Occupational Lead Exposure: What Are the Risks?

This is in response to the comments by Kang *et al.* (Letters, 29 Feb., p. 935) regarding a 1975 report (*1*) on the mortality of lead workers which I coauthored with W. R. Gaffey. I am sorry we did not have an opportunity to prepare a reply for publication in the same issue.

The letter raises two related but different questions pertaining to this and other epidemiologic studies. The first deals with the type of statistical test appropriate for estimating the significance of deviations of observed numbers of deaths from those expected. The second is the interpretation of any excesses or deficiencies in establishing relationships between specific environmental exposures and effects on health. A separate letter by Gaffey responding to criticism of the method of estimating statistical significance follows this letter.

There are many considerations involved in the interpretation of results that are more important than confidence intervals or statistical significance. Apparent associations that have low or borderline levels of statistical significance must be treated with special caution, because of the many ways in which a study population may differ from the population used for comparison. Internal comparisons, between groups that differ in duration, time, or level of exposure, provide opportunities to detect trends which may be more important than any of the individual standardized mortality ratios (SMR's).

An example of such a problem is provided by our inability to control for cigarette smoking as a variable in our study of lead production facility (smelter) and lead battery plant workers. As Lundin *et al.* (*2*) have pointed out, a difference in the proportion of heavy smokers in a population of uranium miners could have explained a 49 percent excess (SMR, 149) of respiratory cancer, but not the fivefold (SMR, 560) that was observed. In the same monograph (*2*, p. 25), the authors attributed a doubling of respiratory cancer in potash industry employees to heavy smoking. Such considerations, and the fact that we found no internal trends pointing to lead, even though many exposures were very high, led to the conclusion, included in another report based on the same data (*3*): "The present study does not suggest that lead is a potent carcinogen, in view of the relatively small excess of cancer deaths in a heavily exposed group. It does, however, suggest that in the industries studied, there are factors that may increase the cancer risk, and lead has not been ruled out as a co-factor. Continuing studies to obtain additional data and to identify causative agents are warranted."

Kang *et al.* contend that, because 59 percent of the smelter workers and 36 percent of the battery plant workers had "latency periods" of less than 20 years, our study might have underestimated the incidence of diseases that do not appear until long after exposure begins. They ignored the fact that we included a separate analysis of all men hired before 1946, who accounted for 60,883 of the total of 103,301 person-years of observation reported. In these, 25 or more years could have elapsed since first exposure; their pattern of mortality from malignancy was similar to that in the total population.

There has been a further study of the mortality of the same populations during the period 1970 to 1975; 491 additional deaths were analyzed (*4*). The SMR for malignant neoplasms in production facility workers was 89 and that for battery plant workers was 136. The SMR's for lung cancer were 121 and 128, respectively. There were no excess tumors of the digestive tract and only one death from a kidney tumor was observed. Again, no correlation was found between elevated SMR's and duration or reported level of exposure to lead. The complete report of this updated study has been widely distributed and has been made available to regulatory agencies (*4*).

By the end of 1980, for 70 percent of the smelter workers and 75 percent of the battery plant workers 20 or more years could have elapsed since their first exposures to lead; for 41 percent and 64 percent, 30 or more years could have elapsed. A study of the mortality of these workers for the years 1976 through 1980 should provide very useful information.

In ongoing epidemiologic studies and the reports they generate, we plan to follow, whenever possible, the guidelines suggested by the Epidemiology Work Group of the Interagency Regulatory Liaison Group (IRLG) (*5*). These describe disclosure and documentation of methods, and the provision of sufficient information to permit independent evaluation of epidemiologic studies. The constraints of space imposed by published summaries often lead to the omission of details that are contained in more complete reports of research. This was true for our lead study, where the 151-page report prepared for the International Lead and Zinc Research Organization and made available to the National Institute for Occupational Safety and Health (NIOSH) and the Occupational Safety and Health Administration contained much information omitted from the article published in the *Journal of Occupational Medicine* (*1*). It appears that epidemiologists in NIOSH have also been confronted with this problem, as attested by the paucity of information in many of their published reports (*6*). I am sure that we will all benefit by being provided with more details.

