Miller, Diane M. (CDC/NIOSH/EID)

From:
Sent: Friday, April 24, 2009 5:09 PM
To: NIOSH Docket Office (CDC)
Cc: Niemeier, Richard W. (CDC/NIOSH/EID)
Subject: NIOSH Docket Number 144
Attachments: Comments.doc

Thank you for the opportunity to comment on the *NIOSH Criteria Document Update: Occupational Exposure to Hexavalent Chromium*. My comments are attached. If you have any questions, please do not hesitate to contact me.

Sincerely,

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April 24, 2009

NIOSH Docket Office
4676 Columbia Parkway
MS C-34
Cincinnati, OH 45226

Subject: NIOSH Docket Number 144

Dear Sir or Madam:

Thank you for the opportunity to comment on the NIOSH Criteria Document Update: Occupational Exposure to Hexavalent Chromium. My comments address the first three questions on which NIOSH is seeking comment as outlined in its Federal Register notice of October 14, 2008.

1. Are the critical studies presented clearly and adequately?

- The document states on page 92: "Based on a categorical analysis, the exposure-race interaction was found to be due largely to an excess in lung cancer mortality evident among whites in the range 0.03-0.09 mg/m^3-yr of chromium cumulative exposure and a deficit in the range 0.37-1.1 mg/m^3-yr. While an explanation for this observed disparity on race was not provided it was argued that a biological basis is unlikely." Presumably, the statement that "While an explanation for this disparity on race was not provided...." refers to Park et al. since a racial disparity was not discussed in Gibb et al. (2000), but that is not clear. The document goes on to state on page 92 that confounding is unlikely but that exposure misclassification is quite plausible. Park et al. (2004) was more explicit regarding their observations on race stating that a biological basis for a chromium-race interaction was unlikely and that more plausible explanations include, but are not limited to, misclassification of smoking status, misclassification of chromium exposures, or chance." That language should be repeated here. Certainly the use of pack-years at age of hire as a measure of smoking status presents an uncertainty as described in response to question #2 below.
- After discussing the potential source of the race disparity, the document goes on to argue that models without the race-chromium interaction term would provide an unbiased estimate of the exposure response (top of page 93). That argument assumes, however, that the racial disparity reported by Park et al. is due to exposure misclassification by race and ignores other potential causes. It would be better to state that if the presumed racial disparity is a result of exposure misclassification, models without the race-chromium interaction term would provide an unbiased estimate of the exposure response.
- On page 96, the document describes limitations of the EPA (1984) quantitative risk assessment. As noted by NIOSH, EPA (1984) used the data of Mancuso (1975) in its assessment. At the time, it was the best data available. EPA (1984) noted, however, the limitations of the data base and in response to public comment made assumptions

to address the limitations where it could. For example, in contrast to the statement on page 96 of the NIOSH document that EPA assumed that exposure estimates from a 1949 study were constant over the period of the study, EPA assumed that exposures could have been twice as high based on public comments on the risk assessment. The limitations of the data base noted by EPA (1984) were in fact the genesis of the EPA-funded Gibb et al. (2000) study which now forms the basis of the NIOSH quantitative risk assessment. It is inappropriate for NIOSH to criticize the "weakness" of the EPA analysis, which is now a quarter of a century old and based on a study that is over 30 years old, for shortcomings in comparison to the current data base. If the Mancuso (1975) study was all that was available for quantitative risk assessment today, would a NIOSH analysis of that data set be considered weak?

- On page 97, it indicates that Gibb et al. (1986) applied the same models as U.S. EPA (1984) to the data of Mancuso (1975) to derive the same lifetime unit cancer risk estimate and therefore is prone to the same limitations of EPA (1984). Gibb et al. (1986) was a review of the literature on chromium including animal and occupational studies and described quantitative risk assessments using several data sets including that of Mancuso (1975), Braver et al. (1985), Langard et al. (1980), Axelsson et al. (1980), and Pokrovskaya et al. (1973). For the Braver et al., Langard, et al., Axelsson et al. and Pokrovskaya data sets, quantitative assessments were developed by Gibb et al. (1986). For the Mancuso data set, the EPA (1984) analysis was used. Gibb et al. (1986) should not even have been included in this section of the NIOSH document since it is merely a repeat of EPA (1984).

