Benzene Exposure and Leukemia

To the Editor:

In their recent nested case-control study of benzene exposure and lymphohematopoietic cancer, Glass et al.[1] concluded that an excess leukemia risk was found at lower benzene exposures than previously reported, with no evidence of an exposure threshold. I want to offer additional comments on these data, developed while working with the authors as a study advisor.

The authors acknowledge that the reported relative risks are higher than those in similar case-control studies.[2,3] These results are also higher than those found in more highly exposed cohorts[4–6] used in risk assessments. For example, 11- and 98-fold risks are reported for >8 and >16 ppm-years, respectively. More perplexing are the reported 4- to 6-fold risks at >1 ppm-year (ie, 0.02 ppm over a working career). These results imply that either the study has detected high risks from exposures below existing standards or that risks have been overestimated.

Table 3 of the Glass paper[1] shows that the baseline exposure category (≤1 ppm-year) contains 35% of controls and 33% of non-Hodgkin lymphoma/multiple myeloma (NHL/MM) cases, but only 9% of leukemia cases. A critical question is whether 9% (3 cases) represents a valid baseline, because, aside from matching factors, odds ratios (ORs) depend on the case/control ratio in the baseline group. Aside from chance (which cannot be excluded), at least 3 issues are germane to this question: the consistency of these data with the parent cohort study and the wider literature, recall bias, and cutpoint bias.

This study's parent cohort[7] can be used as one way to estimate the number of leukemia cases expected in the baseline exposure group. Gun et al.[7] report 19.5 expected leukemias and 42.3 expected NHL/MM cases, for a ratio of 0.46. A similar ratio would be expected in the case-control study's baseline category, because the matching factor (age) is similar in the 2 groups (see Table 1). Instead, the 3 leukemias and 15 NHL/MM cases yield a ratio of 0.20. The cohort leukemia/(NHL/MM) ratio of 0.46 would predict that 7 cases of leukemia should occur in the baseline group in the case-control study. The cohort also experienced 27 leukemias, an absolute excess of 7.5 cases, further arguing against an unprecedented effect of benzene in these workers.

If leukemia cases or their surrogates preferentially recall benzene exposure, migration of cases from the baseline to higher-exposure groups could result. Glass and colleagues[1] suggest that the effect of recall bias should be small and could not account for the reported benzene/leukemia associations, but this bias could have exaggerated the exposure–risk relationship and hidden an exposure threshold. Although I agree with this observation to some extent, it is important to note that use of narrow cell boundaries could magnify the potential for recall bias and could explain moderately elevated ORs, especially in the lower-exposure categories.

There is also some evidence of "cutpoint bias," ie, different categorical boundaries yielding disparate trends. For example, category boundaries in Table 2 produce unadjusted ORs of 1.0, 4.9, 5.5, 2.2, 5.2, and 18.9, similar to the adjusted ORs depicted in Figure 1. Yet, the boundaries used in Table 6 produce unadjusted ORs of 1.0, 0.7, and 2.9, which conveys a different interpretation of risks at low concentrations.

In summary, although Glass et al.[1] present evidence of a relationship between benzene and leukemia, particularly at higher-exposure categories, the low occurrence of leukemia in the baseline group hinders a stronger interpretation of the study. The feasibility of conducting a collective analysis of similar studies of petroleum workers might be a means of providing further insight on the risk of lower benzene concentrations.

