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**Letter to the Editor**

# Re: Response to Criticisms of "Lung Cancer Case-Control Study of Beryllium Workers" Am. J. Ind. Med. 2001. 39:133–144.

## To the Editor:

Dr. David Deubner et al. have criticized our nested case-control study of the association between beryllium exposure and lung cancer [Sanderson et al., 2001a]. In this study, we estimated the beryllium exposures of workers in a beryllium alloy production plant from the 1940s through the 1970s in order to conduct an exposure-response analysis. A manuscript describing how these exposure estimates were determined was published as a companion paper [Sanderson et al., 2001b]. The following are our responses to these criticisms.

"*It is disappointing to observe that the paper constitutes a biased presentation of the material presented in Sanderson's doctoral thesis*".

Response: We do not believe the paper constitutes a biased presentation of the material presented in Sanderson's doctoral thesis [Sanderson, 1997]. The doctoral thesis contains 63 tables of data, from which the most pertinent data were extracted. The published articles reflect the emphasis and conclusions of the research presented in the doctoral dissertation.

"*It is doubtful whether the objective of the authors to estimate the relationship between exposure and lung cancer is possible because of the lack of exposure data relevant to the very short work tenures of over 63% of cases hired before 1945*."

Response: We acknowledged in the manuscript that uncertainty about the exposure estimates was a limitation of the study, particularly because of the absence of quantitative exposure information before 1947, when many of the cases and controls were first hired. Exposure estimates for the early 1940s were assumed to be equivalent to exposures in the late 1940s. However, the retrospective exposure assessment was based on over 7000 measurements from the late 1940s through the 1970s, as well as a careful reconstruction of plant history and process changes, as described in the accompanying article [Sanderson et al., 2001b]. Any misclassification of exposure in the early 1940s is likely to be nondifferential, as a virtually identical proportion of cases and controls (62.7% of cases and 62.8% of controls) were hired prior to 1945.

"*Furthermore, it is probably unwise to draw conclusions from these short term, war-time workers when nothing else is known about the circumstances of their lives or of other exposures*."

Response: It is true that the majority of the cases and controls were short-term, war-time workers and nothing else is known about their other exposures during the remainder of their lives. However, it is not clear how this might result in the observed association between higher levels of beryllium exposure and lung cancer. Moreover, it is plausible that short-term, high-level exposure to beryllium could result in lung cancer or other chronic effects due to long term retention of beryllium particles in the lung.

"*The study is unusual in that a nested case-control design was undertaken after a retrospective study base had already been investigated through a historical cohort design [Ward et al., 1992]. Given the superiority of cohort studies over case-control investigations, . . .*"

Response: The allegation that our study is unusual, because we utilized a nested case-control design after a retrospective study had been conducted [Ward et al., 1992], is perplexing. All nested case-control studies are undertaken, by definition, after cohort studies. In our case, this design was an efficient option because detailed work histories had not been computerized for all workers in the original cohort (n = 3569). Furthermore, cohort designs are not inherently superior to case-control investigations; in general, well designed case-control studies will give the same answer as well-designed cohort studies. These basic

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points are well described in introductory epidemiology textbooks, including one coauthored by Dr. Trichopoulos [McMahon and Trichopoulos, 1996], who is a coauthor of the letter by Deubner et al.

"*Nowhere in their paper do the authors report data presented in the thesis showing that among people hired after* 1/1/1950 *in the Reading plant there were, if anything, fewer cases of lung cancer than would have been expected...*"

Response: Sanderson's dissertation included four additional years of cohort mortality follow-up beyond Ward's original cohort study. For workers hired before 1950, the lung cancer SMR was 1.30 (95% CI 1.07–1.57); the SMR was similar for workers hired between 1950 and 1960 (SMR 1.25; 95% CI 0.85–1.78); while for workers hired after 1960, it was 0.23 (95% CI 0.03–0.84). Among the possible explanations for the significantly decreased SMR for workers hired in the 1960s are lower beryllium exposure and shorter latency.

