November 18, 2010

Office of Environmental Information Docket
Mail Code: 2822T
U.S. Environmental Protection Agency
1200 Pennsylvania Ave., NW.
Washington, DC 20460


Dear Sir or Madam:

The American Water Works Association (AWWA) appreciates the opportunity to submit these comments on the U.S. Environmental Protection Agency’s (EPA’s) notice on the Draft Toxicological Review of Hexavalent Chromium: In Support of Summary Information on the Integrated Risk Information System (September 30, 2010, 75 Federal Register 60455). AWWA is an international, nonprofit, scientific and educational society dedicated to the improvement of water quality and supply. Founded in 1881, the association is the largest organization of water supply professionals in the world. Our more than 55,000 members represent the full spectrum of the drinking water community: treatment plant operators and managers, environmental advocates, engineers, scientists, academicians, and others who hold a genuine interest in water supply and public health. Our membership includes more than 4,100 water systems that supply roughly 80 percent of the nation’s drinking water. AWWA and its member utilities are dedicated to safe water. AWWA and its member utilities are committed to assisting in the development of science-based regulations that provide meaningful risk reduction to protect public health.

AWWA asked Dr. Douglas Crawford-Brown to review the draft Toxicological Review giving particular attention to the charge questions posed that the agency posed to
its external review panel. His review is attached. In brief, Dr. Crawford-Brown's review identified several specific improvements that are essential to ensuring the final toxicological review is scientifically sound and appropriately informative for risk assessors and risk managers. The document should:

1. Provide a convincing basis for the explicit selection of the linear exposure-response relationship for carcinogenicity, and the implicit basis for non-carcinogenic endpoints, in determining the reference dose (RfD) and the cancer slope factor at environmental levels of exposure.

2. Provide the reviewer the ability to determine the slope of the exposure-response curve in the vicinity of the benchmark dose, which would provide essential information in determining the degree of conservatism that would be required in extrapolating below the benchmark dose.

3. Clearly state and provide evidence to support implicit and critical assumption that mutagenicity / genotoxicity is the primary mode of action at doses of environmental concern.

4. Incorporate studies at lower exposures, like the study currently being conducted by ToxStrategies. The data from the ToxStrategies study should inform extrapolation to the point of departure and the derivation of the RfD.

5. Describe the NTP study fully including: providing data on the full pool of animals dosed, the dosing regimes for all animals, the histopathology and other endpoint measurements performed for all animals, and explain, where only data on a subset of animals is used or available, why this subset was selected and whether it is representative of the full population of animals dosed in the original study.

6. Provide a clear description why epithelial hyperplasia in the duodenum of female mice is considered to be adverse, and a proper basis for a No Observed Adverse Effect (NOAEL) / Lowest Observed Adverse Effect Level (LOAEL) determination, and why it is expected to continue to be adverse or even present at much lower exposures.

7. Explain the basis in the available data (or lack there of) for the uncertainty factors employed in the agency's analysis.

8. Fully explain why mutagenic mode of carcinogenic action is the primary mode of action for hexavalent chromium and why alternative modes of action are not appropriate.
The attached review is consistent with President Obama’s and Administrator Jackson’s call for making EPA decisions more transparent. Dr. Crawford-Brown’s review illustrates how communicating when professional judgment is used and why specific choices are made will result in a more transparent document.

AWWA appreciates the agency’s consideration of the attached technical review. If there are any questions, please direct them to me or Steve Via at (202) 326-6130.

Best regards,

Thomas W. Curtis
Deputy Executive Director
AWWA Government Affairs

cc: Lynn Flowers, EPA/ORD/NCEA
    Christine Ross, EPA/ORD/NCEA
    Ted Berner, EPA/ORD/NCEA
    Edward Ohanian, EPA/OW
    Beth Doyle, EPA/OW/OST
    Cynthia Dougherty, EPA/OW/OGWDW
    Wynne Miller, EPA/OW/OGWDW
The following Review is structured around the Charge Questions to Reviewers provided by the EPA.

1. Is the Toxicological Review logical, clear and concise? Has EPA clearly presented and synthesized the scientific evidence for non-cancer and cancer hazard?

Overall, the document is well prepared, in the sense of leading the reader step-by-step to the conclusions drawn in Chapter 6. There has been a reasonable attempt to summarize a quite large body of data into a report that is of reasonable size. The scientific evidence reviewed is the best available, and there appears to have been no systematic exclusion of data that would lead to contrary conclusions. In this sense, therefore, the document is well balanced and easy to follow.

