This review focuses on information provided in the revised Public Health Goal for Hexavalent Chromium in Drinking Water proposal and published work that has become available since the preparation of the previous proposal in 2005. As pointed out in the earlier proposal, considerable evidence is available from rodent studies and from epidemiological studies of occupational exposures that Cr(VI) is a lung carcinogen. At the time of the earlier proposal, however, there was no clear evidence for oral Cr(VI) carcinogenicity in humans or rodents, and significance of data on the effects of inhaled Cr(VI) on gastrointestinal cancers in humans were not fully appreciated. These deficiencies in the data presented in the previous proposal are largely overcome in the revised proposal. Evidence is now provided to support the following important claims: 1) Inhalation of Cr(VI) is associated with increased gastric, as well as, lung cancers from occupational exposures. 2) Consumption of water heavily contaminated with Cr(VI) is associated with gastric cancers in Chinese villagers. 3) High levels of Cr(VI) in drinking water produce intestinal cancers in rodents. Each of these points will be considered in the following paragraphs along with an expression of concern about the method used to derive a PHG in drinking water from these data.

The current PHG proposal includes a valuable analysis of the large body of studies that report the cancer incidences in lung and other organs, including the stomach, from occupational exposures to high levels of Cr(VI) in air. As pointed out in the proposal, it is indeed likely that a portion of inhaled Cr(VI) is transported out of the lung and into the digestive tract by ciliary action in the upper lung. However, no studies were cited that experimentally characterize this phenomenon for soluble or particulate Cr(VI) compositions, and the level of ingested Cr(VI) following its inhalation remains an important issue to be resolved. Nevertheless, when taken together, the results of at least 10 of the 30 studies that met the inclusion criteria support an association of occupational Cr(VI) exposure with cancers of the stomach, as well as the lung.

Applying the only incident of high-level exposure to Cr(VI) in drinking water of a sufficiently large population group for statistical analysis of results occurred in villagers in Liaoning Province, China between 1970-1978. This study and its interpretation have been the subjects of controversy for reasons described in the proposal and in recent published commentaries (Smith A. Epidemiology 2008;19: 24-26). The most recent effort to glean useful information from this study has been published in a peer-reviewed paper by Beaumont et al. (Epidemiology 2008;19: 12-23). Based on an apparently thorough statistical analysis of the published data, the authors concluded that there was a strong association of increased stomach cancer risk with exposure to Cr(VI) in the study region. Remaining concerns in the interpretation of these results for the present purpose include the fact that Cr(VI) levels in the water were high (up to 20 ppm), that no direct analyses of Cr(VI) in tissues or excreta were conducted, and that the lag period between the time of exposure and the time of the observation period was only
about 14 years. This short lag time for the onset of stomach cancer suggests that perhaps additional carcinogenic stresses may have existed in this population. Indeed, as pointed out in the Beaumont et al. (2008) paper, the prevalence of *H. pylori* bacterial infection of the stomach apparently is extremely high in rural China, i.e. 60-80%, which clearly can be an exacerbating factor in the carcinogenic effects of Cr(VI). A further cautionary note in the interpretation of the human cancer data apparently comes from a study in 453 communities in Nebraska (Bednar CM and Kies C, J Am Water Resour Assoc. 1991;27:631-635.) No association was found in this study between low levels of Cr(VI) in drinking water (up to 10 ppb) with total cancer mortality. This study, to which this reviewer does not have ready access, seems to be highly relevant for the development of safe standards for Cr(VI) in water with relatively low contamination levels, and without obvious exacerbating factors, but was not discussed in the current PHG proposal. Indeed, this latter study apparently can provide dose-response data that could test the validity of the various extrapolation methods used in the PHG proposal to project low dose effects in humans based on high dose exposures in rodents.

The major new experimental findings to be considered in the current proposal are the cited NTP 2007a and 2007b rodent studies of Cr(VI) subchronic and chronic toxicity, respectively. Of particular relevance for the present purpose is the observation of “focal ulceration, hyperplasia, and metaplasia of the glandular stomach” in rats and mice that we exposed to high levels of Cr(VI) (1,000 mg/L) in the drinking water for the 3-month duration of the subchronic exposure experiment. These effects are often considered to be pre-cancerous conditions. Interestingly, an additional possible precancerous effect, histiocytic infiltration, was seen in the duodenum and some other tissues at the lowest Cr(VI) concentrations used in these studies, i.e. 62.5 mg/L. In the chronic exposure studies with rats, tumors were found in the mouth and tongue with significantly greater numbers of tumors in males and females exposed to 516 mg/L Cr(VI) in drinking water. No treatment related increases in tumors of the stomach or lower gastrointestinal tract were observed in this species. In contrast, in mice, treatment-related tumors were observed in the small intestine but not in the mouth. The tumor incidences for all sites in the small intestine were significantly increased at exposure levels of 85.7 mg/L dichromate and higher. Thus, the results of these recent subchronic and chronic studies provide evidence for cancer-related effects in the small intestine of rodents of 62.5 mg/L or higher dichromate in drinking water.

Taken together, these new studies provide evidence for the carcinogenic effects of high levels of Cr(VI) in drinking water. The effort to develop a safe dose standard for Cr(VI) in drinking water, however, is complicated by the fact that the human and rodent cancer studies that were considered in the proposal involved only very high doses of Cr(VI). These high exposures are likely to overwhelm the strong reductive capacity of saliva and gastric juices that have been well documented (c.f. De Flora S, Carcinogenesis 2000;21; 533-541). Published work also suggests that rodents may be more sensitive to oral Cr(VI) toxicity that humans. Thus, published pharmacokinetic studies have reported a several fold greater level of gastric absorption of Cr(VI) in rodents compared to humans, possibly due to the higher pH of rodent gastric juice. An apparently extensive study of the cancer effects of lower water concentrations in humans (Bednar and Kies,
1991), although referred to in a peer-reviewed study authored by CEPA personnel (Beaumont et al. 2008), was not included in the literature survey that was conducted for this proposal. The results of this study may provide information on the validity of the apparently unduly conservative extrapolation of the available cancer data to the establishment of a PHG for Cr(VI) of only 0.06 ug/L (0.06 ppb) in the proposal.

In summary, the proposed PHG for Cr(VI), which is fully six orders of magnitude lower than the active concentrations in mice, is well below current safety standards, appears to be lower than levels in uncontaminated waters, is near the limits of detection with currently available analytical methods, and apparently does not consider the likelihood of a threshold for Cr(VI) biological activity, requires further justification.