NIOSH Criteria Document:
Occupational Exposure to Hexavalent Chromium
NIOSH Response to Hexavalent Chromium Peer Review Comments
December 18, 2012

Background

The *NIOSH Criteria for a Recommended Standard: Occupational Exposure to Hexavalent Chromium* was developed to update the NIOSH evaluation of the scientific literature on occupational exposure to hexavalent chromium (Cr[VI]) compounds and the corresponding recommendations for protecting workers from occupational exposure to Cr(VI) compounds. The finalized criteria document supersedes previous NIOSH documents and policy statements on Cr(VI) compounds [NIOSH 1973, 1975, 1988, 2002, 2005a,b].

The intended audiences for the criteria document are other government agency science and policy experts, occupational safety and health professionals, employers, and workers in workplaces with Cr(VI) exposure. The document provides these audiences with current recommendations for preventing and controlling occupational exposure to Cr(VI) compounds based on the NIOSH evaluation of the available scientific literature.

Cr(VI) Criteria Document History

On October 17, 2008, NIOSH announced the availability of the draft document, *NIOSH Criteria Document Update: Occupational Exposure to Hexavalent Chromium* [NIOSH 1998 draft] for public comment until January 31, 2009 [73 Fed. Reg. 61874 (2008)]. NIOSH extended the public comment period by 60 days to March 31, 2009 subsequent to a public request for more time to gather and submit information [74 Fed. Reg. 4752 (2009)]. Eight submissions of public and stakeholder comments were received by the NIOSH Docket Office for the Cr(VI) docket, NIOSH-144. The *NIOSH Response to Hexavalent Chromium Public and Stakeholder Comments* document is available as a separate document.

On October 17, 2008, NIOSH also announced a public meeting for discussion of the draft NIOSH criteria document to be held at the NIOSH Taft Building, Columbia Parkway, Cincinnati, OH, on January 22, 2009 [73 Fed. Reg. 61874 (2008)]. The public meeting was attended by NIOSH scientists, peer reviewers, and stakeholders including government, union, and industry representatives.

The peer review of the NIOSH draft criteria document began at the same time as the public comment period and continued for 60 days beyond the end of the public comment period to May 31, 2009. NIOSH requested peer reviewers with Cr(VI) expertise to review the draft NIOSH document and the public and stakeholder comments received. The NIOSH Docket Office received five submissions from peer reviewers with expertise in the analytical chemistry, toxicology, epidemiology, and/or risk assessment of Cr(VI) compounds.

The charge to the peer reviewers was to objectively review the document to determine whether: 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.

Peer reviewers were asked to consider the following questions:

1. Are the critical studies presented clearly and adequately?
2. Do all of the presented studies use scientifically valid methods and techniques?
3. Are there additional critical studies relevant to occupational exposure to hexavalent chromium compounds that should be included?
4. Does NIOSH have a transparent and sound basis for its revised Recommended Exposure Limit for hexavalent chromium compounds?
5. Is the new NIOSH policy of providing general exposure assessment recommendations instead of a specific Action Level scientifically justified?
6. Are the NIOSH recommendations for worker protection clear and justified?
7. Are there additional recommendations for worker protection that should be included?

This *NIOSH Response to Hexavalent Chromium Peer Review Comments* document provides the NIOSH response to the peer reviewer submissions received on the draft NIOSH document. The peer reviewers' submissions are divided into shorter comments in this document to clearly respond to all of the comments. The charge to peer reviewers, entire peer review submissions, and other information relevant to the criteria document are available on the NIOSH Hexavalent Chromium Criteria Document docket page: http://www.cdc.gov/niosh/docket/archive/docket144.html

Peer Reviewer Comments and NIOSH Responses

Peer Reviewer #1 (no NIOSH response required)

I have reviewed the captioned document with specific reference to the sampling and analysis of hexavalent chromium and the monitoring procedures since this is my area of expertise. In Chapter Three: Measurement of Exposure, recently developed analytical methods have it made possible to determine hexavalent chromium at lower levels than in the past i.e. 0.02 micrograms per sample. These new methods for the determination of hexavalent chromium are cited: a) NIOSH Method 7605 –Hexavalent Chromium by Ion Chromatography; b) NIOSH Method 7703 – Hexavalent Chromium by Field –Portable Spectrophotometry; c) ASTM Method D6832-02 – Standard Test Method for the Determination of Hexavalent Chromium in Workplace Air by Ion Chromatography and Spectrophotometric Measurement using 1,5-diphenylcarbazide; d) International Organization for Standardization (ISO) Method 16740 – Workplace Air – Determination of Hexavalent Chromium in Airborne Particulate Matter – Method by Ion Chromatography and Spectrophotometric Measurement using Diphenylcarbazide; and d) OSHA Method ID-215.

