Risk of Lymphohematopoietic Malignancies in Uranium Miners

Řericha et al. (2006) analyzed data from Czech uranium miners with respect to incidence of malignancies of the lymphohematopoietic system. Their results, however, do not correspond with those of two recent studies on German uranium miners (Kreuzer et al. 2004; Möhner et al. 2006). Řericha et al. (2006) used a case–cohort design, in which the subcohort was stratified by attained age and duration of employment. Stratification by age is a standard approach in case–cohort studies to optimize data ascertainiment in the subcohort. However, stratification by duration of employment is problematic, because in occupational epidemiology it should be assumed that the duration of employment is highly correlated with cumulative exposure. Therefore, this kind of stratification contradicts the general demand for a random selection of controls with respect to exposure under study. Comparing the ratios of sampling fractions (<12 months vs. ≥12 months duration of employment) between age groups results in a heterogeneous picture (Table 1).

It is not uncommon in occupational cohort studies to include only subjects with a duration of employment of at least a certain number of months into the cohort. An analysis of only those miners with an employment duration of at least 12 months would be in line not only with the standard methodology but also with earlier published results of the authors (Řericha et al. 1998). Hence, the authors should have at least explained their reasoning for including the remaining miners in a second set of strata. In addition, they should have presented separate results for both duration strata to validate the result of the combined analysis.

| Age (years) | RR sampling fractions | IRR |
|-------------|-----------------------|-----|
| 19–35       | 0.52 (0.40–0.69)       | 1.06 (0.47–2.61) |
| 36–45       | 1.11 (0.91–1.37)       | 0.56 (0.27–1.19) |
| 46–55       | 1.16 (1.00–1.34)       | 1.08 (0.63–1.95) |
| 56–65       | 1.54 (1.21–2.00)       | 7.16 |
| (118–292.75) |                       |     |
| 66–90       | 1.24 (0.77–2.07)       | 0.29 (0.05–1.99) |
| M-H combined | 1.09 (0.99–1.20)       | 1.00 (0.71–1.41) |

Homogeneity test: p = 0.000

Given the above-mentioned assumption concerning the relationship between duration of employment and cumulative exposure, I calculated crude incidence rate ratios using data from Table 1 of Řericha et al. (2006). The age-specific odds ratios cover a wide range (0.29–7.16), and a corresponding test yields only borderline homogeneity. Consequently, completeness of matching with the cancer registry needs to be discussed.

According to the study design, the time period between last exposure and begin of follow-up can span up to 27 years; therefore, the healthy-worker survivor effect could be an important issue in this study (Řericha et al. 2006). In light of the discussion on the magnitude of the latency period for leukemia, more detailed results would be useful to get an impression on, for example, the effect of the year of last exposure.

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Lymphohematopoietic Malignancies in Uranium Miners: Kulich et al. Respond

We read with interest the comments by Möhner regarding the analysis and interpretation of the case–cohort study of Czech uranium miners (Řericha et al. 2006). He noted that our results do not agree with two recent German studies that also investigated the link between leukemia and radiation exposure in uranium miners. Kreuzer et al. (2004) conducted a mortality study based on death certificates (although combined with autopsy records) and reported standardized mortality ratios. As noted in our article (Řericha et al. 2006), studies relying on vital statistics underestimate the incidence of cancers such as chronic lymphocytic leukemia (CLL), which are not rapidly fatal or systematically diagnosed. For example, compare our 84 leukemia cases to the 95 cases reported by Kreuzer et al. (2004) that were based on a total follow-up period that was more than 4 times longer. The incidence rates or age differences between Czech and German miners cannot be that different. Möhner et al. (2006) published a well-designed, matched case–control study of cancer incidence with a large number of cases. Their reported results from grouped analyses and excess relative risk models indicated some elevated risk for CLL, which does not conflict with our conclusions. The lack of statistical significance can be explained by the relatively poor power of grouped analyses compared with the non-grouped Cox model we applied. Another important point that can explain seemingly conflicting results of different studies is the high sensitivity of the results to measurement error in exposures. A study that uses less precise estimates of radiation exposures is less likely to identify an existing exposure effect. This affects leukemia analyses more than lung cancer analyses because the effect of radon on lung cancer is much stronger and more difficult to miss.

