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Re: Monitoring of Aromatic Amine Exposures in Workers at a Chemical Plant With a Known Bladder Cancer Excess

In 1991, investigators from the National Institute for Occupational Safety and Health (NIOSH) (*1*) reported a correlation between *o*-toluidine and aniline exposure and an increased incidence of bladder cancer. Letters published in the Journal (*2-4*) identified deficiencies and inaccuracies in the study. The recent article by investigators from NIOSH (*5*) continues the inaccurate portrayal of *o*-toluidine and aniline as human bladder carcinogens.

The bladder cancers were diagnosed in the early 1980s. Since the latent period between exposure and tumor expression averages about 20 years, NIOSH should have examined worker exposure to chemicals used in the early 1960s, but it did not do so. The article (*5*) states, "There were insufficient historical data to characterize exposures at the plant 10-30 years ago, the time period most relevant to the development of industrially related bladder cancers, which have a latent period . . . averaging 20 years. . . ." Therefore, NIOSH admits it has no knowledge of the specific chemicals to which the affected workers were exposed. NIOSH also admits that exposures 10-30 years ago are most relevant to causation but ignores historical exposure information.

There is documentation that workers were exposed in the 1950s and early 1960s to diphenylamine. Diphenylamine often contained 4-aminobiphenyl, a known human bladder carcinogen (*6*). NIOSH admits the possibility of exposure to 4-aminobiphenyl from contact with process chemicals but dismisses 4-aminobiphenyl as a causative agent.

Donald Sherman, M.D., Corporate Medical Director for the affected plant, informed NIOSH that 4-aminobiphenyl was present in the plant from 1957 to mid-1966. He stated that no worker with a start date after 1966 has developed bladder cancer. Dr. Sherman states, "We have believed all along that aniline and *o*-toluidine did not cause the cancers in the Niagara Falls plant. . . . The exposures to aniline and *o*-toluidine from 1966 to the late 1970s did not change significantly, based upon process design and configuration. If *o*-toluidine was the real culprit . . . would we not have seen more bladder cancers? . . . We believe the probable cause was 4-aminobiphenyl. . . ." (Sherman DJ: personal communication to Ward JM, May 23, 1996). This confirmation that workers with bladder cancer were exposed to 4-aminobiphenyl invalidates the conclusions of the NIOSH study that used exposure data from the late 1980s.

NIOSH reported workplace air concentrations of 187 and 412 $\mu g/m^3$ for aniline and *o*-toluidine, respectively, orders of magnitude below the Occupational Safety and Health Administration Permissible Exposure Limits (PELs) of 8000 and 22000 $\mu g/m^3$ and the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs) of 7600 and 8800 $\mu g/m^3$, the concentrations to which workers can be exposed 8 hours per day, 5 days per week, for 30 years without adverse health effects. Furthermore, in 1996, the ACGIH downgraded the classification of aniline and *o*-toluidine from "suspected human carcinogen" to "animal carcinogen." NIOSH apparently refutes the validity of TLVs and PELs as universally accepted safe exposure levels.

There are no data in Ward et al. (*5*) that support the NIOSH conclusion that ". . . occupational exposure to *o*-toluidine is the most likely cause of the bladder cancer excess observed among workers in the . . . plant under study. . . ."

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Ward et al. (*1*) recently presented the results of biologic monitoring of workers for aromatic amine exposure in a chemical plant. They concluded that exposure to *o*-toluidine is the most likely cause of the excess numbers of bladder cancers found in the study population and noted that exposure to aniline cannot be ruled out as a potential cause. This article follows an earlier study in which they found an excess of bladder cancer at the plant (*2*).

Several articles (*3-8*) have linked source of drinking water, total fluid intake, water disinfection methods, or exposure to chlorinated surface water with bladder cancer. Four of these articles (*5-8*) were published before Ward et al.

published their original study of plant workers. Of particular interest is the article published in 1993 by Vena et al. (*3*), which describes a clear dose-related increased incidence of bladder cancer in western New York State and links the increase to total fluid intake (of tap water in particular). The plant studied by Ward et al. is located in the same area. Have they considered the effect of water source and intake in their conclusions related to bladder cancer incidence in the worker population studied?

ELLEN R. STEPHENS

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The First Mississippi Corporation manufactures *o*-toluidine and aniline.

Response

We have published responses (*1,2*) in this Journal to earlier letters (*3,4*) regarding our study of excess bladder cancers in a chemical-manufacturing plant (*5*). To summarize our earlier responses, *o*-toluidine, which has induced bladder tumors in rats (*2*), is used in quantities of 7.2 million pounds per year in the manufacture of an antioxidant at the plant. 4-Aminobiphenyl, which Dr. Freudenthal and Mr. Anderson claim is the cause of the bladder cancers, was present at less than 1 part per million in three of nine current bulk samples of process chemicals used at that plant. Furthermore, average levels of adducts to 4-aminobiphenyl do not differ between workers employed in the department where the antioxidant is manufactured and unexposed control subjects (*6*). We believe that 4-aminobiphenyl levels in the past would not be orders of magnitude greater than what they are currently (*1*). Therefore, the weight of the evidence favors *o*-toluidine as the major etiologic agent in the bladder cancer excess.