The NIOSH and OSHA methods and particularly the ASTM and ISO methods have been developed by consensus and have been tested and validated and are used routinely throughout the world. The results obtained by these methods are acceptable by the scientific community and are considered valid techniques.

The Criteria Document Update references and reviews these methods particularly with regard to possible interferences and precautions that are necessary to prevent loss and/or reduction of Hexavalent Chromium to Chrome(III). The referenced paper: Sampling and Analysis Considerations for the Determination of Hexavalent Chromium in Workplace Air by: Ashley, Howe, Demange and Nygren gives a comprehensive review of the analytical methods and possible interferences and precautions necessary to eliminate possible problems in the procedures. Also sampling techniques and considerations are reviewed with the various options that are available. The sampling methods suggested are the acceptable and validated procedures used routinely world-wide.

The Criteria Document Update delineates the various methods necessary to determine hexavalent chromium in air and workplace atmospheres. The methods referenced provide the following: 1. low limits of detection; 2. high selectivity; 3. validation; 4. ease of use; and 5. minimization of interferences. All of the mentioned procedures provide scientifically valid methods and techniques and are acceptable to the scientific community. The results from these methods should provide the necessary data for sound and transparent recommendations that are made in the Criteria Document Update. The data and studies are presented clearly and adequately.

Peer Reviewer #2

NIOSH Review Question: Are the critical studies presented clearly and adequately?

Comment #1: 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 [of NIOSH peer reviewer charge; see comment #10].

NIOSH response and revision: The text in Section 6.1 was revised as suggested: "Park et al. [2004] concluded 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."

Comment #2: 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.
NIOSH response and revision: The text in Section 6.1 was revised as suggested.

Comment #3: 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?
NIOSH response and revision: NIOSH agrees that the discussion of the limitations of the EPA 1984 assessment is unnecessary given the more recent, improved data set and its assessment. This discussion was removed from the document to maintain the focus on the recent, more robust risk assessments.

Comment #4: 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).
NIOSH response and revision: The description of Gibb et al. [1986] was removed from Section 6.2 as suggested.

Comment #5: 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.
NIOSH response and revisions: The title of Table 6-2 was revised to "Risk Assessments of the Baltimore Cohorts"; the title of Table 6-1 was revised to "Risk Assessments of the Painesville Cohort".

Comment #6: On page 102, there is reference made to Crump (1995). Crump (1995) is not in the list of references.
NIOSH response and revision: The Crump [1995] reference citation was added.

Comment #7: On page A-8, it indicates that Gibb et al. (2000) 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. (2000) which found that hexavalent chromium exposure was significantly associated only with several of these symptoms. Gibb et al. (2000) 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. (2000) rather than state that "there was considerable exposure misclassification" which is vague and can have a range of meanings.
NIOSH response: NIOSH appreciates the reviewer's request for text clarification. However, Appendix A of the external review draft was a finalized NIOSH policy document, the *NIOSH Testimony to OSHA on the Proposed Rule on Occupational Exposure to Hexavalent Chromium*, and cannot be revised. Appendices A and B of the external review draft were the NIOSH Cr(VI) testimony and post-hearing comments to OSHA, respectively [NIOSH 2005a,b]. These policy documents are not appended to the final NIOSH document as some of the recommendations made in these previous policy statements were updated in the criteria document.

