2–3), and hemoglobin-amine adduct concentrations were similarly reduced for AN vs. OT.[7]

The recent update of the RCC[4] for 1,875 workers employed any time during the years 1946 to 2006 was based on incidence information from six state cancer registries: New York State Cancer Registry (i.e., the primary registry of residence), and registries in Pennsylvania, California, Ohio, Texas and Florida (see Appendix, Table A1). Race information was unavailable for more than half of the population but there were only 2 nonwhite bladder cancer cases. Ascertainment required evaluating alternate assumptions for a minority of workers for whom there was an incomplete record of residency following employment. The outcome studied was diagnosis of *in situ* or invasive bladder cancer (International Classification of Diseases for Oncology Third Edition (ICD-O-3) codes 8010, 8070, 8120, 8130 and 8140 and behavior codes 2 and 3). The period of follow-up was 1976 through 2007. A substantially elevated standardized incidence ratio (SIR) of 2.87 (95% CI: 2.02–3.96) based on 37 cases of bladder cancer was reported.[4] A detailed exposure assessment had been performed by the previous investigators using historical environmental air sampling information obtained from the RCC plant in 2005 for the volatized chemicals that were plausible bladder carcinogens: OT, AN, and nitrobenzene (NB).[8] They collapsed the large number of departments into 18 categories, collapsed job tasks to 63 job codes, and ranked chemical exposures taking into account 1) possible dermal contact, 2) probability of regular or irregular exposure by job category, 3) use of personal protective equipment (PPE), and 4) possibly unsystematic sampling addressing worst case conditions.[8] In this ranking effort, the investigators did not distinguish exposures to the individual chemicals which were strongly associated (Fig. 1). This assessment procedure assigned rank scores 0–10 for aggregate exposure to volatile process chemicals in all dept × job categories in five time periods (1: 1954–60, 2: 1961–69, 3:1970–79, 4: 1980–94, 5: 1995–2005). With a job exposure-rank matrix applied to the work histories of workers, time-dependent cumulative rank was calculated for each worker. Previously reported standardized incidence ratio (SIR) and proportional hazards regression analyses of bladder cancer incidence in this population demonstrated highly significant associations with the exposure ranking: in the highest cumulative rank quartile (10 yr lag) the SIR was 6.13 (95% CI: 2.8–11.6).[4]

The present work used data and related files from the recent update of the RCC[4] to conduct a quantitative risk assessment for OT and bladder cancer: producing estimates of excess lifetime risk. A method was developed to derive estimates of excess OT risk using regression analyses based on cumulative chemical exposure ranks. Additionally, the historical air sampling data for OT itself, which was summarized previously[8] and which was incomplete for some department, job and year combinations, was used in the present work to construct an OT exposure matrix parallel to the reported matrix based on ranks for use in risk assessment.

METHODS

Ascertainment of incidence—The original study population was all workers hired since 1946, the year the plant started operating, with at least one day of employment between 1946 and 2006 (n=1,875) and known to be alive at the start of the cancer registry of New York State in 1976 when follow-up began.[4] For some former employees there were gaps in known residency. The investigation of Carreón et al.[4] examined several alternatives in this matter. In this analysis it was assumed that there was complete coverage of incident cancers with uninterrupted follow-up. This could result in incomplete ascertainment of new bladder cancer cases and under-estimation of incidence. Assuming that former workers with incomplete registry coverage did not differ greatly on exposure history it was expected that including the additional 25 percent of bladder cancer cases with the assumption of full coverage would increase statistical power and minimally bias estimates of exposure response.

Exposure variables

Production utilizing aniline and nitrobenzene started in 1954, and OT began to be used in 1957. The exposure rank matrix from Hanley et al.,[8] with ranks assigned to all department, job and time period combinations, was applied to the work history from the RCC plant, using available information (quantitative data, chemical purchases, manufacturing records, and interviews with current and former employees). Exposure ranks were assigned for five time periods: 1954–1960, 1961–1969, 1970–1979, 1980–1994 and 1995–2005. A high-resolution classification table of observation time was constructed with fine stratification jointly on the time-dependent cumulative rank (as rank-years, with 10-year lag) and employment duration variables as well as on demographic categories. In the primary analysis file there were 43 levels of employment duration strata and 110 levels of cumulative rank strata. The resulting table had 35,277 classification cells with associated (non-zero) person-years and incident cases. For use as continuous variables in regression analyses, cumulative rank and duration were the person-year weighted cell-means in the classification table. Exposures after 2004 (the most recent year of air sampling data) were not important due to the 10-year lag applied to the cumulative rank variable.

Alternatively, using the environmental data described by Hanley et al.,[8] an alternate OT exposure matrix was created here assigning mean values to department, job and year combinations (in ppm) when available. When exposure data were absent for any combination, the assigned mean was for department, job and *time period* (not year), and when still absent, it was assigned for department and time period (across all jobs with data).

Statistical model

In this analysis, based on prior general knowledge of carcinogenesis, it was assumed that the low-dose linear model of exposure response is appropriate for OT and bladder cancer. Analysis of the available retrospective exposure and outcome information was judged to not have sufficient statistical power or precision to identify departures from linearity at low exposures. Race when known (46% of workers) was 90.3% White and 9.7% non-White (almost entirely African-American). These proportions, by sex, were randomly assigned to observations with unknown race. Thus about 5% of the population ((1–0.46) ×0.097=0.052) had mis-assigned race and expected rates of bladder cancer incidence.

