

Letters to the Editor

RE: "BENZENE AND LEUKEMIA: A REVIEW OF THE LITERATURE AND A RISK ASSESSMENT"

In their recent paper, Austin et al. (1) conclude that: "In the aggregate, the epidemiologic evidence suggests a link between benzene and leukemia" (1, p. 428). Although we hold the opinion that Austin et al. are unnecessarily tentative in this conclusion, we concur with it. We are concerned, however, by several aspects of their review, and particularly by their discussion of epidemiologic risk assessment. Austin et al. criticize our group for having used a risk assessment model based on a nested case-control study. They suggest that in our estimate of the likelihood of leukemia in persons exposed to benzene we should instead have used data based on a stratification of person-years from our entire cohort; indeed, Austin et al. utilize such an approach in their own risk assessment.

We consider their criticism of our approach to have several shortcomings. One problem is that the exposure categories in a standardized mortality ratio (SMR) analysis are inherently arbitrary; variation in the definitions of the boundaries of these categories can have a profound effect on the calculated risks. This effect is especially likely to be evident when there are few deaths.

By contrast, the case-control approach to risk assessment provides an elegant means for modeling cumulative exposure with the use of an internal comparison group. This is a more appropriate referent group than the United States population and is far less disparate in terms of their general health. Also, in a study of an industrial population, such as our cohort, which might have encountered toxic occupational exposures other than benzene, the case-control approach provides an opportunity to balance out those exposures; both cases and controls should have had equal likelihood for exposure to other materials, such as solvents, as well as for prior exposure to benzene in areas of the factories outside the departments under study. Finally, it has been demonstrated (2) that risk assessment using a properly chosen sample of controls will result in estimates of risk that are nearly identical to those which result from use of the full cohort, and this approach is much more cost efficient than risk assessment based on the full cohort.

Austin et al. (1) have attempted to utilize our SMR analysis, which divides the cohort into four categories of cumulative benzene exposure, and to use the mid-points of these categories to estimate leukemia risk. This methodology is not optimal. Because the person-year distribution in each category is highly skewed to the lower exposure, a more appropriate procedure would have been to use the person-years weighted average exposure for each category. With such an approach, Austin et al. would have obtained a risk estimate closer to ours.

A final point in the review by Austin et al. (1) with which we take issue is their dismissal of the possible etiologic association between benzene and hematopoietic malignancies other than acute monoclonogenous leukemia. Two studies cited by Austin—Arp et al. (3) and Checkoway et al. (4)—found elevated relative risks for mortality from lymphocytic leukemia. However, Austin et al. dismiss those findings as "not persuasive" or as possibly due to exposures to "solvents" other than benzene. Austin et al. do not consider the possible etiologic association between benzene and lymphoma. Three recent epidemiologic studies—our own analysis (5) and those by Wong (6) and DeCoulle et al. (7)—have, however, found excess mortality from multiple myeloma and other forms of lymphoma in persons exposed to benzene. Wong (6) argues that mortality from leukemia and lymphoma should not be considered separately in populations exposed to benzene, because of the diagnostic overlap between the two categories of disease, the well known transition or progression of many lymphomas into leukemia and the poor concordance between histopathologic and either immunologic or cytogenetic classification schemes. We suggest that a formal assessment of the possible etiologic association between benzene and lymphoma is required.

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THE AUTHORS REPLY

In a recent Letter to the Editor of the *New England Journal of Medicine* (1) pertaining to a risk assessment by Rinsky et al. (2), we identified a discrepancy between the standardized mortality ratios (SMRs) they estimated and the results of a nested case-control study they did on the same cohort of pliofilm workers. We also pointed out that their use of the nested case-control analysis was inefficient because benzene exposures had been estimated for all cohort members and therefore there was no reason for restricting their risk assessment to nine leukemia cases and 90 controls. We also noted in this letter and in our review article (3) that Rinsky's risk assessment result was considerably higher than all others, including ours.

We agree with Rinsky et al. (4) that a nested case-control study should yield results nearly identical to those of a full cohort analysis of the same data set. Indeed, this is the reason we were surprised that their SMR and case-control analyses were so disparate. Their letter implies erroneously that we believe that the risk assessment should have been based on their SMRs. Although we did use the SMRs, we did so because SMRs were the only results available on the entire cohort. Cox's proportional hazards model (5), or other suitable methodology, should have been used to analyze the complete cohort. Rinsky et al. contend that their case-control study is "elegant" because 1) it allows for modelling of cumulative exposure while controlling for potential confounders, 2) it permits evaluation of effect modification, and 3) an internal comparison group can be used. However, these objectives could have been achieved more efficiently by appropriate analysis of the complete cohort study. It is not "elegant" to discard information needlessly.