Comment #8: On page A-20, it states that NIOSH Method 7703 has a limit of quantitation of 0.27 µg/m^3, but the recommended REL is only 0.2 µg/m^3. The limit of quantitation is higher than the REL?
NIOSH response and revisions: NIOSH Method 7703 is a method for measuring Cr(VI) levels by field-portable spectrophotometry; it is designed to be used in the field with portable laboratory equipment. It has a higher limit of quantitation (LOQ) than other methods; its estimated LOQ is 0.27 µg [Boiano et al. 2000]. In the final draft document Method 7703 is not recommended for assessing exposures below its LOQ. The other information about Method 7703 in the document remains unchanged.

NIOSH Methods 7605 and OSHA Method ID-215, which have LOQs of 0.06 and 0.03 ug, respectively, can quantitatively assess worker Cr(VI) exposure at the REL of 0.2 $\mu g/m^3$. In the final draft document NIOSH Method 7605, and other validated equivalents, are recommended for assessing workplace exposures relative to the REL.

Comment #9: 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).
NIOSH response and revisions: More specific text was added to sections 6.1 and 7.4.1 as suggested: "packs per day were available for most workers" was revised to "packs per day were available for 70 percent of the cohort".

NIOSH Review Question: Do all of the presented studies use scientifically valid methods and techniques?
Comment #10: 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.
NIOSH response: Park et al. [2004] used packs/day at hire, not pack-yrs at hire, as stated in the Methods section of that study. Based on packs/day at hire, cumulative pack-yrs was calculated as a time-dependent variable. The rationale for using pack-yrs as a predictor of lung cancer mortality was primarily biological (exposure response should increase with dose) but model-fit also supported that choice. No change was made to the document.

Comment #11: 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 [CDC 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.

NIOSH response: The model results are incorrectly interpreted in this comment, possibly due to unclear exposition in Park et al. [2004]. The smoking effect was observed to largely depend only on the first 30 pack-yrs of exposure; additional cumulative smoking exposure accruing beyond 30 pack-yrs did not appreciably increase lung cancer risk. Thus a worker with greater than 30 pack-yrs is estimated to have the effect of 30 pack-yrs (a highly significant and elevated effect) plus a smaller additional, non-significant effect of the pack-yrs exceeding 30. This is not an inverse relationship but rather an apparent plateau effect. This observation is consistent with many findings where the exposure response for a carcinogen tends to attenuate with increasing cumulative exposure [Stayner et al. 2003]. The NIOSH findings confirm that Cr(VI) at lower exposures does not reach the level of risk associated with heavy smoking. However, the excess lifetime lung cancer mortality risk established by Park et al. [2004] of 255/1000, based on the OSHA PEL for Cr(VI) at that time, exceeds the average excess risk in the general smoking population. No change was made to the document.

NIOSH Review Question: Are there additional critical studies relevant to occupational exposure to hexavalent chromium compounds that should be included?
Comment #12: 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.
NIOSH response and revision: Information from Chen et al. [2008] was added to Section 3.3.1.1, Measurement of chromium in urine.

Peer Reviewer #3

NIOSH Review Question: Are the critical studies presented clearly and adequately?
Comment #1: Section 4.1.1.1.1: I'd suggest that the authors explicitly state that the 1994 Castle Hayne study [Pastides et al. 1994a] 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.
NIOSH response and revisions: The analyses of the few available human studies that are best suited for quantitative risk assessment are presented in Chapter Six, Assessment of Risk, rather than indicating whether each study in Chapter Four, Human Studies, is suitable for quantitative risk assessment or not. Many of the Cr(VI) epidemiology studies do not contain adequate data for quantitative risk assessment. Although this was already stated at the end of Section 4.1.1.1, the following statement was added at the end of the of Chapter Six overview to clarify this approach: "Analyses of epidemiologic studies with the most robust data for quantitative risk assessment are described in Chapter 6, Assessment of Risk."

The draft document already stated that the confidence intervals of Pastides et al. [1994a] are 90%. However, this note was added in parentheses to the last paragraph of Section 4.1.1.1, Pastides et al. [1994a]: (Note that the authors reported 90% confidence intervals,

rather than 95%.) Additional revisions to address this comment include: the term "for mortality" was added before the odds ratio on page 41 and "cancer OR" was revised to "OR for cancer".

