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Bladder Cancer in Workers Exposed to Aniline

In their very interesting study of bladder cancer in workers exposed to aniline and ortho-toluidine (*o*-toluidine), Ward et al. (*1*) conclude that "contamination by 4-aminobiphenyl is an unlikely cause of the excess number of bladder cancer cases because 4-aminobiphenyl levels were so low in the bulk samples analyzed by NIOSH." This conclusion is unwarranted in the absence of specific exposure data on individuals in the factory.

4-Aminobiphenyl is the most potent known experimental bladder carcinogen and also the most potent known human bladder carcinogen (*2*). Our studies on smoking and bladder cancer provide strong evidence that 4-aminobiphenyl is a causative agent (*3,4*), although it may also be a surrogate for other aromatic amines in cigarette smoke (*5*).

The ratios of hemoglobin adducts for *o*-toluidine and 4-aminobiphenyl in smokers and non-smokers indicate comparable levels of exposure to the hydroxylamine formed from each compound (*3*). *o*-Toluidine adducts are approximately a factor of two higher than 4-aminobiphenyl in smokers, but the biological potency of 4-aminobiphenyl is at least thousands of times greater. In fact, *o*-toluidine must be fed at levels of g/kg body weight to show evidence of carcinogenicity in the mouse (*6*), while doses of 1 mg per mouse per week were sufficient to cause bladder tumors with 4-aminobiphenyl (*7*). Therefore, I suspect that even trace levels of 4-aminobiphenyl are potentially extremely hazardous.

Why is this important? If 4-aminobiphenyl is indeed the culprit in chemical plants using aniline and aniline derivatives, then appropriate controls and biomonitoring may have an important preventive action. It is almost impossible to prevent 4-aminobiphenyl formation from aniline, and air monitoring will not reveal contaminated surfaces. Therefore, only personal monitoring (testing of blood or urine) will reveal a cryptic exposure.

Ward et al. suggest from their study that aniline and *o*-toluidine are risk factors for bladder cancer in smokers. Cigarette smoke contains several aromatic amine carcinogens more potent than *o*-toluidine, including 4-aminobiphenyl, 3-aminobiphenyl, and 2-naphthylamine. In my opinion, the combined evidence would favor 4-aminobiphenyl as the causative agent in both smoking and occupational exposure.

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Response

Ortho-toluidine (*o*-toluidine) is a carcinogen in both mice and rats and has induced bladder tumors in rats in two experiments (*1-4*). *o*-Toluidine is used in quantities of 7.2 million pounds per year as one of the starting materials in the manufacture of an anti-oxidant at the chemical plant investigated in our study (*5*). *o*-Toluidine was present in air samples at a mean level of 418 $\mu g/m^3$ in the anti-oxidant department and was present in post-shift urine samples of workers at a mean level of approximately 100 μg/L, which is about 40 times greater than the mean level among unexposed workers at the same plant (*6*). 4-Aminobiphenyl was present in trace amounts (less than 1 ppm) in three of nine current bulk samples of process chemicals. Although the exact level of historical contamination cannot be quantitatively determined, based on information from chemical suppliers, company process chemists, and review of the literature, we believe that 4-aminobiphenyl levels present in feedstocks or formed in the process stream in the past would not be orders of magnitude greater than they are currently. Dr. Tannenbaum believes that trace contamination with 4-aminobiphenyl is more likely to account for the 6.5-fold bladder cancer excess among workers in the anti-oxidant department than exposure to *o*-toluidine itself. He bases his conclusion on an assertion that 4-aminobiphenyl is "thousands of times" more potent than *o*-toluidine, but neither his letter nor his references explain this calculation. Assessing the relative potency of carcinogens in animals and extrapolating to human health effects is a difficult undertaking. Gold et al. (*7,8*) have attempted to compare the carcinogenic potencies of these and other carcinogens, using a consistent procedure to estimate the 50% effect dose (TD_{50}) for various tumor sites. Table 1 lists TD_{50}s for the most sensitive site for 4-aminobiphenyl and *o*-toluidine bioassays which were evaluated by Gold et al.

