Analysis of the Schubauer-Berigan et al Cancer Risk Estimate for Beryllium Exposed Workers: How Flawed Assumptions Lead to Flawed Conclusions

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Draft 16 August 2011

This study[1] combines data from three beryllium materials manufacturing plants which was produced by three separate job-exposure matrices to estimate cumulative, mean and maximum exposures. It was analyzed using Cox proportional hazards regression of lung cancer, using age based risk sets, with lagging of exposure 10 years. The cohort consists of 5436 male workers employed for at least 2 days at one of three beryllium-processing plants, in Elmore, Ohio, Hazleton, Pennsylvania, and Reading, Pennsylvania, between 1940 and 1970. The cohort was followed for mortality through 2005.

Flaw 1: Excess Risk in the Three Plants

Of the three plants only Reading had excess risk of lung cancer (SMR = 1.20, 95% confidence limits 1.04-1.37)[2]. The Elmore (1.01, 0.74-1.36) and Hazleton (1.03, 0.70-1.47) plants had rates of lung cancer almost exactly predicted by the age and time-specific USA rates of lung cancer. The use of these two lower-exposure and no-excess-risk plants to extrapolate risk gradients to very low levels of beryllium exposure is inherently fallacious. If there is an excess risk gradient, it would occur between the higher levels of exposure at the Elmore and Hazleton plants and the even higher range of exposure at the Reading plant.

A further illustration of the fallacy of extrapolating excess risk to very low levels of exposure when there is no excess risk below a moderate level of exposure is: maximum exposure. In these three plants the SMR for the lowest category of maximum exposure, <10 $\mu g/m^3$, was 0.83 (CI 0.67-1.02)[2] indicating no excess risk in this category and suggesting that if there were an excess risk gradient, it would be above this level.

Flaw 2: Confounding Bias not Fully Controlled in the Analysis

The age based risk set analysis used in this study[1] has been shown to be affected by confounding bias[3]. The bias is not fully controlled with adding fine categories of date of birth to the analysis. The broad lower category for in this study, <1900, would control confounding even less. The bias is due to simple confounding by time from hire due to the following conditions. First, lung cancer in this study is associated with time from hire[2]. Second, when exposure is lagged, time from hire becomes associated with lagged exposure, application of risk modeling to confounded relationships leads to erroneous conclusions.

Flaw 3: Excess Risk Models Anchored With Risk = 1 at Zero Exposure.

The authors anchored all their modeling analyses at risk = 1.0 at zero exposure. Values over 1.0 were interpreted as excess risk. This however does not match the facts. As cited above, at lower exposures the standard mortality ration for maximum exposure is less than 1.0. What the authors

interpreted as an excess risk gradient was actually a gradient within the range of lowered risk. The results cannot be interpreted as pertaining to excess risk.

Flaw 4: Extrapolation is Not Science

Extrapolation into un-measureable regions is not science. Science is systematized knowledge derived from observation, study, and experimentation. A lifetime beryllium-exposure attributable risk of a common cancer such as lung cancer of 10^{-3} is not observable in practice, and is not subject to practical study or experimentation. Therefore, it is impossible to determine scientifically whether the calculation of an exposure associated with a lifetime lung cancer risk as small as 10^{-3} is valid or not.

In this case, not only is a risk that small not observable, but the putative exposure value associated with that risk, average exposure 0.033 $\mu g/m^3$, is below the level of detection or quantification in the data used to construct the job exposure matrices. Therefore, the calculation falls outside the range of observation and can possibly be described as a hypothesis, but cannot be described as a scientific observation.

Summary

The calculations of Schubauer-Berigan et al on the relationship of beryllium exposure to 10^{-3} are:

Not in the realm of science as the result is not verifiable,
Based on relationships distorted by confounding bias, and
Fallacious in that risk is labeled excess when it is not.

References

1. Schubauer-Berigan MK, Deddens JA, Couch JR, Patrersen MT. Risk of lung cancer associated with quantitative beryllium exposure metrics within an occupational cohort. Occup Environ Med 2011; 68:354-360
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3. Rothman KJ, Mosquin PL. Confounding after risk-set sampling in in the beryllium study of Sanderson et al. Annals Epidem. DOI:10.1016/j.annepidem.2011.03.008