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REFERENCES

1. Glass DC, Gray CN, Jolley DJ, et al. Leukemia risk associated with low-level benzene exposure. *Epidemiology*. 2003;14:569–577.
2. Rushton L, Romaniuk H. A case-control study to investigate the risk of leukemia associated with exposure to benzene in petroleum marketing and distribution workers in the United Kingdom. *Occup Environ Med*. 1996;54:152–166.
3. Schnatter AR, Armstrong TW, Nicolich MJ, et al. Lymphohematopoietic malignancies and quantitative estimates of exposure to benzene in Canadian petroleum distribution workers. *Occup Environ Med*. 1996;53:773–781.
4. Rinsky RA, Hornung RW, Silver SR, et al. Benzene exposure and hematopoietic mortality: A long-term epidemiologic risk assessment. *Am J Ind Med*. 2002;42:474–480.
5. Collins JJ, Ireland B, Buckley CF, et al. Lymphohaematopoietic cancer mortality among workers with benzene exposure. *Occup Environ Med*. 2003;60:676–679.
6. Bond GG, McLaren EA, Baldwin CL, et al. An update of mortality among chemical workers exposed to benzene. *Br J Ind Med*. 1986;43:685–691.
7. Gun RT, Pratt NL, Griffith EC, et al. Update of a prospective study of mortality and cancer incidence in the Australian petroleum industry. *Occup Environ Med*. 2004; in press.

To the Editor:

Surveillance bias could potentially create a major flaw in the study by Glass et al.[1] reported in the September 2003 issue of EPIDEMIOLOGY. In a nested case-control study of workers in Australian petroleum refineries, the authors reported an excess total leukemia incidence in association with cumulative lifetime benzene exposure levels as low as >2–4 parts per million (ppm)-years.

However, conditional logistic regression analysis of the association of leukemia subtype with the lowest level of

Editors' note: *The author states, "For the record, I am a consultant on toxic tort cases involving benzene, for both plaintiff and defense."*

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cumulative benzene exposure in this analysis (>4–8 ppm-years) showed an odds ratio (OR) of only 0.52 (95% confidence interval = 0.05–5.0) for acute nonlymphocytic leukemia, the form of leukemia most commonly related to benzene exposure. In contrast, at these low benzene levels, the OR for chronic lymphatic leukemia was 2.76 (0.42–18.1). This suggests that much of the effect reported at the lowest benzene levels may have been the result of chronic lymphatic leukemia, a disease that has not been shown conclusively to be caused by benzene. This subtype accounted for 11 of the 33 leukemia cases in the study.

The potential flaw is that case discovery of chronic lymphatic leukemia is often inadvertent—found with a routine blood count for an unrelated condition. The average life expectancy for a case of this leukemia subtype diagnosed solely on the basis of blood findings is more than 12 years, with long periods in which the disease is likely to go undetected. In contrast, for acute nonlymphocytic leukemia, life expectancy is less than 1 year and disease manifestations occur rapidly. The usual practice at refineries in much of the world is to do routine blood count surveillance on those workers who are more heavily exposed to benzene, but not the entire workforce. Glass et al. report that all employees except head office personnel were part of their study. If, in fact, blood counts were only performed on those workers at the refineries who were more heavily exposed to benzene, it is likely that the cases of chronic lymphatic leukemia would have been preferentially chosen from workers with higher exposures. Because the controls would be from the entire workforce (including those who, in the absence of surveillance, could have an undiagnosed case of early chronic lymphocytic leukemia), this surveillance bias might account for the unusually low levels of benzene exposure associated with leukemia. Information responsive to the possibility of surveillance bias is needed to evaluate the potential significance of the findings reported by Glass and colleagues.

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The authors respond:

We are grateful for the opportunity to reply to the recent correspondence.

We agree with Dr. Schnatter[1] that the exposure–risk relationship is subject to considerable uncertainty, particularly because the baseline group contains only 3 cases. However, we do not believe that our results are inconsistent with the parent cohort, which has an excess of leukemia but not of non-Hodgkin lymphoma (NHL) or multiple myeloma (MM).[2–4]

The observed ratio of leukemia to NHL/MM in the lowest benzene exposure category was lower than the ratio for the whole cohort, but this would be expected if leukemia is related to exposure; more cases would appear in the higher exposure groups.