Evidence for extreme potency of 4-aminobiphenyl in mice, which was suggested in Dr. Tannenbaum's letter, is apparently based on studies by Clayson et al. (*9,12*). A comparison of the carcinogenic potencies of 4-aminobiphenyl and *o*-toluidine, based on data from Clayson et al. for 4-aminobiphenyl, would yield a ratio of TD_{50}s of 759:1 (Table 1). However, the TD_{50} of 4-

Table 1. Comparison of potency estimates calculated by Gold et al. based on rodent bioassays of 4-aminobiphenyl and *o*-toluidine

Chemical	Sex and species	Strain	Route	TD_{50},* mg/kg per d	Ratio† 4-amino-biphenyl:*o*-toluidine	Reference No.
4-Aminobiphenyl	Female mouse	(C57 × IF)F_1	Gavage in arachis oil	0.993	759	(*9*)
4-Aminobiphenyl HCl	Male mouse	BALB/c	Drinking water	32.6	23.1	(*10*)
4-Aminobiphenyl HCl	Female rat	Sprague-Dawley	Gavage in emulphor	0.897	26.0	(*11*)
o-Toluidine HCl	Female mouse	(C57BL/6 × C3H)F_1	Feed	754		(*4*)
o-Toluidine HCl	Male rat	Fischer 344	Feed	23.3		(*4*)

*TD_{50}s calculated by Gold et al (*7,8*).
†Calculated by authors by taking the ratio of TD_{50}s of 4-aminobiphenyl:*o*-toluidine in the same species.

aminobiphenyl derived from the Clayson et al. data contrasts sharply with the 33-fold lower potency reported in the more recent and more extensive drinking water study of Schieferstein et al. (*10*). Use of the Schieferstein et al. data for 4-aminobiphenyl results in a mouse TD_{50} ratio of 23:1. The analysis by Gold et al., based on the best available rat bioassay for 4-aminobiphenyl by Tanaka et al. (*11*), suggests that in the rat, 4-aminobiphenyl is 26 times more potent than *o*-toluidine.

The above comparisons of the ratio of the TD_{50} of 4-aminobiphenyl to that of *o*-toluidine ignore differences in animal strains and sexes, routes and duration of exposure, numbers of animals, and sites of tumorigenesis. Therefore, it is not entirely clear which represents the "best" estimate of the ratio of carcinogenic potencies. Even if the actual TD_{50} ratio were known with perfect accuracy, the issues of low-dose extrapolation and animal-to-human extrapolation would still complicate any attempt to apply the animal bioassay data to quantitative estimates of human risk. Estimating the range of 4-aminobiphenyl:*o*-toluidine exposure in the past is also difficult. Information on the level of 4-aminobiphenyl contamination in feedstocks such as aniline is very limited (*13*), and the levels of 4-aminobiphenyl in present bulk samples may not reflect the extent of 4-aminobiphenyl formation in the past. We continue to seek additional documentation on historical 4-aminobiphenyl levels and are evaluating the feasibility of analyzing blood and urine samples of current workers to confirm that 4-aminobiphenyl levels among workers in the anti-oxidant department are similar to levels in unexposed workers. We nonetheless believe that the weight of available evidence favors *o*-toluidine as the major etiologic agent in this bladder cancer excess. Based on this study and reviews of human and animal data in the literature, the National Institute for Occupational Safety and Health has concluded that *o*-toluidine is a potential occupational carcinogen, as defined in the OSHA carcinogen policy (29 CFR 1990) (*14*).

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Investment in Cancer Research Pays Off for Other Diseases

I have read with considerable interest your "News" article "Investment in Cancer Research Pays Off for Other Diseases," and I certainly concur with its conclusion (i.e., "the cross-feeding

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