Freudenthal and Anderson state, "There is documentation that workers were exposed in the 1950s and early 1960s to diphenylamine. Diphenylamine often contains 4-aminophenyl." However, as we have stated before (*2*), our review of historical plant records indicated that diphenylamine was an additive to a product that was manufactured intermittently from 1972 to 1985. Freudenthal and Anderson incorrectly quote Donald Sherman, M.D., Corporate Medical Director for the affected plant, when they state that he informed NIOSH that 4-aminobiphenyl was present in the plant from 1957 to mid-1966. What Dr. Sherman did say in a letter dated May 23, 1996, to NIOSH was, "We postulate that something else occurred in the Niagara Falls plant process between start-up in 1957 and the mid-1960s that was responsible for the bladder cancers in our workers. We believe that the probable cause was 4-aminobiphenyl, created in the early process at levels which initiated the cancers but were later reduced by operational changes in the '60s and '70s. We cannot state that conclusively, as there are no exposure data from that period, but we believe it to be a more plausible hypothesis."

Freudenthal and Anderson also state that no bladder cancers have been observed among workers who started after 1966. Table 1 in (*5*) clearly shows that three workers with bladder cancer began their employment in the exposed jobs after 1966. Even if the risk of bladder cancer was lower among employees hired after 1966, it could not be concluded that the bladder cancer excess was based on a contaminant in the process. Reduced risk might also be related to lower exposure to *o*-toluidine and aniline resulting from process controls.

Our conclusion that the bladder cancer excess was most likely related to *o*-toluidine exposure does not refute "the validity of TLVs [Threshold Limit Values] and PELs [Permissible Exposure Limits] as universally accepted safe exposure levels," as stated by Freudenthal and Anderson. There are no air-sampling data available prior to 1975, the time period when most individuals with bladder cancer started work in the antioxidant department, so we cannot associate the bladder cancer excess with specific levels of exposure to aniline and *o*-toluidine. Secondly, TLVs and PELs are based on research data and may change on the basis of new information.

Freudenthal and Anderson state that "in 1996, the ACGIH [American Conference of Governmental Industrial Hygienists] downgraded the classification of aniline and *o*-toluidine from 'suspected human carcinogen' to 'animal carcinogen' " (*7-9*). The reclassification is of limited practical significance, as ACGIH recommends that "for A2 and A3 carcinogens, worker exposure by all routes should be carefully controlled to levels as low as possible below the TLV" (*9*).

Dr. Stephens asks whether we have taken into account studies that have associated source of drinking water with bladder cancer. The study she quotes (*10*) does not report an increased incidence of bladder cancer in western New York; rather it compares risk factors between bladder cancer case patients and residents of the same neighborhood. Intake of total fluids and daily cups of tap water consumed were associated with bladder cancer; the odds ratio was 3.38 for the highest quartile of fluid con-

sumption. In our study of workers employed at the chemical plant (*5*), the 753 individuals who never worked in the antioxidant department did not have an increased risk of bladder cancer compared with other residents of New York State (two observed bladder cancers versus 1.43 expected) and those exposed to the antioxidant department had over a sixfold increase (seven observed versus 1.08 expected). There is no reason to believe that workers in the antioxidant department had different exposures to drinking water than workers in the unexposed department, nor would even a moderate difference in drinking water consumption account for a bladder cancer excess of this magnitude.

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Note

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A Hidden Paradox in Carcinogenesis Bioassays

The suitability of preclinical studies has sound implications on the toxicologic risk of drugs or environmental pollutants both during the subsequent clinical investigation and during marketing. Unfortunately, data from long-term carcinogenicity tests often give rise to limited or equivocal evidence of carcinogenicity.

Inasmuch as the procedures for chemical risk assessment used by the U.S. Environmental Protection Agency (EPA) have been criticized for many years and for many reasons, we wish to point out to the scientific community an overlooked but paradoxical aspect of assessment procedures that we only recently discovered.

Most standard risk-assessment experiments expose rodents to large doses of a test chemical for about 2 years (i.e., the natural life-span of the rodent). These animals, generally Sprague-Dawley rats, Fischer rats, or (C57BL/6 × C3H)F_1 mice (hereafter called B6C3F_1), have a higher natural incidence of tumors than humans, and this incidence has also changed with time (*1*) (i.e., spontaneous liver tumors in B6C3F_1 mice increased from an average of 32% to about 50% in less than 10 years). The body weight of adult rodents has increased from 20% to 30%; degenerative diseases and tumor incidence also have increased, whereas survival has dramatically decreased. For example, at the Merck Research Laboratory (Rahway, NJ) (*1*) in the 1970s, the survival rate of control Sprague-Dawley rats at age 2 years was 58%; in the 1980s, it was 44%; in the 1990s, it has dropped to 24%.

Even though the recently emphasized (*2,3*) role of excess weight on the health and longevity of humans or rodents (fed ad libitum) is unquestionable, we would like to bring up the question of food constituents, which can contribute to the great tumor-expression variability of tests in various laboratories (i.e., from 10% to 76% in the male B6C3F_1 mice). Indeed, most standardized diet formulations that we received from numerous laboratories around the world that were conducting cancer research experiments contain the well-known mutagenic/carcinogenic element manganese (*4-6*) at the same level and, in some cases, at an even higher level (up to ninefold) compared to that used to study the carcinogenicity of manganese itself (*7*). The optimal dietary intake (*8*) of manganese for laboratory animals should not exceed 0.35 mg/day (0.74 mg/day for humans, who have a slower metabolism than rodents). In other words, the animal diet should contain no more than 45 mg/kg of this element per weight of the chow.

To increase the reliability of long-term bioassays, the EPA should simply establish protocols in which animal diet constituents should be more carefully considered to avoid invalidating cancer bioassays.

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