**Summary**

Reviewers agree that the document provides adequate information to show that metallic chromium and other substances containing hexavalent chromium can be absorbed through the skin and can cause localized health hazards. One reviewer agrees that exposure creates systemic health hazards, while another reviewer acknowledges that studies provide data showing systemic effects, but thinks that information related to the study needs to be expanded. Reviewers disagree on whether there are immune-mediated responses associated with dermal exposure to the chemical. Regarding the clarity of assigned notations, there are differing opinions and recommendations, as outlined below.

**Recommendations**

- Information related to the Lin et al, 2009 study, described in the document, needs to be expanded. (Q1, Q2 Reviewer 2)
- Add elicitation “NOEL”– as exposure is ubiquitous. (Q3, Q6 Reviewer 1)
- In the first line (SYS) of Table 1, revise “Available Data” column to “Limited human data; absence of animal data.” (Q9, Reviewer 2)
- In Table 2 and accompanying text, it should be conveyed that the designations of carcinogenic potential refer to lung cancers resulting from inhalation exposure, not to oral or other exposures. (Q9, Reviewer 2)
- The systemic effects of hexavalent chromium from non-dermal routes of exposure should be briefly summarized. (Q10, Reviewer 2)
- Provide more clinical interpretation. (Q11, Reviewer 1)
- For clarity to the reader, revise the abbreviation “Cr” for hexavalent chromium to Cr+6, CrVI, or similar. (Q11, Reviewer 2)
- NB Add statement re data (or lack of) on:
  a) Photoirritation
  b) Photoallergic Contact Dermatitis
  c) “Validity” of penetration algorithm (Q13, Reviewer 2)

**Suggested additional scientific data to review:**

Verbatim Reviewer Comments

1. Does this document clearly outline the systemic health hazards associated with exposures of the skin to the chemical? If not, what specific information is missing from the document?

Reviewer 1:
Yes

Reviewer 2:
The document provides adequate information to show that hexavalent chromium can be absorbed through the skin of humans.

As far as systemic effects from skin exposure, the document describes a case study (Lin et al., 2009) in which a worker whose legs were exposed to 1.42 M chromic acid for 10 minutes experienced systemic symptoms (acute pulmonary edema, liver function impairment, anemia, and acute renal failure). This is the only data provided on systemic effects from skin exposures. The information related to this case study needs to be expanded, as discussed in Question 2, below.

2. If the SYS or SYS (FATAL) notations are assigned, is the rationale and logic behind the assignment clear? If not assigned, is the logic clear why it was not (e.g., insufficient data, no identified health hazard)?

Reviewer 1:
NA

Reviewer 2:
In order to strengthen the logic and rationale for the SYS notation, it should be discussed whether or not the effects in the single case reported by Lin et al. (2009) are consistent with the known systemic effects of hexavalent chromium (by other exposure routes) in humans and/or experimental animals.

3. Does this document clearly outline the direct (localized) health hazards associated with exposures of the skin to the chemical? If not, what specific information is missing from the document?

Reviewer 1:
Yes. Add elicitation “NOEL”– as exposure is ubiquitous.

Reviewer 2:
The document clearly shows that skin contact with hexavalent chromium causes direct effects including corrosive effects.

4. If the DIR, DIR (IRR), or DIR (COR) notations are assigned, is the rationale and logic behind the assignment clear? If not assigned, is the logic clear why it was not (e.g., insufficient data, no identified health hazard)?

Reviewer 1:
Yes
Reviewer 2:
The rationale for the assignment of the DIR(COR) notation is clearly presented.

5. Does this document clearly outline the immune-mediated responses (allergic response) health hazards associated with exposures of the skin to the chemical? If not, what specific information is missing from the document?

Reviewer 1:
No. As exposure is ubiquitous, as elicitation "NOEL". See extensive documentation presented to EPA about 3 years ago.

Reviewer 2:
The document clearly shows that hexavalent chromium has been definitively shown to cause immune-mediated responses after skin contact.

6. If the SEN notation is assigned, is the rationale and logic behind the assignment clear? If not assigned, is the logic clear why it was not (e.g., insufficient data, no identified health hazard)?

Reviewer 1:
No. Add elicitation "NOEL" because of ubiquitous exposure.

Reviewer 2:
The rationale for the SEN notation is clearly presented.

7. If the ID^{SK} or SK were assigned, is the rationale and logic outlined within the document?

Reviewer 1:
NA

Reviewer 2:
Not applicable

8. Are the conclusions supported by the data?

Reviewer 1:
No. See #5 and #6 above.

Reviewer 2:
Not applicable.

9. Are the tables clear and appropriate?

Reviewer 1:
Yes

Reviewer 2:
I have the following comments on the tables:

Table 1, first line (SYS) - suggest revising "Available Data" column to "Limited human data; absence of
animal data."

Table 2(carcinogenic designations) - It should be conveyed in the table, and also in the text discussing the table, that these designations of carcinogenic potential refer to lung cancers resulting from inhalation exposure, not to oral or other exposures. Until the completion of the recent (2007) National Toxicology Program oral cancer bioassay of chromium in drinking water, the carcinogenic potential by the oral route was unknown. Governmental agencies are currently just starting to consider the results of this study as the basis for the oral cancer risk assessment for hexavalent chromium. This is important because the lung cancers caused by inhalation are thought to be a result of direct contact of the lungs, and so would not necessarily be considered relevant to dermal exposures.

10. Is the document organized appropriately? If not, what improvements are needed?

Reviewer 1:
Yes

Reviewer 2:
The document is organized appropriately. As above, the systemic effects of hexavalent chromium from non-dermal routes of exposure should be briefly summarized.

11. Is the language of the manuscript acceptable as written? If not, what improvements are needed?

Reviewer 2:
Yes. More useful by providing clinical interpretation – per #5 and #6.

I suggest that the abbreviation "Cr" for hexavalent chromium be revised to Cr+6, CrVI, or similar. Even though the abbreviation "Cr" is defined as meaning "hexavalent chromium" in the document, it might be confusing to the reader who might mistakenly believe that it refers to total chromium, including trivalent chromium.

12. Are you aware of any scientific data reported in governmental publications, databases, peer reviewed journals, or other sources that should be included within this document?

Reviewer 1:
Yes. See #5 above.

Reviewer 2:
An additional reference reviewing the information on hexavalent chromium and contact dermatitis is:

13. What is your final recommendation for this manuscript? (Do you agree with the scientific rationale that serves as a basis for the skin notation assignments?)

Reviewer 1:
Acceptable. Points noted in #5 would help users.

NB Add statement re data (or lack of) on:
a) Photoirritation
b) Photoallergic Contact Dermatitis
c) "Validity" of penetration algorithm

Reviewer 2:
I agree without qualifications with the DIR(COR) and SEN notations.

I agree with the SYS notation pending the addition of the information noted in Question 2, above, and only if this information supports the conclusion that the systemic effects are consistent with the known systemic effects of hexavalent chromium.