Where there is much less clarity, reducing the scientific basis of the conclusions, is in the selection of the exposure-response function to be assumed. Inherent in the document is the assumption that linearity is to be assumed below the point of departure. The authors have explained clearly how the POD was determined using Benchmark Doses, including the selection of the 10% incidence point as the POD. It is a simple matter to follow the reasoning from the primary data selected to develop the BMDs to the creation of a POD, and then onwards to the RfD and cancer slope factor (CSF).

However, the report fails to provide to provide a convincing basis for the explicit selection of the linear exposure-response relationship for carcinogenicity, and the implicit basis for non-cancer endpoints, in determining the RfD and the CSF at environmental levels of exposure. For the endpoints selected in both cancer and non-cancer, the available data showing statistically significant increases in incidence are at levels of exposure several orders of magnitude above those likely to be encountered in environmental exposures, and especially in drinking water systems. This requires significant extrapolation downwards, which therefore brings focus on the information provided in the data on the slope in the vicinity of the POD.

The derivation of the RfD is presented clearly, as it follows standard EPA procedures for building conservatism into regulatory limits. There should be a slightly better presentation of the development of the final value of the BMD and POD in this non-cancer case, so the reader can see the original data on which it is based; the fit to those data using the selected exposure-response function; and the identification of the BMD/ POD. This is described in the text, but a visual display of these data and the curve fit for the BMD is a much better approach and is necessary if the reviewer is to determine the reasonableness of the fit and the slope of the exposure-response curve in the vicinity.
of the BMD. As written, the document does not provide the reviewer the ability to determine the slope of the D-R curve in the vicinity of the BMD, which would provide essential information in determining the degree of conservatism that would be required in extrapolating below the BMD. We note that this remains a significant problem within EPA determinations of non-cancer and cancer extrapolations to PODs and development of RfDs and CSFs, despite continuing recognition within the Agency scientific staff that this slope of the D-R data (near the BMD) is critical in informing the approach to conservatism in regulatory limits. It is disappointing to see that it remains unconsidered in the present document.

Development of the CSF remains similarly unclear. The authors do state categorically that Cr-6 can act by genotoxicity/mutagenicity, and appear to use this conclusion to justify linear extrapolation below the POD. Their statement is based on the data they present showing interactions of metabolic products of Cr-6 with DNA, and at least limited mutagenicity. However, when one examines the primary data they cite, the evidence for mutagenicity and genotoxicity is confined to exposures orders of magnitude above those expected environmentally. Implicit (and unstated) in the document, therefore, is the assumption that mutagenicity/genotoxicity is the PRIMARY mode of action of Cr-6 and metabolites at these higher exposures and for these particular tumors examined in the male mice, as well as the assumption that this will remain true at much lower exposures of environmental concern.

The document neither states this crucial set of assumptions, nor provides any evidence to support it. One might argue that this is a common set of assumptions in Agency regulatory assessments, and so needs no further justification in the present document, but it is precisely this issue that has been at the heart of scientific scrutiny within the Agency and the NRC over the past decade, leading in part to the NexGen program. There is strong evidence that the MOA can change across the scale of exposures, with the balance between genotoxic and mutagenic mechanisms on the one hand and stimulated proliferation on the other changing with exposure. This is an especially critical issue in the current document since so many of the critical effects are related to issues of hyperplasia. Again, it is disappointing to see the issue unaddressed clearly in the present document. At the least, these assumptions must be clearly stated, and the evidence for their selection provided, so this aspect of the assessment can be debated.

2. Please identify any additional studies that would make a significant impact on the conclusions of the Toxicological Review.

The authors have assembled the relevant base of data from amongst the currently available studies. However, as these studies are all at exposures well above those of environmental interest, there is a need to develop better data at exposures below those used to develop the PODs in the current document. Groups such as ToxStrategies are currently conducting studies at these lower exposures to help inform the process of extrapolation, and at the least these studies should be considered before a final IRIS entry is made. An alternative is for the authors of the current document to do a much better job
of presenting an assessment of the slope of the data in the vicinity of the POD, which can also be used to assess the reasonableness of different extrapolation models.

Chemical-Specific Charge Questions:

(A) Oral Reference Dose (RfD) for Hexavalent Chromium

1. A two-year drinking water study of sodium dichromate dihydrate in rats and mice (NTP, 2008) was selected as the basis for the derivation of the RfD. Please comment on whether the selection of this study as the principal study is scientifically supported and clearly described. Please identify and provide the rationale for any other studies that should be selected as the principal study.