"*The method of selecting controls introduced a serious bias that strongly influences the outcome of the analysis.*"

Response: Five controls per case were selected by matching on the age attained by the case at the time of death, having worked at the plant, and race. Incidence density sampling, with age at the index case's death as the matching or time variable for forming risk sets, and subsequent selection of a sample from the risk set (five controls for each case in our study) is standard practice in nested case-control studies. It does not create a bias; nor does it inherently mean that the age of hire of cases will differ from controls. The fact that cases had more exposure after a 20-year lag is likely due to the fact that beryllium causes lung cancer, not any bias from study design. Again, a basic presentation of incidence density sampling in nested case-control studies can be found in McMahon and Trichopoulos, [1996].

"*This paper does nothing to refute the suspicion that confounding by acid mists and vapors was responsible, at least in part, for the alleged association between beryllium exposure and lung cancer risk.*"

Response: There is no basis for this suspicion at the study plant. Unlike the sulfate extraction process used at other beryllium plants, the plant under study (located in Reading, Pennsylvania) used a fluoride extraction process to remove beryllium from the ore [Breslin, 1966]. Sulfuric acid was not used at the Reading plant, and with the exception of a few workers who pickled beryllium alloy products in nitric acid baths (5.6% of cases vs. 8.9% of controls), workers were not exposed to acid mists.

Substantial exposures to fluorides did occur at the Reading plant and the potential confounding effects of fluorides are discussed in the manuscript. Fluoride exposure was highly correlated with beryllium exposure levels. However, there is very limited toxicological evidence that fluorides are carcinogenic, but there is strong toxicological evidence that beryllium is carcinogenic in animals [Groth et al., 1980a; Groth, 1980b]. This supports the argument that increased cancer risk seen in this plant population would more likely be due to beryllium exposures than fluoride exposures.

"*It is particularly disturbing that these authors have chosen to ignore direct information concerning tobacco smoking that is available for a subsample of cases and controls.*"

We considered the sample size of 9 cases and 68 controls with smoking data too small to directly evaluate confounding by smoking of the beryllium exposure-lung cancer relationship in our study which included 142 cases and 710 controls. We therefore looked at the issue indirectly. Using smoking data from a USPHS study conducted in 1968 on 368 members of the 3569 person cohort, we evaluated whether smoking could have confounded the association between beryllium exposure levels and lung cancer risk. Confounding requires, by definition, an association between the confounder and the exposure of interest, as well as an association between the confounder and disease. Indeed, there was an apparent association between cumulative exposure and smoking among these 368 men with smoking data. However, this was due to the inclusion in this group of professionals (white collar workers) who had low beryllium exposure and a low prevalence of current and former smokers. We showed that after stratifying on professional status (white collar and blue collar), there was no association between smoking and level of beryllium exposure, so that smoking was unlikely to act as a confounder within strata of professionals or non-professionals. About 10% of the cohort were professionals. Case control analyses of just the blue-collar workers found virtually the same results as analyses of all cases and controls.

Duebner et al. suggest a different approach to estimate confounding by smoking. They rely on smoking data for the 9 cases and 68 controls for which smoking data are available (out of 142 cases and 710 controls). They proceed to note that among these cases and controls smoking is associated with lung cancer, even providing a *P*-value. They follow this unsurprising result by a calculation purporting to show the degree of confounding of the beryllium-lung cancer association to be expected due to confounding by smoking in our case-control study; they calculate a confounding "relative risk" of 1.43. However, in this calculation, there is no reference to exposure status without which no effect of confounding can be calculated. We suspect they were seeking to calculate the likely effect of confounding by smoking on the observed exposure-disease association [Greenland, 1987; Axelson and Steenland, 1988], but misunderstood the method.

*Overall conclusion: "In summary we believe that the study design, matching methodology, and analytic methods employed in this study are fatally flawed and have led the* *authors to an erroneous conclusion on the relation of beryllium exposure and lung cancer risk in this population."*

Response: We respond that the methods employed in both the retrospective exposure assessment and the case-control study are standard and well accepted by experts in the fields of industrial hygiene and epidemiology. We appreciate the opportunity to address the criticisms by Duebner et al. and remain confident in our original conclusions regarding beryllium exposure and lung cancer risk.

Sincerely,
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