Comment #2: Sections 4.1.1.1.2-4.1.1.1.3: it would benefit the discussion to more clearly describe the relative strengths and limitations of the Gibb et al. (2000) 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).
NIOSH response and revisions: More detailed information was added to these two study descriptions in Chapter Four as suggested. Text was added to Chapter Six, Risk Assessment, in the introduction and Sections 6.1 and 6.5 to clarify the NIOSH decision to select the Gibb data set for analysis. Goldbohm et al. [2006] and van Wijngaarden et al. [2004] were cited in Chapters Six and Four, respectively (see also the NIOSH response to Peer reviewer 3, comments 4, 6, and 7.)

Comment #3: Section 4.1.1.1.3: 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.
NIOSH response and revision: This text was revised as suggested. "A rationale for selection of these categories was not described" was replaced with the explanation provided on page 452 of Luippold et al. [2003], "to allow for nearly equal numbers of expected deaths from cancer of the trachea, bronchus, or lung in each category".

Comment #4: 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).
***NIOSH response and revisions*:** These study descriptions were expanded as suggested. More cohort characteristics and exposure findings were added to Section 4.1.1.1.3, Luippold et al. [2003]; person-years total were added to the Section 4.1.1.1.2 description of Gibb et al. [2000]. The reader was also referred to other sections of the document and other sources with more detailed descriptions of the epidemiologic studies used in risk assessment.

NIOSH Review Question: Do all of the presented studies use scientifically valid methods and techniques?
Comment #5 (no NIOSH response required): Yes, the Baltimore and Painesville cohort studies appear to be well-conducted epidemiological investigations with reasonable approaches to exposure assessment and statistical analysis.

NIOSH Review Question: Are there additional critical studies relevant to occupational exposure to hexavalent chromium compounds that should be included?
Comment #6: 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 Update. The paper also comments on the appropriateness of performing a pooled analysis of the Baltimore and Painesville data.

NIOSH response and revisions: A description of the Birk et al. [2006] epidemiologic study was added to Chapter Four, Human Health Effects, as suggested. Goldbohm et al. [2006] was cited in the introduction of Chapter Six, Assessment of Risk. A sentence was added noting the Van Wijngaarden et al. [2004] analysis in the description of Luippold et al. [2003] in Chapter Four, Section 4.1.1.1.3.

NIOSH Review Question: Does NIOSH have a transparent and sound basis for its revised Recommended Exposure Limit for hexavalent chromium compounds?
Comment #7: 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 μg/m^3 vs. 0.2 μg/m^3, respectively, based on a linear relative risk model (which assumes no threshold) and the information provided on page 100 (3rd paragraph) of the Criteria Document Update.
NIOSH response and revisions: Some basic epidemiology and risk assessment information was added to the introduction to Chapter Six, including the Goldbohm et al. [2006] reference as suggested. An explanation of the NIOSH selection of the Gibb et al. [2000b] data for analysis was also added to the Chapter Six introduction. Text stating why NIOSH determined that the Gibb et al. [2000b] data was the best data set available for quantitative risk assessment was added to the document where the basis for the REL is presented including Sections 6.4 and 7.4 of the document; it was already stated in Section 7.9.

The Baltimore and Painseville cohorts [Gibb et al. 2000b; Luippold et al. 2003] are the best studies for predicting Cr(VI) cancer risks because of the quality of their exposure estimation, large numbers of workers available for analysis, extent of exposure, and years of follow-up [NIOSH 2005a]. NIOSH selected the Baltimore cohort [Gibb et al. 2000b] for analysis because it had the greater number of lung cancer deaths, better smoking histories, and a more comprehensive retrospective exposure archive.

Comment #8: 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 μg/m^3?
NIOSH response: Using just the ever-smoker data as of date of hire produced a significant degradation in model fit. NIOSH would predict that the model without cumulative smoking would somewhat overestimate the Cr(VI) effect and result in a lower proposed REL because the estimated cumulative smoking and cumulative Cr(VI) levels would be positively associated (both generally increasing with age).