It is still my opinion that the evidence derived from our studies is insufficient to justify classifying lead as a carcinogen in humans. The only type of malignancies convincingly demonstrated in lower animals have been tumors of the renal cortex, following near-lethal dosage. This is consistent with the observation that lead inclusion bodies in renal epithelial cells are a characteristic finding in animals and humans after the absorption of large amounts of lead. The absence of an excess of renal tumors in 1758 certified deaths in 7032 workers is an important negative finding, particularly in view of the excessive exposures to lead that many of them had experienced. This fact, the lack of internal correlations with available evidence of lead exposures, and inability to control for a number of variables, including cigarette smoking, make overinterpretation of low levels of association premature and unwise. The evidence is certainly not strong enough to support regulatory decisions based on carcinogenesis.

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As coauthor with Cooper of the lead workers mortality study that was the subject of the letter by Kang *et al.*, I should like the opportunity to reply. I will confine myself to the specific statistical issues raised by Kang *et al.*

Kang and his colleagues allege that an incorrect formula for the standard error of the SMR was used and that an incorrect z value was used for the 1 percent level of significance. In fact, these were both typographical errors. The square root sign that was missing in our report was in fact used in the actual tests. A missing line of type in the part of the text referring to z values created the erroneous impression as to which critical values were used. The text (but not the calculations) is indeed in error. Incidentally, the description by Kang *et al.* of my use of the "technique developed by Chin Long Chiang" is incorrect. I used Chiang's work to satisfy myself that the SMR did not follow the Poisson distribution and that the Poisson assumption was probably conservative. The responsibility for the choice of test was mine alone.

The important issue raised by Kang and his colleagues is that of whether a one-sided or a two-sided test should have been used. Concluding that a one-sided test should have been used, the remainder of the letter contains references to "apparent errors," "the need for use of appropriate . . . statistical analyses," and so forth. Yet one of the authors of the letter—Infante—appears to use two-sided tests in other studies of a similar nature (*1*). Since Infante *et al.* (*1*) do not adhere to the IRLG guidelines, it is impossible to tell what test was used. It is easy, however, to verify that the one-sided test Kang *et al.* use in their reanalysis of our data was *not* used in (*1*). In addition, the use of two-sided tests is more generally accepted than Kang *et al.* suggest. In a copy of a journal issue entitled "Occupational carcinogenesis" (*2*), I found four articles (*3*) by NIOSH authors (nine persons in all) in which two-sided tests had been used. My own view is that significantly low SMR's may have much to tell us. For example, in the case of cancer mortality, in which the healthy worker effect is not strong, a significantly high SMR for one site combined with a significantly low SMR for a second site invites suspicion that there may be some consistent errors in cause of death certification. Other causes of death can be interpreted as socioeconomic indices, and low values may be informative about selection bias in the study population. My views on this matter appear to be shared by a substantial body of experienced investigators at NIOSH.

The next issue in the letter by Kang *et*

al. concerns whether the appropriate two-sided test is a critical ratio or a confidence interval. There will be some marginal cases in which an excess SMR will be statistically significant by the first test but not by the second. I nevertheless prefer the confidence interval. This avoids the logical contradiction, with the critical ratio, of sometimes finding an SMR significantly greater than 100 but with a confidence interval that includes 100. An additional consideration not addressed by Kang *et al.* is that the formula for the standard error of the SMR is, in any case, an approximation. The argument then comes down to whether one approximation is better than another. In view of the fact that all significance statements in a cohort study of this kind are plagued by the multiple comparison problem, any reasonable investigator must regard significance levels, however they are determined, as nominal figures only.

The final reference by Kang *et al.* to the Epidemiology Work Group of the IRLG puzzles me. The implication is that this work group has laid out prescriptions for proper study design and analysis. In fact, the IRLG guidelines confine themselves to prescriptions for disclosure. That document specifies what constitutes good practice in disclosing the details of a study design and analysis and is very wisely silent about prescribing study designs. Although the study by Cooper and me antedated by 5 years the promulgation of the IRLG document, we appear to have provided enough detail about what we did to give Kang and his colleagues the basis for a critique.

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Is Evacuation the Best Policy?

If a serious nuclear reactor accident were to occur, those charged with the health and safety of the public would have to decide whether or not to order an evacuation. Various factors should influence their decision, including the risk of additional deaths due to traffic accidents and heart attacks, psychological stress on the entire population, and, most important, possible increase in radiation