

2. Budnick LD, Finkel A. Medical examinations and appeals for NJ public service workers. *New Jersey Medicine*. 2001;98:39–43.
3. Cocchiarella L, Anderson GBJ (eds). *Guides to the Evaluation of Permanent Impairment*, fifth edition. Chicago: American Medical Association; 2001;2–9.
4. Budnick LD. Firefighter with amputation – follow-up. Available at: <http://lists.unc.edu/read/messages?id=3783599>. Accessed February 22, 2007.
5. US Department of Commerce. The economic consequences of firefighter injuries and their prevention. Final report. NIST GCR 05–874. August 2004;ii:45.
6. Centers for Disease Control and Prevention. Fatalities among volunteer and career firefighters – United States, 1994–2004. *MMWR*. 2006;55:453–455.

DOI: 10.1097/JOM.0b013e318093f49b

Re: Exposure to Beryllium and Occurrence of Lung Cancer: A Reexamination of Findings From a Nested Case-Control Study

To the Editor: We read with interest the recent reanalysis conducted by Levy and colleagues¹ of a case-control study by Sanderson and colleagues.² The authors' interpretation of their reanalysis is that it casts doubt on the purported association between beryllium and lung cancer, observed in the original analyses.²

We believe the reanalysis by Levy and colleagues contains several methodological problems that call into question this reinterpretation of the original study. Our concern centers around three main points in their reanalysis: 1) their rejection of log-transformation of the exposure variable; 2) the assertion that the older average age at death of controls (compared with cases) is problematic in incidence-density sampled cohorts; and 3) the validity of their analysis matching controls to within 3 years of the date of death or last observation. We also offer an alternative explanation for their observation that cases were hired 4 years younger, on average, than were controls.

Regarding the first issue, Levy et al imply that a log transform of the

independent variable in the regression analysis was conducted in the original study to improve its normality. We concur that normality of the independent variable is irrelevant. However, as described by Breslow and Day (pp. 227–238),³ a log transform is commonly employed to improve model fit for exposure data expressed as a dose rate: “Postulating a log-linear relation of the form $\log RR(x) = \alpha + \beta \log(x)$ means that risk itself is proportional to a power of dose, x^β , a relationship known to occur frequently from both human and animal studies.” The categorical results in the original analyses² suggest a power model provides a more appropriate fit, which was confirmed by the analyses of exposure expressed as a continuous variable. Thus, the results shown in Table 2 of the reanalysis¹ are consistent with those in the original analysis.² The observation by Levy et al¹ that the regression coefficients for the untransformed beryllium variables are close to zero, while those for the log-transformed variables are positive, is consistent with the categorical results in Table 3 of the original analyses,² which showed an elevated lung cancer rate ratio in the second-lowest exposure category and then slight increases or attenuation in rate thereafter. These categorical analyses (with their implication for choice of appropriate exposure transformation) are not mentioned in the reanalysis by Levy et al.¹

Many other studies of occupational carcinogens have found that log-transforming exposure variables improves fit over untransformed data, and a number of hypotheses have been advanced to explain this observation.⁴ To facilitate using a log transform for those with zero exposure, a small value must be added to each person's exposure. In Breslow and Day's example,³ a value of one is added to each g/d estimate of tobacco and alcohol consumption. Levy et al criticize the

choice of small value used in the original analysis. However, our own recent reanalysis of the original study found the association of the log of 10-year-lagged average and maximum beryllium exposure to be relatively insensitive to the choice of small value added (ie, comparing 0.01 with half the minimum non-zero exposure value within the study group) (Schubauer-Berigan MK, Deddens JA, Steenland K, Sanderson WT, Petersen MR. Adjustment for temporal confounders in a reanalysis of a case-control study of beryllium and lung cancer. *Occ Environ Med*. Submitted).

Our second major criticism of the reanalysis by Levy et al¹ is its suggestion that risk set sampling methodology introduced a bias in the study because it requires the control to have been under observation at the time of case occurrence. This requirement of a density-sampled nested case-control study leads to its approximation of a Cox proportional hazards model (CPHM).⁵ As is common in studies of cancer, age is the most important time-related factor in lung cancer risk; therefore, age was selected as the time scale in the original analysis.² Thus, all workers hired at an age younger than the case's age at death and who lived to an older age than the case are within that case's risk set. Conditional logistic regression analysis based on exposures truncated at the case's death age for the entire matched set has been shown to provide unbiased estimates relative to an age-based CPHM.⁶ This necessarily results in the trivial observation that cases have younger ages at death than do matched controls.