Comment #9: 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 Update could expand on this issue.
NIOSH response and revisions: The NIOSH risk assessment was conducted on data from workers whose primary exposure was to Cr(VI) compounds, chromate production workers. One of the advantages of the chromate production data is its relative lack of potentially confounding exposures. This allowed for the derivation of a REL providing the best available assessment of risk of occupational exposure to Cr(VI) compounds. NIOSH agrees that many workers with Cr(VI) exposure, including welders, are exposed to complex mixtures in the workplace. There is not a dataset currently available that is suitable for conducting a quantitative risk assessment of Cr(VI) exposure in welders or

other Cr(VI) workplaces other than chromate production. Text was added in the introduction to Chapter Six and Section 7.4 stating that data is not currently available for the quantitative risk assessment of welders or other Cr(VI)-exposed workers other than chromate production.

Although a quantitative risk assessment of welders' risk is not possible, a qualitative assessment suggests a comparable, if not greater, risk. The stainless steel welding studies which address Cr(VI) exposures are limited but rough estimates of risk are possible that demonstrate potential risk in these workers. In a large European study of welders [Simonato et al. 1991], there were 20 lung cancer deaths in welders predominantly working with stainless steel (versus 122 lung cancer deaths in the Baltimore chromate cohort). Among stainless steel welders in the European cohort with more than 30 years' since first exposure, the SMR was 3.12 (95% CI: 1.15-6.79) but based on only 6 cases. Among those stainless steel welders with > 0.5 mg-yr/m^3 Cr(VI), there were 8 lung cancer deaths corresponding to SMR = 1.75 [Gerin et al. 1993]. The four cases with the highest cumulative exposure had a mean cumulative exposure to Cr(VI) of 2.5 mg-yr/m^3. In the Baltimore cohort, there were 24 lung cancer deaths in the range 0.37-5.3 mg-yr/m^3 Cr(VI) for an SMR = 3.41 [Park et al. 2004]. Thus the excess lung cancer mortality among European stainless steel welders exposed to Cr(VI) was roughly comparable to that observed in chromate workers. A review of welder lung cancer risk by Moulin [1997] identified 5 studies in addition to the Simonato et al. [1991] study, with estimated relative risks for lung cancer in stainless steel welding in the range from 1.23(95% CI: 0.75-1.90) to 3.3(95% CI: 1.20-9.30).

Cr(VI) exposures in welding fume differ in particle size from those in many other industrial settings such as chromate production. Welding condensation fume consists of relatively small particulates while dust exposures, even when sampled for the respirable fraction, will include much larger particles. This would argue for higher deposition rates in the lungs for welding emissions and, for otherwise equivalent chromium compounds, possible higher potency of welding fume for lung diseases.

NIOSH recommends that workers' exposure to welding fume mixtures be reduced to the lowest concentration technically feasible for each chemical in the welding mixture [NIOSH 1988]. This is the best practice that can be recommended for this mixed exposure until adequate data become available for quantitative risk assessment of welding fume mixtures. More information about welders' Cr(VI) exposures, the variables affecting Cr(VI) exposure, and recommendations for controlling welding exposures were added to Chapters Two and Eight.

Comment #10: 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), there are several studies with quantitative exposure assessment demonstrating adverse male reproductive effects.

NIOSH response and revisions: It may be possible to use benchmark modeling to assess the reproductive risk of exposure to Cr(VI) compounds if adequate exposure-effect data are available. NIOSH has not conducted quantitative analyses of the reproductive data. NIOSH selected lung cancer as the critical effect of occupational airborne exposure to Cr(VI) compounds. The REL, which is intended to protect workers against lung cancer death, should also protect workers against non-cancer health effects.

A new section, 5.3.6, Reproductive Studies, was added to Chapter Five providing information about other agencies' reviews of the reproductive effects of Cr(VI) compounds, including the California EPA assessment.

NIOSH Review Question: Are the NIOSH recommendations for worker protection clear and justified?

Comment #11: 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.

NIOSH response and revisions: More information was added to Chapter Two about Cr(VI) exposure in welders and the variables affecting Cr(VI) exposure in all workplaces. Additional recommendations for controlling workplace exposures, particularly welding exposures, were added to Chapter Eight.