In his letter, Möhner mentioned several other issues that need clarification. First, is stratification by duration of employment problematic, given the strong association of this variable with exposure? In fact, as shown, for example, by Borgan et al. (2000) and Kulich and Lin (2004), stratification on variables correlated with exposure is always highly desirable because it can substantially increase the precision of the analysis at little cost. As long as a correct procedure for estimating parameters from stratified samples is used, the estimates are valid and their standard errors are reduced. Stratification by age is a similar case; in these data, age is also strongly related to exposure.

The reasoning for including miners who worked <12 months was that they represent a natural comparison group with low exposures. Many occupational studies exclude workers with short employment periods [Kreuzer et al. (2006) included those with ≥6 months exposure]. Both approaches have pros and cons. Including miners with short working periods may increase power and is relevant when the primary interest is to compare incidences at high exposures with those at low exposures. In contrast, miners who left their jobs early may have done so because of health reasons, which could induce a healthy-worker effect. We decided to include all miners before the
data were analyzed, and we presented the planned analysis in our article (Řericha et al. 2006). We did a separate analysis of miners who worked > 12 months underground and found generally stronger radiation effects on incidence. For example, for CLL the estimated relative risks comparing 110 working level months (WLM) to 3 WLM would be 3.13 [95% confidence interval (CI), 1.22–8.08; \( p = 0.02 \)] based on 39 cases and 1,596 subcohort subjects. The CI was wide but the conclusion was not changed.

The odds ratios (ORs) in Möhner’s Table 1 would look less extreme if the last three groups were combined. The OR of 7.16 is based on a single case and the OR of 0.29 is based on three cases. Hence, the alleged heterogeneity does not look very convincing to us. Finally, the issue of latency period and late follow-up was addressed by separate analyses based on time since exposure. As we reported (Řericha et al. 2006), exposures acquired > 25 years ago had no noticeable effect on current incidence, whereas the most recent exposures (2–15 years ago) showed the strongest association.

In conclusion, we believe that our study (Řericha et al. 2006) offers the important advantage of having included incident cases and that the analysis was appropriate. The conclusions of the study do not depend on whether or not the analyses are restricted to miners with longer working periods.

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Ozone and Semen Quality
Sokol et al. (2006) reported an inverse association between environmental ozone and sperm concentration. They performed longitudinal analyses of > 5,000 semen samples from 48 semen donors over a 2-year period and concluded that exposure to average O₃ levels in the range of 20 ppb adversely affect semen quality.

Sokol et al. (2006) did not discuss available evidence on this issue from the occupational arena. Welding of metals with gas shielding of the weld, for example, tungsten inert gas (TIG) and metal inert gas (MIG) welding, confers an exposure to O₃ that may reach a concentration of 400–600 ppb in the welder’s breathing zone (Korczynski 2000). In three cross-sectional semen studies and one longitudinal study, lower sperm counts were not reported among TIG and/or MIG welders compared with appropriate reference groups of nonwelding metal workers (Bonde 1990a, 1990b; Hjollund et al. 1998; Jelnes and Knudsen 1988).

The O₃ exposure levels are some 20 times higher among the welders than among the residents in Los Angeles, California. Moreover, the environmental O₃ measurements in Los Angeles performed outdoors, and indoor levels may be considerably lower. O₃ is generated by ultraviolet radiation of oxygen and has a short half-life. Therefore, it can be assumed that the exposure of citizens is highly influenced by the time spent outdoors, which were not accounted for by Sokol et al. (2006). Could the weak associations they observed in their environmental study be artifacts of complex statistical analyses? In all circumstances, it seems too early to conclude that O₃ alters semen quality.