Our third major criticism of the reanalysis by Levy et al¹ concerns their analyses restricted to controls whose age at death or date last observed is within 3 years of that of the matching case. This matching technique violates the assumptions that are required in order for the analysis to estimate a CPHM. Information about the control that occurs after the

time (age at death) of the case may not be used to select controls without introducing a potential bias. Furthermore, while it may be appropriate to match on calendar time (or, equivalently, date of birth) when using age-based density sampling for selecting controls if birth cohort is an important potential confounder, this is not what Levy et al have achieved. Consider a case who dies at age 65 in 1975 (born in 1910). The corresponding age-based risk set would consist of any worker hired before age 65 who was still alive at age 65. If one matches also on calendar year within 3 years, then the risk set would be restricted to workers who reached age 65 between 1972 and 1978 (ie, were born between 1907 and 1913). Many of these workers in the risk set could have lived to ages well beyond this time. However, the risk set obtained by the suggested matching methodology of Levy et al would include only workers who died between age 65 and 68 or who reached that age alive on December 31, 1992 when follow-up ended. It is difficult to see how such a matching technique could lead to an unbiased result. We contend, therefore, that the analyses in Tables 3 and 4¹ are of little value.

Of some interest is the observation by Levy et al¹ that the average age at hire for cases was approximately 4 years younger than that of controls. In our reanalysis (Schubauer-Berigan MK, Deddens JA, Steenland K, Sanderson WT, Petersen MR. Adjustment for temporal confounders in a reanalysis of a case-control study of beryllium and lung cancer. *Occ Environ Med*. Submitted), we attribute this finding to the fact that hire age is highly correlated with year of birth (Pearson's $r = -0.91$), for which the original analysis did not control.² Birth year is a potentially important confounder of the beryllium-lung cancer association because background lung cancer risk due to smoking was expected to be lower for workers born before 1900 (25% of the case-control

group) than for workers born later. This is associated with beryllium exposure because workers hired during the WWII era were more likely to be older than those hired during other periods (many were born before 1900). These older workers tended to die of other diseases during the 10- and (especially) 20-year latency period and thus had minimal or zero lagged exposure. By adjusting for birth year, we found that cumulative beryllium exposure was not associated with lung cancer risk at any lag. However, the significant positive association of lung cancer with both average and maximum beryllium exposure remained after this adjustment (Schubauer-Berigan MK, Deddens JA, Steenland K, Sanderson WT, Petersen MR. Adjustment for temporal confounders in a reanalysis of a case-control study of beryllium and lung cancer. *Occ Environ Med*. Submitted). It is not appropriate to simultaneously adjust for age at hire because of its high correlation with birth year, and the lack of an a priori rationale for hire age as a source of confounding.

Other, more minor, errors in the reanalysis by Levy et al¹ include the incorrect flagging of some *P* values in Table 1. According to the original analysis,² the *P* value for the trend of the log of 20-year-lagged employment duration with lung cancer mortality was below 0.05, and the values for the log of 20-year-lagged average and maximum exposure were below 0.01. Thus, not "some" (as reported by Levy et al¹) but nearly all exposure metrics were significantly elevated in the original lagged analysis. Sanderson et al² demonstrated an increase in beryllium-associated lung cancer risk when lagging exposures by 10 years. The fact that exposure-related lung cancer risk did not increase further when the exposure was lagged by 20 years should not be construed as evidence against an etiologic association, as implied by Levy et al.¹

Finally, we note that, in contrast to their implication that the designation by the International Agency

for Research on Cancer (IARC) of beryllium as a group 1 carcinogen relied upon the case-control study by Sanderson et al,² IARC's designation predates that study by 8 years.

Mary K. Schubauer-Berigan, PhD
James A. Deddens, PhD
Martin R. Petersen, PhD
National Institute for Occupational Safety and Health
Division of Surveillance, Hazard Evaluations and Field Studies
Cincinnati, OH

References

1. Levy PS, Roth HD, Deubner DC. Exposure to beryllium and occurrence of lung cancer: a reexamination of findings from a nested case-control study. *J Occup Environ Med*. 2007;49:96–101.
2. Sanderson WT, Ward EM, Steenland K, Peterson MR. Lung cancer case-control study of beryllium workers. *Am J Indust Med*. 2001;39:133–144.
3. Breslow NE, Day NE. *Statistical Methods in Cancer Research, Vol 1—The Analysis of Case-Control Studies*. Lyon: World Health Organization. IARC Scientific Publication No. 32; 1980.
4. Stayner L, Steenland K, Dosemeci M, Hertz-Piccioto I. Attenuation of exposure-response curves in occupational cohort studies at high exposure levels. *Scand J Work Environ Health*. 2003;29:317–324.
5. Prentice RL, Breslow NE. Retrospective studies and failure time models. *Biometrika*. 1978;65:153–158.
6. Beaumont JJ, Steenland K, Minton A, Meyer S. A computer program for incidence density sampling of controls in case-control studies nested within occupational cohorts. *Am J Epidemiol*. 1989;129:212–219.

DOI: 10.1097/JOM.0b013e3180d09e9c

Authors' Response

To the Editor: The major points made by Schubauer-Berigan et al on our reanalysis¹ of the Sanderson et al nested case-control data² reflect their non-acceptance of an artifact that we found can occur under certain patterns of employment when incidence density sampling is used to match controls to cases and then exposure is lagged for purposes of investigat-