Responses to Major Comments on Technical Support Document

Public Health Goal

For

Uranium

In Drinking Water

Prepared by

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INTRODUCTION

The following are responses to major comments received by the Office of Environmental Health Hazard Assessment (OEHHA) on the proposed public health goal (PHG) technical support document for uranium as discussed at the PHG workshop held on November 5, 1999, or as revised following the workshop. Some commenters provided comments on both the first and second drafts. For the sake of brevity, we have selected the more important or representative comments for responses. Comments appear in quotation marks where they are directly quoted from the submission; paraphrased comments are in italics.

These comments and responses are provided in the spirit of the open dialogue among scientists that is part of the process under Health and Safety Code Section 57003. For further information about the PHG process or to obtain copies of PHG documents, visit the OEHHA Web site at www.oehha.org. OEHHA may also be contacted at:

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RESPONSES TO MAJOR COMMENTS RECEIVED

Comments from Office of Water, U.S. Environmental Protection Agency

Comment 1: "The study used to derive the PHG is a Report to Medical Services Branch on a Study Conducted by the Radiation Protection Bureau of the Health Protection Branch of Health Canada (1998). This report has not undergone peer review nor has it been published in a peer-reviewed journal. Thus, the use of such a report for developing PHGs [is not] recommended since it will be hard to defend it in the scientific community. Although the authors claim that there is a statistically significant increase in the levels of gamma glutamyl transferase (GGT) and beta-2-microglobulin (BMG) in the urine of exposed individuals indicating proximal kidney tubule effects, the levels are still within the normal range. Another study done by Zamora et al. (1998), also from Health Canada, found increased levels of alkaline phosphatase (ALP), BMG and glucose in individuals exposed to high levels of uranium in their well waters compared to the ones exposed [to] 1 μg/l; however, levels of ALP and BMG though on the high side were within the normal range; the levels of glucose were slightly above the normal range; it's significance however is not known as yet. Also, this last study is done on 50 individuals only."

Response 1: We agree that the Health Canada study on which the proposed public health goal (PHG) was based provided a relatively weak endpoint for calculation of health-protective levels of uranium in drinking water. Because it appears to be a valid scientific study and the use of this study was judged acceptable by our University of California peer reviewer, we continue to cite it. However, the PHG has been revised and is now based on the carcinogenic hazards from ionizing radiation, using the U.S. EPA's 1999 guidance report on cancer risk coefficients for environmental exposures to radionuclides.

Comment 2: "USEPA's draft MCL is based on a study by Gilman et al. (1998). This is a 91-day study in SD rats given uranyl nitrate hexahydrate in DW. The LOAEL identified in this study is 0.06 mg/kg/day based on histopathological effects seen in the kidney, the severity of which was dose related. Similar effects were seen in New Zealand White rabbits also. Since both these studies have been published in a peer reviewed journal, I feel this is a better study for calculating the MCL or for that matter the PHG. In the Summary Section, the authors of this PHG document also state that 'histopathological lesions of kidney tubules…are considered adverse effects….'"

Response 2: The studies by Gilman et al. (1998) could be appropriate studies on which to base a PHG. We have calculated values based on these studies and presented them in the document. These values were not used for the final PHG because we believe the carcinogenic effects of ionizing radiation provide a more compelling and appropriate endpoint. However, the animal data of Gilman et al. and, the Health Canada human study provide strong supportive evidence for a public health protective level based on the carcinogenic endpoint. The health-protective levels we calculate from the Gilman et al. data (0.3 ppb for adults, 0.08 ppb for a child) and the Health Canada data (0.3 ppb) are very similar to the level (0.6 ppb) based on the carcinogenic endpoint.

Comment 3: "We would like to clarify a few statements mentioned in this document concerning U.S. EPA":

Comment 3a: "In 1991 USEPA used 20% as the absorption of uranium from the gut, the current estimate of GI absorption used by USEPA is 2%, based on new information."

Response 3a: The document has been amended to show this change.