- On page 102, the title of Table 6-2 is "Risk assessments based on the Hayes cohort....". The table includes analyses by Gibb et al. (1986), Crump (1995), Park et al. (2004) and Park et al. (2004). The Park et al. analyses are based on the Gibb et al. cohort, not the Hayes cohort. The Hayes cohort included workers employed before 1950; the Gibb et al. cohort did not.

- On page 102, there is reference made to Crump (1995). Crump (1995) is not in the list of references.

- On page A-8, it indicates that Gibb et al. (2000b) were not able to link many morbidity outcomes usually associated with chromium to the exposure measures available suggesting that there was considerable exposure misclassification. It is unclear what is meant by this statement. A significant proportion of the cohort experienced irritated nasal septum, ulcerated nasal septum, perforated nasal septum, bleeding nasal septum, irritated skin, ulcerated skin, dermatitis, burn, and/or conjunctivitis. Presumably, NIOSH is referring to the results of the proportional hazards model by Gibb et al. (2000b) which found that hexavalent chromium exposure was significantly associated only with several of these symptoms. Gibb et al. (2000b) noted, however, that the reason for the association with only some of the symptoms may be that the ambient hexavalent chromium concentrations used in the proportional hazards model represent annual averages rather than a possibly more relevant shorter term average. It would be more appropriate for NIOSH to cite the reasoning by Gibb et al. (2000b) rather than state that "there was considerable exposure misclassification" which is vague and can have a range of meanings.

- On page A-20, it states that NIOSH Method 7703 has a limit of quantitation of 0.27 $\mu g/m^3$, but the recommended REL is only 0.2 $\mu g/m^3$. The limit of quantitation is higher than the REL?
- The risk assessment analysis in the current document relies on the quantitative analysis by Park et al. (2004). Park et al. relied on pack-years from the Gibb et al. data file as a measure of smoking. The NIOSH document states that smoking information was available for 91% of workers (pages 90, 112) and that "packs per day were available for most workers". For 91% of the cohort, smoking information (yes/no for cigarettes, pipes, and cigars was available), but pack year data were available for only 70% of the cohort. While the statements on pages 90 and 112 are not incorrect, the reader should be made aware of the more limited nature of the pack-year data (it is misleading to indicate that smoking data was available for 91% of the cohort when that data was not used in the analysis).

2. Do all of the presented studies use scientifically valid methods and techniques?

- Park et al. (2004) used pack-year data collected at the age of hire as his smoking metric. The median age of hire was 28.6, and the median length of follow-up was 31.2 years. The pack-years for any individual would have changed considerably over a 30+ year period, the smoking status probably less so. Park et al. (2004) argued that models using cumulative smoking fit better than did the models using simple categorical classification (yes/no), but model fit should not be an argument for selection of data.
- Concern regarding the use of pack-years as the smoking metric is heightened by the fact that Park et al. (2004) found that there was no lung cancer risk associated with smoking more than 30 pack-years and only a 1.07 (95% CI 1.04, 1.07) risk of smoking less than 30 pack-years (see Table IV, Park et al. 2004). This anomaly relates to the fact that a reference U.S. male population which includes both smokers and nonsmokers was used in the risk model, but it may also relate to the uncertainty of the cumulative smoking data. Smoking is estimated to account for almost 88% of lung cancer deaths in the U.S. male population [MMWR 54(25):625-8]. Gibb et al. (2000) found that smoking as a yes/no variable was a stronger predictor of lung cancer risk than was hexavalent chromium exposure. In any case, a model predicting an inverse dose response relationship for smoking and no lung cancer risk for those smoking > 30 pack-years is open to considerable question.

3. Are there additional critical studies relevant to occupational exposure to hexavalent chromium compounds that should be included?

Chen, C. J., T. S. Shih, et al. (2008). "The total body burden of chromium associated with skin disease and smoking among cement workers." Sci Total Environ **391**(1): 76-81.

I hope that you find these comments to be helpful. Please do not hesitate to contact me if you have any questions.

Sincerely,