Models of bladder cancer incidence were fit using Poisson regression with a linear relative rate specification on cumulative rank and with an offset for the expected number of incident cases such that standardized incidence ratios (SIR) were modeled.[9–11] Population reference rates were obtained from the New York State cancer registry (excluding New York City).[4] Exposure effects were based on both stratified (as quartiles by incident cases) and continuous cumulative exposure ranks (or powers of ranks) over time lagged by 10 years. In order to allow for a possible *healthy worker survivor effect* (HWSE),[12,13] employment duration was included as a multiplicative term in the model:

$$\begin{aligned}&\mathrm{CaOut} \;=\; \exp(\mathrm{a0} + \mathrm{b1} \times \mathrm{rac0} + \mathrm{c1} \times \mathrm{dur}) \times (1 + \mathrm{c2} \times \mathrm{cumOTr}) \times \mathrm{expt} \;\; \text{where,}\\ &\quad \textit{CaOut} \text{ is predicted incident cases, } \textit{rac}0 \text{ is indicator of non} - \text{White race } (0, 1),\\ &\quad \textit{dur} \text{ is employment duration, } \textit{cumOTr} \text{ is lagged cumulative exposure rank as rank} - \text{years,}\\ &\quad \text{and } \textit{expt} \text{ is expected cases using reference rates}\end{aligned}$$

$$\mathrm{SIR} \;=\; \mathrm{CaOut}/\mathrm{expt} \;=\; \exp(\mathrm{a0} + \mathrm{b1} \times \mathrm{rac0} + \mathrm{c1} \times \mathrm{dur}) \;+\; \exp(\mathrm{a0} + \mathrm{b1} \times \mathrm{rac0} + \mathrm{c1} \times \mathrm{dur}) \times \mathrm{c2} \times \mathrm{cumOTr}$$

and the excess relative rate (ERR) is:

$$\mathrm{ERR} \;=\; \exp(\mathrm{a0} + \mathrm{b1} \times \mathrm{rac0} + \mathrm{c1} \times \mathrm{dur}) \times \mathrm{c2} \times \mathrm{cumOTr}$$

This specification allows the background risk to change with increasing employment duration as could occur if population susceptibility was declining with duration, perhaps by attrition of high-risk individuals. An alternate model was evaluated in which susceptibility to OT exposure is unaltered but overall risk declines due to selection out of employment of workers at risk due to other exposures such as smoking:

$$\begin{aligned}\mathrm{SIR} \;&=\; \exp(\mathrm{a0} + \mathrm{b1} \times \mathrm{rac0}) \times (\exp(\mathrm{c1} \times \mathrm{dur}) + \mathrm{c2} \times \mathrm{cumOTr})\\ &=\; \exp(\mathrm{a0} + \mathrm{b1} \times \mathrm{rac0} + \mathrm{c1} \times \mathrm{dur}) \;+\; \exp(\mathrm{a0} + \mathrm{b1} \times \mathrm{rac0}) \times \mathrm{c2} \times \mathrm{cumOTr}\\ \mathrm{ERR} \;&=\; \exp(\mathrm{a0} + \mathrm{b1} \times \mathrm{rac0}) \times \mathrm{c2} \times \mathrm{cumOTr}\end{aligned}$$

In this model, the OT exposure effect estimate, *c2*, and *ERR* are not dependent on employment duration.

It was possible that the ranking based on expert industrial judgment could have introduced a non-linear relationship between the assigned ranks and the actual effective OT air concentrations. To investigate this, for the better-fitting model cumulative rank was also calculated as $\Sigma(\text{rank}^{a})$ where the possible scaling parameter, *a,* took on values $\alpha \in \{0.5, 1, 1.2, 1.5, 2.0, 2.5\}$.

The same models predicting bladder cancer incidence were fit using the cumulative OT exposure metric estimated directly from the observed OT concentrations as ppm-years (not using rank).

Risk assessment

From the Poisson regression, an excess relative rate (ERR) for incident bladder cancer was estimated in relation to cumulative rank of rubber chemical exposures. In order to perform a risk assessment for OT, a means to calibrate rank in terms of OT (ppm) was sought. In the high-exposed production departments (Departments 245, 255) over the years 1976–2005 in samples collected by the employer, the annual geometric mean OT (TWA) concentrations varied largely in the range 0.06 to 0.20 ppm (Fig. 2) which were thought to be non-representative due to attention to worst cases conditions.[14] Samples performed by NIOSH in 1990 suggest lower levels in the same production departments (Fig. 3) with geometric mean levels (corresponding to rank=10) in the range 0.08 to 0.10 ppm OT.[15] For Departments 245–255 over the time Periods 3, 4, and 5 covering 1970–2005, the reported levels appeared to decline about three-fold from 0.2 to 0.06 (Fig. 2); over the same periods the assigned ranks (adjusted for PPE use, and other factors) were respectively 10, 8 and 3 (Appendix, Table A2), also a three-fold reduction. In Period 3 (1970–79), the highest exposures (in Department 245) were assigned rank 10; estimates for corresponding OT geometric means reasonably fall in the range from 0.15 to 0.20 ppm (Fig. 3) but with representative sampling would likely be lower. Using the actual OT sampling data linked to work history, an aggregate time-weighted arithmetic average OT exposure for workers in Department 245 in Period 3 was calculated (0.36 ppm). The OT exposure corresponding to ranks 1–9 were assumed to be proportional on rank to that of rank 10.

One can calculate the ERR for OT as follows, where *beta* is the exposure response from the regression on cumulative rank and *betax* is the exposure response for cumulative OT:

$$
\begin{aligned}
&\text{beta} \times (\text{cum}(\text{rank} = 10)) = \text{betax} \times \text{cum}(\text{ X=Xmax }) = \text{betax}_{36} \times (\text{cum}(X = 0.36)) \\
&\text{betax}_{0.36} = \text{beta} \times (\text{cum}(\text{rank} = 10))/(\text{cum}(X = 0.36)),\ \text{where, beta} = 0.3184 \text{ (from Table2, model 5)} \\
&\text{betax}_{0.36} = 0.3184 \times \text{cum}(\text{rank} = 10)/\text{cum}(X = 0.36) = 0.3184 \times 10/0.36 = 8.84 \\
&\text{with duration} - \text{related attenuation: } \text{ERR}_{0.36} = \exp(a0 + b1 \times rac0 + c1 \times dur) \times 8.84 \times \text{cumX} \\
&\text{without duration} - \text{related attenuation: } \text{ERR}_{0.36} = \exp(a0 + b1 \times rac0) \times 8.84 \times \text{cumX} \text{ where cumX is} \\
&\text{ppm} - \text{yrs of OT at concentration X}
\end{aligned}
$$

Applying the ERR for OT in a lifetable for risk assessment according to the BEIR VII procedure[16] (*lifetime attributable risk*) one can estimate excess lifetime risk at specified levels of OT. Similarly, applying the estimate of exposure response obtained directly from the model prediction using actual OT exposure history, an alternate estimate of lifetime risk was obtained.

