Letter to the Editor

On the Carcinogenicity Risk Assessment of Chromium Compounds

To the Editor:

The evaluations of the potential carcinogenicity of metallic chromium and trivalent chromium by several international and national agencies [International Agency for Research on Cancer (IARC), 1990; Agency for Toxic Substances and Disease Registry (ATSDR), 1993; Canadian Environmental Protection Act (CEPA), 1994; United States Environmental Protection Agency (US EPA), 1998; United States National Toxicology Program (US NTP), 2002] and individual scientists [Langård, 1990; Lees, 1991; Hayes, 1998] are unanimous that the evidence is inadequate in humans. For some occupational sources of chromium exposure (e.g., ferrochrome industry and manufacture of chrome pigments) and for some occupations (e.g., leather tannery workers, painters, and chromium platers) there are increased risks, but almost invariably in the epidemiologic studies the available data do not permit discrimination between simultaneous exposure to trivalent chromium and hexavalent chromium. Although the chromium compound that increases the risk of lung cancer and sinonasal cancer has yet to be identified, there is fairly general agreement that hexavalent species are responsible for these diseases and that the trivalent and metallic species are not.

Gibb et al. [2000] claimed that their study on lung cancer among workers in chromium production offers the best quantitative evidence to date of the relations between hexavalent chromium exposure and lung cancer. This may well be the case, but their conclusion that “cumulative hexavalent chromium exposure was not” warrants a critical comment. In an effort to refute the conclusion drawn by Mancuso [1997] according to which all forms of chromium are carcinogenic, Gibb et al. modeled for the separate effects of cumulative hexavalent chromium, Cr(VI), exposure and cumulative trivalent chromium, Cr(III), exposure on the risk of death from lung cancer.

Proportional hazards models using age as the time variate, cumulative exposure as a time-varying covariate, and smoking as a confounding covariate were applied to assess the relation between cumulative chromium exposure and lung cancer mortality risk. When one exposure variate at a time was included in the model, cumulative Cr(VI) exposure and cumulative Cr(III) exposure were found to have separately almost equivalent, statistically significant risk (or hazard) ratios for each tenfold increase in cumulative exposure: 1.38 (95% confidence interval 1.20–1.63) and 1.32 (95% confidence interval, 1.15–1.51), respectively. Despite the very strong correlation between the log of cumulative Cr(VI) exposure and the log Cr(III) exposure (correlation coefficient \( r = 0.95 \)), Gibb et al. made an attempt to analyze the adjusted effects of exposure to the two types of chromium compounds. The inclusion of both exposure variates as risk factors in the same model resulted in cumulative Cr(VI) exposure remaining statistically significant, although at a lower significance level, and the risk ratio attained a higher value, 1.66 (confidence interval was not given but it was presumably wide). On the other hand, the association between cumulative Cr(III) exposure and lung cancer risk did not retain its statistical significance, and apparently the risk ratio was less than unity, 0.84 (correcting for the given erroneous value of 0.17).

A likely explanation for these results is that Cr(III) acts like a proxy variate for Cr(VI). In this case, the estimated risk ratios will change drastically from the ones obtained from separate analyses, and the confidence intervals for the risk ratios will become very wide. Such changes are to be anticipated whenever the values of the regression variates are
highly correlated, as was the case in the Gibb et al. study. The phenomenon is well known in statistics and termed collinearity [Breslow and Day, 1980, Section 6.10]. In this situation, the predictor variates are so strongly correlated that it is difficult or impossible to come up with reliable estimates of the actual risks. Although collinearity does not affect the ability of a regression model to predict the risk, it poses a serious problem if the purpose of the study is to estimate the variates’ individual abilities to predict the disease risk. Even when the correlation is weaker, the proxy’s coefficient influences somewhat the coefficient of the proper risk factor that one would like to estimate well.

The multivariate regression analysis performed by Gibb et al. does not exclude the theoretical possibility that trivalent chromium could be a causal risk factor. However, when two highly correlated variates are entered jointly into a model, it happens that the risk factor, which has the stronger association of the two with the disease risk, remains statistically significant, whereas the other risk factor apparently loses its significance, even though it would have a causal relation with the disease risk. Although an unambiguous answer is simply not possible in the presence of collinearity, one could speculate that if the effect of trivalent chromium in humans indeed is carcinogenic, its potency is most probably much less powerful than that of hexavalent chromium.

Unfortunately, collinearity rendered the otherwise well-conducted study by Gibb et al. inconclusive. While waiting for new epidemiologic data to become available, that is, data where simultaneous exposure to the two chromium species does not confound the risk assessment, a tentative judgment as to whether trivalent chromium is likely to play a causal role in carcinogenesis would have to be made based on other relevant data and information. These sources include experimental animal data, knowledge about chromium metabolism and plausible carcinogenic mechanisms. If such a judgment cannot be made, one must simply admit that precise identification of the factor(s) responsible for the carcinogenic effect is impossible.

REFERENCES