Peer Reviewer #4

General Comments (no NIOSH response required):

I have carefully reviewed the NIOSH Hexavalent Chromium Criteria Document Update with particular consideration of whether the conclusions and recommendations in the document are scientifically reasonable, appropriately protective, and transparently documented. Overall, I am quite satisfied on all counts. The document is quite well written and appears to be relatively error free. The review of the scientific evidence for the health effects of Cr(VI) is thorough and balanced. The derivation of the REL is adequately supported and clearly described, and I agree with the NIOSH recommendations for protection of workers. Specific comments are provided below.

Comment #1: The summary of the risk assessment in Section 7.4.3 needs to be expanded. There are a number of important considerations that are to some extent discussed elsewhere in the document but need to be presented together here in order to

provide an appropriate perspective on the REL. These considerations should also be briefly summarized in the introduction, where the REL is first mentioned:

- In the studies on which the REL is based, the average exposures were on the order of 50 micrograms per cubic meter, more that 100-fold higher than the REL. There is strong evidence that at the relatively high concentrations observed in the workplace studies Cr(VI) exposure would be associated with oxidative stress and genotoxicity. However, there are a number of factors that suggest the cellular effects of Cr (VI) are highly dose-dependent, such that carcinogenic potencies observed in these studies would overestimate, perhaps significantly, the potency at the REL.
- The REL is based on studies where the exposure was to soluble forms of Cr(VI). However, there is evidence from animal studies that less soluble Cr(VI) compounds may be more potent than the soluble forms. Therefore the risks at the REL may be higher in different workplace exposures.
- NIOSH estimates that lifetime occupational exposure at the REL would be associated with an increased risk of roughly 1/1000, which is a level of risk consistent with those for other carcinogens in recent OSHA rules. However, until recently OSHA's stated intent was to limit worker risks to 1/10,000, which is more consistent with the lifetime risk for noncancer fatalities in the workplace. Moreover, OSHA's acceptance of 1/1000 risk is driven to a large extent by the regulatory requirement that OSHA balance costs and benefits.

***NIOSH response and revisions*:** The reviewer suggests that potency increases more than proportionately with increasing exposure concentration, i.e. a positive dose-rate effect, and therefore occupational studies may be overestimating low dose risk. In a study examining this and other features of the Cr(VI)-lung cancer exposure-response relationship, the dose-rate effect in the Baltimore chromate worker cohort was observed to be slightly negative but with considerable uncertainty [Park and Stayner 2006]. This finding offers weak evidence favoring a negative dose-rate effect, which argues against overestimation and for underestimation of risk at low exposure levels from the Baltimore chromate study. In occupational studies even with an extensive exposure history and as large as this one, it would be difficult to obtain a precise estimate of the dose-rate effect.

The information about the REL was added to Section 1.3 as suggested. This information was already presented in Section 7.4, Basis for the REL, and Section 7.5, Applicability of the REL to All Cr(VI) Compounds so it was not added to additional sections. Section 7.4.3 is intended to be a summary of the risk assessment information only.

Comment #2: Given the above considerations as a whole, I am comfortable with the REL. However, I am not comfortable with the implication that 1/1000 risk can be justified as a generally reasonable level of protection for the worker. For example, I would be very uncomfortable with a REL for vinyl chloride that was associated with 1/1000 risk, because I believe that the carcinogenic potency of vinyl chloride can be estimated very accurately. In the case of Cr(VI) I am comfortable with the REL because, as I described in the first bullet above, I believe the carcinogenic potency at the REL is greatly over-estimated. My concern is that the criteria document update should clearly describe the considerations that factor into the selection of the REL, and should not set a precedent for general acceptance of a 1/1000 lifetime cancer risk increase in workers.

***NIOSH response and revisions*:** The updated Cr(VI) REL was selected based on the results of the Park et al. [2004] quantitative risk assessment at a risk of approximately one excess lung cancer mortality per 1000 workers. This level of risk is consistent with recent NIOSH recommendations. Text consistent with recent NIOSH policy documents was added to Section 7.4, Basis for the NIOSH REL, to clarify this NIOSH policy. In addition a risk table, Table 7-1, was added to Chapter Seven which presents the exposure levels associated with an array of risks.

As described in Chapter Seven, NIOSH derived the REL based on the characteristics and effects of Cr(VI) compounds and quantitative risk assessment results. Analytical feasibility and achievability in the workplace were additional considerations.