RESULTS

Prediction of bladder cancer incidence

Calculation of SIRs in strata of cumulative rank (10 year-lagged) by Poisson regression with a categorical model produced estimates close to those published based on a standardized incidence ratio (SIR) analysis (Table 1).[4] The numbers of incident cases here were higher (46 vs. 37) than in the published analysis due to exclusions in the published study related to uncertain registry coverage. The overall estimate of bladder cancer incidence relative risk was SIR = exp(0.9468) = 2.58 (95%CI: 1.91,3.46) (Table 2, model 1).

Exposure metrics

Although the original assignment of ranks was for generic volatile rubber chemical exposures (including dermal contributions), the ranking would also apply approximately to OT itself if the different major chemical concentrations were strongly associated. In the compiled dataset of plant air-sampling exposures, OT was linearly associated with AN and with NB (Figure 1; on the log scales the slopes were close to 1.0). A linear concordance was observed predicting individual OT exposure concentrations from assigned ranks (slope=0.0135 with SE=0.0022, intercept =−0.04) but the R^2 was only 0.074.

Poison regression models

Several different models of increasing complexity were fit with terms for employment duration and cumulative rank (or exposure) (Table 2). With linear relative rate Poisson models, applying an offset for reference rates, employment duration exhibited a significant positive effect (SIR=1.03, 95%CI 1.01, 1.05) or a 3% increase for each year employed (Table 2, model 3). The effect of race (2 non-White cases) was insignificant. Cumulative rank was a highly significant predictor of bladder cancer incidence, the rate increasing by 5.7% for each rank-year of exposure (likelihood ratio test (LRT): chi square = 26.8; Table 2, model 4). However, including both the cumulative rank and duration terms revealed a strong negative duration effect corresponding to 4% decline per year of employment, and a stronger exposure effect, with the incidence rate increasing 32% (above the low background) for each rank-year of chemical exposure (Table 2, model 5). This result suggests that considerable HWSE was present. The estimate of the background risk was considerably less than expected from reference rates (SIR(0)=0.45) and further declined with duration of employment (Table 2, model 5). Thus, after 12 years at a rank 5 exposure (and after a 10 year lag; cumulative rank = 2×5=10) the baseline SIR is 0.45×exp(−0.04×12) = 0.28, the ERR is 10×0.318 = 3.2 and the SIR is 0.28× (1+ 3.2) = 1.18 of which most (3.2/4.2) is estimated to be attributable.

An alternate model examining HWSE that could arise because of removal of workers at higher risk from another cause, like smoking, revealed no such effect (Table 2, model 6): this was a less well-fitting model (compared to model 4) and the duration effect was statistically insignificant (LRT: 0.07). To assess whether a scaling transformation would improve model fit based on cumulative rank, choices of *a* from 0.5 to 2.5 in calculating $\Sigma(\text{rank}^a)$, summed over time, were evaluated. The optimum model fit occurred with *a*=1 (Table 3).

Prediction-model fit based on the actual available OT exposure history (Table 4) was similar to that based on ranks (Table 2) except that the duration terms were no longer significant predictors when appearing together with cumulative OT (Table 4, models 5, 6) with chi squares (1 degree of freedom (df)) of 0.33 and 2.22, respectively. The net contribution of the duration and cumulative exposure terms for the rank-based model (Table 2, model 5) in terms of model fit was 32.6 (chi square, 2df) and somewhat larger than that for the actual OT-based model: 29.3 (chi square, 2df).

To examine the possibility that exposures in earlier periods, e.g., prior to 1975, were higher than what had been determined in the previous exposure assessment, an analysis of bladder cancer incidence was performed including a term for calendar time. The secular trend in chronological time was statistically insignificant (p=0.08; data not shown) and resulted in a small reduction in the effect estimate for cumulative OT by 5%.

Risk assessment

The excess lifetime risk calculations follow a hypothetical worker population exposed at fixed levels for a 45 year working life; these risks are expressed as excess cases per 1000 workers. Including the *duration* term allows predicting outcomes following the same population during which there is an apparent reduction in the expected rate of bladder cancer incidence with duration of employment possibly due to higher risk workers (i.e., higher susceptibility) becoming cases and leaving exposure or some other selection effect (“with HWSE adjustment”). Not including the *duration* term would be appropriate for short-term, high-turnover employment for a hypothetical population in which terminating employees are continually replaced over the 45 year period of working lifetime; thus higher risk workers are replenished and the equivalent aggregate population risk is higher (“without HWSE adjustment”). An intermediate case where worker duration effects are capped at 5 years, is also presented (Table 5). At a constant exposure of 1 ppb OT, the excess risk is estimated to be 1.2 per thousand. For the high-turnover equivalent, the excess risk is 7.1 per thousand, and with 5 years maximum duration, the intermediate excess risk is 5.8 per thousand (Table 5). The RCC had a mean employment duration of 8.1 years and a median of 1.4 years,[4] indicating high turnover within many jobs. Control of HWSE in this analysis by applying a multiplicative, exponential decline in background rate could induce a bias in the exposure response estimate if the form of the duration effect was poorly specified. Examination of categorical estimates of exposure effects without an assumed form of the exposure response demonstrated that the shape of the trend of increasing response with cumulative rank was not materially altered with inclusion of the duration term (Appendix, Table A3). The duration term allowing for possible HWSE specified an exponential decline in background rate. Extending to 45 years is far outside the range of observable data. To assess this issue, the final model was modified such that duration of employment greater than 17.2 years (the duration at which the background rate was reduced by half) was fixed at 17.2. This model fit substantially less well (data not shown; $-2\ln(L) = 1078.378$ vs. 1073.709 for Model 5, Table 2).

Excess lifetime risk estimates based on the exposure response derived using the actual OT exposure history but without including the unimportant duration term (Table 4, model 4) were almost identical to that based on ranks with full HWSE adjustment using duration (Table 5).