The risk of leukemia appeared higher and was associated with lower benzene exposures than in previous studies. A partial explanation could be that our study was of cancer incidence and so not directly comparable to previous mortality studies. Mortality risk is less than incidence in the parent HealthWatch cohort.[5] Exposures have been low in the Australian petroleum industry, based on its own hygiene data. We believe our exposure estimates were more reliable than those of other similar studies because they were for subjects in a recent cohort using detailed, complete job histories.[6,7]

We do not believe that recall bias explains the greatly elevated odds ratios. Exposure was estimated from job histories collected largely prospectively during the cohort study and checked against company records. We used standardized job-specific proformas to interview workers; interviewers were unaware of case status and obtained task descriptions carried out by anonymous subjects. If recall bias had occurred, NHL and MM would also have appeared associated with benzene exposure.

Dr. Schnatter highlights the finding of an elevated risk at >1 parts per million (ppm)-year. He used an assumed exposure period of employment of 40 years to estimate a working lifetime average exposure of 0.02 ppm. This is inappropriate, because the mean duration of employment was 20 years (range, 5–40 years). We calculated the risk associated with intensity of highest exposed job in ppm and these data are in our paper.

We discussed the sensitivity of odds ratios to the cutpoints used. Our cutpoints were chosen using 2 predetermined methods of dividing the subjects into groups: by quintile of cumulative exposure for unmatched analyses (not reported in our paper, for brevity, but included in the report on the Australian Petroleum Industry web site[8]) and by exposure-doubling groups for matched analyses. We reported the latter because it was exposure-based and matched. The strong increase in risk in the highest group was clear, unambiguous, and consistent in these analyses.

We acknowledge that the baseline group had few cases. We examined the effect of moving 2 leukemia cases from a higher exposed group to the lowest exposed group and of combining the 2 lowest exposure groups. The association was weaker but still present in the highest exposed group (>16 ppm-years).

In response to Dr. Goldstein,[9] we do not believe that ascertainment bias

can explain the association between leukemia and benzene exposure. We know 4 companies undertook blood screening, usually as part of regular voluntary medicals, but company medical officers do not know of any cases of leukemia identified in this way (Petroleum Company Medical Officer, personal communication, 2004).

We thank both correspondents for their interest in our paper. We believe that our study has demonstrated that the excess risk of leukemia observed in the HealthWatch cohort is associated with exposure to low concentrations of benzene. The precise risk estimates that are calculated do vary with cutpoint. A more precise understanding of any threshold of risk will depend on studies that have larger numbers of cases and controls with well-defined job histories and good estimates of exposure. We support the call for a study of pooled petroleum industry data.

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REFERENCES

1. Schnatter AR. Benzene exposure and leukemia [Letter]. *Epidemiology*. 2004;15:509.
2. Bisby JA, Adams GG. *HealthWatch Ninth Report*. Melbourne: The University of Melbourne Department of Community Medicine; 1993.
3. Bisby JA, Adams GG. *HealthWatch Tenth Report*. Melbourne: The University of Melbourne Department of Public Health and Community Medicine; 1999.
4. Gun RT, et al. *HealthWatch Eleventh Report*. Adelaide: Department of Public Health, Adelaide University; 2000.
5. Gun RT, Pratt NL, Griffith EC, et al. Update of a prospective study of mortality and cancer incidence in the Australian petroleum industry. *Occup Environ Med*. 2004;61:150–156.
6. Glass DC, Adams GG, Manuell RW, et al. Retrospective exposure assessment for benzene in the Australian Petroleum Industry. *Ann Occup Hyg*. 2000;44:301–320.
7. Glass DC, Gray CN, Adams GG, et al. Validation of exposure estimation for benzene in the Australian Petroleum Industry. *Toxicol Ind Health*. 2001;17:113–127.
8. *Lympho-haematopoetic Cancer and Exposure to Benzene in the Australian Petroleum Industry June 2001*. Report to Australian Institute of Petroleum. Available at: http://www.aip.com.au/health/ohs.htm.
9. Goldstein B. Benzene exposure and leukemia [Letter]. *Epidemiology*. 2004;15:509–510.