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Risk of Lymphohematopoietic Malignancies in Uranium Miners

Řeřicha 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). Řeřicha 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 ascertainment 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 (Řeřicha 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.

Table 1. Rate ratios (RRs) of sampling fractions and incidence rate ratios (IRRs) for lymphohematopoietic malignancies (95% confidence intervals), calculated from Rericha et al. (2006).

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
(1.18–292.75)		
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	$p = 0.000$	$p = 0.055$

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 Řeřicha 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 (Řeřicha 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 (Řeřicha 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 (Řeřicha 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 (Řeřicha 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 (Řeřicha 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 (Řeřicha 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 ambient O_3 levels in the range of 20 ppb adversely effect 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 O_3 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 O_3 exposure levels are some 20 times higher among the welders than among the residents in Los Angeles, California. Moreover, the environmental O_3 measurements in Los Angeles performed outdoors, and indoor levels may be considerably lower. O_3 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 O_3 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 O_3 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 O_3 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 O_3 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 O_3 findings were robust to their inclusion in the models. Moreover, the O_3 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 O_3 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 O_3 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 O_3 effects on male fertility and but do not necessarily show causation.

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Fetal Lead Exposure and Infant Mental Development Index

All of the authors of Ronchetti et al. (2006) read with great interest the article of Hu et al. (2006); their excellent experimental data fully supports the hypotheses and conclusions we reported in an our recent literature review on lead neurotoxicity in children (Ronchetti et al. 2006). Hu et al. (2006) show that in predicting the loss of mental development index (MDI) in 2-year-old children, the plasma lead level is better than the whole blood lead level, and measurements made in the first trimester of pregnancy are better than measures obtained later in pregnancy or in cord blood.

One issue that remains unexplained, however, is the enormous scatter of the individual points around the correlation line between plasma lead concentrations and the MDI. Equally wide scatter also emerges in the similar figure reported by Canfield et al. (2003). This finding suggests that plasma lead concentrations (or whole blood lead levels used by Canfield et al.) are not the direct determinants of lead neurotoxicity and that the relationship between lead concentrations measured in blood and the decrease in MDI are significantly influenced by other biological factors (Mushak 1998).

Lead is dissolved in a circular river (blood circulation); every day the river is contaminated by a relatively small affluent (daily lead intake) and purified by some effluents (excretion). however, it is in contact and is heavily influenced by a large lake (long-term bone stores), which can be heavily contaminated. The lead contamination in the lake slowly but continuously influences the lead concentration in the river, and thereby tends to contaminate all the other small lakes (body tissues and organs including brain) with which the river comes in contact. As long as we continue to measure the lead concentration in the river, we will have a proxy variable to define the real situation in the body and in the brain.

This scenario engenders concepts that are important in understanding and preventing lead neurotoxicity. First, when women born after lead was removed from gasoline become mothers, they will be persons whose "big lake" is less contaminated. Second, as Hu et al. (2006) stated, even at the present time we have the means (e.g., calcium supplementation from the beginning of the pregnancy) to close some of the gates between the big lake and the river (we can at least partially avoid maternal bone lead mobilization during pregnancy).

From a scientific point of view, we could understand lead toxicology far better and also plan more effective preventive interventions if we include the measure of bone lead concentrations in mothers and children in epidemiologic studies.

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Infant Mental Development Index: Hu et al. Respond

We thank Ronchetti for his comments on our recent article (Hu et al. 2006). We are aware of what he noted was the wide scatter of points surrounding the correlation line of plasma lead in relation to mental development index (MDI) score. Ronchetti suggests that the scatter might improve if one measured the "lake" of maternal lead burden (in this case, maternal bone lead) as opposed to sampling the "river" of maternal lead represented by lead in maternal venous blood, since the "lake" is presumably the ultimate source of maternal circulating lead and therefore fetal lead exposure. We are quite aware of (and have been a proponent of) this line of reasoning (Hu et al. 1998). Our article (Hu et al. 2006) is just one in a series of reports stemming from a long-running birth cohort study in which we do, in fact, have maternal bone lead measurements (measured noninvasively using K-X-ray fluorescence). In separate analyses we have examined maternal bone lead as an independent predictor of MDI, as well as other outcomes (e.g., Gomaa et al. 2002; Gonzalez-Cossio et al. 1997; Hernandez-Avila et al. 2002; Sanin et al. 2001).

In our study (Hu et al. 2006), our major focus was on comparing the relative contributions of each trimester of lead exposure to fetal neurodevelopment, and we did not include maternal bone lead in our models. If we force maternal tibia lead in the model of first trimester maternal plasma lead and MDI, tibia lead is an independent and significant predictor of lowered MDI and the effect of first trimester plasma lead is attenuated [Table 1; note that the smaller sample size of 113 subjects, compared with 119 subjects in Table 2 of Hu et al. (2006), is due to the smaller number of mothers with bone lead measurements]. This provides some support for maternal bone lead as the best biological marker for predicting lead's impact on fetal neurodevelopment; however, it does not detract from our observation

Table 1. Multivariate model of MDI of offspring (at 24 months of age) using both maternal plasma lead during the first trimester and maternal bone lead (measured in the perinatal period) as markers of prenatal lead exposure ($n = 113$).

Variable	β	*p*-Value
Tibia lead (μg/g)	–0.22	0.03
Maternal plasma lead (μg/L)[a]	–0.97	0.59
Current blood lead (μg/dL)[b]	–0.050	0.22
Sex[c]	2.89	0.18
Mother's IQ	0.035	0.68
Mother's age (years)	0.68	< 0.01
Height-for-age *z*-score	2.16	0.12
Current weight (kg)	–2.27	0.02
Intercept	97.96	0.00

Total model $R = 0.24$.
[a]Measured during the first trimester; log-transformed. [b]Measured at 2 years of age. [c]Male = 1; female = 2.

(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.