May 2, 2009

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4676 Columbia Pkwy
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Re: Peer review of NIOSH Criteria Document Update: Occupational Exposure to Hexavalent Chromium.

Dear Dr. Niemeier,

I have reviewed the NIOSH Criteria Document Update: Occupational Exposure to Hexavalent Chromium. I find that the hazard identification is a reasonable reflection of the available scientific studies; the NIOSH recommendations for protecting workers from occupational exposure to hexavalent chromium are appropriate; and NIOSH has a transparent and sound basis for its revised Recommended Exposure Limit for hexavalent chromium compounds. Below are my responses to the seven questions you requested I consider. Each is presented in turn, followed by my responses.

Q1. Are the critical studies presented clearly and adequately?
Yes, NIOSH has done a commendable job presenting the key studies in clear and comprehensive manner. There is a small error in the mechanisms of toxicity section on page 76. The final paragraph on that page states: "This hypothesis is consistent with studies demonstrating that particle-cell contact and extracellular dissolution were required for lead chromate-induced clastogenesis [Wise et al., 1993; Xie et al., 2004]." It is correct that both studies showed extracellular dissolution was required, however, Xie et al. showed particle-cell contact was not required for human lung cells.

Q2. Do all of the presented studies use scientifically valid methods and techniques?
Yes, all of the presented studies use scientifically valid methods and techniques.

Q3. Are there additional critical studies relevant to occupational exposure to hexavalent chromium compounds that should be included?
Section 5.2 Mechanisms of Toxicity covers many of the important mechanisms, but it is missing recent discoveries with respect to chromosome instability. This section would be strengthened by the addition of discussion of two recent papers:

> Holmes, A.L., Wise, S.S., Sandwick, S.J., Lingle, W.L., Negron, V.C., Thompson W.D. and Wise, Sr., J.P. Chronic Exposure to Lead Chromate Causes Centrosome Abnormalities and Aneuploidy in Human Lung Cells. Cancer Research, 66(8): 4041-4048, 2006.
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> Wise, S.S., Holmes, A.L., Xie, H., Thompson, W.D. and Wise, Sr., J.P. Chronic Exposure to Particulate Chromate Induces Spindle Assembly Checkpoint Bypass in Human Lung Cells. Chemical Research in Toxicology, 19(11):1492-1498, 2006.

There is also more data that establish that many Cr(VI) compounds are genotoxic including some in human lung epithelial cells, and should be added:

> Wise, S.S., Holmes, A.L. and Wise, Sr., J.P. Particulate and Soluble Hexavalent Chromium Are Cytotoxic and Genotoxic to Human Lung Epithelial Cells. Mutation Research, 610(1-2): 2-7, 2006.
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> Holmes, A.L., Wise, S. S., Sandwick, S.J. and Wise, Sr., J.P. The Clastogenic Effects of Chronic Exposure to Particulate and Soluble Cr(VI) in Human Lung Cells. Mutation Research, 610(1-2): 8-13, 2006.
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> Xie, H., Holmes, A.L., Young, J.L., Qin, Q., Joyce, K, Pelsue, S.C., Peng, C., Wise, S.S., Jeevarajan, A., Wallace, W.T., Hammond, D. and Wise, Sr., J.P. Zinc Chromate Induces Chromosome Instability and DNA Double Strand Breaks in Human Lung Cells. Toxicology and Applied Pharmacology. 234: 293–299, 2009.

Also, a key in vitro finding is that Cr(VI) compounds induce transformation of human cells including bronchial epithelial cells. This aspect should be mentioned:

> Xie, H., Holmes, A.L., Wise, S.S., Huang, S., Peng, C. and Wise, Sr., J.P. Neoplastic Transformation of Human Bronchial Cells by Lead Chromate Particles. American Journal of Respiratory Cell and Molecular Biology. 37(5): 544-552, 2007.
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> Xie, H., Wise, S.S. and Wise, Sr., J.P. Deficient Repair of Particulate Chromate-Induced DNA Double Strand Breaks Leads To Neoplastic Transformation. Mutation Research. 649: 230-238, 2008.