Comment 3b: "USEPA has never claimed that U238 is not carcinogenic. Although no epidemiological studies have unequivocally proved its carcinogenic potential due to confounding factors in the available studies, U.S. EPA has always claimed that because U emits ionizing radiation, it is considered a human carcinogen. This needs to be clearly stated in the first paragraph on page 11."

Response 3b: The document has been amended to clarify this point.

Comment 3c: "On page 11, in the second full paragraph, the data from the Health Canada study should be cited rather than saying "see Table 7 of Health Canada, 1998." Reviewers may not have the report with them."

Response 3c: The data table has been added to the document.

Comment 3d: "The PHG document is using the specific activity of U as 0.79 pCi/μg. USEPA has used 1.3 pCi/μg. It is possible that the uranium in California waters has a lower specific activity compared to the average specific activity that the USEPA uses."

Response 3d: California natural uranium in drinking water does have a lower specific activity. The source of this information is cited in the document.

Comments from University of California, Davis

Comment 1: "The PHG derived from the Health Canada Study is supported by the data. However, it might be worthwhile to have an additional consideration in the document: with a level of 0.2 μgU/L drinking water, the "standard" daily intake can be expected to be 0.4 μg or, for a 70 kg man, 0.006 μg/kg. According to the Zamora study (described on page 13), the lowest value indicative of disturbed kidney function was found to be 0.004 μg/kg/day. It needs explanation why the PHG might be in excess of a level found to have detectable effects of kidney damage in man."

Response 1: The Zamora (1998) study was an ecological study that compared a "high exposure group" with a "low exposure group." The high exposure group had daily intakes ranging from 0.004 to 9 μg/kg. Higher urinary glucose levels were seen in the high exposure group relative to the low exposure group. The data were not adequate to determine a lower level at which this effect began. The lower end of the "high exposure" range is therefore not necessarily an effect level. The text is being changed to clarify this point.

Comment 2: "In 1983, a NRC council came up with a SNARL in drinking water of 35 μg/L based on non-carcinogenic response in adults. This is almost 200 times higher as the currently proposed PHG. Since a great deal of toxicity data on U was available in 1983, it would be interesting to consult the NRC

report and discuss why, at the time being, U was considered to be that much less toxic and provide an explanation. On what data was the then recommendation based and what has changed since that made U so much more toxic?"

Response 2: The suggested no-adverse-response-level (SNARL) was based on a 1949 one-year dog feeding study by Maynard and Hodge. In this study, 1 mg/kg-day was found to be "the highest dietary level tolerated by dogs with no decreases in body weight or symptoms of renal involvement." The SNARL was calculated as follows:

$$\text{SNARL} = \frac{\text{NOAEL} \times \text{bw} \times \text{RSC}}{\text{UF} \times 2\ \text{L/d}} = \frac{1.0\ \text{mg/kg-d} \times 70\ \text{kg} \times 0.1}{100 \times 2\ \text{L/d}} = 0.035\ \text{mg/liter or } 35\ \mu\text{g/L}$$

The kidney effects looked for in this study were elevations in blood nonprotein nitrogen and urea nitrogen, and transient urinary sugar and proteinuria. This study was less informative than the more recent studies on kidney effects, because the number of data points and the length of exposure was less. Text has been added to the document to further explain the SNARL.

Comment 3: "Is there any epidemiological evidence to suggest that in populations exposed to high U levels in drinking water (like the Zamora population) have increased incidence of kidney disease?"

Response 3: To our knowledge there are no epidemiological studies on incidence of renal disease in populations exposed to uranium at these levels.

Comment 4: "There is a serious problem with the references in this document."

Response 4: The missing references have been added, and the whole document has been checked for problems with the references.

Comment 5: "Throughout the document, amounts and concentrations of U are sometimes given as weight (mg, µg or ppb) or as radioactive units (pCi). This is very confusing and made even more so since it is never clear whether there is a one to one ratio: right at the beginning of the document it is stated that the PHG will be 0.2 ppb (0.2 pCi/L), implying that 1 µg corresponds to 1 pCi. However, on page 23, line 24, 20 µg/L are equated with 30 pCi; whereas on page 23, line 4 from bottom, 35 µg/L corresponds to 23 pCi/L."