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Ozone and Semen Quality: Berhane and Sokol Respond
We thank Bonde for his interest in our article (Sokol et al. 2006) and for drawing to our attention the literature on the effects of the welding occupation on male fertility. Although we agree with Bonde that the findings in the occupational studies he cited, for the most part, do not show a correlation between welding and abnormal semen parameters, one of his studies does report such an association (Bonde 1990), as does an article by Mortenson (1988). We find these data intriguing and puzzling, but we also would like to make the following points.

First, our study (Sokol et al. 2006) was population based and hence not directly comparable to the occupational studies.

Although our study directly investigated the effects of ozone, albeit from the ambient point of view and not via personal monitoring of exposure, the evidence from the occupational studies (Bonde 1990; Mortenson 1988) is an indirect and implied one. In these studies, direct O₃ exposure information is not provided. In one of the negative studies (Hjollund et al. 1998), no differences in urine concentrations for the trace metals associated with welding were detected between welders and nonwelders, suggesting that “the negative results could be due to generally low exposure of the study base” (Hjollund et al. 1998).

The longitudinal design of our study (Sokol et al. 2006) gave us the opportunity to examine within-subject (over time) effects of O₃ on male fertility in a sample that guarantees validity of the asymptotic inferences we made from the data.

The modeling techniques we used in the analysis have become fairly standard in analysis of longitudinal data such as ours; these techniques properly account for the within-subject correlation in the repeated measures for each subject. It is very unlikely that the O₃ findings are artifacts of our modeling approach.

Finally, we carefully examined the potential confounding effects of weather, seasonality, and long-term time trends, and the O₃ findings were robust to their inclusion in the models. Moreover, the O₃ effects were robust to inclusion of other pollutants in the model.
That said, we readily acknowledge the excellent point that Bonde raised with respect to indoor–outdoor ratio of O₃ exposure and possible misclassification of exposure due to the ambient nature of our exposure assignment. Ideally, we would have liked to assign direct personal exposure values or use a microenvironmental model (Navidi and Lurman 1995) to assign personal exposure values according to time–activity patterns, but this was not possible because of the retrospective nature of our study. However, we believe that the longitudinal design of our study (Sokol et al. 2006) gives us more confidence in the results, assuming consistent within-subject time–activity patterns.

We hope that future research will replicate our study (Sokol et al. 2006) in other locations around the world, preferably allowing for personal monitoring of exposure. We also hope that occupational studies will focus on direct assessment of O₃ exposure to allow for direct comparisons with population-based studies whenever possible. Finally, we acknowledge that our epidemiologic findings of strong associations only add to the evidence in support of O₃ effects on male fertility and but do not necessarily show causation.

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(Hu et al. 2006) that if one focuses on the individual trimesters in order to examine the question of the greatest window of vulnerability during gestation, the impact of first trimester fetal lead exposure appears to be greater than the impacts of the other trimesters. Moreover, the increase in the variance explained by the model with bone lead compared with the model without bone lead is modest ($R^2$ values of 0.24 vs. 0.22 when the analysis is restricted to the 113 subjects with bone lead), which translates into a relatively minor improvement in the scattered nature of the points.

In our view, rather than denoting the continued absence of a superior biomarker of lead burden, the scattered nature of the points reflects the general challenge of studying a relationship in which all predictors are measured with a substantial amount of random error; no doubt, there are many other predictors of MDI that remain completely unmeasured (e.g., genetics, nutrition, other potential neurotoxicants). Future studies may be able to improve scatter by improving such measures (and increasing study sample sizes) while, of course, public health measures are hopefully taken to continue reductions in population levels of lead exposure.

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**ERRATUM**

The November 2006 Focus article “Fertile Grounds for Inquiry: Environmental Effects on Human Reproduction” [Environ Health Perspect 114:A644–A649 (2006)] contains a potentially misleading typo on page A646. The National Survey on Family Growth defined fertility as a married woman being able, not unable, to become pregnant within 12 months. EHP regrets the error.