

NCEH/ATSDR Comments on IRIS Hexavalent Chromium Documents  
Submitted by: Paula Burgess MD, MPH

We find the Charge to External Reviewers appropriate and the Toxicological Review well written, especially the section on mode of action. The oral RfD of  $9 \times 10^{-4}$  mg/kg-day is consistent with ATSDR's chronic oral MRL for hexavalent chromium, on which the analysis was based.

**Specific comment on cancer**

Hexavalent chromium appropriately has been classified as likely to be carcinogenic to humans by the oral route of exposure. Previous to the publication of the NTP (2008) study, the cancer classification of hexavalent chromium by the oral route of exposure was indeterminate. The weight of evidence is scientifically supported and clearly described. However, there is statement on page 172; line 29 that perhaps is too strong. It states "The available studies show that hexavalent chromium induces tumors in the stomach of humans (Beaumont et al., 2008)..." This statement could be viewed as inconsistent with "likely to be carcinogenic to humans" and is also inconsistent with other discussions of the human cancer data in TR. For example, page 168, lines 10- 14: "A moderately elevated risk of stomach cancer mortality was seen in Jinzou (Liaoning Province, China), but this risk has not been established (or examined) in other populations exposed to drinking water contaminated with hexavalent chromium. The epidemiologic data are not sufficient to establish a causal association between exposure to hexavalent chromium by ingestion and cancer."

**Minor comments and edits**

Page 10, lines 15-20: References are needed when specific data are presented.

Page 15, line 6-8: In the sentence: "While these studies demonstrate placental transfer of chromium, they are of limited use for assessing embryonic exposure to chromium due to maternal oral exposures to hexavalent chromium" I suggest changing "due to" to "as a result of"

Section 3.5: The TR uses the term "physiologically-based toxicokinetic models (PBTK)" but "physiologically-based pharmacological models (PBPK)" is more universally recognized.

Page 27, line 24: Here and everywhere – Kerger et al. (2009) is not in the reference list.

Page 60, line 7: Typo "stidu" should be "study"

Page 68, lines 15 and 16: The sentence: "An increase in the incidence of mild-to-moderate fatty change was observed in females only at  $\geq 0.94$  mg hexavalent chromium/kg-day." Change to: "An increase in the incidence of mild-to-moderate fatty change was observed only in females at  $\geq 0.94$  mg hexavalent chromium/kg-day."

Page 94, line 28: Typo “coulc” should be “could”

Page 96, line 4: In the sentence: “The NTP studies were designed to replicate the Zahid et al. (1990) study (described above) and thereby provide data to either refute or confirm findings of adverse male reproductive effects.” I suggest that “expand or” be added before the word “replicate”. NTP did more than just replicate the Zahid study.

Page 101, line 9: “necropsy; organ weights (liver, kidneys, right cauda epididymis right epididymis, prostate” needs a comma after “cauda epididymis”.

Page 114, end: Section 4.3 on reproductive and developmental toxicity studies goes on for 30 pages. A summary of all these studies would have been helpful.