Comment #3: I found it difficult to put the epidemiological studies into context because there was often an inadequate characterization of the workplace exposure concentrations. For example, on page 42 of the document I was able to estimate an average exposure concentration of around 43 micrograms per cubic meter for Gibb's Baltimore study only because the average length of employment was given as about 3.3/3.7 years (for whites/non-whites) and the mean cumulative exposure was given as 0.13 and 0.18 micrograms per cubic meter - years. It wasn't until I reached appendix B (NIOSH post-hearing comments to OSHA) that I was able to verify my estimate (p. B4). Since the effects of Cr(VI) are highly concentration dependent, the mean and range of exposures should be provided for all studies. If exposure concentrations were not measured, this should be stated.
***NIOSH response and revisions*:** The mean cumulative Cr(VI) or CrO_3 exposure and/or range was included in the descriptions of the three studies with air concentration sampling data. The average concentrations for the Luippold et al. [2003] study were added to the text as reported in a separate paper by Proctor et al. [2003] (the study description had referred readers to that paper.) The average found by the reviewer in Appendix B [NIOSH 2005b] was calculated using the Gibb et al. information noted by the reviewer. The average concentration was added to the text, Park and Stayner [2006] and NIOSH [2005b] were cited.

Note: Appendix B of the external review draft was the NIOSH post-hearing comments to OSHA on its Cr(VI) rulemaking [NIOSH 2005b]. Appendices A and B of the external review draft, the NIOSH testimony and the NIOSH post-hearing comments on the OSHA Cr(VI) rulemaking, respectively, are not appended to the final NIOSH document as some of the recommendations in these earlier policy statements were updated in response to external review comments.

Comment #4: I could not find an adequate discussion of the implications of measuring total Cr(VI) exposure rather than inhalable or respirable. My understanding is that all of the standard methods referred to in the document are for total inhaled Cr(VI). The implications of this are that for insoluble Cr(VI) compounds, larger-sized particles that would be deposited in the nasopharynx and swept into the GI tract would be included in the estimate of lung cancer incidence along with the smaller particles that actually reach the lung. This would tend to, in part, offset the fact that the less soluble forms may be

more potent than the soluble forms on which the REL is based. Apparently, although it is not clear, DECOS would have preferred using Cr(VI) in inhalable dust (p.95). Was there a rationale for this?
***NIOSH response*:** The determination of total Cr(VI) or inhalable Cr(VI) is determined by the type of sampling conducted rather than the analytical methods used to analyze the samples. Inhalable sampling actually collects a greater mass than "total" mass. International voluntary consensus analytical standards rely on the sampling of inhalable, thoracic or respirable fractions. In the industrial hygiene community there is a movement away from the recommendation of the measurement of 'total' particulate matter towards inhalable and other relevant fractions.

The NIOSH criteria document focuses on total Cr(VI) measurements as this is how the available workplace data was collected and measured. The data on which the NIOSH REL is based are dust samples measured as total Cr(VI). Therefore the NIOSH REL and the recommendations in the criteria document are for total Cr(VI). NIOSH will provide updated information about workplace sampling and analysis as it becomes available in the NIOSH Manual of Analytic Methods, available at:
http://www.cdc.gov/niosh/docs/2003-154/

DECOS [1998] assumed that total dust measurements did not differ considerably from inhalable dust measurements due to the relatively small aerodynamic diameters of these particulates. NIOSH is not aware of the rationale for this conversion from total to inhalable measurements.