The NTP study is the relevant one to use in this report, and is the most complete and recent study available to the authors. It should be supplemented with the ToxStrategies study when the latter is available, but at least at the moment the NTP database is the best available.

The authors state clearly how they have used the NTP results, subject to the problems identified in the opening section of this review concerning the inability of the reader to see how the D-R curve appears in the vicinity of the POD. More problematic is the difficulty by at least the current reviewer to determine whether all of the data generated in the NTP study were used. Since these data are critical in developing the RfD, the current document should describe the full pool of animals dosed; provide the dosing regimes for all animals; provide the histopathology and other endpoint measurements performed for all animals; and explain, where only data on a subset of animals is used or available, why this subset was selected and whether it is representative of the full population of animals dosed in the original study. As currently described in the document under review, the reader cannot assess these issues, greatly reducing the ability to determine the robustness of the conclusions to other data that might have been generated in the NTP study but are not summarized or used in the document. The reviewer should not be left to go back to the NTP to uncover the full set of data generated.

2. Diffuse epithelial hyperplasia in the duodenum of female mice was selected as the critical effect for the RfD. Please comment on whether the selection of this critical effect is scientifically supported and clearly described. Please identify and provide the rationale for any other endpoints that should be selected as the critical effect.

This effect is relevant to the determination of critical effects, and the NOAEL/LOAEL. The reason for selecting this endpoint is discussed clearly in the document, so the reader can understand why it was selected as the basis for a NOEL/LOEL determination, at least under current Agency practice. Missing from the document, however, is any clear description as to why this same effect is considered to be adverse, and hence a proper basis for a NOAEL/LOAEL determination, and why it is expected to continue to be adverse or even present at much lower exposures. Hyperplasia is particularly problematic because it can be induced by a number of mechanisms that are known scientifically to be
significant at high exposures but to disappear, or at least become much less significant in the overall MOA, at lower exposures of environmental interest. These differences are both in the relationship between exposure, uptake and dose (such as in the potential saturation of chemical transformation mechanisms in the stomach when Cr-VI is delivered in large quantities, allowing for greater fractional uptake into the epithelium of the GI tract at high intakes); and in the relationship between dose and degree of hyperplasia. Therefore, the weakness of the present document is not so much in choosing this particular effect to produce the POD, but rather in failing to explain the basis for considering it adverse at levels of environmental interest.

3. Benchmark dose (BMD) modeling was applied to the incidence of diffuse epithelial hyperplasia in the duodenum of female mice to derive the point of departure (POD) for the RfD. Has the BMD modeling been appropriately conducted and clearly described? Is the benchmark response (BMR) selected for use in deriving the POD (i.e., a 10% increase in the incidence of diffuse epithelial hyperplasia) scientifically supported and clearly described?

Development of the BMD follows standard Agency practice in both BMD and BMR development. The authors have chosen the correct body of data to use, conditional on their assumption that adverseness continues at low exposures (see Comment 2 above), and provide a reasonable verbal description of the process they used. As noted earlier in this review, this description would be greatly improved by showing the original data graphically, showing the curve fit, and showing the selected BMD/BMR and POD on that same figure. This would allow the reader to grasp the slope of the curve in the vicinity of the BMD/BMR and POD. The authors should then include an explanation, referring to this figure, of the implications of this “near BMD/BMR slope” for the extrapolation to lower exposures that are relevant to development of the RfD. Absent this, critical scientific information is being lost through too-rote application of existing Agency methods that do not reflect scientific advances such as the Agency’s NexGen program.

4. Please comment on the rationale for the selection of the uncertainty factors (UFs) applied to the POD for the derivation of the RfD. Are the UFs scientifically supported and clearly described? If changes to the selected UFs are proposed, please identify and provide a rationale.

There is no description of the rationale for selection of the UFs, except to state why the factor of 100 was applied as resulting from the two components of inter-species differences and inter-subject variability. The selection of these particular numerical values appears to be simply because there are no data on which to develop factors other than 10 and 10, although this is not stated explicitly. One can understand the selection of these two factors seen through the lens of current Agency practice (the selection here is consistent with that practice), but there is no explanation as to why that practice itself is reasonable. As mentioned previously, selection of a UF should reflect at least in part the slope of the D-R curve in the vicinity of the POD, and this either is not the case in the present document or has not been discussed. Significant improvements can be made here in the text without requiring a long discussion.
(B) Carcinogenicity of Hexavalent Chromium

1. Under EPA’s 2005 Guidelines for Carcinogen Risk Assessment, hexavalent chromium is likely to be carcinogenic to humans by the oral route of exposure. Is the cancer weight of evidence characterization scientifically supported and clearly described?

