

Carbon Black Risk Assessment Comparison Is Flawed

By: Irva Hertz-Picciotto, Jeff Korte, [Mark Schulz](#), Tung-Chin Chiang, and Louise M. Ball

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Although the effort of Valberg and Watson (1996) to incorporate epidemiologic data into an assessment of the plausibility of carcinogenicity estimates is to be commended, their analysis contains a fundamental flaw. The authors equate comparison of observed rates with expected rates, a common technique in epidemiology, to a comparison of the number of observed events with an expected number of events. The two comparisons are *not* equivalent. The only circumstance in which they are equivalent is when the same denominator of person-time produces both the observed and the expected events.

More specifically, a standardized mortality or incidence ratio is calculated by: (1) stratifying on age, gender, and possibly other variables; (2) determining the stratum-specific observed number of events and the corresponding person-time that gave rise to those events; (3) calculating the comparable expected number of events based on the same person-time distribution (i.e., identical with respect to age, gender, etc., but differing with respect to an exposure of interest); (4) dividing the sum of the observed rates by the sum of the expected rates. When done correctly, one can re-place the rates with the number of events, since the denominators for both are identical.

In comparing mortality predicted from animal data with mortality observed in an epidemiologic study, the same principle must apply: the expected number of events must be derived from the same "person-time." Valberg and Watson (1996) instead compared the lung cancer events observed in carbon black workers by 1980 ($n = 13$) with the expected number of events ($n = 14.7$) predicted for a population in which every subject is observed for an entire lifetime. This comparison is meaningless. Since only about 10% of the person-time was at ages >55 years, few workers had reached the typically used 70- or 75-year "lifetime." In contrast, the unit risk derived using the rodent assay relates a quantified exposure to the probability of lung cancer death for a *full lifetime*. The fundamental point, which has been made previously (Hertz-Picciotto and Holtzman 1991; Hertz-Picciotto 1995) but which is not well understood by risk assessors, is that the structure of data from an animal study differs from the structure of data from a human study: animals can be observed for their entire lifetime, while humans usually cannot. The data from an animal carcinogenicity bioassay are, therefore, "lifetime risks" (the standard assumption is that a 2-year rat bioassay covers the animal lifetime), whereas the data from human studies are age-specific rates.

After the last worker in the carbon black cohort either dies or reaches age 70, it will be possible to validly compare the observed number of deaths to the expected number of deaths. In the meantime, partial lifetime risks for the human population can be compared with animal-based risk estimates that have been scaled to partial lifetimes.

How can this scaling be done? Clearly, most of the lifetime lung cancer deaths that will have occurred by the time the last worker reaches the age of 70 (or 75, or whatever is deemed to be a full lifetime) have simply not yet been observed. This problem is accentuated by the fact that the rise in lung cancer mortality with age is not linear, but is far steeper—approximately the fourth power of age.

If one examines the pattern of human lung cancer mortality, one can estimate the proportion of lifetime risk that is incurred at any specific age. Using multiple decrement lifetables constructed from 1990 U.S. male lung cancer and all-cause mortality rates (the latter are used to correct for competing risks), we have calculated the proportion of cumulative lifetime risk experienced by persons of different ages. Allowing age 75 to represent the lifetime of risk that is of interest, the total accumulated risk for lung cancer mortality is 0.050; the accumulated risk by age 55 is 0.007, or about one-seventh of the total. Accordingly, the figure of 14.7 lung cancer deaths predicted by the animal bioassay should be divided by 7 to obtain the partial-lifetime-predicted number of deaths.

Thus, to scale the animal predictions, one would need, at a minimum, the age distribution of the entire cohort at the end of follow-up. A predicted lung cancer risk for partial lifetime could then be calculated for each worker, and these could be summed for comparison with observed deaths.

Other weaknesses in the analysis of Valberg and Watson stem from defects in the original analysis by Robertson and Ingalls (1980). For instance, because the follow-up time analyzed by these authors only included “active” person-years (years in which the workers were employed) and years after retirement, but not person-years after a worker left employment at the plant for reasons other than retirement, their results are subject to strong bias from the healthy worker survivor effect (Fox and Collier, 1976; Pearce *et al.*, 1986). It has been well established that workers who leave the work force are, in general, in poorer health than those who remain on the job, even after adjusting for age (Delzell and Monson, 1981; Arrighi and Hertz-Picciotto, 1994). Valberg and Watson also make assumptions about length of service that are not supported by the statements of Robertson and Ingalls, who assert that the average size of the workforce during the last 25 years of follow-up was 1250 and that the turnover was 2% annually. These problems would also need to be addressed in a proper analysis comparing the epidemiologic data on carbon black workers with the animal-based predictions.

Any comparison of human and animal data involves a degree of conjecture; nevertheless, since regulatory policy routinely assumes some comparability, the attempt to validate animal-based risk projections is a worthwhile venture, provided that it is done correctly. Direct comparisons of animal and human data can elucidate situations in which risks have been overestimated by extrapolation from animal experiments, e.g., ethylene dibromide (Hertz-Picciotto *et al.*, 1988) and cadmium (Hertz-Picciotto and Hu, 1994). However, without a comparison based on the age distribution of the carbon black cohort, it is not possible to know whether, in this case, the animal-based risk assessment overestimates human lung cancer mortality or not.

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