DISCUSSION

Findings

This risk assessment found excess lifetime risk with exposures of 1 ppb OT to be about 1 per thousand in the context of what appears to be a depletion of more susceptible workers or some equivalent selection process. Derivation of the estimate of actual OT exposure from the assigned exposure rank was uncertain as it was based on calibrating air sampling using rank 10 exposures in Period 3. A significant and possibly comparable contribution to bladder cancer risk in the RCC by aniline cannot be ruled out. However, in addition to lower urinary concentrations and serum HB adduct levels comparing AN and OT in a sample of workers, there is also *in vitro* genotoxicity evidence that AN is a less potent carcinogen than OT. In a human tissue culture study of histone phosphorylation activity, a marker for genotoxic events, was considerably higher for OT vs. AN.[17] If AN was actually contributing bladder cancer risk comparable to that of OT in the RCC population, the lifetime risks attributed to OT in this work would have been over-estimated by about a factor of two. A possible contribution to risk by nitrobenzene co-exposures (not an aromatic amine) has been considered and was thought to be small;[4] the NB concentrations were not strongly associated with those of OT (Figure 1b).

In the RCC workforce, OT exposure occurred not only from inhalation of airborne OT (as vapor and mist) but also from vapor and liquid phase dermal absorption which could have played a major role in the observed exposure response for OT. Air levels would have resulted from routine emissions of incompletely enclosed or otherwise insufficiently controlled production processes but also from irregular releases due to minor leaks, breakdowns, maintenance activities and other process or design features. These air concentrations result from evaporation from the liquid phase (including mists) or as mists condensing from emissions of OT vapors at elevated temperatures. Measured air concentrations would capture both the inhalation route dermal uptake from vapor of mist but would miss the route via liquid phase contact whereas urine levels of OT would reflect all sources. The strong association observed between air and urine OT levels (Figure 4) suggests that liquid contact was playing a minor role in the overall population exposure while perhaps dominating worker exposures in some jobs or tasks. The Health Hazard Evaluation conducted by NIOSH in 1990 examined dermal exposure issues using glove deposition and passive badge sampling and found that substantial liquid contact was infrequent but could have been more important earlier.[13] The urinalysis database for this population was limited and strongly focused on high risk jobs and thus not a useful basis for this quantitative risk assessment, but is clearly an important tool in investigating and preventing events that result in liquid contact.

Exposures in Period 3 (1970–1979, where rank 10 exposures occurred) could have had associated substantial dermal exposures to OT, with less protection than was likely common in later years. If as much as half of the effective exposure in this study came via a dermal pathway, then the OT air concentrations corresponding to various lifetime risks would be doubled under conditions of rigorous control of dermal exposure. Thus for a target risk of one per thousand for which the corresponding estimate of OT concentration is 1.0/1.2 = 0.83 ppb (from first risk column, Table 5) the relevant OT concentration would be as high as 0.83×2 = 1.7 ppb with control of dermal exposure. The OSHA Permissible Exposure Limit for OT is 5 ppm or 5,000 ppb and the ACGIH TLV is 2,000 ppb.

Limitations and other uncertainties

A major limitation in this risk assessment was the absence of OT exposure information prior to 1976 and a key step was the informal imputation of OT concentrations corresponding to the chemical exposure ranks assigned in the environmental assessment. Uncertainty could arise from non-representative (worst case) air sampling which would over-estimate exposure assignments and under-estimate corresponding risks, but this problem was recognized in the assigning of ranks. Although there could be large errors in exposure estimates, these errors are likely to be non-differential with respect to case status and any resulting bias is unlikely to largely explain the moderately large excess in OT-induced bladder cancer observed in this cohort. The analysis examining a linear secular trend in the exposure response attributable to underestimation of early exposures suggests that the magnitude of the resulting bias was small, on the order of 5%.

Incomplete cancer registry coverage might have caused some incident bladder cancer cases to be missed. The overall SIR (2.58) was somewhat smaller than that reported for the analysis restricted to known coverage (2.87).[4] If the latter SIR were applied to the larger observed population (incomplete coverage) one would expect the total number of cases to be about 46 ×2.87/2.58 = 51, or an additional 5 cases representing 10% of total.

The observations here using exposure rank assignments are consistent with a large survivor effect related to variable susceptibility. The form of the duration dependence specified to adjust for the HWSE was exponential. While this term was a statistically significant addition to the model (LRT= 5.8 (1df), p=0.016) there appeared to be insufficient statistical power to assess possible improvements requiring additional parameters; the observations with high duration were relatively sparse.

When duration and cumulative OT exposure ranks were predictors of bladder cancer incidence, the baseline risk was about 50 percent of expected (SIR=exp(−0.789) = 0.45, Table 2, model 4) and further declined another 33 percent at 10 years of duration (exp(10*0.0402) = 0.67) (Table 2, model 4). Some higher-susceptibility workers in the study population (which was all workers hired after 1946) could have become bladder cancer cases following introduction of OT in 1957 but prior to the start of follow-up in 1976 thus presenting a lower risk population by 1976 and an example of “left truncation” in case ascertainment.[18] In a study of bladder cancer incidence and chemical dye workers in the U.K., Cartwright et al.[19] observed that cases among dye workers were 15 times more likely to be “slow acetylators” via *N*-acetyltransferase than unexposed cases (OR = 14.8, 95% CI 1.9, 114, based on Table IV in Cartwright et al.[19]). Almost all (96%) dye worker cases were slow acetylators vs. 50–60 percent of cases in Caucasian populations. However, workers in the Cartwright study might have been exposed to multiple aromatic amines with competing metabolic pathways. The low estimated background incidence rate could also result from incomplete cancer registry coverage. The latter contribution was likely to be small because most follow-up occurred in New York State with full registry coverage. Unless observation time lacking registry coverage was strongly associated with cumulative exposure rank, there would be minimal impact on estimates of exposure effect other than reducing the statistical power of the analysis. In contrast, regression analyses using the actual OT exposure history instead of exposure ranks did not identify a duration effect consistent with HWSE. There is no clear explanation for this difference, but one possibility is that exposure misclassification arising from non-representative air sampling (i.e., elevated worst-case estimates) was declining over time and partially compensating for declining baseline risk due to a survivor effect. Alternatively, the analyses based on actual OT air concentrations (Table 4) while better estimating the airborne contribution to exposure response might have fit the bladder cancer incidence data less well than those based on exposure ranks (Table 2) which accounted for dermal contributions, PPE use and task-based probability of exposure. This misclassification could inflate the intercept estimates in Table 4. Finally, medical surveillance procedures by the employer in later years might have increased or hastened the detection of bladder cancer which could impact the exposure response estimate and lower the estimate of intercept.