Response 5: The PHG level has been recalculated as 0.6 ppb (0.5 pCi/L) based on the change to a carcinogenic hazard from radioactivity endpoint. The concept of different cancer potencies for different isotopes has been addressed earlier and hopefully more clearly. The three different values for the specific activity of natural uranium which have been used by regulatory agencies make the subject inherently confusing, but these are all discussed in the document. The equilibrium specific activity is 0.67 pCi/µg. This value has been known for a long time, and was used in 1983 to convert the SNARL of 35 µg/L to 23 pCi/L. Later, the U.S. Environmental Protection Agency used 1.3 pCi/µg (based on a national survey of natural uranium in drinking water sources) as the specific activity to convert an MCL of 20 µg/L to 30 pCi/L. The Office of Environmental Health Hazard Assessment (OEHHA) has used a specific activity of 0.79 pCi/µg (based on a survey of California drinking water sources) for its conversions. An attempt has been made to make the terminology and units as consistent as possible throughout the document.

Comment 6: "In the same line, it should be specified whenever toxicities are given in mass whether the number refers to the complete molecule or only to the cation. See for example page 8, Subacute, noncarcinogenic effects: adverse effects of dogs were observed at 0.2 g/kg of uranyl nitrate -- this is clear. But Morrow then exposed dogs to UF6/UO2F2 and toxicity is only defined in 10 μg/kg body weight (line 9 from bottom) -- is this alone or the compound? The document needs to be scrutinized for such ambiguities."

Response 6: The Morrow study reported an absorbed dose of 10 μg U^{6+}/kg body weight. This has been clarified in the document, and the document has been checked for similar ambiguities.

Comment 7: "On page 13, a 91-day study in rats yields a lowest-observed-adverse-effect-level (LOAEL) of 0.06 mg/kg/day. In rabbits the subchronic LOAEL is 0.05 mg/kg/day. The text then goes on: (page 13, line 15: "The findings of effects on human kidney function resulting from quite low exposure of uranium levels of U in drinking water (0.004 μg/kg-d to 9 μg/kg-d) tends to support the animal data…" (??) These data (unless there is a typo somewhere) seem to suggest to me that man is 1000 times more sensitive. On page 17, line 11 it is stated: (Uncertainty factor): 1 (one) for interspecies differences since the responses in humans and experimental animals appear very similar. How does this make sense?"

Response 7: The sentence comparing the rat LOAEL with the range of exposures in the Zamora (1998) study has been taken out of the text. This was not a good comparison because the figures from the Zamora study merely represented the range of exposures in the study. The calculation of a health protective concentration based on the rat data has been changed to include a 10-fold UF for interspecies differences.

Comment 8: Page 5, line 9: "What is the significance of this difference in absorption between summer and winter samples?"

Response 8: We do not know if this is significant. It is merely an observation reported by the investigators. No subsequent publications investigated possible seasonal differences in absorption.

Comment 9: Page 5, line 25: "What is the basis for this assumption?"

Response 9: As discussed in the PHG document, neonates have been shown to have enhanced intestinal absorption of certain metals, including iron, lead, and cadmium. Certain constituents have been shown to enhance the absorption of metals. It seems a reasonable assumption that uranium, a metal, would also be absorbed more readily under the same conditions.

Comment 10: Page 6, third paragraph: "Why give amount per 5,000 g of bone instead of concentration?"

Response 10: This is the way the authors (Wrenn et al.) reported the results, apparently putting the emphasis on the whole body burden of uranium. The concentration can be easily calculated from these figures, i.e., 25 μg uranium per 5 kg bone is 5 μg/kg, or 5 ppb. The recalculation to 5 μg/kg has been added to the document.

Comment 11: Page 6, fourth paragraph: "What is "occupationally exposed"? What route? What compound? How much? How long?"

