

## CORRESPONDENCE

### An Alternative Hypothesis for Bladder Cancer Among Workers Exposed to Ortho-Toluidine and Aniline

Ward et al. (1) reported an excess in bladder cancer incidence among workers with potential exposure to ortho-toluidine (*o*-toluidine), aniline, and other chemicals and attributed this excess to *o*-toluidine. The authors did not discuss the inconsistency of their results with a prior mortality study of workers exposed to these chemicals (2). There are alternative plausible hypotheses for the bladder cancer findings: 1) the aniline used at the plant during the 1950s and 1960s may have contained the bladder carcinogen 2-naphthylamine or 2) an amine carcinogen may have been produced in the process. These possibilities merit careful evaluation of the evidence for causality regarding *o*-toluidine or aniline versus alternative hypotheses.

Only two published epidemiologic studies are relevant. The first (3), cited by Ward et al. (1), found one bladder cancer death versus 0.84 expected for the "aniline only" subcohort. [Ward et al. (1) gave 0.54 expected.] In a more pertinent study, Ott and Langner (2) studied 342 organic dye workers who had used aniline and *o*-toluidine in separate batch processes from 1914-1958. Mortality follow-up covered 1940-1976. Given the presumed exposure levels in this early process, if either of the two amines were potent carcinogens, one would have expected substantial mortality from bladder cancer. Yet, there were no bladder cancer deaths versus a total of 1.5 expected (95% confidence interval = 0-2.5). Five-year bladder cancer survival was 42% for 1940 to 1949 (4), increasing to 73% by 1976 (5).

We detail one alternative hypothesis: 2-naphthylamine and possibly 2-amino-fluorene were present as aniline impur-

ities in quantities sufficient to produce bladder cancer. This hypothesis results from considering the source of aniline in the 1950s and evaluating whether likely impurities are known human bladder carcinogens (6). This hypothesis also fits the concentration of bladder cancer among workers employed soon after start-up of antioxidant production in 1957 [cf. "definitely exposed" cases in Table 1 (1)].

Production at that plant began during a transition in the manufacture of benzene—the key raw material for aniline. In 1955, about 65% of benzene in the United States was a byproduct of coke from coal (7); by 1975, more than 90% came from petroleum (8). Commercial aniline includes impurities originating in benzene. Benzene produced as a byproduct of coal included quantities of naphthalene, fluorene, and other aromatic hydrocarbons (8), whereas petroleum-derived benzene lacked these impurities. During aniline production (9), these impurities would have been converted to the corresponding aromatic amines (i.e., 2-naphthylamine and 2-aminofluorene). Exposure to aniline impurities would have occurred wherever there was aniline exposure. However, because of the switchover in benzene production, exposures to these impurities would have declined with time, and cancer risk should manifest a corresponding decline.

This hypothesis can be tested. Aniline could be made using the methods of the 1950s and then could be analyzed for impurities. Further, extension of the study of Ward et al. (1) prospectively should demonstrate that the bladder cancer excess is restricted to workers employed in the early years of antioxidant production. Finally, ongoing epidemiologic studies by our company and other companies of *o*-toluidine or aniline workers will provide further insight into the proposed association of these chemicals with bladder cancer.

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## Response

Acquavella et al. cite the results of two prior mortality studies of workers exposed to aniline (1) and aniline and *o*-toluidine (2) as inconsistent with our results of excess bladder tumor incidence among workers exposed to *o*-toluidine and aniline (3). It has been our experience that using mortality as an end point in studying occupational bladder cancer is likely to yield falsely negative results. For example, in the population described in our report (3), none of the 15 incident bladder cancer case patients has died with bladder cancer as the underlying cause of death. In prior National Institute for Occupational Safety and Health (NIOSH) studies of workers exposed to beta-naphthylamine, 13 bladder cancers versus 3.3 expected (standardized incidence ratio = 3.9; 95% confidence interval = 2.2-6.8) were ob-

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served in an incidence study (4), whereas a mortality study of the same population found only two bladder cancer deaths observed and 0.7 expected (standardized mortality ratio = 2.9; 95% confidence interval = 0.35-10.3) (5). Thus, in the NIOSH studies of *o*-toluidine and aniline (3) and betanaphthylamine (4,5), only the incidence studies were able to adequately detect the increased risk of bladder cancer. The mortality studies (1,2) mentioned by Acquavella et al. had inadequate statistical power to assess bladder cancer mortality. Based on the data in Table 2 of the mortality study by Case et al. (1), the total number of expected deaths was actually 0.54 for the class "Aniline without magenta contact," thus yielding 80% statistical power to detect only a 7.2-fold excess of bladder cancer deaths. The total number of expected deaths from malignant neoplasms of urinary organs in the study by Ott and Langner (2) was 1.5, yielding 80% statistical power to detect only a 4.1-fold excess of bladder cancer deaths. Moreover, approximately 70% of the workers studied by Ott and Langner were potentially exposed to aniline and/or *o*-toluidine for under 5 years, while the excess bladder cancer risk observed in our study was concentrated among workers exposed for 10 or more years. Thus, neither of these studies provides strong negative evidence about the carcinogenicity of aniline and/or *o*-toluidine in humans.

Acquavella et al. also advance the hypothesis that the bladder cancer excess resulted from impurities in aniline that were present because the aniline was manufactured from coal-derived benzene. We have contacted many of the companies that supplied aniline to the study plant, as well as other industry sources. Some of the suppliers state that they used petroleum-derived benzene as early as the 1940s, while others used both coal-derived benzene and petroleum-derived benzene through the 1960s. However, a major producer of coal-derived benzene during the 1940s through 1960s states that its coal-derived benzene was processed to 99.9% purity, with 0.1% of trace aliphatics.

Acquavella et al. cite a Stanford Research Institute document (6) as evidence for the presence of naphthalene and fluorene in coal-derived benzene. We found no such information about benzene contamination in this document. The document does report the high level of naphthalene relative to the level of benzene in coal tar. The higher the naphthalene-to-benzene ratio, the greater the potential for naphthalene contamination in benzene distilled from coal tar. But given the low level of total impurities (0.1%), the vast majority of the impurities are likely to be compounds whose volatility is more similar to that of benzene, such as some aliphatics, toluene, or xylenes. The boiling point of naphthalene is 138 °C higher than that of benzene. Moreover, purification of the crude aniline would remove even further traces of impurities derived from naphthalene or fluorene. Technical specifications from the study plant, as far back as 1955, require that the aniline purchased have a minimum purity of 99.8%. Company records also indicate that, in 1962, an analysis of aniline obtained from three suppliers found even lower levels of impurities, less than 500 ppm, in each sample.

Given the carcinogenicity of *o*-toluidine in experimental animals and the relatively low probability of significant contamination of even that portion of the aniline used at the plant that was derived from coal tar products, we believe that the alternative hypothesis proposed by Acquavella et al. to explain the bladder cancer excess at this plant is an unlikely one.

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## Proliferation Rate in Hereditary Nonpolyposis Colon Cancer

We have read with great interest the study by Lynch et al. (1), in which the rectal epithelial proliferation rate has been re-evaluated in a Native-American family with hereditary nonpolyposis colon cancer (HNPCC) 7 years after initial proliferation measurements by Lipkin et al. (2). Labeling indices were found for the laboratory involved to be in the normal range, i.e., less than 10%, with the exception of one patient, in whom colonic cancer meanwhile had developed. Lynch et al. suggested that this unexpected finding might be due to a prevailing low-risk diet or lifestyle in this family.

Another explanation might be that the rectum is not the optimal site for the in-

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