The statistical significance of the bladder cancer incidence association with cumulative exposure-ranking, exhibiting no improvement with scaling adjustment, is inconsistent with a high level of exposure rank misclassification. This result favors a role of expert industrial hygiene judgment in constructing job exposure matrices for individual occupational epidemiological analyses.

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Appendix

Table A1

Time coverage of cancer registries in six states

Year new registry began	States with cancer registries	Time coverage
1976	NY[a]	1/1/1976 – 12/31/1984
1985	NY PA	1/1/1985 – 12/31/1987
1988	NY PA CA	1/1/1988 – 12/31/1991
1992	NY PA CA OH	1/1/1992 – 12/31/1994
1995	NY PA CA OH TX	1/1/1995 – 12/31/1996
1997	NY PA CA OH TX FL	1/1/1997 – 12/31/2007

[a]NY reference rates excluding New York City.

Abbreviations: NY, New York; PA, Pennsylvania, CA, California; OH, Ohio; TX, Texas, FL, Florida

Table A2

o-Toluidine assigned rank in high-exposed production departments (Departments 245–255) of a chemical manufacturing plant over three periods

	n	Mean OT rank
Period 3 1970–79	27	10
Period 4 1980–94	205	8
Period 5 1995–07	127	3

Personal TWA air samples

Table A3

Effect of categorical duration adjustment on excess relative rate estimates from standardized incidence ratio model of bladder cancer in workers from a chemical manufacturing plant

	ERR (from SIR) (lag = 10 yr)		
	Loglinear model		
Cumulative rank (unit-days)^2	Without duration term -2ln(L)=1083.035	With duration term -2ln(L)=1082.302	Ratio with/ without duration term[a]
<11 000	0.082	0.17	2.1
11 000–<27 000	2.33	3.71	1.6
27 000–<48 000	4.31	6.75	1.6
48 000+	5.44	9.65	1.8

[a]As applied in model 5, Table 2

Notes: Models with cumulative o-toluidine rank in 4 strata (s1Tol, s2Tol, s3Tol, s4Tol).

```
proc nlin data=otolANL01_1 nohalve method=gauss eformat sigsq=1 ; * without
dur ;
  parameters s1=0 s2=0 s3=0 s4=0 ;
  model.CaOut = exp(s1*s1Tol+s2*s2Tol+s3*s3Tol+s4*s4Tol) * expt ;
  _weight_ = 1/model.CaOut ;
  dev = Deviance(‘Poisson’, CaOut, Model.CaOut) ;
 _loss_ = dev/_weight_;
run;
proc nlin data=otolANL01_1 nohalve method=gauss eformat sigsq=1 ;  * with
dur ;
  parameters c1=0 s1=0 s2=0 s3=0 s4=0 ;
  model.CaOut = exp(c1*dur+s1*s1Tol+s2*s2Tol+s3*s3Tol+s4*s4Tol) * expt ;
  _weight_ = 1/model.CaOut ;
  dev = Deviance(‘Poisson’, CaOut, Model.CaOut) ;
 _loss_ = dev/_weight_;
run;
```

Interpretation:

The form of the exposure response based on cumulative rank analyzed categorically in 4 levels appeared not to be materially altered with inclusion of the duration adjustment

SAS code for calculation of excess lifetime risk

Code for calculating NRC: Lifetime Attributable Risk, LAR, for lagged exposure based on BEIR VII[2] ;

```
*   Prepare basic lifetable for age >= 20 starting with table from SSA1 ;

*create merge category: IA  ;
data otol.LTable01; set otol.LTableCM01;
    IA=int(age/5)-2 ; if IA>15 then IA=15 ; * IA=1 ~ 15–19,... ;
run ;

* merge bladder cancer rates by age ;
data otol.LTable02; merge otol.LTable01 otol.NYSxNYCCa188IR3; by IA ; run ;

data otol.XLTR001; set otol.LTable02;
  retain PSrvPop p20 pyrs ;    *  PSrvPop: prior surviving population ;
  if _N_ = 1 then pyrs=0.0;
  if age < 20 then PSrvPop=start - dths;
  if age = 20 then p20=PSrvPop;
  if age => 20 then do;
   sdths=dths*PSrvPop/start;  * sdths: deaths expected at age-year in
surviving population ;
   SrvPop=PSrvPop - sdths;   * SrvPop: surviving population ;
   pyrs=pyrs+PSrvPop;
   PSrvPop=SrvPop;
  end;
  if age < 19 then delete;
run;
```

/* From Table 2 model 5:

```
proc nlin data=otol.otolanl01 nohalve method=gauss eformat sigsq=1 ;
  model.CaOut = exp(a0+b1*rac0+c1*dur) * (1+c2*cumrank) * expt ;
   ...
                Parameter  Estimate  Std Error  Approximate 95% Confidence
Limits
                a0      −0.7895    0.6894   −2.1408   0.5618
                b1       0.4967    0.7242   −0.9227   1.9160
```

```
                c1      −0.0402   0.0152   −0.0700  −0.0105
                c2       0.3184   0.2942   −0.2581   0.8950
[dur in yrs; cumrank in rank-yrs;
```