We requested that either an analysis of the full cohort be reported or that an explanation be provided as to why the analysis was restricted to a subset of the cohort (1). Neither was provided (6). Instead, they contend that our SMR analysis would have yielded a risk assessment result closer to what they obtained in the case-control study if we had used different scores for the exposure categories. This point is largely irrelevant and certainly is not an adequate explanation for the disparity between the results of the cohort and case-control analyses. Furthermore, the contention is not substantiated with data, although such data could have been provided easily by Rinsky et al.

Our review evaluated several case-control studies of leukemia among rubber workers. Two studies reported a positive relation between benzene and lymphocytic leukemia (7, 8). However, the relative risks pertaining to other solvents in both studies were nearly identical to those for benzene. We pointed out that the investigators of one of these studies also

expressed the concern that the association between benzene and lymphocytic leukemia may have been confounded by other solvents (8). The International Agency for Research on Cancer also has recently stated that "mixed exposure patterns" in these case-control studies has rendered interpretation of the studies difficult (9). Thus, Rinsky et al.'s apparent acceptance of a causal relation between benzene and lymphocytic leukemia is credulous; we are not surprised that they judge our consideration of this issue as "cavalier."

We did not evaluate the epidemiologic data pertaining to benzene and malignant neoplasms of lymphatic and hematopoietic tissue, other than leukemia, nor did we include these malignancies in our risk assessment. The three studies cited in Rinsky's letter include only the three from these other malignant neoplasms with about 11.8 expected (SMR = 136, 95 per cent confidence interval 77-220). Such a weak and imprecise association does not warrant being included in a risk assessment. Their other arguments for including these other malignancies also are not compelling. We point out that Rinsky et al. did not include these other malignancies in their own risk assessment (2).

Infante (a coauthor of Rinsky's on the original report on the pliofilm cohort (10)) and DiStasio have recently discussed benzene and leukemia (11), and in so doing, they used a risk assessment result nearly identical to ours. They state that their estimate of the effect of benzene on leukemia mortality is similar to that of most others accepted by the Occupational Safety and Health Administration. Rinsky et al.'s risk assessment yields a result four times as high. It is our belief, and apparently that of most others, that Rinsky et al.'s risk assessment result is too high and cannot be used.

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RE: 'MORTALITY OF LEAD SMELTER WORKERS'

The provocative account by Selevan et al. (1) of the epidemiologic relation existing between exposure of smelter workers to lead and the manner of their fatal issue well documents one of the most common sources of plumbum. Those engrossed in the fields of forensic medicine and pathology have, on occasion, become aware of another, albeit unusual, encounter with this element.

Over 100 years ago, a case was described of a man who had received a gunshot wound to the knee and who succumbed 12 years later with symptomatology closely mimicking chronic lead intoxication (2). Since then, there have been numerous reports of similar cases, all having in common the long tissue retention of lead missiles, mostly in and around the large joints of the extremities (3). Recent clinical evaluation of some has revealed hematologic findings of anemia, reticulocytosis, and basophilic stippling of red blood cells, all consistent with lead poisoning. Elevations of blood lead levels up to 5 µg/dl are recorded. The normal level is less than 0.6 µg/dl.

Clinical findings relating to chronic nephritis and acute renal failure are often present together with lead encephalopathy, the precipitating cause of death. The latter is marked anatomically by cerebral swelling, uncal herniation, and brain stem hemorrhages (4, 5). The hepatocytes and renal tubular cells revealed characteristic intranuclear inclusions. The respiratory system is not primarily affected in these instances because the silica of quarried ~~is~~ is not expressly related with the gunshot.

Of great relevance to the hazard of retained lead is the epidemiology of clinical lead toxicity. Lead bullets, striking dense bone of an extremity, are frequently fragmented. The pieces may enter into the joint space where they are exposed to synovial fluid that possesses the ability to dissolve lead, slowly, but consistently

(6). The solubilized lead ions are absorbed through the thin walls of capillaries which invade into the area of injury during the phase of inflammatory repair. Some of these vessels persist for long periods. Thus, over an extended time, small amounts of lead leave the embedded missile and enter the circulation, to travel widely within the body and reach distant vulnerable organs such as the kidney and brain. The resultant clinical and pathologic alterations may, over a span of years, become as devastating as those observed in the organs of lead smelter workers.

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Editor's note: Dr. Selevan and his co-authors were given the opportunity to respond to this letter, according to Journal policy, but chose not to do so.

RE: 'CONFOUNDING CONFOUNDING'

In a recent article, Grayson (1) argued that a definition of confounding based on change in a parameter's value upon covariate control (noncollapsibility) was fundamental. We think that both Grayson's description of the problem and his conclusion are seriously in error. There are four major reasons for these errors: First, Grayson failed to distinguish effect measures from parameters that do not measure effects.

Second, like several earlier authors (2), Grayson failed to recognize that an odds ratio can be an unbiased measure of effect even if it is not collapsible (i.e., even if the crude odds ratio differs from the stratum-specific odds ratios). Third, Grayson failed to recognize that, in causal inference, "confounding" can be viewed as a more fundamental concept than "confounder". Fourth, Grayson failed to note that ignoring noncom-