The answer here must be given in two parts. First, following standard Agency practice, the basis for classifying CR-6 as a likely human carcinogen is provided clearly, based on the findings of carcinogenicity in one or more lab animal species that have formed the basis for many such determinations on other contaminants. And the authors have stated clearly that the available epidemiological data do not allow classification as a known human carcinogen. They are correct in this. So the authors have provided a reasonable description of their judgment reflecting past practice.

Where there is a much less satisfactory explanation is around the issue of whether it is justified scientifically to conclude that carcinogenicity is a simple yes/no determination. Since the MOA can change appreciably with level of exposure, it is not valid to assume that demonstrated carcinogenicity at the high exposures reviewed in the document implies carcinogenicity at levels of environmental interest. The document authors make no attempt to address this issue, or to support the choice of concluding that Cr-6 is likely to be a carcinogen in humans at exposures of environmental interest. The current reviewer realizes that this scientific issue is not currently part of standard Agency practice in producing carcinogen classifications, but it is at least implicit in the evolving science underlying Weight of Evidence determinations, and so should be at least mentioned in the current document on Cr-6.

Having said this, the carcinogenicity classification is not that critical in producing a CSF value, and hence a regulatory limit on exposures. In producing a CSF, the more interesting question is over selection of the D-R curve to use in extrapolating to exposures of environmental interest.

2. A mutagenic mode of carcinogenic action by all routes of exposure is proposed as the primary mode of action for hexavalent chromium. Please comment on whether this determination is scientifically supported and clearly described. Please comment on data available for hexavalent chromium that may support an alternative primary mode of action.

This is a particularly weak aspect of the current document. The description in 4.7.3.3 is cursory and inconclusive. It describes what the authors were thinking in choosing the mutagenic mode of action, and provides the evidence they used to support this judgment, but does not describe systematically why this particular MOA is a more likely explanation than modes such as removal of apoptosis or non-cytotoxic modes of stimulating proliferation and hyperplasia.
As mentioned previously in this review, the available data do suggest that there is some genotoxicity and mutagenicity at high exposures. The document completely fails, however, in presenting a coherent scientific argument as to why this is the dominant mode of action even at these high exposures, or why it is assumed this will be a dominant or even existing mode of action at the much lower exposures of environmental interest. This is a particularly important issue because the cancer endpoints examined in the document all point to some form of hyperplasia, and presumably proliferation, playing a significant role in the particular tumors observed. Whether this role is sufficient to call into question the assumption that genotoxicity/mutagenicity is a critical aspect of the MOA cannot be determined from the current document, because the authors offer little insight into this issue. This doesn’t mean they are incorrect in their decision, only that the scientific basis for this decision is not provided in the document. Again, provision of a graphical summary of the D-R data on carcinogenicity, and formal quantitative assessment of the slope of this curve in the vicinity of the BMD/BMR, would provide evidence one way or the other.

3. A two-year drinking water study in rats and mice (NTP, 2008) was selected for the derivation of an oral slope factor. Please comment on whether the selection of this study for quantification is scientifically supported and clearly described. Please identify and provide the rationale for any other studies that should be considered.

Given the caveats provided in the previous review comments, the selection of this particular study is appropriate and has been correctly analyzed.

4. The incidence of adenomas and carcinomas combined in the small intestine of male mice from the NTP (2008) two-year drinking water study were selected to serve as the basis for the quantitative cancer assessment. Please comment on whether this selection is scientifically supported and clearly described. Please identify and provide the rationale for any other endpoints that should be selected to serve as the basis for the quantitative cancer assessment.

Again, given the caveats provided in the previous review comments, the selection of this particular cancer endpoint is appropriate and has been correctly analyzed. Where the document needs significant improvement is in describing why the significantly reduced incidence in other species, and in females, has not been factored into development of a final CSF, or at least an explanation provided of the implications of this reduced response.

5. The oral slope factor was calculated by linear extrapolation from the POD (i.e., the lower 95% confidence limit on the dose associated with 10% extra risk of tumors of the small intestine in male mice). Has the modeling been appropriately conducted and clearly described?

This approach follows standard Agency practice, and the procedure has been described at least verbally. As mentioned previously, however, the document requires a graphical and quantitative depiction of the D-R data, including the implications of the slope of the D-R
curve in the vicinity of the POD. As the document stands currently, the reader cannot determine the reasonableness of the assumption of linearity below the POD.