Response 11: The individual is described as "a chemical operator in a uranium processing plant." The route, compound and other details of exposure are not given in the original paper. However, the paper does give data on the yearly uranium excretion from this individual. He excreted a total of 118.3 mg of uranium over a period of 20 years. This level of detail is not needed in the PHG document, because this report is cited only to describe the relative amounts of uranium that were found in the major tissues at autopsy. The length of exposure (20 years) has been added to the document.

Comment 12: Page 8, table 1: "LD_{50} is not necessarily the lethal dose -- it is what it says -- the lethal dose for half the population."

Response 12: The text has been changed to indicate "median lethal dose."

Comment 13: Page 9, line 11: "Would the Braunlich and Fleck studies allow to estimate to what extent young or old individuals [are] more or less sensitive? Why was alkaline phosphatase no good [for] measurements in young or old rats?"

Response 13: The Braunlich and Fleck study was a study of the effects of a single dose of uranyl nitrate (6 mg/kg). For this reason it is of limited value in trying to understand the age dependence of chronic effects. Chronic effects are of concern for PHGs. For some reason the young (15 day old) and old (240 day old) rats did not show as much of an alkaline phosphatase response as the 20 day and 33 day old rats. The authors speculate that the absence of response in the "neonates" may be due to "absence or incompleteness of enzyme pattern of tubular cells at this age," and that in the old rats the "enzyme activities are low in comparison with adult animals."

Comments from Association of California Water Agencies and Sacramento Department of Utilities

Comment 1: It is inappropriate for OEHHA to use the 1998 Health Canada study in the uranium PHG calculation because:

a) the relative uranium exposure from all sources is not known,
b) the exposed population is small, unique and is not characteristic of California,
c) the study contained no zero-exposed control group,
d) the changes noted are not scientifically linked to actual adverse effects, and
e) the effects of measurement error were not considered."

Response 1: We agree that the Health Canada study on which the proposed public health goal (PHG) was based provided a relatively weak endpoint for calculation of health-protective levels of uranium in drinking water. Because it appears to be a valid scientific study and the use of this study was judged acceptable by our University of California peer reviewer, we continue to cite it. However, the PHG has been revised and is now based on the carcinogenic hazards from ionizing radiation, using the 1999 radiation hazard estimates of the U.S. EPA.

Comment 2: "The PHG for uranium should be delayed until the USEPA completes its risk assessment for uranium and other radionuclides. USEPA is set to release a Notice of Data Availability this spring for many radionuclides, including uranium, that may prove beneficial to OEHHA in finalizing this PHG."

Response 2: The U.S. EPA final rule for radionuclides including uranium was published in December, 2000 (40 CFR Parts 9, 141, and 142, Vol. 65, No. 236, Dec. 7, 2000), and has been considered in the revised PHG estimate. The U.S. EPA's risk assessment is based on radioactive effects while noting potent kidney toxicity, as is ours. The PHG for uranium appears to be based on the same radioactivity assessment as the U.S. EPA final radionuclide rule. The newly promulgated federal MCL for uranium is 30 μg/L, revised upward from 20 μg/L in the 1991 proposed rule. This level (including the revision upward) is based on a cost benefit analysis, and is acknowledged to exceed a 10^{-6} cancer risk level, calculated with a no-threshold assumption. The U.S. EPA maximum contaminant level goal (MCLG), more analogous to the PHG, remains set at zero.

Comment 3: "If OEHHA proceeds to establish the PHG for uranium at this time, it should base the calculation of the PHG on the Gilman et al (1998) study. However, OEHHA should follow the international consensus conclusions from the 1998 U.S. EPA workshop on uranium, in which OEHHA participated, regarding use of this study for calculating a public health goal."

Response 3: OEHHA participated in the workshop as a way of exchanging relevant information with scientists from U.S. EPA and Canada. The workshop had no mechanism for reaching "consensus" on a public health goal among the participants, and the contractors summary purporting to describe a consensus was in error, as we noted in our comments on the draft returned to the contractor. However, this is somewhat moot, after revision of our evaluation to use risk from ionizing radiation as the endpoint.