Excess lifetime risk:

```
    c2×cumrank(max) = c2× 10 = betax × cumOT(max) = betax × 0.36
        (cumOT is equivalent cumulative exposure to OT )
        betax = 0.318×10/0.36 = 8.84
           ERR = exp(a0+b1×rac0+c1×dur) × betax × cumOT    with duration-
related attrition
           ERR = exp(a0+b1×rac0) × betax × cumOT      without duration-
related attrition
   ncasex=exp(a0+b1×rac0+c1×dur) × betax × cumOT × rate × PSrvPox ;
with duration-related attrition
   ncasex=exp(a0+b1×rac0) × betax × cumOT × rate ×
PSrvPox ;                     without duration-related attrition
        ( rate is age-, sex-, race-specific bladder cancer incidence rate )
*/

%macro hrltr(x=.);
data XLTRI01; set otol.XLTR001;  retain PSrvPox tcasex;
   X=&X;
   if _N_ = 1 then do;
    tcasex=0;
    PSrvPox=start - dths;
    delete;
   end;
   if _N_ > 1 then do ;
    dur=age-20; if age>65 then dur=45 ;
*   if dur>5 then dur=5 ;       *  DUR =< 5 ************ ;
*   cumOT=X*(age-19.5);  if age> 65 then cumx=X*45; * lag=0 ;  * unlagged
XLTR ;
    cumOT=0;  if age> 29.5 then cumOT=(age-29.5)*X;  if age> 75 then
cumOT=X*45; lag=10 ;
    ncasex=exp(−0.7895–0.0402*dur) * 8.84*cumOT * rate * PSrvPox ; * with
duration-related attrition ;
*   ncasex=exp(−0.7895) * 8.84*cumOT * rate * PSrvPox ;        * without
duration-related attrition ;
    sdthx=dths*PSrvPox/start ;
    SrvPox=PSrvPox - ncasex - sdthx ;
    PSrvPox=SrvPox ;
    tcasex = tcasex  + ncasex ;
    xltr = tcasex/p20 ;
```

```
   end ;
   if age = 85 then do ;
     put lag 4.0 X 8.4 cumOT 8.2 tcasex 12.4 xltr 10.4 ;
   end;
run ;
%mend ;

%hrltr(x=1.00);
%hrltr(x=.500);
%hrltr(x=.200);
%hrltr(x=.100);
%hrltr(x=.0500);
%hrltr(x=.0200);
%hrltr(x=.0100);
%hrltr(x=.0050);
%hrltr(x=.0020);
%hrltr(x=.0010);
%hrltr(x=.0005);
%hrltr(x=.00020);
%hrltr(x=.00010);
```

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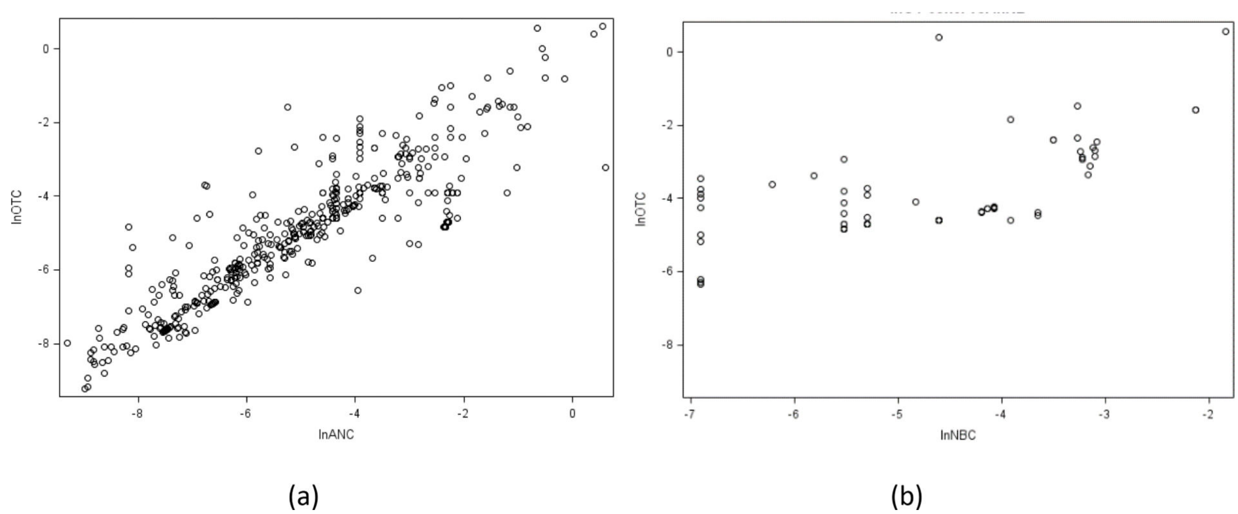

Figure 1.

Historical association of paired air concentrations of o-toluidine (OTC) with (a) aniline(ANC) and (b) nitrobenzene (NBC) (as natural log in ppm: lnOTC=log[OT], lnANC=log[AN]), and lnNBC=log[NB] reported for workers from a chemical manufacturing plant[8,14]).

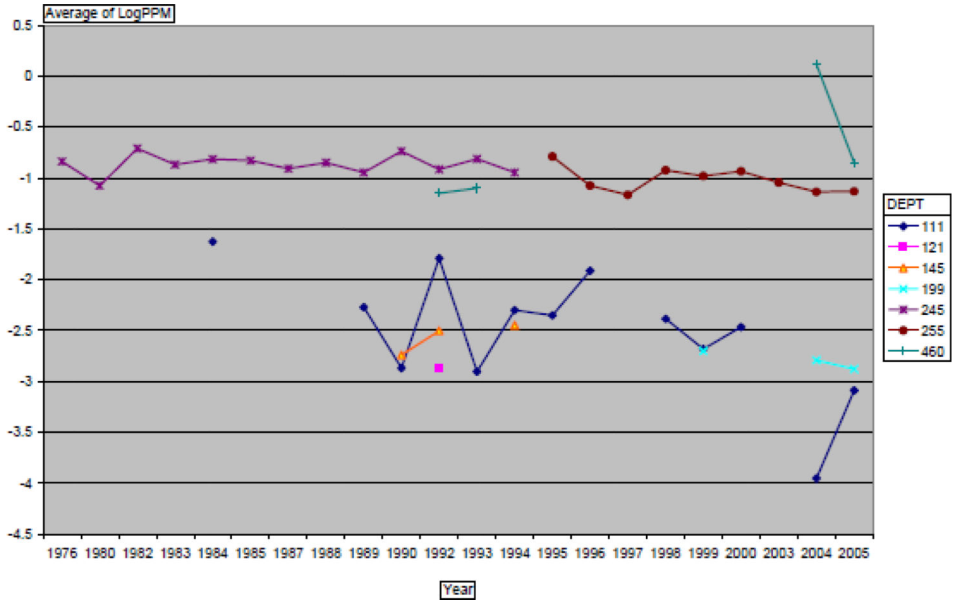

Figure 2.

o-Toluidine (OT) air concentrations during 1976–2005 by major departments in a chemical manufacturing plant, as $\log_{10}$(PPM): −1.2 ~ 0.06 ppm OT, −1.1 ~ 0.08 ppm OT, −0.8 ~ 0.16 ppm OT, −0.7 ~ 0.20 ppm OT (source: NIOSH[14])

