

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

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**From:**

**Sent:** Saturday, April 25, 2009 2:33 PM

**To:** NIOSH Docket Office (CDC)

**Subject:** peer review of NIOSH Docket Number 144

**Attachments:** Review of NIOSH Criteria Document Update for Hexavalent Chromium.doc

Dear Sir or Madam,

Attached are my comments on the NIOSH Criteria Document Update: Occupational Exposure to Hexavalent Chromium. Thank you for the opportunity to review this document.

Sincerely,

April 25, 2009

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

Re: NIOSH Docket Number 144

Dear Sir or Madam,

Thank you for the opportunity to review the NIOSH Criteria Document Update: Occupational Exposure to Hexavalent Chromium. Enclosed are my comments which pertain primarily to the discussion of the epidemiological evidence for human health effects of occupational exposure to hexavalent chromium and its use in quantitative risk assessment.

Sincerely,

A large rectangular area of the document is redacted with a light gray box, obscuring the signature and any handwritten notes.

**Review of NIOSH Criteria Document Update: Occupational Exposure to Hexavalent Chromium (NIOSH Docket Number 144)**

1. Are the critical studies presented clearly and adequately?

- Section 4.1.1.1.1 (pages 40-41): I'd suggest that the authors explicitly state that the 1994 Castle Hayne study due to the small number of events does not provide sufficient information for use in quantitative risk assessment. Also, please point out that the reported confidence limits are 90% confidence intervals, which are narrower than the usual 95% confidence intervals (and consequently may show statistical significance whereas 95% confidence limits would not). It is also unclear if the odds ratios reported on page 41 are for total mortality or specific causes of death; I assume it is the former given the small number of total deaths;
- Sections 4.1.1.1.2-4.1.1.1.3 (pages 41-43): it would benefit the discussion to more clearly describe the relative strengths and limitations of the Gibb et al. (2000a) and Luippold et al. (2003) studies, and their impact on selecting one study over another for risk assessment purposes. The difference in study populations may have consequences for comparability across the two studies; Painesville workers with less than 1 year of employment were excluded from further study, whereas a large proportion of the Baltimore cohort included workers employed for less than 1 year. It is therefore possible that workers in the Baltimore cohort may have different risk profiles than the Painesville cohort. In addition, the average exposure was lower and the exposure range smaller in the Baltimore study. These factors likely introduced some heterogeneity in study findings between the two study cohorts (as discussed in Goldbohm et al. 2006 and van Wijngaarden et al. 2004, see below).
- Section 4.1.1.1.3 (page 43): the five categories of hexavalent chromium exposure were most likely based on ensuring an equal number of expected lung cancer deaths in each category (see Table 3 in Luippold et al. 2003, with about 4.4 expected deaths in each category). Similarly, in Crump et al. 2003 ten exposure categories were created based on approximately 2.2 expected deaths per category;
- Sections 4.1.1.1.2-4.1.1.1.3: Given the importance of these two studies, the description of their characteristics and findings could be expanded in these sections (or include a Table for a quick overview of the 2 studies in terms of follow-up period, average duration of employment, sample size, exposure assessment, covariates, and exposure-response findings).

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

- Yes, the Baltimore and Painesville cohort studies appear to be well-conducted epidemiological investigations with reasonable approaches to exposure assessment and statistical analysis.

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

I would suggest that the following manuscripts be acknowledged:

- Birk T, Mundt KA, Dell LD, Luippold RS, Miksche L, Steinmann-Steiner-Haldenstaett W, Mundt DJ. Lung cancer mortality in the German chromate industry, 1958-1998. *J Occup Environ Med* 2006;48(4):426-433. Given that the Castle Hayne report was discussed in some detail despite

the small number of deaths, it would seem reasonable to include a description of the Birk et al. 2006 study as well since it also used quantitative measures of exposure;