The Color Pigment Manufacturer's Association mentioned the need for including a study by Nestmann and Zhang. That study does consider pigments directly, but it incorrectly states that all other studies have "artificially enhanced" aqueous solubility. In fact, most lead chromate studies have not enhanced aqueous solubility, the only one that did was Douglas et al. The Nestmann and Zhang study, however, is flawed because they used very large particles in CHO

cells and Wise et al., 1992 (Wise, J.P., Leonard, J.C. and Patierno, S.R. Clastogenicity of Lead Chromate Particles in Hamster and Human Cells. Mutation Research, 278: 69-79, 1992), showed that very large lead chromate aggregates are nontoxic. The Wise et al., 1993 (Wise, Sr., J.P., Stearns, D.M., Wetterhahn, K.E. and Patierno, S.R. Cell-Enhanced Dissolution of Carcinogenic Lead Chromate Particles: The Role of Individual Dissolution Products in Clastogenesis. Carcinogenesis, 15: 2249-2254, 1994.) showed that CHO cells require particle cell contact for genotoxicity to occur. Finally, the Nestmann study exposes cells for 18 h, while previously published studies all used 24 h. It is possible that exposures were simply not long enough in the Nestmann study to exert an effect. Thus, the Nestmann study would be expected to be negative due to the large particle sizes and short exposures. While it would be of value to evaluate the pigment itself, it should be done using respirable-sized particles applied to cells for at least 24 h.

There are other recent papers further showing that unadulterated lead chromate particles are genotoxic to CHO cells, such as:

Grlickova-Duzevik E., Wise, S.S., Munroe, R.C., Thompson, W.D. and Wise, J.P., Sr. XRCC1 Protects against Particulate Chromate-Induced Chromosome Damage and Cytotoxicity in Chinese Hamster Ovary Cells. Toxicological Sciences, 92(1): 96-102, 2006.

Duzevik, E.G., Wise, S.S., Munroe, R.C., Thompson, W.D. and Wise, Sr., J.P. XRCC1 Protects against Particulate Chromate-Induced Chromosome Damage and Cytotoxicity in Chinese Hamster Ovary Cells. Toxicological Sciences, 92(2): 409-415, 2006.

Savery, L.C., Grlickova-Duzevik, E., Wise, S.S., Thompson, W.D., Hinz, J.M., Thompson, L.H. and Wise, Sr., J.P. Role of the Fancg Gene in Protecting Cells from Particulate Chromate-Induced Chromosome Instability. Mutation Research, 626(1-2): 120-127, 2007.

Camrye, E., Wise, S.S., Milligan, P., Gordon, N., Goodale, B., Stackpole, M., Patzlaff, N., Aboueissa, A. and Wise, Sr., J.P. Ku80 Deficiency Does Not Affect Particulate Chromate-Induced Chromosome Damage and Cytotoxicity in Chinese Hamster Ovary Cells. Toxicological Sciences, 97(2):348-54, 2007.

Stackpole, M.M., Wise, S.S., Goodale, B.C. Duzevik, E.G., Munroe, R.C., Thompson, W.D., Thacker, J., Thompson, L.H., Hinz, J.M. and Wise, Sr., J.P. Homologous Recombination Protects Against Particulate Chromate-Induced Genomic Instability in Chinese Hamster Cells. Mutation Research. 625: 145-154, 2007.

Q4. Does NIOSH have a transparent and sound basis for its revised Recommended Exposure Limit for hexavalent chromium compounds?
Yes, NIOSH has a transparent and sound basis for its revised Recommended Exposure Limit for hexavalent chromium compounds.

Q5. Is the new NIOSH policy of providing general exposure assessment recommendations instead of a specific Action Level scientifically justified?
Yes, the NIOSH policy of providing general exposure assessment recommendations instead of a specific Action Level is scientifically justified.

Q6. Are the NIOSH recommendations for worker protection clear and justified?
Yes, the NIOSH recommendations for worker protection are clear and justified.

Q7. Are there additional recommendations for worker protection that should be included?
No, the document provides appropriate recommendations for worker protection.

Sincerely yours,