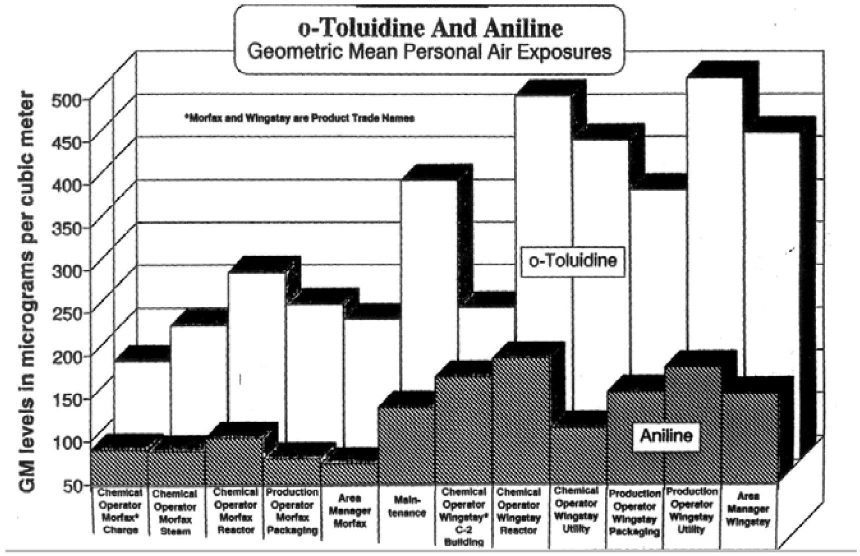

Figure 3.

Average o-toluidine and aniline air concentrations by department in a chemical manufacturing plant, March 1990. Source: NIOSH Health Hazard Evaluation[11] (350 µg/m^3 ~ 0.08 ppm o-toluidine, 450 µg/m^3 ~ 0.10 ppm o-toluidine)

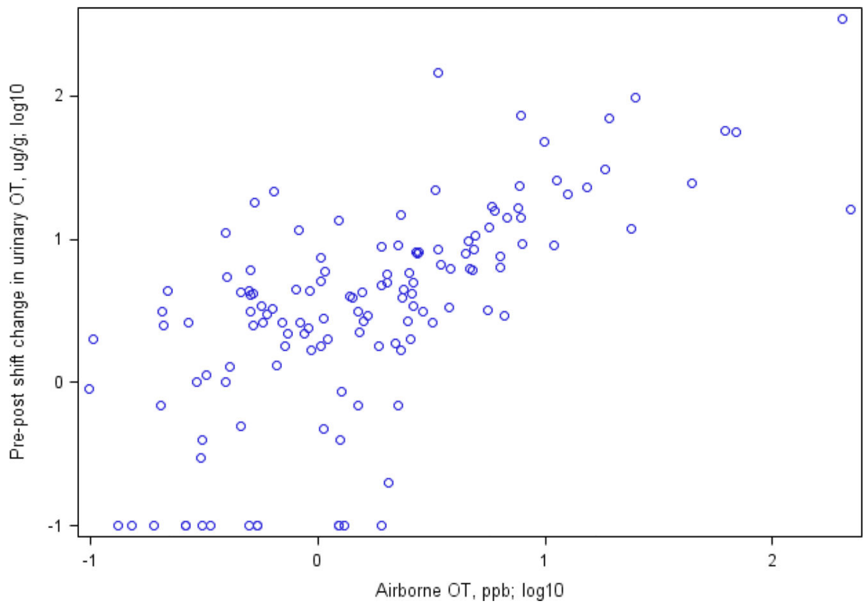

Figure 4.

Association of o-toluidine (OT) urinalysis determinations with OT air concentrations during 1999–2000 in workers from a chemical manufacturing plant. Each plotted point is for means of workers' paired air/urinalysis samples: arithmetic mean for pre-post change in urine OT (creatinine adjusted, µg/g) and arithmetic mean for air concentration of OT (ppb) compared for same day, department and job, and both plotted on logarithmic scale. Points at −0.1 for urinary OT were (low) samples where post-shift level was lower than per-shift.

Table 1

Comparison of study findings with previously published results for bladder cancer incidence associated with o-toluidine cumulative exposure rank (10-year lag) in workers from a chemical manufacturing plant (n=1,875)

	Present Analysis[a]	Published analysis[b]
Bladder cancer cases (person-years)	46 (47,640)	37 (35,155)
Overall SIR, lag = 10 yr (95% CI)	2.58 (1.91, 3.46)	2.87 (2.02, 3.96)
SIR by cumulative rank (unit-days)[c]		
<11 000	1.08	1.32
11 000–<27 000	3.33	3.37
27 000–<48 000	5.31	5.44
48 000+	6.44	6.13

[a]From single Poisson regression model, no intercept, unadjusted for healthy worker survival effect.

[b]Table 2, Carreón et al., 2014.[4]

[c]Derived from unit-years by multiplication by 365.

Abbreviations: CI, confidence interval; SIR, standardized incidence ratio.

Table 2

Models of standardized incidence ratios for bladder cancer by Poisson regression using cumulative o-toluidine exposure rank prediction with reference population rates[a] (10year lag) in workers from a chemical manufacturing plant (n=1,875)

Parameter		SIR Estimate[b]	Std Error	Approx. 95% CI (Wald)[c]	Model deviance or chi square to remove variable
1	**CaOut = exp(a0) × expt**				**-2ln(L) = 1106.686**
	a0	0.9468	0.1474	0.65,1.24	
2	**CaOut = exp(a0+b1×rac0) × expt**				**-2ln(L) = 1106.346**
	a0	0.9309	0.1508	0.64,1.23	
	b1	0.451	0.723	−0.97,1.87	
3	**CaOut = exp(a0+b1×rac0+c1×dur) × expt**				**-2ln(L) = 1096.590**
	a0	0.3499	0.2672	−0.17,0.87	
	b1	0.595	0.7248	−0.83,2.02	
	c1	0.0319	0.0102	0.012,0.052	9.8
4	**CaOut = exp(a0+b1×rac0) × (1+c2×cumOTr) × expt**				**-2ln(L) = 1079.482**
	a0	−0.323	0.4207	−1.15,0.50	
	b1	0.5849	0.7233	−0.83,2.00	
	c2	0.0573	0.0315	−0.004,0.12	26.8
5	**CaOut = exp(a0+b1×rac0+c1×dur) × (1+c2×cumOTr) × expt**				**-2ln(L) = 1073.709**
	a0	−0.7895	0.6894	−2.14,0.56	
	b1	0.4967	0.7242	−0.92,1.92	
	c1	−0.0402	0.0152	−0.070,-0.011	5.8
	c2	0.3184	0.2942	−0.26,0.90	22.6
6	**CaOut = exp(2a0+b1×rac0) × (exp(c1×dur)+c2×cumOTr) × expt**				**-2ln(L) = 1079.407**
	a0	−0.2868	0.4536	−1.18,0.60	
	b1	0.5794	0.7238	−0.84,2.00	
	c1	−0.0101	0.0545	−0.12,0.097	0.07
	c2	0.0575	0.0306	−0.003,0.12	17.2