Comment #5: Minor comments:
a) p. 34, line 192: "urinary Cr(VI) levels" should be "urinary Cr levels"
***NIOSH response and revisions*:** Revised as suggested.
b) p. p. 37, lines 272-273: This sentence is confusing. 8-OHdG excretion in urine could not possibly be induced by Cr(VI) exposure *in vitro*. It appears that Gao is not an *in vitro* study.
***NIOSH response and revisions*:** This text was rewritten to clarify the results of Gao et al. [1994].
c) p.73, line 57: Liu et el. 1997 a or b?
***NIOSH response and revisions*:** Liu et al. 1997a; this was revised.
d) p. 74, line 72: "Tsapakos 1983a" should be "Tsapakos and Wetterhahn 1983"
***NIOSH response*:** This was cited correctly as Tsapakos and Wetterhahn [1983] in the external review draft.
e) p. 93, lines 134-137. I found this sentence confusing. Does it mean that, if there is a threshold, it is likely to be below 16/29 micrograms per cubic meter?
***NIOSH response*:** This sentence describes the threshold models that were evaluated using profile likelihood. The best estimate (point estimate) at this time is that if there is a threshold, it is < 0.5 $\mu g/m^3$ Cr(VI); these observations are consistent with a threshold of 0.0 . The upper confidence limit for such a threshold consistent with the observed data is 16 or 29 $\mu g/m^3$ Cr(VI), for models with and without the exposure-race interaction, respectively, for the Cr(VI)-lung cancer effect. No change was made to the document.

Comment #6 (no NIOSH response required): Opinion regarding Action Levels: I agree with the new NIOSH policy to provide general exposure assessment recommendations instead of specific action levels. I believe action levels are better determined on a workplace-specific basis, considering the variability of exposures, monitoring methods, etc., in order to assure protection of the worker at the level of the REL.

Peer Reviewer #5

General Comments (no NIOSH response required): 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.

NIOSH Review Question: Are the critical studies presented clearly and adequately?
Comment #1: 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.
NIOSH response and revisions: This text in Section 5.2 was revised to clarify the results of Wise et al. [1993] and Xie et al. [2004].

NIOSH Review Question: Do all of the presented studies use scientifically valid methods and techniques?
Comment #2 (no NIOSH response required): Yes, all of the presented studies use scientifically valid methods and techniques.

NIOSH Review Question: Are there additional critical studies relevant to occupational exposure to hexavalent chromium compounds that should be included?
Comment #3: 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:
1) 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.
2) 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.

NIOSH response and revisions: Holmes et al. [2006a] and Wise et al. [2006b] were added to Section 5.2 as suggested.

Comment #4: 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:
1) 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.
2) 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.
3) 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.
NIOSH response and revisions: Wise et al. [2006], Xie et al. [2009], and Holmes et al. [2006b] were added to Section 5.2 as suggested.

Comment #5: 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:
1) 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.
2) 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.
NIOSH response and revisions: Xie et al. [2007, 2008] were added to Section 5.2 as suggested.

Comment #6: 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:
1) 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.
2) Grlickova-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.
3) 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.
4) 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.
5) 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.
NIOSH response: This information and these references were used in the response to the public comments regarding the carcinogenicity of lead chromate.

NIOSH Review Question: Does NIOSH have a transparent and sound basis for its revised Recommended Exposure Limit for hexavalent chromium compounds?
Comment #7 (no NIOSH response required): Yes, NIOSH has a transparent and sound basis for its revised Recommended Exposure Limit for hexavalent chromium compounds.

NIOSH Review Question: Is the new NIOSH policy of providing general exposure assessment recommendations instead of a specific Action Level scientifically justified?
Comment #8 (no NIOSH response required): Yes, the NIOSH policy of providing general exposure assessment recommendations instead of a specific Action Level is scientifically justified.

NIOSH Review Question: Are the NIOSH recommendations for worker protection clear and justified?
Comment #9 (no NIOSH response required): Yes, the NIOSH recommendations for worker protection are clear and justified.

NIOSH Review Question: Are there additional recommendations for worker protection that should be included?

Comment #10 (no NIOSH response required): No, the document provides appropriate recommendations for worker protection.

NIOSH Conclusion

NIOSH followed a rigorous peer, stakeholder and public review process in order to develop the *NIOSH Criteria for a Recommended Standard: Occupational Exposure to Hexavalent Chromium.* This *NIOSH Response to Hexavalent Chromium Peer Review Comments* documents the policy and content changes and additions to the criteria document made by NIOSH in response to the peer review comments received during the external review process. NIOSH appreciates the time and effort taken by these expert peer reviewers to provide their comments and expert input to strengthen this document. The final document, *NIOSH Criteria for a Recommended Standard: Occupational Exposure to Hexavalent Chromium,* will be published and made available on the NIOSH Web site when approved for public dissemination by the NIOSH Office of the Director.

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