Comments from City of Riverside, Public Utilities Department

Comment 1: "Riverside, like ACWA, is particularly concerned that the very "limited" Canadian study referenced in the proposed PHG document could be used to propose an unnecessarily too stringent PHG for uranium. The Kitigan Zibi Community data is not typical of community water systems in California. For example, the community profile of the data suggests statistical bias towards female gender because only 15 of the 54 data samples were associated with the male gender."

Response 1: The revised PHG acknowledges these concerns by basing the public health level on risks from ionizing radiation rather than the Canadian study.

Comment 2: "Our experience suggests that wells with high levels of uranium may have higher levels of turbidity and other associated dissolved contaminants. The Canadian study did not provide the water chemistry and as such, the observed health outcomes may not be entirely associated with uranium in drinking water."

Response 2: The effects of water chemistry on the toxicity of uranium are an important factor that deserves further study. It would have been an improvement if the Health Canada study had included a complete analysis of the water supplies. However, the kidney effects observed in the study are exactly those that have been associated with uranium exposure in numerous previous studies. The observed kidney changes in this community are important to consider in the overall evaluation of uranium effects, although the PHG is no longer based upon these kidney effects.

Comment 3: "Water is a relatively insignificant source of uranium intake by adults according to the January 1988 Canadian Guidelines for Drinking Water Quality -- Supporting Documents for Uranium. Estimates of daily intake of uranium by adults are 1.5 μg from food in contrast to 0.075 μg from water."

Response 3: As cited in the PHG document, the National Council on Radiation Protection and Measurements (NCRPM, 1984) estimated that humans take in approximately the same amount of uranium from food and water. The proportions may vary considerably from place to place, depending of course on how much uranium is in the local water supply. The PHG is intended to deal with uranium in drinking water, and is most relevant where the uranium level in water is relatively high and is thus proportionately greater, compared with food sources.

Comment 4: "The relative contribution of uranium from other sources of exposures are not known, and over reliance on the total fluid intake resulted in distorted conclusions as shown in Figure 1 of the proposed PHG document and attached Figure 1. Our preliminary analyses of the Canadian study suggest that the urine volume of some of the subjects greatly exceed the total fluid intake as shown in the attached Table 2 and Figure 3. As such, we reanalyzed the dependence as shown in Table 3 and Figure 4 by not including the sample data of those subjects where the urine volume exceeded the total fluid intake."

Response 4: In the evaluation of this study, the relative contribution from "other sources" has been assumed to equally affect the groups with high exposure from drinking water and those with low exposure. The rationale for this assumption is that foods consumed in a community would not be expected to reflect the uranium content of the drinking water wells from which the individuals are obtaining their drinking water.

The rationale for excluding those subjects for whom the urine volume exceeded the total fluid intake is not clear. Perhaps it is based on an assumption that it should not be possible for urine volume to exceed total fluid intake. This would not be a correct assumption. The water part of urine is made up of water from three sources: 1) water from fluid intake, 2) water from solid foods, and 3) water produced metabolically by the oxidation of hydrogen in organic compounds. Since fluid intake is only one part of the water of urine, there is no reason to expect that the urine volume cannot exceed the fluid intake. There is therefore no reason to exclude these subjects from the analysis. The results of epidemiological studies can often be changed by arbitrarily excluding certain groups of individuals. A rationale must be provided for such exclusions. Another thing to keep in mind is that the fluid consumption data are based on the subjects' recall of how much they drank, and this may not be very accurate.

Comment 5: "The expected health outcomes that formed the basis for setting the PHGs are not severe and may be reversible after the exposure to the uranium ceases (Page vii of Canadian study). California population is highly mobile."

Response 5: The health outcomes described in the Canadian study (such as increased beta microglobulin excretion) are not severe in themselves, but are indicative of changes in the kidney tubules which may progress to severe effects. The purpose of setting health-protective levels is to avoid any adverse health effects, even ones that are not life-threatening or "severe." While it is true that much of the California population is highly mobile, not all individuals in the population are mobile. Some individuals may remain in the same location for decades, continuing to drink the same water. Risk assessments have traditionally assumed that individuals will be exposed for a lifetime.