Note: CaOut – predicted incident cases of bladder cancer, expt – expected cases from reference population,

rac0 – indicator of non-white race (0,1), *dur* – employment duration, *cumOTr* – cumulative exposure rank, in unit-years.

[a]Reference rates for six states (Pennsylvania, California, Ohio, Texas, Florida, and New York excluding New York City).

[b]c2 is the estimate for the exposure response, or, excess relative rate per rank-year of exposure.

[c]Wald CI not appropriate for linear relative rate term: c2.

Abbreviations: CI, confidence interval; SIR, standardized incidence ratio.

Table 3

Effect of scaling choices for parameter *a* in cumulative rank [cumOTr = $\Sigma(\text{rank}^a)$] summed over time, for predicting bladder cancer incidence in workers from a chemical manufacturing plant (n=1,875); largest chi square indicates best fit.

Parameter *a*	**0.5**	**1.0**	**1.2**	**1.5**	**2.0**	**2.5**
chi square (2df)	30.04	32.64	32.12	30.15	27.67	25.84

Notes: chi square (2df) values for parameters c1, c2 from final model (Table 2, Model 5); chi square (2df) = change in -2ln(L) with removal of *dur* and *cumOTr* terms.

Model: CaOut = exp(a0+b1×rac0+c1×dur) × (1+c2×cumOTr) × expt.

Abbreviation: df, degrees of freedom.

Table 4

Models of standardized incidence ratios for bladder cancer by Poisson regression using cumulative estimated o-toluidine exposure prediction with reference population rates[a] (10-year lag) in workers from a chemical manufacturing plant (n=1,875)

Parameter		SIR Estimate[b]	Std Error	Approx. 95% CI (Wald)[c]	Model deviance or chi square to remove variable
1	**CaOut = exp(a0) × expt**				**-2ln(L) = 1108.680**
	a0	0.9476	0.1474	0.66, 1.24	
2	**CaOut = exp(a0+b1×rac0) × expt**				**-2ln(L) = 1105.226**
	a0	0.887	0.1543	0.58, 1.19	
	b1	1.1292	0.5233	0.10, 2.15	
3	**CaOut = exp(a0+b1×rac0+c1×dur) × expt**				**-2ln(L) = 1095.015**
	a0	0.2923	0.2698	−0.24, 0.82	
	b1	1.2373	0.5245	0.21, 2.27	
	c1	0.0326	0.0102	0.013, 0.053	10.2
4	**CaOut = exp(a0+b1×rac0) × (1+c2×cumOT) × expt**				**-2ln(L) = 1076.304**
	a0	0.2048	0.2612	−0.31, 0.72	
	b1	1.2167	0.5236	0.19, 2.24	
	c2	0.5879	0.2506	0.097, 1.080	28.9
5	**CaOut = exp(a0+b1×rac0+c1×dur) × (1+c2×cumOT) × expt**				**-2ln(L) = 1075.97**
	a0	0.1384	0.2903	−0.43, 0.71	
	b1	1.2436	0.5258	0.21, 2.27	
	c1	0.00796	0.0133	−0.018, 0.034	0.33
	c2	0.474	0.2592	−0.034, 0.980	19.1
6	**CaOut = exp(2a0+b1×rac0) × (exp(c1×dur)+c2×cumOT) × expt**				**-2ln(L) = 1074.088**
	a0	−0.0997	0.357	−0.80, 0.60	
	b1	1.2523	0.5242	0.23, 2.28	
	c1	0.0233	0.0161	−0.008, 0.05	2.22
	c2	0.7135	0.3522	0.023, 1.40	20.9

Note: CaOut – predicted incident cases cases of bladder cancer, expt – expected cases from reference population,

rac0 – indicator of non-white race (0,1), *dur* – employment duration, *cumOT* – cumulative OT exposure, in ppm-years

[a]Reference rates for six states (Pennsylvania, California, Ohio, Texas, Florida, and New York excluding New York City).

[b]c2 is the estimate for the exposure response, or, excess relative rate per ppm-year of exposure

[c]Wald CI not appropriate for linear relative rate term: c2

Abbreviations: CI, confidence interval; SIR, standardized incidence ratio.

Table 5

Excess lifetime risk of incident bladder cancer in workers from a chemical manufacturing plant, attributable to o-toluidine airborne exposure (ppm) from model based on cumulative rank and assuming different dependencies on employment duration, and from model based on estimated o-toluidine concentrations

	Excess lifetime risk (per 1000) applying different model estimates			
o-toluidine, ppm	**OT ranks with unrestricted durations**[a]	**OT ranks with durations <5yr**[a]	**OT ranks with duration = 0**[a]	**OT concentration (no duration term)**[a]
0.2	212	601	653	217
0.1	114	407	463	118
0.05	59	242	284	61
0.02	24	108	130	25
0.01	12	56	68	13
0.005	6.2	29	35	6.4
0.002	2.5	12	14	2.6
0.001 (1 ppb)	1.2	5.8	7.1	1.3
0.0005	0.6	2.9	3. 5	0.6
0.0002	0.2	1.2	1.4	0.3
0.0001	0.1	0.6	0.7	0.1

Notes: OSHA PEL: 5 ppm; ACGIH TLV: 2 ppm

[a]Based on OT exposure ranks with Rank 10 equivalent OT concentration = 0.36 ppm, and calculating lifetime risk with different treatments of duration (from Table 2, Model 5).

[b]Based on actual reported air concentrations of OT (from Table 3, Model 4).

Abbreviation: OT, o-toluidine.