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RESPONSE TO "CASE STUDY 'CARCINOGENS': THE MBOCA TLV EXAMPLE"

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The study conducted by Ward et al.[1,2] was initiated by a request from the Michigan Department of Public Health (MDPH) to the National Institute for Occupational Safety and Health (NIOSH) to investigate bladder cancer incidence among workers at a plant in southern Michigan that had manufactured MBOCA from 1968 through 1979. The MDPH had documented extensive exposure to MBOCA both within the study plant and in the surrounding community and was concerned about the potential effects on workers.[3,4] NIOSH investigators visited the plant in 1981, and collected information about the MBOCA process and potential exposures, as well as the characteristics of the workforce. We determined that this was not an ideal cohort for an epidemiologic study to determine the carcinogenicity of MBOCA.[2] However, we proceeded with a study of bladder cancer incidence because there was evidence that plant workers may have been heavily exposed, and we wished to address the public health concerns raised by the MDPH.[2] Although we recognized that a study at the plant would be unlikely to yield definitive information about the carcinogenicity of MBOCA, we could not identify any other U.S. cohorts that would be more appropriate for an epidemiologic study. The results of the study have been presented in two publications.[1,2]

The major criticism of the study raised by Dr. Hogan was that the exposure characterization was "inadequate and incompletely reported." At the time we began the study, we requested from company management a list of all chemicals used or produced at the facility along with an estimate of the time period and the amount. We were informed by the company president that the company made many products on a short-term or pilot scale and did not have records adequate to compile the information requested. The information provided by the company was limited and gave no evidence that any of the well-accepted human bladder carcinogens (such as benzidine, betanaphthalamine, or 4-aminobiphenyl) had been used or produced at the plant. We believe that these compounds represent the major potential confounding exposure in studies of occupational bladder cancer, as they have been associated with bladder cancer risks on the order of 10-fold or greater.[5,6]

An important part of the exposure assessment, which was omitted from Dr. Hogan's discussion, was a review of data collected by the MDPH, which included urinary MBOCA concentrations among employees of the chemical plant as well as environmental sampling both in the plant itself and the surrounding community.[3,4] The urinary MBOCA concentrations ranged as high as 59 000 μg/L, and surface sampling revealed contamination with MBOCA throughout the plant.[3] MBOCA contamination in the community surrounding the plant was so extensive that the area has been declared a Superfund site.[7] An additional aspect of the exposure assessment by NIOSH investigators was to review the toxicity data on MBOCA, which has been summarized elsewhere.[4,8]

Dr. Hogan mentions a number of chemicals "present" in the plant as putative risk factors for bladder cancer without providing information on the time periods and quantities, or potential for worker exposure to these chemicals. He also does not describe the criteria by which he has classified chemicals as potential bladder carcinogens, nor does he provide a thorough and systematic review of the literature to support his judgments. For example, Dr. Hogan states that "All workers with MBOCA exposure also were exposed to one of its raw ingredients, formaldehyde, which has been implicated as a cause of bladder cancer in human epidemiologic studies."[9] Three review articles, including the article cited by Dr. Hogan,[9] either conclude that there is no epidemiologic evidence for an association between formaldehyde exposure and bladder cancer[9,10] or do not even mention this cancer site.[11] In fact, the article cited by Dr. Hogan reported a meta-analysis yielding a combined relative risk estimate for bladder cancer of 1.0 for studies of professional workers and 1.1 for studies of industrial workers.[9] All three review articles implicate the upper respiratory tract as the most likely site for a potential carcinogenic effect of formaldehyde. Dr. Hogan also cites the presence of polybrominated biphenyls (PBBs), stating that "One animal study found a bladder tumor after short-term dosages of PBBs."[12] However, a single tumor in an animal bioassay is not usually considered a significant finding, and two recent review articles provide no indication that PBBs are potential bladder carcinogens in either animals or humans.[13,14]

Of some concern is the information provided by Dr. Hogan that 4,4'-methylenedianiline, 4-chloro ortho-toluidine (4-COT), aniline, and ortho-toluidine (OD) were used at the study plant. 4,4'-methylenedianiline is an animal carcinogen[15] that has been suspected of being a human bladder carcinogen,[16] and recent evidence has associated 4-COT,[17,18] aniline, and OT[19] exposure with high increased risks of bladder cancer in occupationally exposed populations. These chemicals were not identified in our previous reviews of material safety data sheets and CAS numbers of trade name products produced by the company. Since these compounds are the most likely significant confounders identified by Dr. Hogan, it would be useful to know how they were identified (i.e., were they starting products, intermediates, or end products; what processes were they used or generated in; and in what years and quantities were they estimated to be present?).

In summary, while we acknowledge that the NIOSH study included only a limited assessment of other chemicals present at the facility, our efforts were limited by the lack of company records from which to determine whether these other chemicals presented a significant risk of exposure. Dr. Hogan's assessment lacks information on quantities and time periods during which chemicals were used and categorizes chemical substances present at the plant as potential bladder carcinogens based on minimal or highly selected data. The case histories for the three individuals with bladder tumors provided by Dr. Hogan do not add substantial information to their case histories as presented in our original articles, nor do the histories identify important bladder cancer risk factors other than MBOCA exposure. Thus, while Dr. Hogan's article raises criticisms of the exposure assessment in our study, it does not provide an adequate alternative.

We did not conclude, as implied by Dr. Hogan, that our study confirmed MBOCA as a human carcinogen. As was discussed in the two published articles regarding the study, the interpretation of the results was limited by the absence of a comparison population. The bladder tumors were detected by cystoscopy in three individuals who did not have clinical symptoms of a bladder tumor. The appropriate comparison population would be individuals in a similar age range who had cystoscopy in the absence of any clinical symptoms or known increased risk of bladder cancer. It would be unethical, because of the risks of the procedure, to subject individuals to cystoscopy solely to obtain background prevalence data, and we were unable to find data on tumor prevalence in a comparable population in the literature. Thus, it was impossible to calculate the number of tumors expected and develop a quantitative estimate of the risk and its statistical significance. However, based on the low incidence of clinically apparent bladder tumors in young men, the strong animal evidence of MBOCA's carcinogenicity, and the structural similarity between MBOCA and other aromatic amines known to induce human bladder cancer, we concluded that our findings of our study were "consistent with the hypothesis that MBOCA induces bladder neoplasms in humans."[1]

Based on the evidence of oncogenic results in three animal test species, NIOSH recommended in 1978 that MBOCA be treated as a potential human carcinogen.[20] The data from our study reinforce the importance of treating MBOCA as a potential occupational carcinogen.

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