- Goldbohm RA, Tielemans EL, Heederik D, Rubingh CM, Dekkers S, Willems MI, Dinant Kroese E. Risk estimation for carcinogens based on epidemiological data: A structured approach, illustrated by an example on chromium. *Regul Toxicol Pharmacol.* 2006 Apr;44(3):294-310. This manuscript describes a framework for quantitative risk assessment using epidemiological data. It discusses in some detail the selection of appropriate studies for hexavalent chromium quantitative risk assessment, derives estimates of risk using the Baltimore and Painesville data, and describes the consistency of the evidence and statistical considerations;
- van Wijngaarden E, Mundt KA, Luippold RS. Evaluation of the exposure-response relationship of lung cancer mortality and occupational exposure to hexavalent chromium based on published epidemiological data. *Nonlinearity Biol Toxicol Med* 2004 Jan;2(1):27-34. The conclusions in this paper regarding the presence of a threshold in the lung cancer exposure-response relationship are consistent with those in the Criteria Document. The paper also comments on the appropriateness of performing a pooled analysis of the Baltimore and Painesville data.

4. Does NIOSH have a transparent and sound basis for its revised Recommended Exposure Limit for hexavalent chromium compounds?

- The document would benefit from a general discussion of the use of epidemiology in risk assessment, such as criteria (e.g., control for confounding, quantitative exposure assessment, statistical precision or risk estimates) for selecting studies of sufficient quality for exposure-response assessment and risk characterization (e.g., see Goldbohm et al. 2006; Hertz-Picciotto 1995) and statistical considerations (e.g., log-linear vs. linear relative risk model), prior to section 6.1. This would increase the transparency of selecting the Baltimore cohort for derivation of the REL over the Painesville cohort, which seems important since the REL based on the latter cohort would be somewhat greater than the proposed REL;  $0.5 \mu\text{g}/\text{m}^3$  vs.  $0.2 \mu\text{g}/\text{m}^3$ , respectively, based on a linear relative risk model (which assumes no threshold) and the information provided on page 100 (3<sup>rd</sup> paragraph) of the Criteria Document;
- Park et al. 2004 used for their final exposure-response assessment a statistical model with smoking cumulative exposure using imputed data (based on smoking information at hire) since this model fit the data best (page 91). However, since it relies on imputed data it would be informative to know what the REL would be based on a statistical model that used only observed smoking data (smoking at hire: yes, no, unknown). Would it be consistent with proposed REL of  $0.2 \mu\text{g}/\text{m}^3$ ?
- It appears that occupational exposure to hexavalent chromium at present primarily occurs among workers also exposed to a variety of other harmful agents (Table 2-3, page 11). For example, welders exposed to chromium (stainless steel alloy) are also likely to be exposed to nickel, another lung carcinogen (Antonini et al. *Am J Ind Med* 2003;43:350-360). This raises concerns about the relevance of the Baltimore and Painesville data to these workers and whether the proposed REL is sufficiently (or overly) protective. Perhaps the Criteria Document could expand on this issue.
- Regarding non-cancer risk assessment, would it be possible to derive exposure limits using epidemiological data on male reproductive effects of occupational exposure to hexavalent chromium exposure, perhaps using benchmark dose modeling? As recently discussed by the Office of Environmental Health Hazard Assessment, California Environmental Protection Agency

in their draft hazard identification document for hexavalent chromium ([http://oehha.ca.gov/prop65/hazard\\_ident/pdf\\_zip/chrome0908.pdf](http://oehha.ca.gov/prop65/hazard_ident/pdf_zip/chrome0908.pdf)), there are several studies with quantitative exposure assessment demonstrating adverse male reproductive effects.

5. Is the new NIOSH policy of providing general exposure assessment recommendations instead of a specific Action Level scientifically justified?

No comments.

6. Are the NIOSH recommendations for worker protection clear and justified?

More detailed information on determinants of hexavalent chromium exposure in the different workplace environments where such exposure occurs would help to evaluate the appropriateness and effectiveness of the NIOSH recommendations for worker protection.

7. Are there additional recommendations for worker protection that should be included?

No comments.